Untersuchungen und Identifikationsmöglichkeiten von minderwertigen und gefälschten Arzneimitteln zur Verbesserung der Arzneimittelqualität in Ländern mit niedrigem und mittlerem Einkommen

Dissertation

der Mathematisch-Naturwissenschaftlichen Fakultät
der Eberhard Karls Universität Tübingen
zur Erlangung des Grades eines
Doktors der Naturwissenschaften
(Dr. rer. nat.)

vorgelegt von
Cathrin Evelyn Marie Hauk
aus Ellwangen

Tübingen
2021

Gedruckt mit Genehmigung der Mathematisch-Naturwissenschaftlichen Fakultät der Eberhard Karls Universität Tübingen.

Tag der mündlichen Qualifikation:	17. Dezember 2021
Dekan:	Prof. Dr. Thilo Stehle
1. Berichterstatter:	Prof. Dr. Lutz Heide
2. Berichterstatter:	PD Dr. Bertolt Gust

Erklärung

Ich erkläre hiermit, dass ich die zur Promotion eingereichte Arbeit mit dem Titel: „Untersuchungen und Identifikationsmöglichkeiten von minderwertigen und gefälschten Arzneimitteln zur Verbesserung der Arzneimittelqualität in Ländern mit niedrigem und mittlerem Einkommen“ selbständig verfasst, nur die angegebenen Quellen und Hilfsmittel benutzt und Zitate als solche gekennzeichnet habe. Ich erkläre, dass die Richtlinien zur Sicherung guter wissenschaftlicher Praxis der Universität Tübingen (Beschluss des Senats vom 25.5.2000) beachtet wurden. Ich versichere an Eides statt, dass diese Angaben wahr sind und dass ich nichts verschwiegen habe. Mir ist bekannt, dass die falsche Abgabe einer Versicherung an Eides statt mit Freiheitsstrafe bis zu drei Jahren oder mit Geldstrafe bestraft wird.“

Tübingen, den

Cathrin Hauk

Inhaltverzeichnis

Abkürzungsverzeichnis

BP	British Pharmacopoeia, Britisches Arzneibuch
COVID-19	Coronavirus disease 2019, Coronavirus-Krankheit-2019
EML	Essential Medicines List, Liste der unentbehrlichen Arzneimittel
EPN	Ecumentical Pharmaceutical Network, Ökumenisches Pharmazeutische Netzwerk
Difäm	Deutsches Institut für ärztliche Mission e.V.
DR Kongo	Demokratische Republik Kongo
DC	Dünnschichtchromatographie
GDF	Global Drug Facility
GPHF	Global Pharma Health Fund e.V.
HPLC	High performance liquid chromatography, Hochleistungsflüssigkeitschromatographie
HR-MS	High resolution MS, hochauflösende Massenspektrometrie
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LC	Liquid chromatography, Flüssigchromatographie
LMICs	Low- and middle-income countries, Länder mit niedrigem und mittlerem Einkommen
LOAs	Limits of agreement, Grenzen der Übereinstimmung
MEDQUARG	Medicine Quality Assessment Reporting Guidelines
MDR-TB	Multidrug-resistant tuberculosis, multiresistente Tuberkulose
MP	Mega Pixel
MS	Mass spectrometry, Massenspektrometrie
NCD	Non-communicable disease, Nichtübertragbare Krankheit
NGO	Non-governmental organization, Nichtregierungsorganisation
Penicillin V	Phenoxymethylpenicillin
Ph. Int.	International Pharmacopoeia, Internationales Arzneibuch
QA	Quality assurance, Qualitätssicherung
QC	Quality control, Qualitätskontrolle
QCA	Quality control agent, Qualitätskontrollbeauftragter
RSD	Relative standard deviation, relative Standardabweichung

SDGs	Sustainable Development Goals, Ziele für nachhaltige Entwicklung
SF	Substandard and falsified, minderwertig und gefälscht
TB	Tuberkulose
TLC	Thin-layer chromatography, Dünnschichtchromatographie
UN	United Nations, Vereinten Nationen
USP	United States Pharmacopeia, US-amerikanisches Arzneibuch
WHO	World Health Organization, Weltgesundheitsorganisation

Zusammenfassung

Die weltweite Sicherstellung der Arzneimittelqualität ist eine der großen gesundheitspolitischen Herausforderungen unserer Zeit und Grundlage für eine allgemeine Gesundheitsversorgung, die als Ziel 3.8 in den nachhaltigen Entwicklungsziele der Vereinten Nationen verankert ist. Schätzungen der WHO zufolge ist eins von zehn Arzneimitteln in Ländern mit niedrigem und mittlerem Einkommen minderwertig oder gefälscht. Im Rahmen dieser Doktorarbeit wurde diese Schätzungen durch zwei Studien zur Qualität von Antibiotika und Arzneimitteln gegen nichtübertragbare Krankheiten bestätigten, die eine Prävalenz von 8% in Togo und 18,6% in Kamerun und der DR Kongo zeigten. Drei der 506 in Kamerun und der DR Kongo gesammelten Proben (0,6%) enthielten nicht den deklarierten Wirkstoff.

Einer der Gründe für die große Heterogenität der berichteten Prävalenzdaten von minderwertigen und gefälschten Arzneimitteln ist die Wahl unterschiedlicher Toleranzgrenzen. In einer nachfolgenden Studie wurde daher der Einfluss unterschiedlicher Toleranzgrenzen, die bei der Gehaltsbestimmung zur Unterscheidung zwischen „innerhalb der Spezifikation“ und „außerhalb der Spezifikation“ herangezogen werden, untersucht. Es wurde gezeigt, dass bei Verwendung desselben Probensatzes die Rate an Proben „außerhalb der Spezifikation“ abhängig von der Wahl der Toleranzgrenze zwischen 2,4% und 34,3% variierte. In derselben Studie wurden Authentizitätsanfragen an Hersteller und Vertreiber geschickt, die sich als effektive Methode zur Identifizierung von Fälschungen erwiesen. Von den 601 Proben, die in diese Studie miteinbezogen wurden, konnten sieben, nach Arzneibuchanalyse unauffällige Proben, als gefälschte Arzneimittel identifiziert werden.

In einer weiteren Studie wurden gefälschte Chloroquin Tabletten analysierte, die im März und April 2020 in Kamerun und in der DR Kongo gefunden wurden und sichtbar machten, wie die COVID-19 Pandemie, insbesondere in Ländern mit niedrigem und mittlerem Einkommen und schwachen regulatorischen Kotrollmechanismen, zu einer Zunahme an minderwertigen und gefälschten Arzneimitteln geführt hat.

Die Global Drug Facility (GDF) ist der weltweit größte Anbieter von qualitätsgesicherten Antituberkulotika für den öffentliche Sektor. Im Rahmen dieser

Doktorarbeit wurde eine Evaluierung der Qualitätssicherungs- und -kontrollverfahren der GDF durchgeführt. Die Analysenergebnisse der Arzneimittelhersteller wurden dafür mit denen des externen Qualitätskontrolllabors rückwirkend über einen Fünfjahreszeitraum mittels Bland-Altmann-Analyse verglichen. Signifikante Unterschiede wurden im Fall von Rifampicin und Kanamycin festgestellt, die auf unterschiedliche Analysemethoden zurückgeführt wurden.

In einer abschließenden Studie wurde eine Smartphone-Imaging-App entwickelt und validiert. Diese kann zur Quantifizierung unentbehrlicher Arzneimittel, die mittels Dünnschichtchromatographie nach den Methoden des Global Pharma Health Fund (GPHF) Minilab analysiert wurden, eingesetzt werden. Mithilfe dieser App soll die Arzneimittelprüfung vor Ort in Ländern mit niedrigem und mittlerem Einkommen verbessert und gestärkt werden.

Summary

Ensuring the quality of medicines worldwide is one of the urgent health challenges of our time and key to achieve universal health coverage, which is included as target 3.8 in the Sustainable Development Goals of the United Nations. The WHO estimates that one in ten medicines in low- and middle-income countries (LMICs) is substandard or falsified. In the course of this dissertation, two studies of the quality of antibiotics and medicines against non-communicable diseases confirmed these estimates, showing a prevalence of substandard and falsified medicines of 8% in Togo, and of 18.6% in a study in Cameroon and the DR Congo. Three of the 506 samples (0.6%) collected in Cameroon and the DR Congo did not contain the declared active ingredient.

In a subsequent study, one of the reasons for the high heterogeneity of the prevalence data reported for substandard and falsified medicines was addressed, i.e. the different tolerance limits used to distinguish “in-specification” and “out-of-specification” samples in regard to the content analysis. It was shown that, using the same data set, the rate of out-of-specification samples varied between 2.4% and 34.3% depending on the choice of tolerance limits. In the same study, authenticity inquiries were sent to manufacturers and distributors, and were found to be an effective method to identify falsifications. Of the 601 samples included in this study, seven sample, that had remained inconspicuous in the pharmacopeial analysis, could be identified as falsified medicines by these inquiries.

In a further study, cases of falsified chloroquine tablets were identified in March and April 2020 in Cameroon and the DR Congo, revealing how the COVID-19 pandemic has led to an increase in substandard and falsified medicines, particularly in low- and middle-income countries with weak regulatory control mechanisms.

The Global Drug Facility (GDF) is the largest provider of quality-assured anti-tuberculosis medicines to the public sector worldwide. In the course of this dissertation, an evaluation of GDF's quality assurance and control procedures was carried out, using Bland-Altmann analysis to retrospectively compare the analysis results provided by the manufacturers with those of the external quality control agent over a five-year period. In the case of rifampicin and kanamycin, significant differences were found, which were attributed to different analytical methods.

In a final study, a smartphone imaging app was developed and validate. If can be used for the quantitative evaluation of thin-layer chromatographic analyses of essential medicines carried out according to the methods of the Global Pharma Health Fund (GPHF) Minilab. This app may improve and strengthen medicines testing on site in low- and middle-income countries.

Publikationen und Präsentationen

Akzeptierte Publikationen

„Quality of medicines in southern Togo: Investigation of antibiotics and of medicines for non-communicable diseases from pharmacies and informal vendors"
Schäfermann S., Wemakor E., Hauk C., Heide L.;
PLOS One, 2018;13(11): e0207911

„Substandard and falsified antibiotics and medicines against noncommunicable diseases in western Cameroon and northeastern Democratic Republic of Congo"
Schäfermann S., Hauk C., Wemakor E., Neci R., Mutombo G., Ngah Ndze E., Cletus T., Nyaah F., Pattinora M., Wistuba D., Helmle I., Häfele-Abah C.,
Gross H., Heide L.;
The American Journal of Tropical Medicine and Hygiene, 2020; 103(2):894-908

„Identification of falsified chloroquine tablets in Africa at the time of the COVID-19 Pandemic"
Gnegel G., Hauk C., Neci R., Mutombo G., Nyaah F., Wistuba D., Häfele-Abah C., Heide L.;
The American Journal of Tropical Medicine and Hygiene, 2020; 103(1):73-76

„Quality assurance in anti-tuberculosis drug procurement by the Stop TB Partnership-Global Drug Facility: Procedures, costs, time requirements, and comparison of assay and dissolution results by manufacturers and by external analysis"
Hauk C., Schäfermann S., Martus P., Muzafarova N., Babaley M., Waning B., Heide L.;
PLOS One. 2020, 15(12):e0243428.

„Identification of substandard and falsified medicines: Influence of different tolerance limits and use of authenticity inquiries"
Hauk C., Hagen N., Heide L.;
The American Journal of Tropical Medicine and Hygiene. 2021; 104(5):1936-1945

„Trade in falsified and substandard medicines"
Hauk C.*, Hagen N.*, Heide L.
Buchkapitel im Sammelband: Maihold G, Müller M, Vorrath J, eds. „Geographies of the illicit: sectoral and spatial dimensions of illegal markets linking the Global South and Europe" in der Reihe „Weltwirtschaft und internationale Zusammenarbeit", Nomos Verlag. Akzeptiert zur Publikation

Noch nicht eingereichte Manuskripte

„Medicine quality screening: TLCyzer, an open-source smartphone-based imaging algorithm for the quantitative evaluation of thin layer chromatographic analyses using the GPHF Minilab"
Hauk C.*, Boss M.*, Schäfermann S., Lensch H., Heide, L.

Weitere Veröffentlichungen

„Die Global Drug Facility: Qualitätsgesicherte Tuberkulose Medikamente"
Hauk C., Muzafarova N, Waning B.
Pharmakon. 2018;6(5): 399

„Tradition trifft Moderne" – Museum of Materia Medica in Toyama, Japan
Hauk C., Hagen N., Heide L.
Pharmazeutische Zeitung. 2019;164(25):1812-3

Mündliche Präsentationen

„Investigating medicine quality in Togo, Cameroon and DR Congo"
German and Japanese perspectives on global substandard & falsified medicines Mini-Symposium, Kanazawa, Japan, März 2019

„Falsified and substandard medicine" und "Pharmacy in Global Health"
Workshop, International Pharmaceutical Students' Federation (IPSF) World Congress in Kigali, Rwanda, August 2019

„Study report on quality of medicines in African countries"
Kurs „Pharmacy in Global Health", Tübingen, Oktober 2019

„Quantifizierung von Arzneistoffen mit der TLCyzer App"
Workshop beim Online Kurs „Pharmacy in Global Health", Tübingen, März 2021 (online)

„Medicine quality study in Cameroon and DR Congo. Detection and identification of substandard and falsified medicines"
Institute of Tropical Medicine Antwerp, Belgien, Januar 2021 (online)

Erklärung der Eigenanteile

„Quality of medicines in southern Togo: Investigation of antibiotics and of medicines for non-communicable diseases from pharmacies and informal vendors"
Schäfermann S., Wemakor E., Hauk C., Heide L.;
PLOS One, 2018;13(11): e0207911

- Simon Schäfermann
    - Planung der Studie
    - Dokumentation der gesammelten Medikamente
    - Durchführung und Auswertung der Gehaltsbestimmung und Wirkstofffreisetzungsprüfung

  - Vorbereiten der Abbildungen
  - Schreiben des Manuskripts

- Emmanuel Wemakor
  - Involviert in die Planung der Studie
  - Durchführung der Probensammlung in Togo
  - Unterstützung bei der Durchführung der Wirkstofffreisetzungsprüfung

- **Cathrin Hauk**
  - Involviert in die Planung der Studie
  - Etablierung der analytischen Methoden
  - Durchführung und Auswertung von Gehaltsbestimmung

- Lutz Heide
  - Initiierung und Planung der Studie
  - Betreuung des Projekts
  - Entscheidend an Auswertung der Daten und Diskussion der Ergebnisse beteiligt
  - Schreiben des Manuskripts

„Substandard and falsified antibiotics and medicines against noncommunicable diseases in western Cameroon and northeastern Democratic Republic of Congo"

Schäfermann S., Hauk C., Wemakor E., Neci R., Mutombo G., Ngah Ndze E., Cletus T., Nyaah F., Pattinora M., Wistuba D., Helmle I., Häfele-Abah C., Gross H., Heide L.;

The American Journal of Tropical Medicine and Hygiene, 2020; 103(2):894-908, doi:10.4269/ajtmh.20-0184

Autorenanteile:

- Simon Schäfermann
  - Planung der Studie
  - Kommunikation mit den Partnern in der DR Kongo und Kamerun

  - Dokumentation der gesammelten Medikamentenproben
  - Wirkstofffreisetzungsprüfung der gesammelten Proben
  - Statistische Auswertung der Ergebnisse
  - Vorbereiten der Abbildungen
  - Schreiben des Manuskripts

- **Cathrin Hauk**
  - Involviert in die Planung der Studie
  - Etablierung der analytischen Methoden
  - Durchführung der Gehaltsbestimmung der gesammelten Proben
  - Involviert in Schreiben des Manuskripts

- Richard Neci
  - Feedback zur Studienplanung
  - Sammeln der Medikamentenproben in der DR Kongo
  - Durchführung und Dokumentation der Untersuchung mit dem GPHF Minilab

- Edward Ngah Ndze, Tambo Cletus, Fidelis Nyaah und Manyi Pattinora
  - Feedback zur Studienplanung
  - Sammeln der Medikamentenproben in Kamerun
  - Durchführung und Dokumentation der Untersuchung mit dem GPHF Minilab

- Valentine Basolonduma Pondo
  - Feedback zur Studienplanung
  - Sammeln der Medikamentenproben in der DR Kongo
  - Durchführung und Dokumentation der Untersuchung mit dem GPHF Minilab

- Dorothee Wistuba
  - Durchführung der LC-HR-MS/MS Analysen und Unterstützung bei der Auswertung

- Irina Helmle
    - Durchführung der ^{1}H und ^{13}C NMR Messung und Unterstützung bei der Auswertung

- Harald Groß
    - Betreuung der ^{1}H und ^{13}C NMR Messung und Überprüfung der Auswertung

- Christine Häfele-Abah
    - Involviert in die Planung der Studie
    - Herstellung des Kontakts zu Studienpartnern in der DR Kongo und Kamerun

- Lutz Heide
    - Initiierung und Planung der Studie
    - Betreuung des Projekts
    - Entscheidend an Diskussion der Analysenergebnisse beteiligt
    - Schreiben des Manuskripts

„Identification of falsified chloroquine tablets in Africa at the time of the COVID-19 Pandemic"

Gnegel G., Hauk C., Neci R., Mutombo G., Nyaah F., Wistuba D., Häfele-Abah C., Heide L.;

The American Journal of Tropical Medicine and Hygiene, 2020; 103(1):73-76

Autorenanteile:

- Gesa Gnegel
    - Planung der Studie
    - Durchführung der HPLC Analyse
    - Vorbereiten von Abbildungen
    - Schreiben des Manuskripts

- **Cathrin Hauk**
    - Mitwirkung bei der HPLC Analyse
    - Vorbereiten von Abbildungen

- Georges Mutombo und Fidelis Nyaah
    - Involviert in die Planung der Studie
    - Sammeln der Medikamentenproben
    - Durchführung der Untersuchung mit dem GPHF Minilab

- Dorothee Wistuba
    - Durchführung der LC-HR-MS Analysen und Unterstützung bei der Auswertung

- Christine Häfele-Abah
    - Involviert in die Planung der Studie

- Lutz Heide
    - Planung und Initiierung der Studie
    - Schreiben des Manuskripts

„Quality assurance in anti-tuberculosis drug procurement by the Stop TB Partnership-Global Drug Facility: Procedures, costs, time requirements, and comparison of assay and dissolution results by manufacturers and by external analysis"

Hauk C., Schäfermann S., Martus P., Muzafarova N., Babaley M., Waning B., Heide L.;

PLOS One, 2020, 15(12):e0243428.

Autorenanteile:

- **Cathrin Hauk**
    - Planung der Studie

  - Aufbereitung der Daten
  - Auswertung von Daten
  - Vorbereitung der Abbildungen
  - Schreiben des Manuskripts

- Simon Schäfermann
  - Initiierung und Planung der Studie
  - Auswertung von Daten

- Peter Martus
  - Statistische Auswertung und Beurteilung der Studienergebnisse
  - Vorbereitung der Abbildungen
  - Schreiben des Manuskripts

- Nigorsultan Muzafarova
  - Initiierung und Planung der Studie
  - Bereitstellung und Aufarbeitung von Daten
  - Involviert in Schreiben des Manuskripts

- Magaly Babley
  - Bereitstellung und Aufarbeitung von Daten
  - Involviert in Schreiben des Manuskripts

- Brenda Waning
  - Initiierung der Studie
  - Betreuung der Studie
  - Involviert in Schreiben des Manuskripts

- Lutz Heide
  - Planung der Studie
  - Betreuung der Studie
  - Entscheidend an Auswertung der Daten und Diskussion der Ergebnisse beteiligt

- Vorbereiten von Abbildungen
- Schreiben des Manuskripts

„Identification of substandard and falsified medicines: influence of different tolerance limits and use of authenticity inquiries"

Hauk C., Hagen N., Heide L.;

The American Journal of Tropical Medicine and Hygiene. 2021; 104(5):1936-1945

Autorenanteile:

- **Cathrin Hauk**
  - Planung der Studie
  - Schreiben und Verschicken der Authentizitätsanfragen an Hersteller und Vertreiber der in der DR Kongo und in Kamerun gesammelten Proben
  - Kommunikation mit den Herstellern und Vertreibern
  - Vorbereiten und Erstellen von Abbildungen
  - An Diskussion der Ergebnisse beteiligt
  - Schreiben des Manuskripts

- Nhomsai Hagen
  - Schreiben und Verschicken der Authentizitätsanfragen an Hersteller und Vertreiber der in Malawi gesammelten Oxytocin- und Misoprostol Proben
  - An Diskussion der Ergebnisse beteiligt

- Lutz Heide
  - Planung der Studie
  - Entscheidend an Diskussion der Ergebnisse beteiligt
  - Schreiben des Manuskripts

„Medicine quality screening: TLCyzer, an open-source smartphone-based imaging algorithm for the quantitative evaluation of thin layer chromatographic analyses using the GPHF Minilab"

Hauk C.*, Boss M.*, Schäfermann S., Lensch H., Heide, L.

Vorbereitet zur Publikation

Autorenanteile:

- **Cathrin Hauk**
  - Planung der Studie
  - Planung und Durchführung der Validierung
  - Auswertung und Diskussion der Ergebnisse
  - Erstellen der Abbildungen
  - Schreiben des Manuskripts

- Mark Boss
  - Involviert in die Planung der Studie
  - Entwicklung der Smartphone Imaging Software
  - Schreiben des Manuskripts

- Simon Schäfermann
  - Planung der Studie
  - Schreiben des Manuskripts

- Hendrik Lensch
  - Betreuung der Studie

- Lutz Heide
  - Planung der Studie
  - Betreuung der Studie
  - Beteiligt an Diskussion der Ergebnisse
  - Schreiben des Manuskripts

Einleitung

Qualität von Arzneimitteln in Ländern mit niedrigem und mittlerem Einkommen

Minderwertige und gefälschte Arzneimittel stellen eine Bedrohung für die globale Gesundheit dar und gehören zu den großen aktuellen gesundheitlichen Herausforderungen, deren Auftreten mit einer Pandemie verglichen wurde.[1] Etwa ein Drittel der Weltbevölkerung hat derzeit keinen Zugang zu Medikamenten, Impfstoffen und anderen wichtigen Gesundheitsprodukten.[2] Der Zugang zu sicheren, qualitativ hochwertigen und erschwinglichen Arzneimitteln wurde aus diesem Grund als Ziel Nr. 3.8.4 in die Ziele für nachhaltige Entwicklung (Sustainable Development Goals, SDGs) der Vereinten Nationen (UN) aufgenommen.[3] Schätzungen der Weltgesundheitsorganisation (WHO) zufolge sind etwa 10,5% der Arzneimittel in Ländern mit niedrigem und mittlerem Einkommen (LMICs) minderwertig oder gefälscht.[4] Zuverlässige Daten zur Prävalenz sind jedoch immer noch spärlich und weisen eine teils hohe Heterogenität auf.[5-7]

Die Auswirkungen von minderwertigen und gefälschten (substandard and falsified, SF) Arzneimitteln sind weitreichend und umfassen sowohl gesundheitliche als auch wirtschaftliche und sozioökonomische Aspekte. Arzneimittel, die den falschen Wirkstoff oder gar giftige Chemikalien enthielten, wie beispielsweise als Diazepam etikettierte Haloperidol Tabletten, und mit Diethylenglycol verunreinigter Paracetamol Sirup, hatten schwerwiegende, mitunter tödliche Folgen.[8, 9] Therapieversagen, Verlängerung von Krankheit und Arbeitsausfall, verstärkte Nebenwirkungen, Infektionen aufgrund fehlgeschlagener Prophylaxe, als auch die Zunahme von Resistenzen gegen Antiinfektiva stellen weitere Auswirkungen dar.[4] Schätzungen der WHO zufolge führt das durch SF-Arzneimittel bedingte Therapieversagen jährlich zum Tod von 72.000 bis 169.000 mit Lungenentzündung erkrankten Kindern und allein in Subsahara-Afrika zum Tod von 31.000 bis 116.000 Malariapatienten.[4] Die Anwendung von SF-Malariamedikamenten, die nur subtherapeutische Dosen der Wirkstoffe enthielten, konnte zudem in mehreren Studien mit einer Erhöhung der Resistenz gegen Malariamittel in Verbindung gebracht werden.[4]

Unwirksame oder gar gesundheitsgefährdende SF-Arzneimittel belasten zudem das begrenzte Budget von Gesundheitssystemen und Krankenkassen, und können insbesondere in LMICs, in denen ein großer Teil der Kosten für Gesundheitsausgaben aus eigener Tasche bezahlt werden müssen (37%, im Vergleich zu 14% in Ländern mit hohem Einkommen) zu finanziellen Notlagen für Patienten und ihre Familien führen.[4]

Um effizient auf dieses Problem reagieren zu können, sind zuverlässige Schätzungen der Prävalenz von SF-Arzneimitteln für unterschiedliche geografische Regionen, verschiedene Abschnitte der Lieferkette und Arzneimittelklassen von wesentlicher Bedeutung.[4]

Ein Großteil der veröffentlichten Studien zu minderwertigen und gefälschten Arzneimitteln haben sich auf Malariamedikamente konzentriert, einige auf Antibiotika und antivirale Arzneimittel. Die Qualität von Arzneimitteln gegen nichtübertragbare Krankheiten wurde bisher nur in wenigen Studien untersucht. Angesichts der steigenden Zahl an Todesfällen durch nichtübertragbare Krankheiten (weltweit jährlich 41 Millionen) und der Tatsache geschuldet, dass heute bereits 77% dieser Todesfälle in Ländern mit niedrigem und mittlerem Einkommen auftreten, bedarf es weiterer Studien.[10] In einer kürzlich veröffentlichten Studie wurde darauf aufmerksam gemacht, dass minderwertige und gefälschte Herz-Kreislauf-Medikamente, bisher wenig Beachtung gefunden haben und möglicherweise ein ernstes Problem für die öffentliche Gesundheit darstellen.[11] Wie das seit 2013 existierende globale Überwachungs- und Kontrollsystem für SF-Medikamente (Global Surveillance and Monitoring System for SF medical products, GSMS) der WHO zeigt, sind alle Arten von Arzneimitteln, von Krebsmedikamenten bis hin zu Verhütungsmitteln und Schmerzmitteln, Originalpräparaten und Generika, teure sowie billige Medikamente und alle Regionen der Welt von der Problematik der SF-Medikamente betroffen.[12] Systematische Übersichtsarbeiten zur Arzneimittelqualität von Ozawa at al. (2018),[13] Almuzaini, Choonara und Sammons (2013)[14] sowie McManus und Naughton (2020)[15] berichteten über Prävalenzen von SF-Arzneimitteln zwischen 13,6% und 28,5% in LMICs. Auffallend war, dass aufgrund der Heterogenität der Methodik und der Definitionen, die Zahlen minderwertigen und gefälschten Arzneimittel in diesen Übersichtsarbeiten nicht getrennt aufführt werden konnte. Um die Heterogenität der Daten zu reduzieren und eine Vergleichbarkeit von Studien zu ermöglichen, ist die Einhaltung von Leitlinien und Checklisten bei der Durchführung von

Arzneimittelqualitätsstudien essenziell.[16, 17] Daneben ist eine allgemeingültige Definition von SF-Arzneimittel von entscheidender Bedeutung, um dieses Problem besser zu verstehen und anzugehen. Die Weltgesundheitsversammlung (World Health Assembly) hat nach vielen Jahren der Kontroverse im Jahr 2017 eine verbindliche Definition von gefälschten und minderwertigen Arzneimitteln eingeführt.[18] „Minderwertig“ bezieht sich auf zugelassene Arzneimittel, die entweder ihre Qualitätsstandards, ihre Spezifikationen oder beides nicht erfüllen. „Gefälschte“ Arzneimittel geben absichtlich oder in betrügerischer Absicht ihre Identität, Zusammensetzung oder Herkunft falsch an. Diese Definitionen schließen sich gegenseitig aus, d.h. eine Probe kann entweder als minderwertig oder als gefälscht eingestuft werden.[18] Bei der Definition von „minderwertigen“ Arzneimitteln ist zu beachten, dass die Toleranzgrenzen der Gehaltsbestimmung (und auch Wirkstofffreisetzungsprüfung) für das gleiche Arzneimittel in unterschiedlichen Arzneibüchern, wie z.B. der International Pharmacopoeia (Ph. Int), der United States Pharmacopeia (USP) oder der British Pharmacopoeia (BP) variieren. Daher kann ein bestimmtes Produkt nach den Kriterien eines Arzneibuchs „innerhalb der Spezifikation“ und nach den Kriterien eines anderen „außerhalb der Spezifikation“ sein. Dies kann die Prävalenzraten von „minderwertigen“ Arzneimitteln in Arzneimittelqualitätsstudien stark beeinflussen, zumal in einigen Studien auch willkürliche anstelle von Arzneibuchgrenzwerten verwendet wurden.[5, 19, 20] „Minderwertige“ Arzneimittel werden in der WHO Definition als Arzneimittel „außerhalb der Spezifikation“ bezeichnet.[18] Die beiden Begriffe sind jedoch nicht synonym zu verwenden, da „außerhalb der Spezifikation“ laut U.S. Food and Drug Administration (FDA) alle Testergebnisse umfasst [21] und nicht unterscheidet ob es sich um ein „minderwertiges“ Arzneimittel handelt, das z.B. durch Mängel bei der Herstellung oder falscher Lagerung die Spezifikation nicht erfüllt oder vorsätzlich gefälscht wurde. Um Missverständnisse zu vermeiden, weist die WHO in einer Fußnote der Definition darauf hin, dass Arzneimittel als „gefälscht“ betrachtet werden sollen, wenn der zugelassene Hersteller die Qualitätsstandards oder die Spezifikationen aufgrund falscher Angaben zu Identität, Zusammensetzung oder Herkunft absichtlich nicht einhält.[18, 22]

Offensichtlich ist es nicht immer möglich, Informationen über die Absicht des Herstellers zu erhalten, und eine Analyse nach Arzneibuch allein reicht nicht aus, um ein Arzneimittel eindeutig als minderwertig oder als gefälscht einzuordnen. Eine

detaillierte Verpackungsanalyse sowie Authentizitätsanfragen an die deklarierten Hersteller und Vertreiber der Proben können dabei helfen Fälschungen aufzudecken.[23, 24]

Maßnahmen zur Sicherstellung der Arzneimittelqualität

Eingeschränkter oder fehlender Zugang zu qualitätsgesicherten Arzneimitteln, schwache regulatorische Kontrollmechanismen und unzureichende technische Möglichkeiten begünstigen, insbesondere in Kombination, das Auftreten von minderwertigen und gefälschten Medikamenten.[12] Schlüsselelemente zur Bekämpfung von SF-Medikamenten sind laut WHO die Prävention und Erkennung dieser Medikamente und die Zusammenarbeit aller beteiligten Akteure weltweit.[12] Die COVID-19 Pandemie hat die komplexen Lieferketten von Wirkstoffen und Arzneimitteln noch verwundbarer gemacht. Die weltweit sprunghaft angestiegene Nachfrage nach persönlichen Schutz- und Hygieneprodukten, Medikamenten und Impfstoffen wurde vielfach von Kriminellen ausgenutzt und führte zum vermehrten Auftreten von SF-Produkten.[25, 26]

Eine der wirksamsten Maßnahmen zur Prävention des Auftretens von SF-Arzneimitteln ist die Stärkung der Qualitätssicherung bei der Arzneimittelbeschaffung. Zwar gibt es dafür allgemeine Empfehlungen[27-30], jedoch fehlt es in der wissenschaftlichen Literatur an detaillierten empirischen Daten zu Verfahren, Kosten und Zeitbedarf der Qualitätssicherung und Qualitätskontrolle (quality assurance, QA und quality control, QC) bei der Arzneimittelbeschaffung. Vielfach werden in LMICs spezifische geberfinanzierte Gesundheitsprogramme von internationalen Organisationen implementiert, die die Bereitstellung qualitätsgesicherter Medikamente übernehmen. Die stagnierende Gesundheitsfinanzierung durch internationale Geber zwingt jedoch viele dieser Länder ihre Beschaffungsprozesse nun selbst zu koordinieren.[31] Daher wurde gerade für mit Gebermitteln beschaffte, unentbehrliche Arzneimittel vorgeschlagen, die Ergebnisse der Qualitätssicherung mit verschiedenen Interessengruppen zu teilen.[28]

Die Beschaffung von Antituberkulotika wird in vielen LMICs durch den Global Fund to Fight AIDS, Tuberculosis and Malaria und die United States Agency for International

Development (USAID) organisiert. Der Großteil dieser Antituberkulotika und -Diagnostika für Tuberkulose (TB)-Kontrollprogramme stammt von der Global Drug Facility (GDF) der Stop TB Partnership, die 2001 gegründet wurde, um einen unterbrechungsfreien Zugang zu qualitätsgesicherten Antituberkulotika sicherzustellen. Die GDF ist heute der weltweit größte Anbieter von TB-Produkten für die nationalen TB-Kontrollprogramme. Im Jahr 2017 lieferte GDF Antituberkulotika und Diagnostika im Gesamtwert von 304 Millionen US$ an 119 Länder.[32] Minderwertige Antituberkulotika gehören zu den Treibern für das Auftreten arzneimittelresistenter Erreger.[33, 34] Vor der COVID-19 Pandemie war Tuberkulose, vor HIV/AIDS, die häufigste Todesursache durch einen einzelnen Infektionserreger.[35] Bei arzneimittelempfindlicher TB lag der Behandlungserfolg einer sechsmonatigen Therapie mit den vier Erstlinienmedikamenten (Rifampicin, Isoniazid, Ethambutol und Pyrazinamid) 2019 bei durchschnittlich 85%.[35] Die multiresistente TB (MDR-TB) stellt dagegen eine noch größere Bedrohung dar. Die Behandlung ist länger, teurer (>1.000 US$ pro Patient) und verursacht mehr Nebenwirkungen.[35] Durch die COVID-19 Pandemie wurden durch eingeschränkten Zugang zu Diagnostik und Behandlung viele Fortschritte im Kampf gegen Tuberkulose wieder zunichte gemacht und die Zahl der Todesfälle durch Tuberkulose ist zum ersten Mal seit zehn Jahren wieder gestiegen.[35]

Zur Durchführung einer Analyse nach Arzneibuch werden hochqualifiziertes Personal, sowie technisch aufwendige und teure Geräte benötigt. In Ländern und Gebieten mit begrenzten Ressourcen und technischen Möglichkeiten werden diese daher kaum durchgeführt.[36] Screening-Geräte ermöglichen dagegen eine einfache und vergleichsweise kostengünstige Qualitätsuntersuchung und spielen daher in diesen Ländern eine wichtige Rolle.[12, 37] Verdächtige Arzneimittel können schnell und relativ unkompliziert vor Ort untersucht werden, wodurch der Schaden von SF-Medikamenten, die sich in der Zwischenzeit ungebremst ausbreiten können, minimiert werden kann.[38, 39] Screening-Tools mit hoher Selektivität können zudem dazu beitragen Kosten zu senken, indem eine Vorauswahl getroffen wird, welche Proben einer vollständige Arzneibuchanalyse unterzogen werden sollen.[40]
Die Zahl der entwickelten Screening-Geräte nimmt stetig zu, jedoch eignet sich nicht jede Technologie gleich gut für den Einsatz an unterschiedlichsten Stellen der Arzneimittelversorgungskette.[37, 38, 41, 42] Um Empfehlungen für die Wahl des

optimalen Tools zu geben, sind Studien zur Bewertung von Screening-Methoden einschließlich eines umfassenden Validierungsprozesses unerlässlich.[38, 40, 43] Die USP hat dafür vor kurzem einen Leitfaden für die Beurteilung und Validierung von Screening-Tools eingeführt.[41]
Das Minilab des Global Pharma Health Fund (GPHF) ist mittlerweile in 98 Ländern weltweit vertreten ist und wird von der WHO und dem USAID-Programm Promoting the Quality of Medicines Plus gefördert.[44] Es besteht aus einem Kofferlabor, das alles beinhaltet, was zur Durchführung einer DC-Analyse und eines Zerfallstests benötigt wird. Das dazugehörige Handbuch umfasst Untersuchungsmethoden für mehr als 100 unverzichtbare Wirkstoffe in verschiedenen Darreichungsformen.[45]

Die semiquantitative Auswertung der DC-Analyse erfolgt durch visuellen Vergleich der Probenspots mit einem 100% - und 80% Referenzspot unter UV-Licht oder nach Anfärben mit Färbereagenzien. Ist der Spot der Probe schwächer als der 80% Spot, wird die Prüfung als nicht bestanden angesehen. Die Minilab-Untersuchung ist daher nicht darauf ausgelegt Abweichungen von weniger als 20% zu erkennen.
Während sich das Vorhanden- oder Nichtvorhandensein des deklarierten Wirkstoffs mit dem Minilab zuverlässig nachweisen lässt, ist die Identifizierung von Proben, die nicht die richtige Menge des angegebenen Wirkstoffs enthalten oft unzuverlässig.[46-49] Die Auswertung der Spots ist immer subjektiv, erfordert sowohl Sehschärfe als auch ein geschultes Auge.[49-52] Durch die Entwicklung von Densitometern ist mittlerweile auch eine ist zuverlässige quantitative Auswertung der automatisierten Hochleistungs-Dünnschichtchromatografie (HPTLC) möglich.[53-55] Erste Versuche diesen Ansatz auf Screening-Geräte zu übertragen wurden bereits gemacht, so konnte Yu et al. ein Smartphone-basiertes Bildgebungssystem entwickeln, das Bilder von DC-Platten analysieren kann.[56] Geplant ist, dass das Minilab des GPHF in Zukunft mit einer Smartphone Software kombiniert wird, um eine objektive und bessere Quantifizierung von Spots zu ermöglichen.[45]

Zielsetzung

Studien zur Qualität von Antibiotika und Arzneimitteln gegen nichtübertragbare Krankheiten wurden in Togo, in Kamerun und in der DR Kongo durchgeführt, um die Datenlage zur Prävalenz von minderwertigen und gefälschten Arzneimitteln in Ländern mit niedrigem und mittlerem Einkommen (LMICs) zu verbessern. Die vorliegende Arbeit soll zudem zu einer Verbesserung der Methodik von Arzneimittelqualitätsstudien und zu einer besseren Vergleichbarkeit von Prävalenzdaten beitragen, sowie mögliche Kriterien zur Unterscheidung von minderwertigen und gefälschten Arzneimitteln entwickeln. Konkret soll gezeigt werden, wie stark die Prävalenzrate von den verwendeten Toleranzgrenzen abhängt und wie mithilfe von Authentizitätsanfragen an Hersteller und Vertreiber von Arzneimitteln Fälschungen identifiziert werden können. Fälle von Chloroquin Fälschungen in Kamerun und der DR Kongo, die in Zusammenhang mit der COVID-19 Pandemie auftraten, wurden im Rahmen dieser Arbeit untersucht, und Gründe und Ursachen für das Auftreten von minderwertigen und gefälschten Arzneimitteln diskutiert.

Die Global Drug Facility der Stop TB Partnership ist der weltweit größte Anbieter von Antituberkulotika für den öffentlichen Sektor.[32] Die Arzneimittelqualitätssicherung und -kontrolle der GDF wurde retrospektiv über einen Fünfjahreszeitraum evaluiert, indem Analysenzertifikate der Arzneimittelhersteller mit denen des externen Qualitätskontrolllabors mittels Bland-Altmann-Analyse verglichen wurden. Ein solcher Vergleich wurde bisher nicht durchgeführt, und es sollte gezeigt werden, welchen Nutzen dieser sowohl für die GDF als auch andere Arzneimittelbeschaffungs-organisationen bringt, um eine zuverlässige Qualitätskontrolle sicherzustellen.

Die Qualitätsuntersuchung von Arzneimitteln mithilfe einfacher und preisgünstiger Screening-Methoden hat in LMICs einen hohen Stellenwert. Um die quantitative Auswertung von Analysen mit dem GPHF Minilab zu verbessern, wurde eine Box zum Fotografieren von DC-Platten und eine Smartphone App entwickelt, die die Probenspots anhand ihrer Intensität quantifiziert. Diese Erweiterung des Minilabs wurde anhand des USP Leitfadens zur Bewertung von Screening-Technologien evaluiert und validiert. Im Speziellen wurde die Robustheit der Methode, der Einfluss unterschiedlicher Faktoren auf die Auswertung und der Schulungsaufwand, der notwendig ist, um zuverlässige Ergebnisse mit der App zu erzielen, untersucht.

Ergebnisse

Studien zur Arzneimittelqualität in Togo, DR Kongo und Kamerun

Zur Verbesserung der Datenlage zur Prävalenz minderwertiger und gefälschter Arzneimittel in Ländern mit niedrigem und mittlerem Einkommen (LMICs), wurde eine Pilotstudie in Togo, gefolgt von einer größeren Hauptstudie in der DR Kongo und in Kamerun, durchgeführt. Beide Studien wurden auf Basis der WHO-Leitlinien[16] und den MEDQUARG-Leitlinien[17] zur Durchführung von Arzneimittelqualitätsstudien konzipiert und durchgeführt. Für die Studie in Togo, wurden sieben Antibiotika und fünf Medikamente gegen nichtübertragbare Krankheiten aus der Liste der unentbehrlichen Arzneimittel der Republik Togo ausgewählt: Amoxicillin, Amoxicillin/Clavulansäure, Sulfamethoxazol/Trimethoprim, Ciprofloxacin, Phenoxymethylpenicillin (Penicillin V), Metronidazol, Doxycyclin, Metformin, Atenolol, Hydrochlorothiazid, Furosemid, alle in Form von Tabletten oder Kapseln. Für die Studie in der DR Kongo und Kamerun wurden die gleichen Arzneimittel ausgewählt, mit dem Unterscheid, dass in Kamerun Glibenclamid anstelle von Atenolol gesammelt wurde, da dieses dort selten verwendet wird. Alle Arzneimittel sind in den Listen der unentbehrlichen Arzneimittel der Republik Kamerun[57] und der Demokratischen Republik Kongo[58] enthalten.

In Togo fand die Probensammlung im Februar 2017 im Süden des Landes, in den Regionen Maritime und Plateaux statt. Sechs informelle Händler und die jeweils geographisch nächstgelegene Apotheke aus der Liste der zugelassenen Apotheken[59] wurden ausgewählt. Gekauft wurde, falls verfügbar, eine Menge von 100 Tabletten bzw. Kapseln unter dem Vorwand, dass diese für die Verwendung in einer medizinischen Einrichtung bestimmt sind, die von einem Verwandten betrieben wird.

Für die Hauptstudie wurden zwischen August 2017 und November 2018 im Nordosten der DR Kongo (Provinzen Ituri, Nord-Kivu, Süd-Kivu und Tanganyika) und im Westen Kameruns (Regionen Adamawa, Centre, Littoral, Northwest, Southwest und West) Proben gesammelt. Kirchliche und staatliche Gesundheitseinrichtungen, private Apotheken und informelle Händler wurden dafür unter Berücksichtigung der

Sicherheitslage zufällig ausgewählt. Der Mystery Shopper Ansatz wurde hier für den Einkauf bei informellen Händlern verwendet.
Nicht alle ausgewählten Medikamente waren an allen Stellen verfügbar, und so konnten von 26 Stellen in Kamerun und 34 Stellen in der DR Kongo insgesamt 506 Arzneimittelproben gekauft werden. Ergebnisse zu Preisen und Verfügbarkeit wurden separat veröffentlicht.[60] In Togo konnten von den geplanten 144 Proben, 94 erworben werden (zwei davon wurden aufgrund zu kleiner Tablettenzahl von der Analyse ausgeschlossen).
An der Universität Tübingen wurden alle gesammelten Proben dokumentiert und einer Verpackungsanalyse unterzogen. Eine Analyse nach den Monografien der United States Pharmacopeia (USP) 39 (2016) bzw. 41 (2018) wurde bei beiden Studien an der Universität Tübingen durchgeführt. Es wurde eine Identitätsprüfung des deklarierten Wirkstoffs, eine Gehaltsbestimmung (Assay), beide mittels HPLC, und eine Wirkstofffreisetzungsprüfung (Dissolution Test) durchgeführt. Die Proben der Hauptstudie wurden zudem einer Prüfung auf Gleichförmigkeit einzeldosierter Arzneiformen (Uniformity of Dosage Units; Weight Variation) laut USP Vorschrift unterzogen. Die lokalen Partner in Kamerun und der DR Kongo führten für 451 der gesammelten Proben zusätzlich eine Untersuchung mit dem Minilab des Global Pharma Health Fund (GPHF) durch. Diese umfasste eine visuelle Inspektion und eine Untersuchung mittels Dünnschichtchromatographie (DC) mithilfe eines Referenzstandard und eines Zerfallstests.[61]
Von den 92 Proben aus Togo enthielten alle den bzw. die deklarierten Wirkstoffe und bei der Verpackungsanalyse wurden keine Hinweise auf Fälschungen beobachtet. 85 der Proben entsprachen den Spezifikationen der USP 39 sowohl für den Gehalt als auch für die Wirkstofffreisetzung. Die Abweichung wurde jeweils in „moderat“ und „extrem“ eingeteilt. Als „extrem“ wird eine Abweichung von mehr als 20% vom deklarierten Gehalt oder eine durchschnittliche Wirkstofffreisetzung von weniger als 25% unter dem Arzneibuchgrenzwert (Q-Wert minus 25%) bezeichnet, wie von der WHO 2011[49] vorgeschlagen. Sechs Proben zeigten eine moderate Abweichung, eine Probe eine extreme Abweichung. Dabei handelte es sich um Amoxicillin Kapseln, die nur 47% des deklarierten Gehalts enthielten. Möglicherweise wurden diese Kapseln als 250mg - und nicht wie auf dem Etikett angegeben als 500mg Amoxicillin Kapseln hergestellt. Eine absichtliche Falschdarstellung, die auf eine Fälschung hinweisen würde, kann dabei nicht ausgeschlossen werden.

In der Studie in der DR Kongo und Kamerun wurden drei (0,6%) der Proben als gefälscht identifiziert, da sie den deklarieren Wirkstoff nicht enthielten. Abbildung 1 zeigt diese drei Fälle: A) Als „Augmentin® GlaxoSmithKline - SmithKline Beecham Pharmaceuticals (amoxicillin 500 mg/clavulanic acid 125 mg tablets)“ deklariertes Präparat: die Verpackung und Tabletten zeigte keine Hinweise auf eine Fälschung, jedoch enthielten die Tabletten keinen nachweisbaren Wirkstoff. B) „Penicillin-V Tablets, Oxford Pharma Co. Ltd., Belgium“: der Wirkstoff wurde fälschlicherweise als „Phenoxymetgyl“ und nicht als Phenoxymethylpenicillin auf dem Etikett deklariert. Der angegebene Hersteller „Oxford Pharma, Belgien“ existiert nicht. Die Tabletten enthielten kein Penicillin V, sondern 50mg Paracetamol pro Tablette wie mittels LC-HR-MS/MS-Analyse festgestellt werden konnte. C) „Metronyl® Metronidazole Tablets B.P., Mac’s Pharmaceuticals Ltd., Kenia“: wurden von einem informellen Verkäufer in der DR Kongo erworben, der diese in einem bereits geöffneten Plastikbehälter verkaufte. Mittels LC-HR-MS/MS und 1D- und 2D-NMR-Analyse konnte gezeigt werden, dass es sich bei dem unbekannten Inhaltsstoff um Metronidazolbenzoat handelte. Dieser wird in pädiatrischen Formulierungen und in der Veterinärmedizin eingesetzt.[62] Der Gehalt lag hier jedoch nur bei 93mg pro Tablette im Gegensatz zu den deklarierten 200mg freien Metronidazols. In allen drei Fällen zeigte bereits die Untersuchung mit dem Minilab vor Ort, dass die Proben nicht den deklarierten bzw. gar keinen Wirkstoff enthielten. Die Proben wurden direkt an die Universität Tübingen zur Bestätigungsanalyse geschickt und in zwei der Fälle wurde ein WHO Medical Product Alert veröffentlicht.[63, 64]

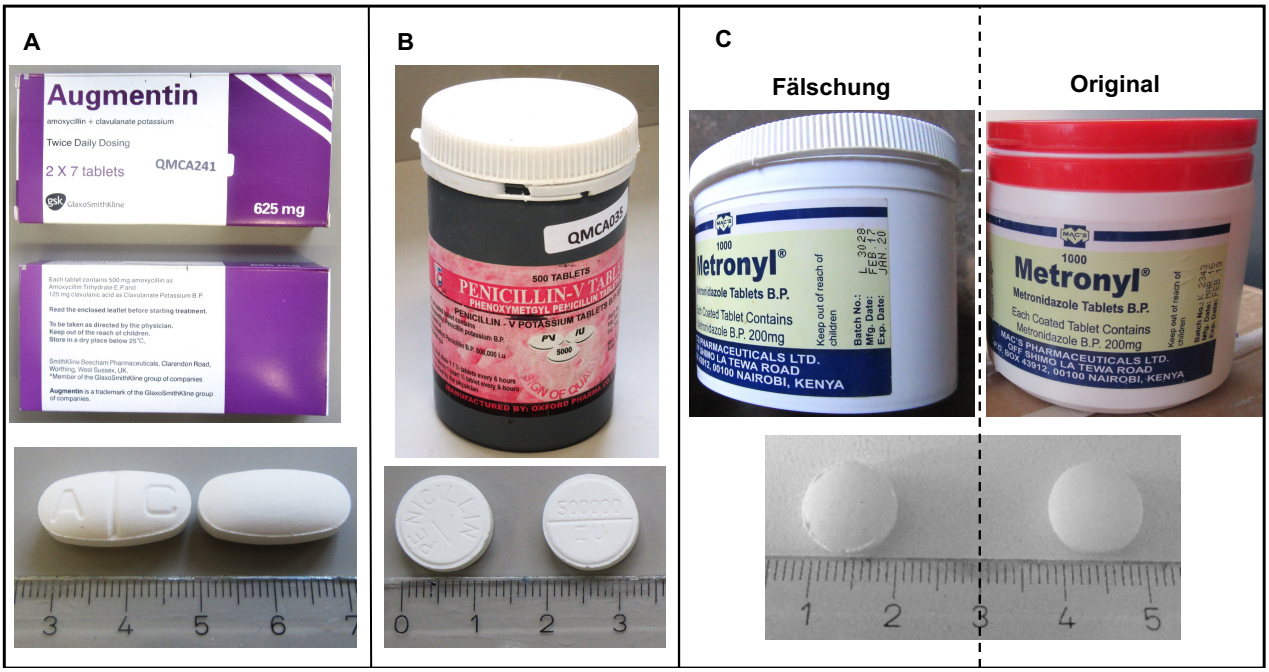
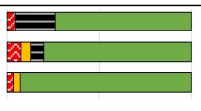
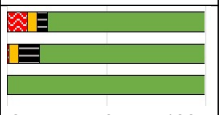
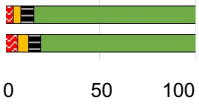
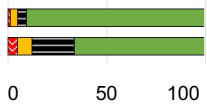
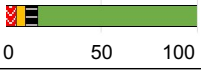
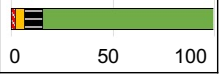


Abbildung 1: Fotos der Proben, die als gefälschte Arzneimittel identifiziert wurden, da sie den deklarierten Wirkstoff nicht enthielten. A) Gefälschte „Augmentin®“ Tabletten, die keinen nachweisbaren Wirkstoff enthielt. B) Gefälschte Penicillin V Tabletten, die Rechtschreibfehler auf dem Etikett aufweisen und 50mg Paracetamol pro Tablette enthielten. C) Gefälschte „Metronyl®“, Tabletten, die 94mg Metronidazolbenzoat pro Tablette enthielten, rechts daneben Metronyl® Tabletten, die der USP Monografie entsprachen. *(Modifiziert nach Schäfermann et al.[65])*

Von den Proben haben 8,5% die Gehaltsbestimmung nach USP nicht bestanden, und 11,7% die Wirkstofffreisetzungsprüfung nicht bestanden. Insgesamt haben 16,2% der Proben mindestens eine der Prüfungen nicht bestanden. Diese Zahl erhöhte sich auf 18,6%, bei Berücksichtigung der Prüfung auf Gleichförmigkeit einzeldosierter Arzneiformen. Der Anteil an Proben, die die Gehalts- und/oder Wirkstofffreisetzungsprüfung nicht bestanden haben ist in Abb. 2 dargestellt, aufgeteilt nach angegebenem Herkunftskontinent der Probe, der Arzneimittelklasse und der Einrichtung bzw. dem Händler, bei dem das Arzneimittel gekauft wurde.

	Kamerun			DR Kongo		
Angegebener Herkunftskontinent						
	Gesamt-zahl	Außerhalb d. Spezi-fikation		Gesamt-zahl	Außerhalb d. Spezi-fikation	
Afrika	23	**26%** (6)		40	**20%** (8)	
Asien	156	**20%** (31)		201	**16%** (32)	
Europa	57	**7%** (4)		21	**0**	
Einrichtung						
Staatl. Gesundheitseinrichtung	36	**25%** (9)		42	**7%** (3)	
Kirchl. Gesundheitseinrichtung	71	**14%** (10)		72	**6%** (4)	
Apotheke	70	**6%** (4)		91	**19%** (17)	
Informeller Händler	67	**28%** (19)		57	**28%** (16)	
Kategorie						
Antibiotika	152	**16%** (24)		196	**9%** (18)	
Arzneimittel gegen NCDs	92	**20%** (18)		66	**33%** (22)	
Insgesamt						
	244	**17%** (42)		262	**15%** (40)	

- Beide Prüfungen nicht bestanden
- Gehaltsprüfung nicht bestanden
- Wirkstofffreisetzungstest nicht bestanden
- Innerhalb der Spezifikation

Abbildung 2: Rate an Arzneimittelproben außerhalb der Spezifikation nach Untergruppen aufgeteilt. *(Modifiziert nach Schäfermann et al.[65])*

Medikamente von informellen Anbietern wiesen eine signifikant höhere Rate an Proben außerhalb der Spezifikation auf (28,2%), als von anderen Quellen (12,3%; p<0,0001). In Togo war dieser Unterschied auch zu beobachten, erreichte jedoch keine statistische Signifikanz.[66] Alle drei gefälschten Medikamente stammten von informellen Händlern. Bei den Medikamenten gegen nichtübertragbare Krankheiten lag eine signifikant höhere Rate an Proben außerhalb der Spezifikation (25%) im Vergleich zu den Antibiotika (12%; p=0,0004). Dieser Unterschied war in der DR Kongo besonders ausgeprägt (33% vs. 9%; p<0,0001).

Wie eingangs erwähnt ist das Minilab nicht dafür ausgelegt, moderate Abweichungen, d.h. Abweichungen von weniger als 20% von der deklarierten Wirkstoffmenge zu erkennen. Von den 26 Proben, die laut USP Analyse moderate Abweichungen aufwiesen, haben nur zwei die Untersuchung laut Minilab nicht bestanden. Von den 14 Proben, die extreme Abweichungen zeigten, konnten sechs

mit dem Minilab identifizieren werden. Extreme Abweichungen des Wirkstoffgehalts wurden demnach mit einer Sensitivität von 43% festgestellt.

Der Einfluss von Toleranzgrenzen bei der Gehaltsbestimmung

Trotz der Bemühungen um eine Harmonisierung der Arzneibücher gibt es auch in den allgemein anerkannten und von der WHO empfohlenen Arzneibüchern[16] - USP, International Pharmacopeia (Ph. Int.) und der British Pharmacopoeia (BP) – in Bezug auf die Akzeptanzgrenzen von Arzneimitteln noch immer große Unterschiede. Anhand der Arzneimittelproben, die für die Qualitätsstudie in der DR Kongo und in Kamerun gesammelt wurden, sowie in Malawi gesammelte Oxytocin Injektionen und Misoprostol Tabletten,[67] wurden die Auswirkungen unterschiedlicher Akzeptanzgrenzen auf die resultierenden Prävalenzraten von minderwertigen Arzneimitteln untersucht. Diese Studie umfasste insgesamt 601 Arzneimittelproben, die mit den Methoden der USP bzw. im Fall von Misoprostol mit der Ph. Int. an der Universität Tübingen analysiert wurden. Die Ergebnisse für die Gehaltsbestimmung wurden dann nach den Toleranzgrenzen der USP 42 (2019), Ph. Int. (neunte Ausgabe, 2019) und BP (2020) in „innerhalb -“ und „außerhalb“ der Spezifikation“ eingeteilt.
In Abbildung 3 sind die 601 Testergebnisse, die in den drei Arzneibüchern angegebenen Toleranzgrenzen und die willkürlichen Toleranzgrenzen 95-105% und 90-120%, die in Studien zur Qualitätsbeurteilung von Malaria- und Herzmedikamenten 2016 und 2017 in Studien verwendet wurden[5, 19, 20], gezeigt.

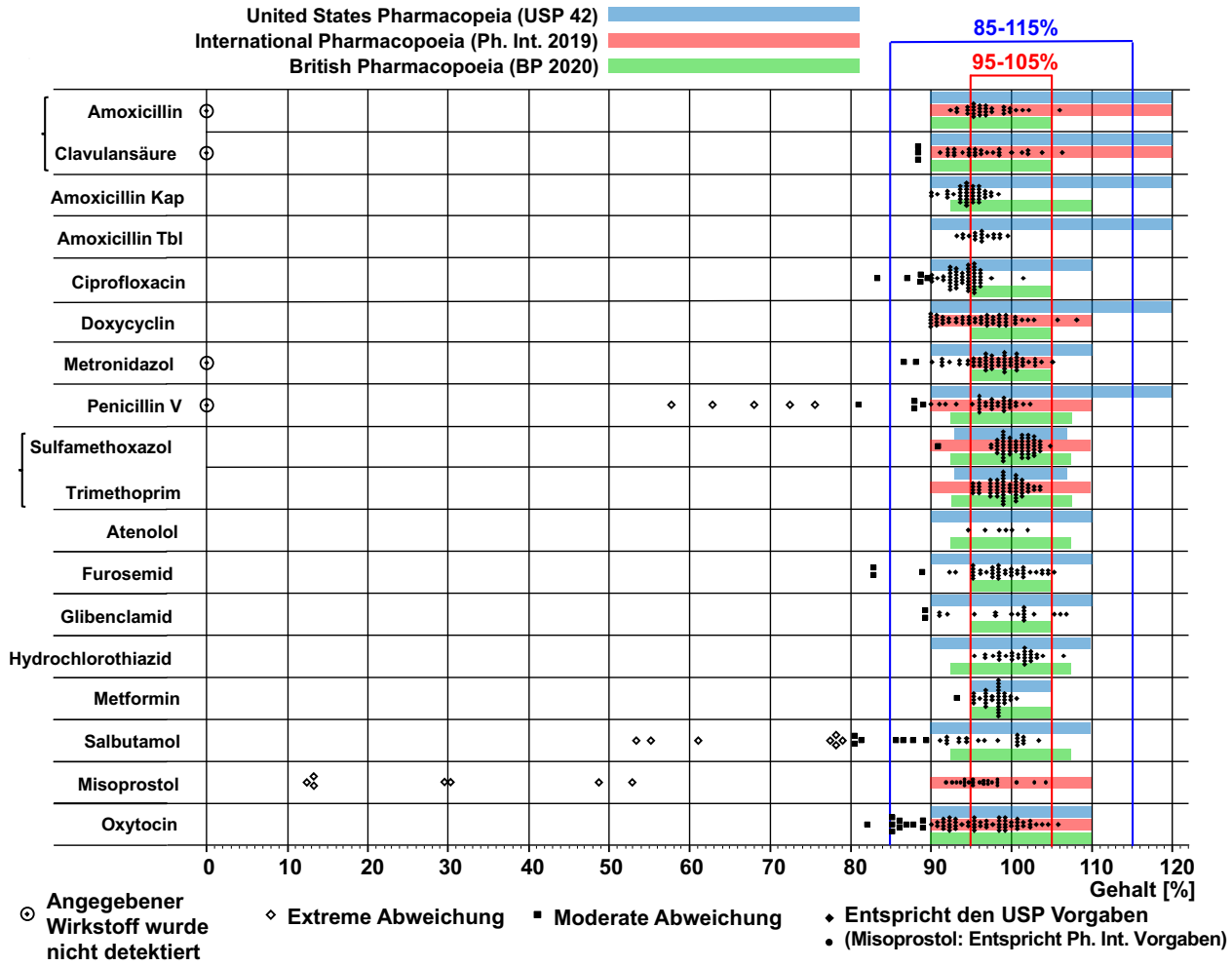


Abbildung 3: Analysenergebnisse für die 601 in Kamerun, der DR Kongo und Malawi gesammelten Arzneimittelproben. Angegeben sind jeweils die Toleranzgrenzen der USP 42, Ph. Int. neunte Ausgabe und BP 2020, sowie die willkürlichen, in Studien verwendeten Toleranzgrenzen, 85-115% [5, 19] und 95-105%[20]. *(Modifiziert nach Hauk et al.[68])*

Bei einigen wenigen Arzneimittelproben, wie Cotrimoxazol (= Sulfamethoxazol und Trimethoprim) oder Metformin Tabletten, war der Anteil minderwertiger Proben, relativ unabhängig von den angewendeten Toleranzgrenzen. Wie in Abb. 3 deutlich sichtbar wird, hatte die Wahl der Toleranzgrenzen bei den meisten Arzneimitteln jedoch einen großen Einfluss auf die resultierende Anzahl der minderwertigen Arzneimittel. So waren z.B. von den 57 gesammelten Ciprofloxacin Proben fünf (8,8%) bei Anwendung der USP-Toleranzgrenzen „außerhalb der Spezifikation", während 43 (75,4%) bei Anwendung der BP-Toleranzgrenze „außerhalb der Spezifikation" lagen. Abbildung 4 zeigt den prozentualen Anteil an minderwertigen Proben, abhängig von den verwendeten Spezifikationen für die 297 Proben, für die

Monografien in allen drei genannten Arzneibüchern existieren. Laut USP und Ph. Int. beträgt die Rate 8,4% bzw. 11,4%, laut BP ist sie deutlich höher (21,9%). Der stärkste Kontrast (34,3% bzw. 2,4%) trat bei Anwendung der willkürlich gewählten Grenzwerte von 85-115% bzw. 95-105% auf.

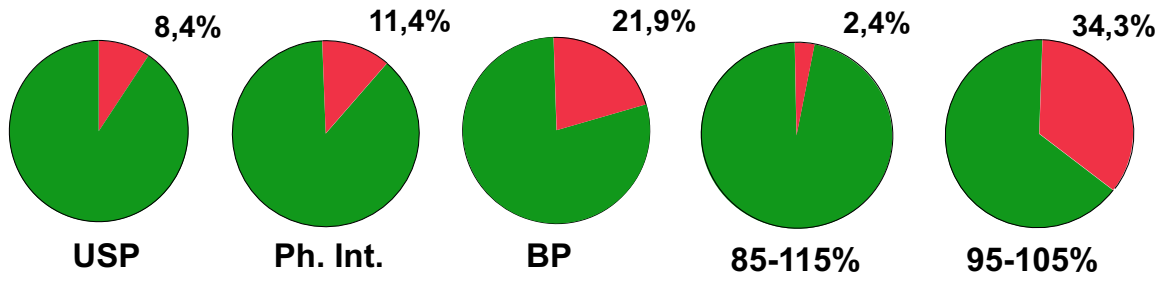


Abbildung 4: Einfluss verschiedener Toleranzgrenzen auf die Rate der minderwertigen Arzneimittel (rot: „außerhalb der Spezifikation"; grün: „innerhalb der Spezifikation"). Die Toleranzgrenzen der USP 42, Ph. Int. neunte Ausgabe und BP 2020, sowie die willkürlichen Toleranzgrenzen 85-115%[5, 19] und 95-105%[20] wurden angewendet. Für diesen Vergleich wurden nur die Testergebnisse der sechs untersuchten Arzneimittel verglichen, für die Monografien in allen drei Arzneibüchern existieren (insgesamt 297 Arzneimittelproben). *(Modifiziert nach Hauk et al.[68])*

Nutzen von Authentizitätsanfragen zur Identifizierung gefälschter Arzneimittel

Um ein Arzneimittel als gefälscht einzustufen, ist nach WHO Definition ein Nachweis krimineller Absicht des Herstellers notwendig.[18] Um diesen nachzuweisen ist eine Verpackungsanalyse zusätzlich zur Arzneibuchanalyse oftmals nicht ausreichend. Authentizitätsanfragen, die an Hersteller und Vertreiber der Arzneimittel gesendet werden, können daher einen zusätzlichen Beitrag zur Identifizierung gefälschter Arzneimittel leisten. Um herauszufinden, wie effektiv diese Methode ist, wurden an die angegebenen Hersteller und Vertreiber, der 601 im vorherigen Kapitel genannten Arzneimittelproben, eine Anfrage (inklusive Fotos und Angaben zur Chargennummer, Herstellungs- und Verfallsdatum, jedoch keine Analysenergebnisse) verschickt mit Bitte um Prüfung der Echtheit der Proben. Die E-Mail-Adressen und Websites dieser Unternehmen wurden anhand des Etiketts oder der Packungsbeilagen sowie mithilfe von Suchmaschinen (Google, Bing und Baidu) im Internet ermittelt. Anfragen wurden

per Post verschickt, wenn keine E-Mail-Adresse gefunden werden konnte oder offensichtlich keine der E-Mail-Anfragen den Empfänger erreichte. Wenn innerhalb von sechs Wochen keine Rückmeldung erfolgte, wurde eine Erinnerungs-E-Mail geschickt. Alle Antworten, die innerhalb von drei Monaten nach der ersten Anfrage eingingen, wurden ausgewertet. Abbildung 5 zeigt die Ergebnisse der 582 Proben für die Authentizitätsanfragen verschickt wurden. Für 288 (49,5%) der Proben wurde eine Antwort mit Erklärung zur Echtheit des jeweiligen Arzneimittels erhalten. Bei 281 Proben wurde diese durch den Hersteller und/oder den Vertreiber bestätigt, während sieben Proben als gefälscht identifiziert wurden. Für 50 der 288 Proben (17,4%) gingen Antworten sowohl vom Hersteller als auch vom Vertreiber ein und die Angaben beider Quellen stimmten überein.

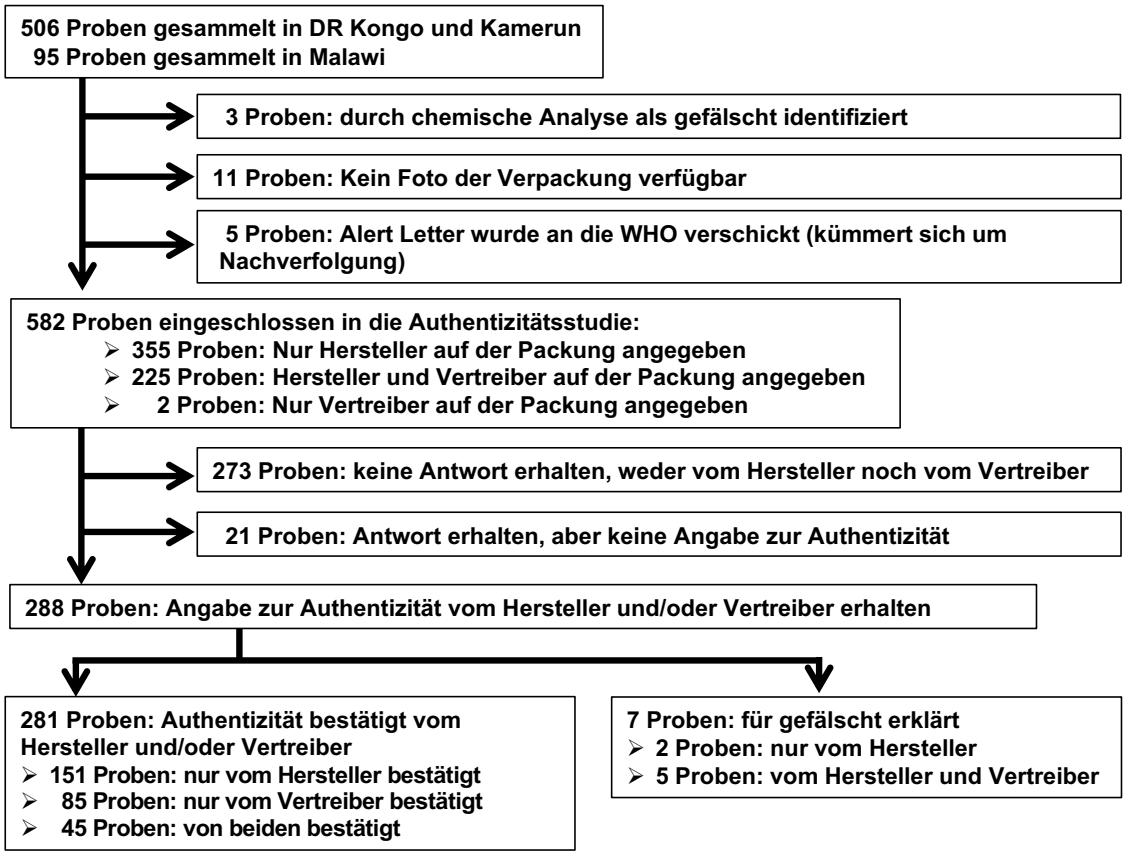


Abbildung 5: Flussdiagramm zur Identifizierung gefälschter Arzneimittel durch Authentizitätsanfragen an Hersteller und Vertreiber. Fünf stark minderwertige Misoprostol Proben wurden ausgeschlossen, da die WHO nach Herausgabe des Alert Letters die Korrespondenz mit den angegebenen Herstellern und Vertreibern aufgenommen hatte. *(Modifiziert nach Hauk et al.[68])*

Tabelle 1 zeigt, dass bei Proben, die Asien oder Europa als Herkunftsort angaben, die Rückmeldequote bei über 50% lag und damit höher als bei Proben, die laut Angabe in Afrika hergestellt wurden (27,4%; p<0,001). Indien und China waren die bedeutendsten Herkunftsländer, der in dieser Studie untersuchten Arzneimittel. Die Rücklaufquoten waren für beiden Ländern ähnlich (53,7% bzw. 50,3%), wobei anzumerken ist, dass für die in China hergestellten Proben in den meisten Fällen nur Rückmeldung von den Vertreibern der Arzneimittel eingingen, die überwiegend in Afrika und Europa ansässig waren, und nicht von den chinesischen Herstellern selbst.

Tabelle 1: Antwortquoten auf die Authentizitätsanfragen, aufgeschlüsselt nach geografischen Regionen

	Anzahl Proben		**Anzahl Hersteller**		**Anzahl Vertreiber***	
	Herkunft	Authentizi-tätsangabe erhalten (%)	Kontaktiert	Authentizi-tätsangabe erhalten (%)	Kontaktiert	Authentizi-tätsangabe erhalten (%)
Asien (alle)	420	220 (52,4%)	83	30 (36.1%)	9	4 (44,4%)
Indien	257	138 (53,7%)	58	28 (48,3%)	7	3 (42,9%)
China & Hongkong	161	81 (50,3%)	24	1 (4,2%)	1	0
Europe und Amerika	96	51 (53,1%)	24	13 (54,2%)	16	7 (43,8%)
Afrika	62	17 (27,4%)	19	6 (31,6%)	17[§]	5 (29,4%)
Total	**582[¶]**	**288 (49,5%)**	**126**	**49 (38,9%)**	**42[§]**	**16 (38,1%)**

* Die Vertreiber befanden sich häufig in einer anderen Region als die Hersteller der jeweiligen Proben.

§ In dieser Studie waren 20 Vertreiber aus Afrika vertreten, für drei (repräsentieren 14 Proben), wurde keine E-Mail-Adresse oder Kontakt-Website gefunden, und sie konnten nicht auf dem Postweg kontaktiert werden, da der Postdienst aufgrund der COVID-19-Pandemie unterbrochen war. Daher konnten nur 42 der 45 in dieser Studie vertretenen Vertreiber kontaktiert werden.

¶ 582 Proben wurden in die Untersuchung einbezogen, aber bei vier Proben war das Herkunftsland unbekannt: Bei drei Proben von Cinpharm war nicht angegeben, ob sie von Cinpharm in Kamerun oder von ihrem Partner Cipla Ltd. in Indien hergestellt worden waren; und bei einer Probe war auf der vorhandenen Verpackung nur der Vertreiber, nicht aber der Hersteller angegeben. *(Modifiziert nach Hauk et al.[68])*

Die mittlere Zeitspanne zwischen der ersten Anfrage und dem Erhalt einer Antwort mit einer Bestätigung der Echtheit lag bei 16 Tage (0-84 Tage). 38 (58,5 %) dieser Hersteller und Vertreiber antworteten bereits auf die erste Anfrage, während in 27 Fällen (41,5%) ein Erinnerungsschreiben erforderlich war.
Es konnte ein signifikanter Zusammenhang (p = 0,0456) zwischen Proben, die den Arzneibuchvorgaben entsprachen und einer höheren Rücklaufquote (51,2%; im Vergleich dazu 39,5% bei Proben außerhalb der Spezifikation) beobachtet werden. Durch die Authentizitätsanfragen wurden sieben weitere Proben (vier verschiedener Marken) als Fälschungen identifiziert, zusätzlich zu den drei Proben, die aufgrund der Verpackung und der chemischen Analyse als "gefälscht" eingestuft worden waren (siehe Abb.1). Daraus resultiert eine Gesamtrate gefälschter Arzneimittel von 1,7%. Die sieben identifizierten Fälschungen sind in Abb. 6 A-D dargestellt und in der Legende näher erläutert. Die „Amoxicillin 500 mg + Clavulanic acid 125 mg BP“ - (A) und „CO-TRIMOXAZOLE (sulfamethoxazole & trimethoprim)" (B) -Tabletten stammten von informellen Händlern in Kamerun, die vier „Furosemide 40 mg BP" Tabletten (C) stammten von kirchlichen Einrichtungen aus vier verschiedenen Regionen im Kamerun. „Metronidazole Tablets BP 250 mg“ (D) stammten aus einer staatlichen Gesundheitseinrichtung in Nord Kivu, DR Kongo. Auffällig ist, dass alle sieben gefälschten Proben die Arzneibuchanalyse (Gehalt- und Wirkstofffreisetzungsprüfung) ohne Abweichungen von den USP-Spezifikationen bestanden hatten. Ähnliche Beobachtungen wurden in der Arbeitsgruppe von Kimura gemacht.[23, 69] Wie in der Legende von Abb. 6 beschrieben, wiesen zwei der Fälschungen (A und B), neben anderen Unstimmigkeiten, Unterschiede in der (Blister-) Verpackung im Vergleich zum Originalprodukt auf. Bei den anderen Fälschungen (C und D) deutet das nicht korrekte Verfallsdatum und die scheinbar korrekte Verpackung möglicherweise darauf hin, dass diese nachträglich manipuliert wurden.

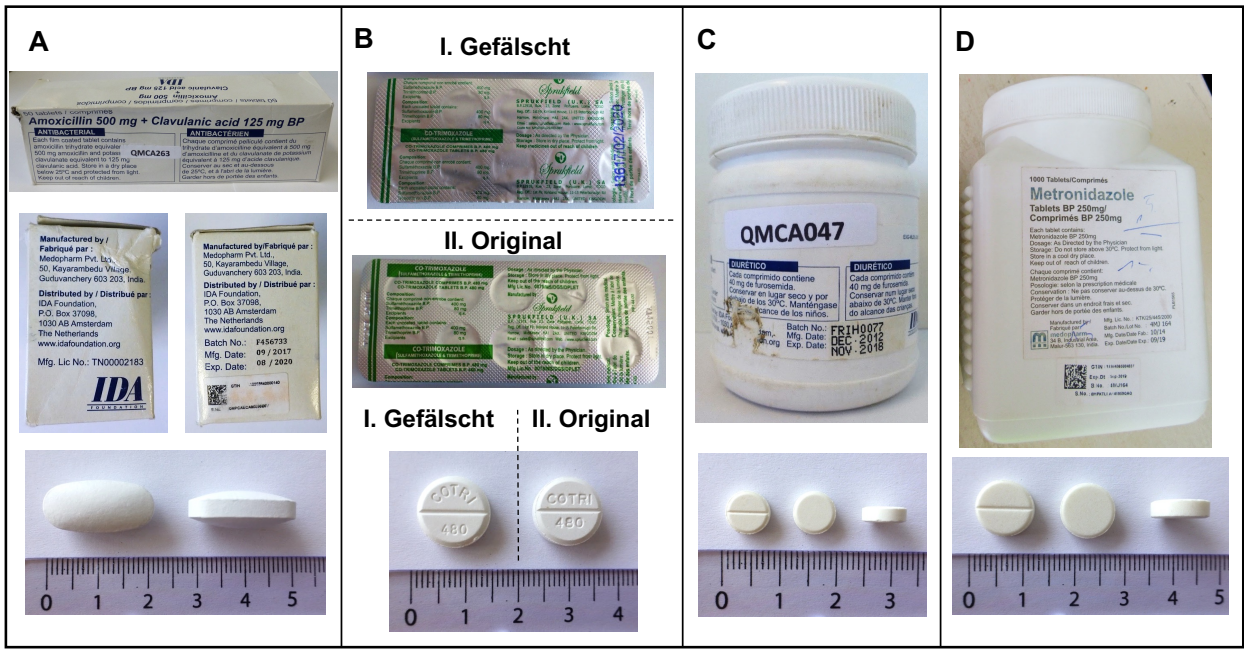
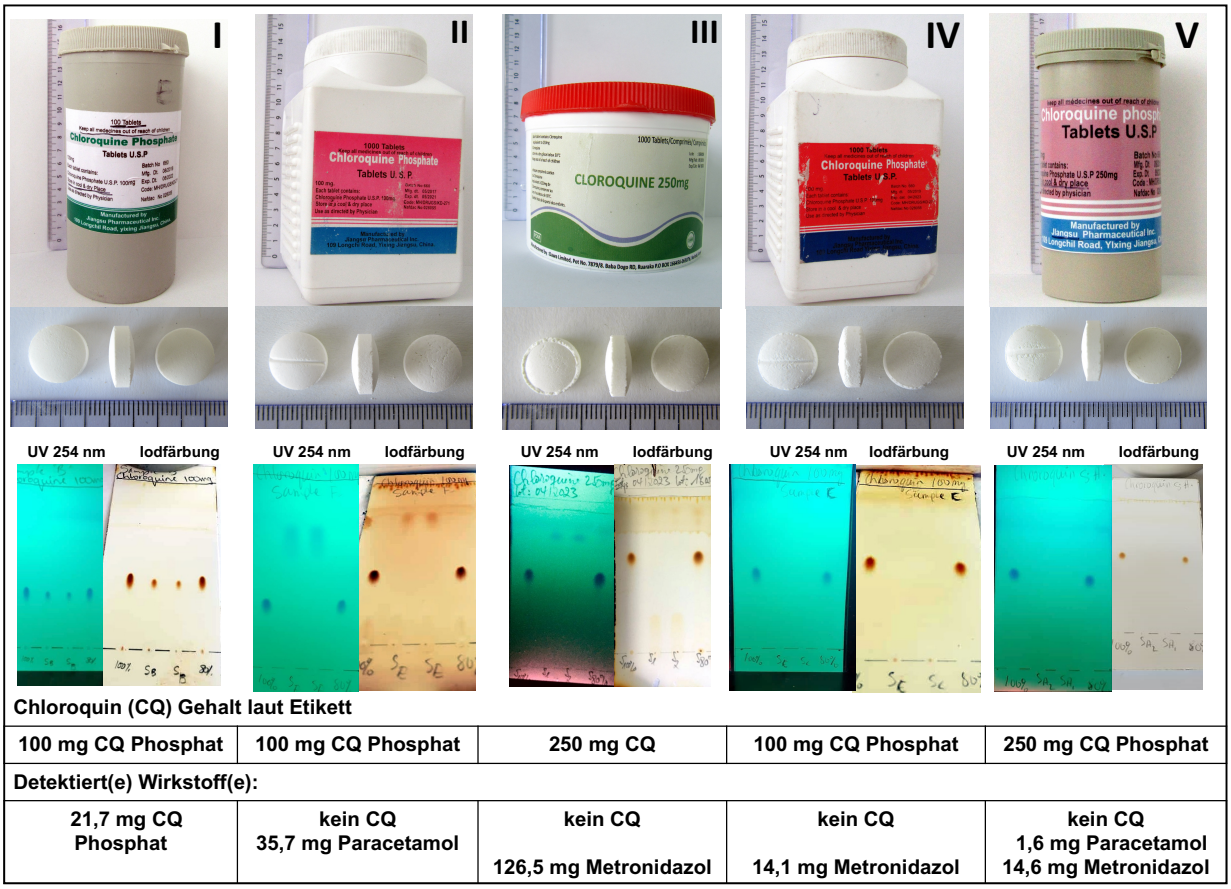


Abbildung 6: Fotos der gefälschten Arzneimittel, die durch Authentizitätsanfragen identifiziert wurden. (A) Gefälschte "Amoxicillin 500 mg + Clavulanic acid 125 mg BP"-Tabletten. Chargennummer, Haltbarkeitsdauer, Blisterlänge und weitere Angaben auf der Etikettierung stimmen nicht mit denen des echten Produkts überein, laut angegebenem Hersteller und Vertreiber. (B) Gefälschte (I) und echte (II) "CO-TRIMOXAZOLE (sulfamethoxazole & trimethoprim)" Tabletten. Die gefälschte Probe weist eine falsche Chargennummer auf. Chargennummer und Verfallsdatum sind auf dem Blister aufgedruckt und nicht eingeprägt; Blisterlänge, Gestaltung und Farbton der Beschriftung des Blisters sowie die Prägung der Tabletten stimmen nicht mit denen des echten Produkts überein. Das gefälschte Produkt war ohne Umverpackung verkauft worden. (C) Eine der vier gefälschten "Furosemide 40 mg BP"-Proben mit manipuliertem Verfallsdatum („NOV. 2018“, anstelle des echten Verfallsdatums „NOV. 2015“). (D) Gefälschte "Metronidazole Tablets BP 250 mg", ebenfalls mit manipuliertem Verfallsdatum („09/19“ statt des echten Verfallsdatums „09/17“). Der zweidimensionale Barcode auf der Verpackung zeigte nach Angaben des Herstellers im Gegensatz zu dem im Etikett das korrekte Verfallsdatum (30. Sept. 2017). *(Modifiziert nach Hauk et al.[68])*

Gefälschte Chloroquin Tabletten in Zusammenhang mit der COVID-19 Pandemie

Berichte über die Wirksamkeit von Chloroquin (CQ) und Hydroxychloroquin gegen COVID-19 haben im Frühjahr 2020 weltweit für Aufmerksamkeit gesorgt. Als Folge davon schoss die Nachfrage nach Chloroquin und Hydroxychloroquin in die Höhe

und es kam zu einem sprunghaften Anstieg von Fälschungen.[26] Lokale Mitgliedsorganisationen des Ökumenischen Pharmazeutischen Netzwerks (EPN) in der DR Kongo und Kamerun, die mithilfe des GPHF Minilabs eine lokale Überwachung der Arzneimittelqualität durchführen[36], berichteten im März und April 2020 von auffälligen Chloroquin Tabletten. Diese stammten vom Schwarzmarkt als auch von privaten Apotheken und zeigten nach DC-Analyse keinen Spot auf Höhe der CQ Referenz. Das Deutsche Institut für Ärztliche Mission (Difäm), das für das Minilab-Netzwerk verantwortlich ist informierte das WHO-Schnellwarnsystem, woraufhin ein WHO Medical Product Alert herausgegeben wurde.[70]
Abbildung 7 zeigt Verpackung, Tabletten und DC-Platten (unter UV-Licht und mit Jod angefärbt) der vor Ort durchgeführten DC-Analyse von fünf auffälligen Proben: In Probe I deutete ein kleiner Spot auf Höhe der CQ Referenz, der auch bei Anfärbung mit Jod sichtbar wurde, auf eine geringe Menge CQ in der Tablette hin. In Probe II-V war CQ hingegen nicht nachweisbar. Spots mit einem anderen Retentionsfaktor deuteten bei Probe II und III auf das Vorhandensein von nicht deklarierten Stoffen hin. An der Universität Tübingen konnten diese Beobachtungen durch HPLC Analyse nach Methoden der USP 42 bestätigt werden. Probe I enthielt nur 21,7% der auf dem Etikett deklarierten Menge an CQ Phosphat. In Probe II-IV war kein CQ nachweisbar. Die unbekannten Verbindungen konnten mithilfe von LC-HR-MS identifizieret und mit HPLC quantifiziert werden. Probe II enthielt 35,7mg Paracetamol, Probe III 126,5mg Metronidazol pro Tablette, Proben IV und Probe V enthielten kleinere Mengen von Metronidazol (14,1mg bzw. 14,6mg pro Tablette) und Probe V enthielt zusätzlich Spuren von Paracetamol (1,6mg pro Tablette). Rechtschreibfehler auf der Verpackung deuteten darauf hin, dass diese nicht von etablierten Herstellern, sondern von Kriminellen hergestellt wurden. Der angegebene Hersteller von Probe III, Dawa Limited, Kenia bestätigte, dass dieses Präparat nicht von ihm hergestellt wurde. Metronidazol hat einen bitteren Geschmack und wurde womöglich eingesetzt, um den sehr bitteren Geschmack von CQ nachzuahmen. Die subtherapeutischen Dosen von Metronidazol in Probe III, IV und V können zur Entstehung antimikrobieller Resistenzen beitragen. Die geringe Menge an Paracetamol könnten auf eine Kontamination aus einer früheren Produktionscharge hindeuten.



Chloroquin (CQ) Gehalt laut Etikett				
100 mg CQ Phosphat	100 mg CQ Phosphat	250 mg CQ	100 mg CQ Phosphat	250 mg CQ Phosphat
Detektiert(e) Wirkstoff(e):				
21,7 mg CQ Phosphat	kein CQ 35,7 mg Paracetamol	kein CQ 126,5 mg Metronidazol	kein CQ 14,1 mg Metronidazol	kein CQ 1,6 mg Paracetamol 14,6 mg Metronidazol

Abbildung 7: Gefälschte Chloroquin (CQ) Tabletten, die in Kamerun und in der DR Kongo gefunden wurden und die Fotos der DC-Untersuchung. Die DC Platten zeigen links und rechts zwei CQ Referenzspots (100% und 80%) und in der Mitte zwei Spots mit der jeweiligen Probe. Fotos der DC-Platten stammen aus der DR Kongo und Kamerun. *(Modifiziert nach: Gnegel et al.[71])*

Der Handel mit minderwertigen und gefälschten Arzneimitteln

Die im Kamerun und der DR Kongo aufgetretenen gefälschten Chloroquin Tabletten sind nur ein Beispiel für den im Zusammenhang mit der COVID-19 Pandemie beobachteten weltweit sprunghaften Anstieg von minderwertigen und gefälschten Arzneimitteln.[26] Durch die gesteigerte Nachfrage nach Medikamenten, Impfstoffen, als auch Schutzmasken und Hygieneprodukten und die Unterbrechung von Lieferketten für Rohstoffe und fertige Arzneimittelpräparate kam es zu einer regelrechten Flut an minderwertigen und gefälschten Produkten. So wurden seit Beginn der Pandemie allein in der englischsprachigen Laienpresse über 845 Artikel zu Qualitätsproblemen mit COVID-19 Impfungen, Medikamente und

Medizinprodukten veröffentlicht.[72] Eingeschränkter oder fehlender Zugang zu qualitätsgesicherten Arzneimitteln, schwache regulatorische Kontrollmechanismen und unzureichende technische Möglichkeiten, führen dazu, dass minderwertige und gefälschte Medikamente in LMICs oft leichtes Spiel haben.[12] Nationale Arzneimittelzulassungsbehörden sind in LMICs oftmals nicht in der Lage die Qualität importierter Arzneimittel vor der Registrierung ausreichend zu prüfen. Gelangen minderwertige oder gefälschte Arzneimittel in das Land, bleiben diese aufgrund schwacher Arzneimittelüberwachungssystemen oft unentdeckt. Hinzu kommt, dass die teils hohen Preise für Arzneimittel aus legalen Quellen, die Patienten auf die Schwarzmärkte treiben.[12]

Die Herstellung von Wirkstoffen, Hilfsstoffen, Verpackungsmaterial, als auch die Herstellung des Produkts und die Verpackung findet meist in unterschiedlichen Ländern statt. Lange und komplizierte Lieferketten und wiederholtes Umpacken machen es Kriminellen leicht, minderwertige oder gefälschte Produkte in die legale Lieferkette einzuschleusen. Vor allem Großhändler stellen eine Eintrittspforte für Fälschungen dar, da sich hier legale und illegale Ströme leicht vermischen können, im Wissen oder Nicht-Wissen der Großhändler. Ein Beispiel an dem die zunehmende weltweite Vernetzung und Komplexität von Lieferketten deutlich sichtbar wird, ist das Auftreten von gefälschtem Avastin® (Bevacizumab), das über Zwischenhändler in Syrien, Türkei, Ägypten, Schweiz, Dänemark und Großbritannien die USA erreichte und dort an Patienten abgegeben wurde.[12]

Viele LMICs sind auf den Import von Arzneimitteln angewiesen. In einigen afrikanischen Ländern machen diese mehr als 80% der im Land erhältlichen Medikamente aus, und die meisten davon sind Generika.[73] Das konnte auch in der Arzneimittelqualitätsstudie in Kamerun und der DR Kongo bestätigt werden: Von 502 untersuchten Proben wurden 71% in Asien (meist in Indien und China) hergestellt und weniger als 3% in dem afrikanischen Land, in dem die Probe gesammelt wurde. Nur 6% stellten Originalpräparate dar.[65]

Indien und China sind zudem auch oft Ursprungsort gefälschter Arzneimittel[74] wobei oftmals eine direkte Verbindung zwischen illegalen Händlern in Afrika und kriminellen Herstellern in Indien oder China besteht.[75] Illegale Produkte, oft in falsch deklarierten Containern verpackt, werden, um Kontrollen zu vermeiden, über reguläre Frachtunternehmen, aber auch über andere Vertriebskanäle von spezialisierten Kurieren transportiert.[75] Wie die UN-Kommission für Kriminalprävention und

Strafjustiz (Commission on Crime Prevention and Criminal Justice) festgestellt hat, sind organisierte kriminelle Gruppen auch am Handel mit SF-Arzneimitteln beteiligt.[76] Der illegale Arzneimittelmarkt, der von kriminellen Netzwerken beliefert wird, ist auch die Hauptquelle für Medikamente, die außerhalb der medizinischen Indikation angewendet werden, wie beispielsweise Tramadol. Der missbräuchliche Einsatz dieses Schmerzmittels hat in Westafrika und im Nahen Osten zu einer regelrechten „Tramadol-Krise“ geführt.[77, 78] Das synthetische Opioid wird aufgrund seiner beruhigenden und euphorischen Wirkung sowie zur Überwindung von Müdigkeit missbräuchlich eingesetzt. Längerer Konsum kann zu Abhängigkeit und schweren Gesundheitsschäden führen und mitunter tödlich enden.[78]

Prävention, Erkennung und Reaktion sind laut WHO Schlüsselelemente bei der Bewältigung des Problems minderwertiger und gefälschter Arzneimittel.[12] Um zu verhindern, dass SF-Arzneimittel in die Lieferketten gelangen, muss die Verfügbarkeit, Zugänglichkeit und Erschwinglichkeit von Arzneimitteln guter Qualität über die legale Lieferkette verbessert werden. Die Qualitätssicherung in der Arzneimittelbeschaffung muss verstärkt werden, wozu auch das „WHO Prequalification of Medicines Program“ einen wichtigen Beitrag leistet.[79] Die Stärkung nationaler Arzneimittelbehörden sowie eine stärkere Vernetzung zwischen Gesundheitsakteuren, Regulierungsbehörden, Strafverfolgung und des Zolls können zu einer Verbesserungen der Arzneimittelüberwachung beitragen.[80] Zudem ist ein internationales Rechtsverständnis notwendig, um dem illegalen Handel mit SF-Arzneimitteln effektiv entgegenzutreten.

Untersuchung der Qualitätssicherung bei der Arzneimittelbeschaffung durch die Global Drug Facility

Die Global Drug Facility (GDF), der weltweit größte Anbieter von Antituberkulotika im öffentlichen Sektor, beschafft diese über die IDA Foundation (Amsterdam, Niederlande). Der internationale Warenprüfkonzern SGS S.A. führte als externer Qualitätskontrollbeauftragter (Quality control agent, QCA) die Qualitätskontrolle dieser Medikamente durch. Um die Ergebnisse dieser Qualitätskontrolle retrospektiv zu analysieren, stellte GDF die Microsoft Excel-Dateien der 13.999 Arzneimittelchargen, die zwischen 2013-2017 beschafft und überprüft wurden, zur

Verfügung. Unter Verwendung eines risikobasierten Randomisierungsverfahrens hat der externe QCA in diesem Zeitraum 1.388 Chargen für die Laboranalyse ausgewählt. Diese Analysenergebnisse wurden nicht in eine Datenbank eingepflegt und standen daher nur in Form von Zertifikaten, als PDF-Dateien zur Verfügung. Die Daten des externen QCA umfassten 51 verschiedene Medikamente, die 26 pharmazeutische Wirkstoffe in verschiedenen Formulierungen, Dosierungen und Kombinationsprodukten repräsentierten.

Die 1.388 Chargen wurden nach Herstellern und Fertigarzneimitteln sortiert und von jedem Wirkstoff jedes Herstellers, wurden, wenn möglich, mindestens fünf Chargen zufällig ausgewählt. Von den resultierenden 196 Chargen wurden die Ergebnisse der Gehaltsbestimmung und der Wirkstofffreisetzungsprüfung manuell aus den PDF-Dateien übertragen. Bei vielen der ausgewählten Arzneimittel handelte es sich um Kombinationenprodukte, die mehrere Wirkstoffe enthielten, zudem waren Injektionen vertreten. Die ausgewählten 196 Proben stellen daher insgesamt 288 Gehaltsanalysenergebnisse und 261 Wirkstofffreisetzungsergebnisse (Mittelwert der sechs Ergebnisse) dar. Die Analysenergebnisse wurden graphisch mittels Streudiagrammen und Bland-Altman-Diagrammen mit den Grenzen der Übereinstimmung (limits of agreements, LOAs)[81] veranschaulicht und analysiert. Darüber hinaus wurden t-Tests durchgeführt, um systematische Unterschiede zu untersuchen und Spearman-Korrelationen berechnet. Die Varianzanalyse wurde angewendet, um die Ergebnisse zwischen Wirkstoffen und Herstellern zu vergleichen. Abbildung 8a und c zeigt Streudiagramme des Vergleichs der Herstelleranalyse mit der externen QCA-Analyse für die Gehaltsbestimmung und die Wirkstofffreisetzungsprüfung. Abbildung 8b und d zeigt die dazugehörigen Bland-Altman-Diagramme.

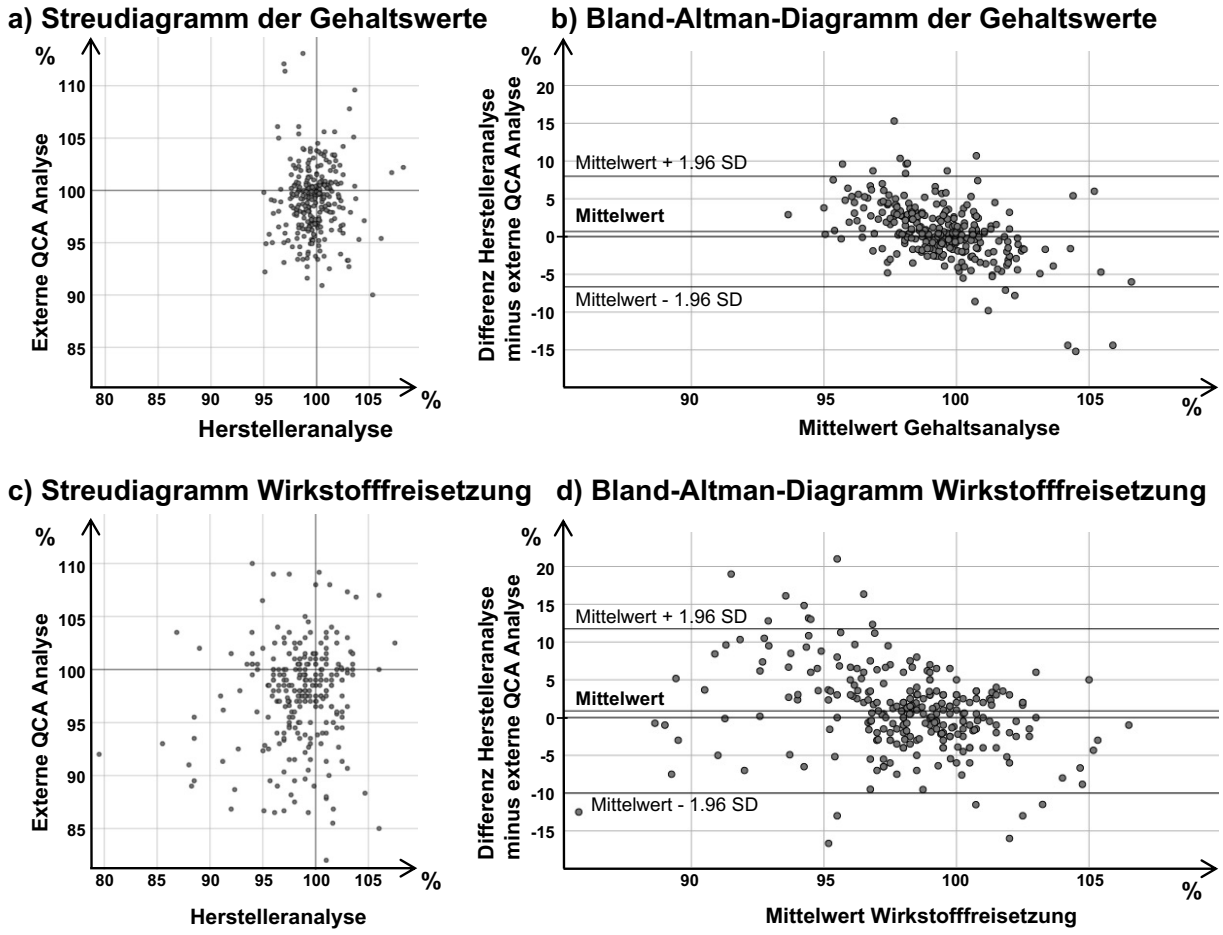


Abbildung 8: Vergleich der Gehalts- und Wirkstofffreisetzungsergebnisse der Herstelleranalyse und der externen QCA-Laboranalyse. Zwischen den Ergebnissen der Herstelleranalyse und der externen QCA-Analyse wurde eine Korrelation von r = 0,035 (p = 0,559) für die Gehaltsbestimmung und r = 0,132 (p = 0,034) für die Wirkstofffreisetzungsprüfung berechnet. Der in dem Bland-Altman-Diagramm dargestellte Bias betrug 0,67% für die Gehaltsbestimmung (zweiseitiger t-Test: p = 0,003) und 0,88% für die Wirkstofffreisetzungsprüfung (zweiseitiger t-Test: p = 0,011). *(Modifiziert nach Hauk et al.[32])*

Die Ergebnisse der Bland-Altman-Analyse sind in Tabelle 2 zusammengefasst. Eine minimale Abweichung wurde sowohl für die Gehaltsbestimmung (0,67%) als auch für die Wirkstofffreisetzungsprüfung (0,88%) beobachtet, wobei die Hersteller höhere Ergebnisse als der externe QCA angaben. Wie bereits anhand der Streudiagramme ersichtlich, zeigte die Bland-Altman-Analyse erhebliche zufällige Schwankungen. Obere und untere 95%-Übereinstimmungsgrenzen lagen bei -6,7% bis 8,0% für den Gehalt und -10,1% bis 11,8% für die Wirkstofffreisetzungsprüfung. In Tabelle 2 sind

die Ergebnisse der vier Erstlinien Antituberkulotika gezeigt. Im Fall von Isoniazid, Pyrazinamid und Rifampicin war der Bias (Verzerrung) statistisch signifikant. Für Isoniazid, Ethambutol und Pyrazinamid waren die Unterschiede in der Wirkstofffreisetzungsprüfung nicht signifikant. Für die schwer wasserlösliche Verbindung Rifampicin lagen die vom Hersteller angegebenen Ergebnisse der Wirkstofffreisetzungsprüfung (Mittelwert = 98,5%) jedoch deutlich über denen des externen QCA (Mittelwert = 94,1%; Bias 4,4%; zweiseitiger t-Test: $p<0,001$). Die Wirkstofffreisetzungsprüfung von Rifampicin ist bekanntermaßen problematisch [82, 83], zudem unterscheiden sind die Vorschriften stark in USP 2018 verglichen mit Ph. Int. 2017. Laut USP 2018 Methode soll zum Testen der Wirkstofffreisetzung von Rifampicin-Kapseln und Rifampicin/Isoniazid-Kapseln 0,1N Salzsäure verwendet werden, jedoch zersetzt sich Rifampicin schnell unter sauren Bedingungen. Da bei neutralem pH-Wert die Löslichkeit von Rifampicin geringer ist, was auf die schlechte Benetzbarkeit von Rifampicin zurückgeführt wird[84] verwendet das Ph. Int. 2017 Natriumdodecylsulfat als Detergens. Für einige Kombinationsprodukte sind keine Arzneibuchmethoden verfügbar in Ph. Int., USP und BP, was dazu führt, dass hausinterne Methoden entwickelt und verwendet werden. Für Rifampicin wurde eine Varianzanalyse durchgeführt, die aber keinen signifikanten Einfluss des Herstellers oder Produkts auf die beobachteten Unterschiede zeigte. Es ist zu vermuten, dass die beobachteten Unterschiede durch unterschiedliche (interne-) Methoden hervorgerufen wurden.

Tabelle 2: Vergleich der Ergebnisse von Gehalts- und Wirkstofffreisetzungsprüfung zwischen Herstelleranalyse und externer QCA-Laboranalyse. Dargestellt sind die Ergebnisse der Bland-Altman-Analyse.

Verglichener Datensatz (Herstelleranalyse minus externe QCA-Analyse)	Anzahl	Differenz (Mittelwert)	Grenzen der Übereinstimmung (LOAs)
Gehaltsbestimmung	288	0,67%**	- 6,69% bis + 8,03%
Wirkstofffreisetzungsprüfung	261	0,88%*	- 10,05 % bis + 11,81%
Isoniazid Gehaltsbestimmung	57	1,60%**	- 5,49 % bis + 8,69%
Ethambutol Gehaltsbestimmung	37	0,71%	- 7,10 % bis + 8,52%
Pyrazinamid Gehaltsbestimmung	37	0,77%*	- 3,21 % bis + 4,75%

Verglichener Datensatz (Herstelleranalyse minus externe QCA-Analyse)	Anzahl	Differenz (Mittelwert)	Grenzen der Übereinstimmung (LOAs)
Rifampicin Gehaltsbestimmung	51	1,30%*	- 5,93% bis + 8,53%
Isoniazid Wirkstofffreisetzungsprüfung	57	0,67%	- 9,91% bis + 11,25%
Ethambutol Wirkstofffreisetzungsprüfung	36	0,04%	- 14,08% bis + 14,16%
Pyrazinamid Wirkstofffreisetzungsprüfung	36	1,00%	- 6,75% bis + 8,75%
Rifampicin Wirkstofffreisetzungsprüfung	51	**4,39%****	- 9,85% bis + 18,63%
Kanamycin Gehaltsbestimmung	81 §	-0,65%	- 14,52% bis + 13,22%
Kanamycin Gehaltsbestimmung, Hersteller 1	55 §	-0,19%	- 15,03% bis + 14,65%
Kanamycin Gehaltsbestimmung, Hersteller 2	16 §	1,39%	- 1,55% bis 4,33%

Der höchste beobachte Bias ist fett gedruckt.

* Der Unterschied ist signifikant mit p<0,05 (zweiseitiger Test)

** Der Unterschied ist signifikant mit p<0,01 (zweiseitige Test)

§ Ursprünglich waren 15 Kanamycin Proben ausgewählt worden. Für die Analyse, die in den letzten drei Zeilen dieser Tabelle dargestellt ist, wurden die Daten aller 81 Kanamycin Proben untersucht, die im Studienzeitraum von dem externen QCA untersucht wurden. *(Modifiziert nach Hauk et al.[32])*

Abbildung 8b zeigt für sechs der untersuchten Proben Unterschiede von >10% zwischen der Gehaltsanalyse des Herstellers und externer QCA. Fünf davon stammen von Kanamycin Injektionen. Aus diesem Grund wurden die Daten aller 81 Kanamycin Proben untersucht, die im Untersuchungszeitraum analysiert wurden. Die Abbildungen 9a und b zeigen das Streudiagramm und das Bland-Altman-Diagramm für diese Daten. Die Bland-Altman-Analysenergebnisse sind in Tab. 2 gezeigt. Die Grenzen der Übereinstimmung (LOAs) lagen bei -14,5% bis +13,2% für die Kanamycin-Gehaltsbestimmung und sind damit deutlich höher als die der Gesamtanalyse aller Wirkstoffe. In diesem Fall zeigte die ANOVA einen deutlichen Einfluss des Herstellers. Dies wird in den Streudiagrammen und den Bland-Altman-Diagrammen der beiden wichtigsten Hersteller, von denen 71 der 81 untersuchten Kanamycin-Proben stammten (Abbildung. 9c, d, e und f) sichtbar. Hersteller 1 (55 Proben) hatte eine mikrobiologische Wertbestimmung für Kanamycin verwendet,

während der externe QCA eine Gehaltsbestimmung mittels HPLC nach den USP Vorschriften durchgeführt hatte. Die Übereinstimmungsgrenzen der Bland-Altman-Analyse waren in dem Fall sehr weit (-15,0% bis +14,7%). Im Fall von Hersteller 2 (16 Proben) hatte sowohl der Hersteller als auch der externe QCA eine mikrobiologische Gehaltsbestimmung durchgeführt, woraus viel engere Übereinstimmungsgrenzen (-1,6% bis +4,3%) resultierten.

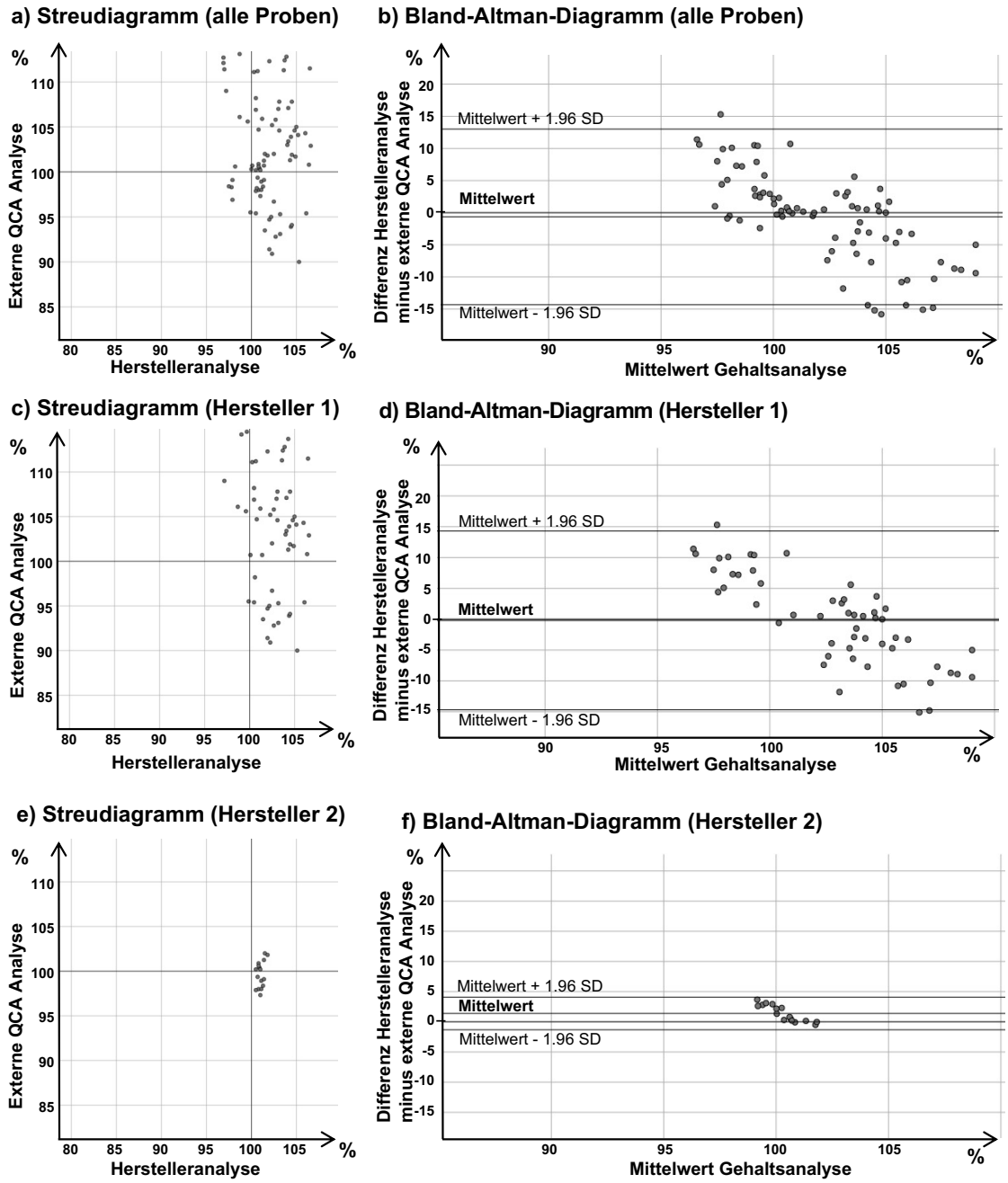


Abbildung 9: Vergleich der Ergebnisse der Kanamycin Gehaltsbestimmung der Herstelleranalyse und externer QCA-Laboranalyse. *(Modifiziert nach Hauk et al.[32])*

Im untersuchten Fünfjahreszeitraum befanden sich zum Zeitpunkt des Versands alle analysierten Arzneimittelchargen innerhalb der Spezifikationen. Jedoch kann sich die Qualität von Arzneimitteln im Laufe der Zeit verschlechtern, besonders (aber nicht ausschließlich) bei unsachgemäßen Transport- und Lagerbedingungen. Zudem hängt die Stabilität der Arzneimittel von der Qualität der Formulierung und Verpackung ab. Eine Untersuchung der Arzneimittelqualität zum Zeitpunkt der Verabreichung an den Patienten ist daher äußert sinnvoll und notwendig. Um diese finanziell, technisch und personell auch in ressourcenschwachen Ländern zu ermöglichen, sind Screening-Technologien unerlässlich.

Die TLCyzer App: Quantifizierung von Arzneistoffen auf Minilab DC-Platten

Das Minilab des Global Pharma Health Fund (GPHF) beinhaltet eine dünnschichtchromatografische Untersuchung zur Identifizierung und semiquantitativen Untersuchung von Arzneistoffen. Zur Automatisierung und Verbesserung der Quantifizierung wurde in Kooperation mit dem Arbeitskreis von Prof. Hendrik Lensch (Fakultät für Informatik, Universität Tübingen) die Smartphone App TLCyzer entwickelt. Mithilfe des Algorithmus kann die Intensität der Spots auf dem Foto einer DC-Platte ausgewertet werden. Der Algorithmus wurde als Android-basierte Smartphone-App entwickelt, die als GPL-Open-Source-Software im Google Play Store und bei F-Droid kostenfrei zur Verfügung gestellt wird.
Basierend auf der von Yu et al. veröffentlichten 3D gedruckten Box[56] wurde eine Holzbox entwickelt (Abbildung 10), die einen Schlitz für die 254nm UV-Lampe (Teil des Minilabs), eine Markierung für die DC-Platte und ein Fenster für eine Smartphone Kamera bietet. Mit dieser Konstruktion können unter Ausschluss von Umgebungslicht qualitativ gute Fotos der DC-Platten unter UV-Licht aufgenommen werden.

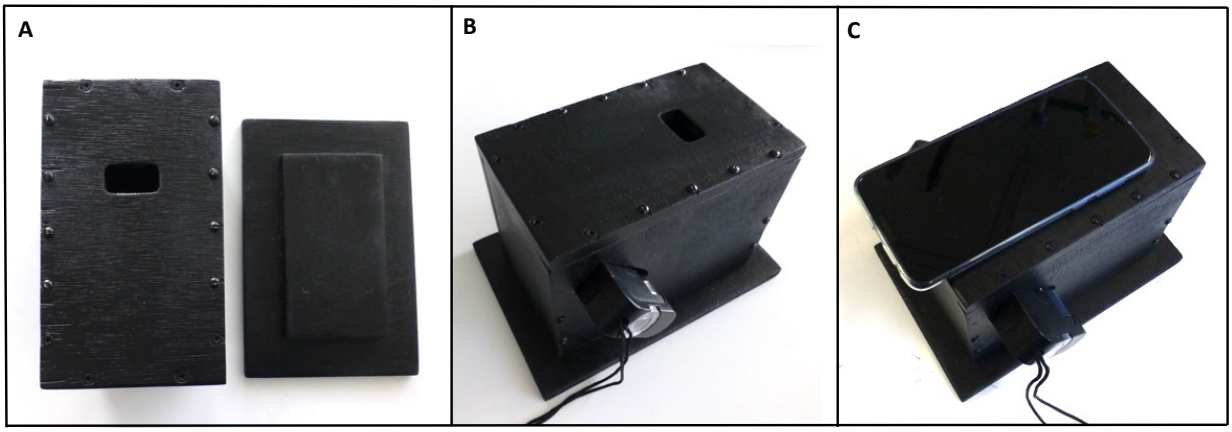
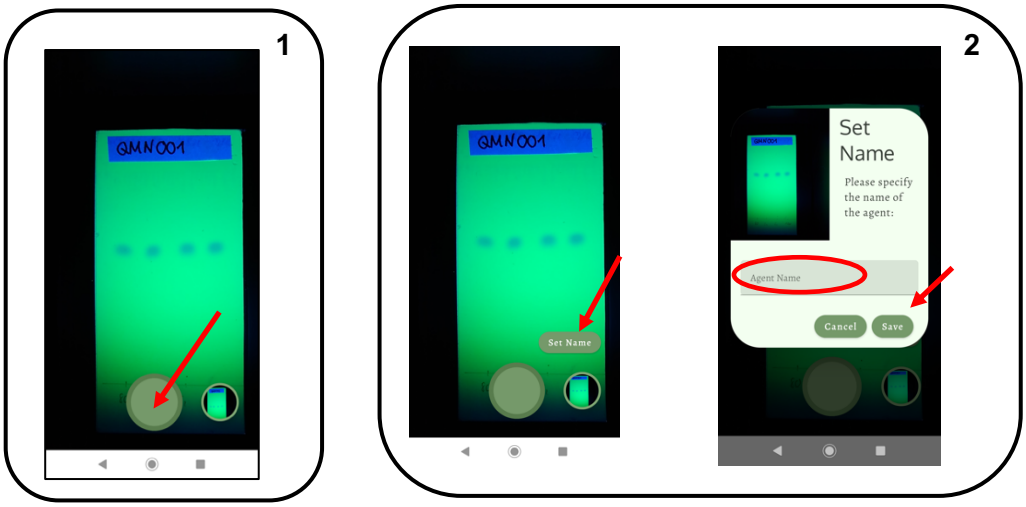
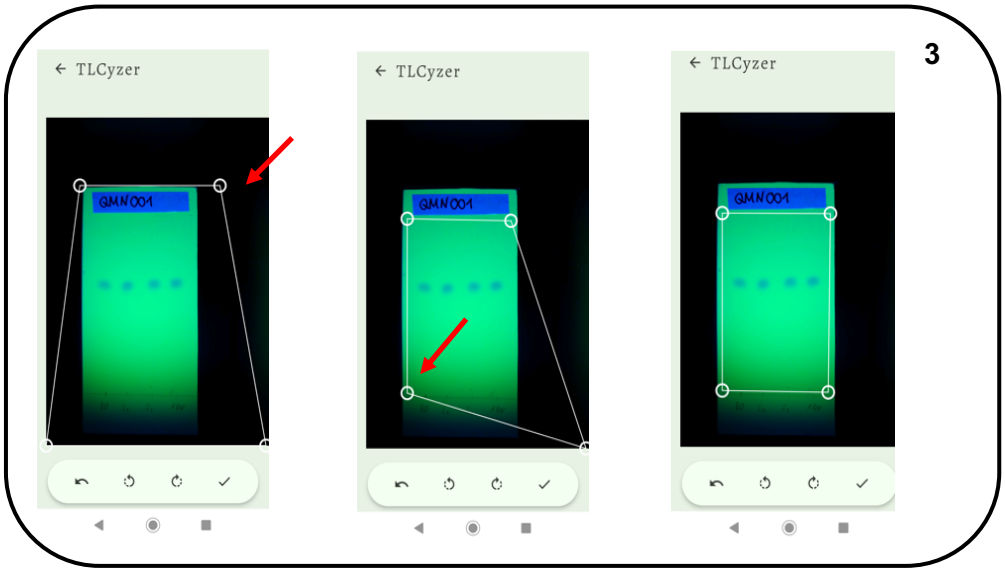


Abbildung 10: Fotos der DC-Holzbox. (A) Die Holzbox besteht aus einem Deckel, um eine dunkle Umgebung zu schaffen und einer Bodenplatte, auf der die Position für die DC-Platte markiert ist. (B) Zusammengebaute Box mit UV-Lampe. (C) DC-Box mit Smartphone. Die Smartphone-Kamera muss sich zum Fotografieren über dem Kamera-Fenster befindet.

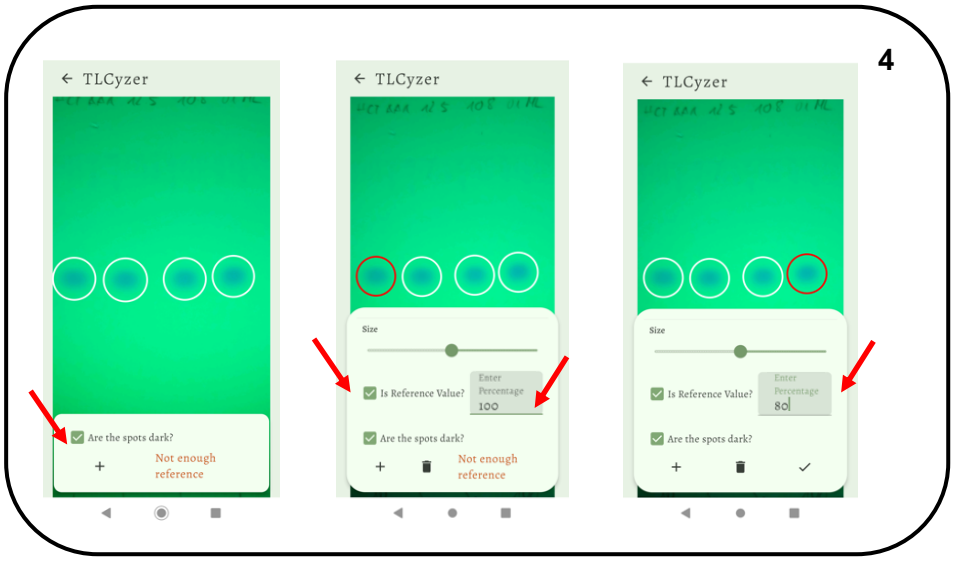
Anhand von 14 verschiedenen Antibiotika und Arzneimitteln gegen nichtübertragbare Krankheiten (Atenolol, Ceftriaxon, Cefuroximaxetil, Chloroquin, Ciprofloxacin, Dexamethason, Fluconazol, Furosemid, Glibenclamid, Hydrochlorothiazid, Metformin, Metronidazol, Sulfamethoxazol und Trimethoprim) wurde die Smartphone App getestet. DC-Platten wurden gemäß Minilab-Handbuch 2020[45] hergestellt. Nach den Minilab Methoden werden für semiquantitative Schätzungen standardgemäß ein 100%- und ein 80% Referenzstandard zusammen mit zwei Probenspots auf die Platte aufgetragen. Laut Minilab Handbuch können jedoch bis zu fünf Spots auf eine 5 x 10cm großen DC-Platte platziert werden. Für die Durchführung der Validierung wurde daher zusätzlich ein 60% Referenzspot auf die Platte aufgetragen. Der genaue Ablauf ist in Abb. 11 anhand einer Schritt-für-Schritt-Anleitung beschrieben.



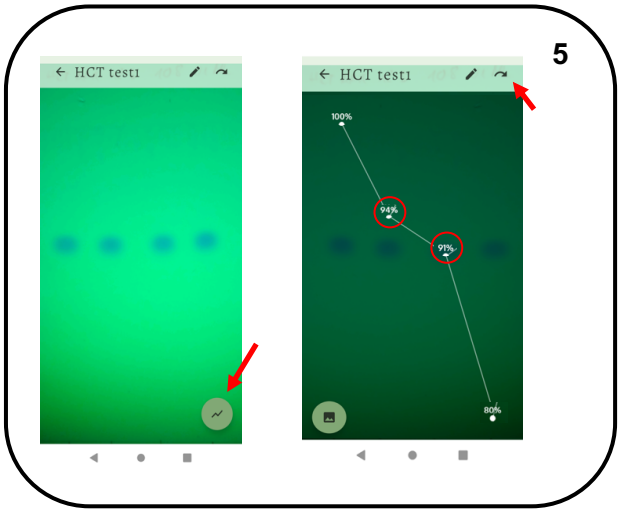
Legen Sie die DC-Platte in die Box und bauen Sie die Box zusammen, schalten Sie die UV-Lampe ein und starten Sie die TLCyzer-App auf Ihrem Smartphone. Nach dem Starten der App schaltet sich die Smartphone-Kamera ein. Sie können ein Foto aufnehmen, indem Sie auf den Kreis tippen (1). Tippen Sie auf „Set Name", geben Sie den Namen der Probe ein und tippen Sie auf „Save" um diesen zu speichern (2).



Wenn die Umrisse der Platte nicht automatisch von der App erkannt werden, müssen Sie diese manuell auswählen. Mithilfe der vier verstellbaren Eckpunkte können die korrekten Umrisse der DC-Platte ausgewählt bzw. korrigiert werden (3). Achten Sie darauf, dass das ausgewählte Rechteck nur die DC-Platte und keine Teile des schwarzen Hintergrunds enthält.



Die Spots werden automatisch erkannt, erkennbar an den weißen Kreisen um die Spots. Das Häkchen bei „Are the Spots dark?" nicht entfernen (4). Wählen Sie die Referenzspots aus, indem Sie den jeweiligen Spot antippen und das Häkchen bei „Is Reference Value" setzen. Geben Sie die jeweilige Konzentration im Feld „Enter Percentage" ein (normalerweise 100% und 80%). Danach tippen Sie auf das Häkchen unten rechts, um die Auswertung zu starten (4). Wenn keine oder nicht alle Spots automatisch erkannt wurden, können mit dem + Zeichen Kreise manuell hinzugefügt werden. Die Größe der Kreise kann am Regler manuell eingestellt werden. Überzählige Kreise können durch Tippen auf den Papierkorb gelöscht werden.



Das Ergebnis der Auswertung wird nun angezeigt. Sie können diese wiederholen, indem Sie auf den Pfeil in der rechten oberen Ecke tippen (5).

Abbildung 11: Schritt-für-Schritt-Anleitung zur Auswertung mit der TLCyzer App

Gemäß USP Kapitel <1850> "Evaluation of Screening Technologies for Assessing Medicine Quality" [41] sollen zur Beurteilung eines Screening-Tools generelle Informationen zur Technologie, eine Validierung und eine Beurteilung der Praxistauglichkeit im Feld durchgeführt werden. Zur Quantifizierung von Wirkstoffen in Arzneimitteln, soll die Richtigkeit (angegeben als Wiederfindungsrate in Prozent), die Genauigkeit (Wiederholbarkeit und „interne Laborpräzision“), Spezifität, Linearität, Robustheit und der Arbeitsbereich validiert werden. Diese Parameter sind Teil mehrerer Richtlinien und Standards, wie beispielsweise der ICH Q2(R1) Richtlinie "Validierung analytischer Verfahren: Text und Methodik".[85] Das USP Kapitel bezieht sich im Gegensatz zur ICH Richtlinie jedoch explizit auf die Validierung eines Instruments und nicht auf die Validierung einer Methode.[41]

Für die Validierung der Smartphone App in Kombination mit der Holzbox wurden zertifizierte Referenzstandards verwendet. Es konnte gezeigt werden, dass die Quantifizierung der 14 verschiedenen Wirkstoffe mit der TLCyzer App genaue und reproduzierbare Ergebnisse lieferte. Die Wiederfindungsrate der Einzelergebnisse lag zwischen 93,4% und 107,9%. Die Genauigkeit, angegeben als relative Standardabweichung (RSD), lag zwischen 0,77% und 5,68%. Die einzelnen Ergebnisse, jeweils vier pro Wirkstoff und Konzentration (70%, 85% und 90%), sind in Abb. 12 dargestellt.

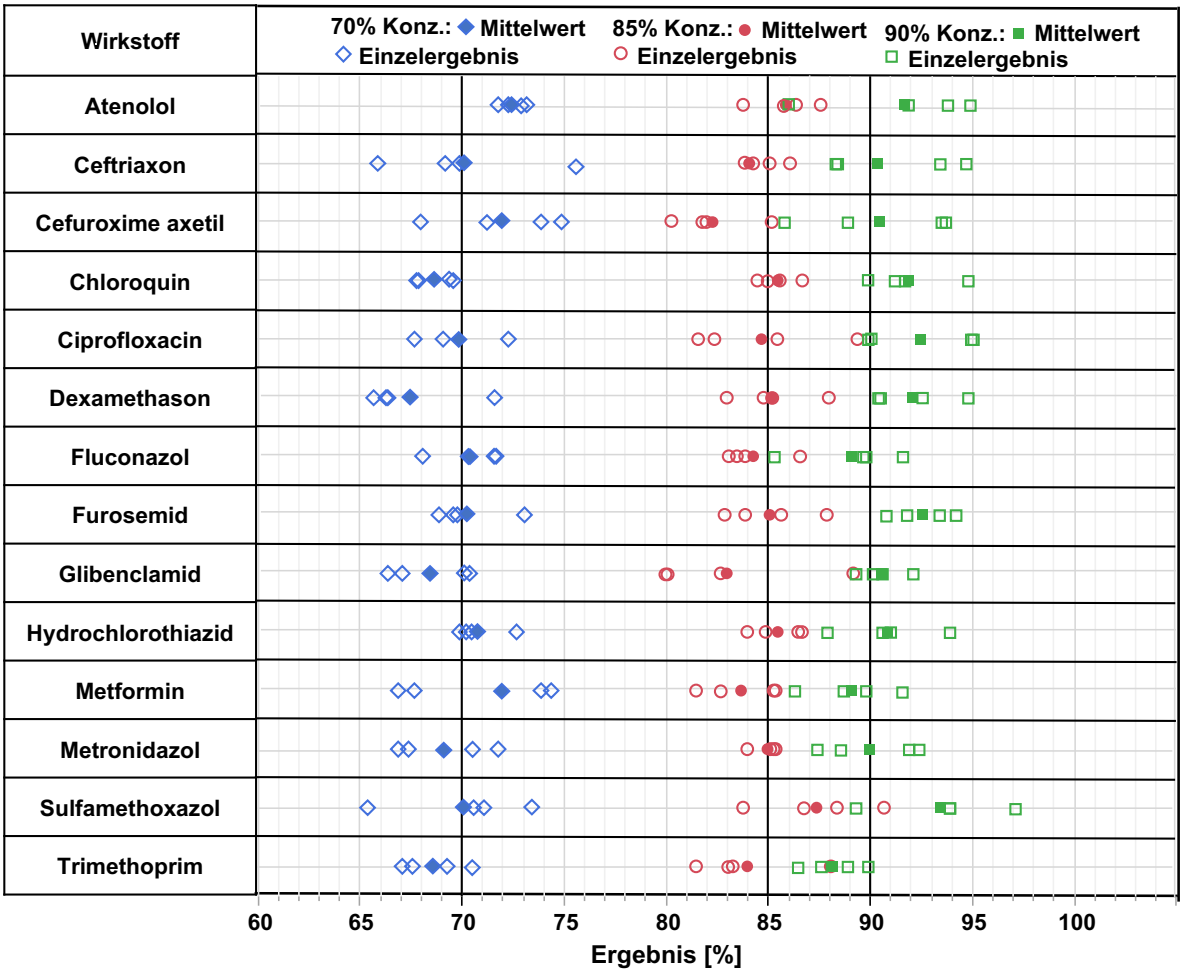


Abbildung 12: Mit der Smartphone-App ermittelte Ergebnisse zur Bewertung der Genauigkeit und Wiederholbarkeit. Für jeden Wirkstoff und jede Konzentration (70%, 85% und 90%) wurden zwei DC-Platten mit je zwei Probenspots erstellt und ausgewertet. Dargestellt sind die Einzelergebnisse und der Mittelwert der Ergebnisse.

Auch Trimethoprim und Atenolol, die beide nur schwach sichtbare Spots zeigen und laut Minilab zur Identifizierung und Quantifizierung mit Jod angefärbt werden sollen, konnten mit der Smartphone-App quantitativ ausgewertet werden (mittlere Wiederfindung 98,3% bzw. 102,2%; RSD 2,48 bzw. 2,33%).
Für die Bestimmung der „internen Laborpräzision“ wurden DC-Platten an zwei verschiedenen Tagen fotografiert und von drei verschiedenen Personen an zwei verschiedenen Tagen mit drei verschiedenen Smartphones ausgewertet. Die Parameter wurden nicht einzeln überprüft, sondern wie in der ICH Richtlinie vorgeschlagen anhand eines Matrix Designs.[85] Die durchschnittliche RSD der 24 Ergebnisse pro Wirkstoff, lag bei 4,46% und damit unter der 5% Schwelle, die weithin als RSD für chromatografischen Methoden akzeptiert wird.[55]
Ziel der App war es, die quantitative Bewertung des Minilabs hinsichtlich der Zuverlässigkeit und Objektivität der Bewertung zu verbessern. Eine Probe mit einem Gehalt unter 80% gilt als „nicht bestanden“ laut Minilab.[45] In Bezug auf die Spezifität der Quantifizierung konnte gezeigt werden, dass alle 70% Spots korrekt als „nicht bestanden“ identifiziert wurden, d.h. ein Ergebnis unter 80% wurde von der App berechnet und die 90% Spots wurden korrekt als „bestanden“ identifiziert, d.h. ein Ergebnis über 80% wurde angezeigt. Außerdem zeigte die App für die 56 untersuchten Spots mit 85% der vom Minilab angegebenen Konzentration immer ein Ergebnis zwischen 80% und 90% an (siehe Abb. 12).
Alle 14 Wirkstoffe zeigten einen linearen Zusammenhang zwischen der Wirkstoffkonzentration des Spots und den mit der App ermittelten Ergebnissen im Bereich von 50% bis 120% bezogen auf die Minilab-Standardkonzentration. Die Ergebnisse der Linearitätsuntersuchung sind in Tabelle 3 abgebildet. Pro Wirkstoff wurden fünf verschiedene Konzentrationen auf drei DC-Platten analysiert. Der Bestimmungskoeffizient R^2 lag zwischen 0,989 und 1,00.

Tabelle 3: Ergebnisse der Linearitätsuntersuchung. In der Tabelle sind die Ergebnisse der linearen Regressionsgerade für jeden der 14 Wirkstoffe gezeigt.

Wirkstoff	y-Achsen-abschnitt	Steigung	Residuen-quadrat-summe	Korrelations-koeffizient R	Bestimmungs-koeffizient R^2
Atenolol	-2,701	1,026	15,52	0,997	0,995
Ceftriaxon	-0,795	0,999	6,77	0,999	0,998
Cefuroximaxetil	1,376	0,984	9,62	0,998	0,997

Wirkstoff	y-Achsen-abschnitt	Steigung	Residuen-quadrat-summe	Korrelations-koeffizient R	Bestimmungs-koeffizient R^2
Chloroquin	1,568	0,984	24,05	0,996	0,992
Ciprofloxacin	3,310	0,958	29,26	0,995	0,989
Dexamethason	0,228	0,991	3,81	0,999	0,999
Fluconazol	-1,060	1,012	3,18	0,999	0,999
Furosemid	0,853	0,992	0,57	1,000	1,000
Glibenclamide	0,645	0,992	7,30	0,999	0,997
Hydrochlorothiazid	0,573	1,007	17,44	0,997	0,994
Metformin	3,782	0,967	18,41	0,997	0,993
Metronidazol	0,460	0,998	1,46	1,000	0,999
Sulfamethoxazol	1,344	0,987	6,97	0,999	0,998
Trimethoprim	1,069	0,992	1,12	1,000	1,000

Die Wiederfindung lag hier zwischen 94,3% und 107,2%, die RSD unter 5%, vorausgesetzt es wurden beim Wirkstoff Sulfamethoxazol (der sehr große Spots zeigt) nur vier statt fünf Spots (kein 60% Referenzspot) auf einer Platte platziert. Dieser Bereich gilt als akzeptabler Arbeitsbereich der App für die untersuchten 14 Wirkstoffe. Ziel des Screening-Tools ist es nicht, stark minderwertige oder gefälschte Proben mit einem Wirkstoffgehalt unter 50% exakt zu quantifizieren.
Trimethoprim (sehr schwache Spots) und Sulfamethoxazol (sehr dunkle Spots) konnten auch bei einer Konzentration von 12% der Minilab-Standardlösung noch zuverlässig mit der App quantifiziert werden können. Diese Beobachtung kann allerdings nicht ohne weiteres auf andere Wirkstoffe übertragen werden, da die Intensität der Spots von der jeweiligen Fluoreszenzlöschung (Quenching) und der in der in der Minilab Methode angegebenen Wirkstoffkonzentration abhängt, deutet jedoch darauf hin, dass die App auch zur Quantifizierung geringerer Wirkstoffmengen verwendet werden kann.
Im Rahmen der Robustheitsuntersuchung wurde die Analyse unter verschiedenen modifizierten Faktoren durchgeführt, um kritische Parameter aufzudecken. Diese betrafen sowohl die Auswertung mit der App (unterschiedlicher Zuschnitt der DC-Platte, mit- und ohne Beschriftung) als auch externe Faktoren (Position und geringe Batterieladung der UV-Lampe, Verwendung einer anderen Box und eines anderen Smartphones). Die Methode zeigte sich als sehr robust, so lag der durchschnittliche Unterschied im Vergleich zu den Ergebnissen unter Standardbedingungen unter 4,7%.

Die USP empfiehlt Handhabung, Wartung und Reparatur sowie Haltbarkeit und Nutzung der entwickelten Technologie zu bewerten. Das GPHF Minilab selbst wird seit vielen Jahren erfolgreich im Feld eingesetzt und wurde bereits in einem Technologie-Review der US Pharmacopeial Convention bewertet.[86] Die entwickelte Box ist stabil gegen Umwelteinflüsse, kann käuflich erworben werden (Pidinger Werkstätten, Piding) oder relativ einfach nachgebaut werden. Ein Schreiner in Simbabwe hat diese bereits anhand unserer Konstruktionspläne nachgebaut. Ein günstiges Smartphone mit einer 12 MP Kamera ist ausreichend und für die Auswertung selbst ist weder eine Internetverbindung noch eine Stromversorgung notwendig. Die Fotos können zur Dokumentation gespeichert werden, als ZIP-Datei verschickt werden, um einen einfachen, schnellen und unkomplizierten Austausch von Fotos und Analysenergebnissen sowie eine erneute Auswertung zu ermöglichen. Die Auswertung ist weitgehend selbsterklärend und konnte bereits erfolgreich über eine online Schulung vermittelt werden.

Diskussion

Die in Togo, DR Kongo und Kamerun gefundene Prävalenz von 8% bzw. 18,6% minderwertiger und gefälschter Medikamente liegt im Bereich der von der WHO im Jahr 2017 geschätzten Prävalenz von 10,5% in LMICs bzw. der von Ozawa et al. geschätzten Prävalenz von 18,7% in afrikanischen Ländern.[13] Auffallend war, dass sich die Zahl an Proben „außerhalb der Spezifikation“ verdoppelt hat, wenn zusätzlich zur Gehaltsbestimmung auch eine Wirkstofffreisetzungsprüfung durchgeführt wurde (16,2% statt 8,6%; und 18,6% mit Prüfung auf Gleichförmigkeit einzeldosierter Arzneiformen). In vielen Studien wurde die relativ aufwendige Wirkstofffreisetzungsprüfung aus Zeitgründen bislang nicht durchgeführt. Diese Beobachtung deutet jedoch darauf hin, dass die Zahl minderwertiger Proben dann als zu niedrig angegeben wird, weshalb die Prüfung in zukünftigen Studien nicht weggelassen werden sollte. Minderwertige Arzneimittel stammten häufiger von informellen Händlern als von anderen Quellen. Das legt nahe, dass eine Lieferantenqualifizierung bei der Arzneimittelbeschaffung sowie eine Durchsetzung des Arzneimittelverkaufsverbots durch informelle Anbieter die Prävalenz minderwertiger und gefälschter Arzneimittel verringern kann. Beim Vergleich der

Arzneimittelklassen fällt auf, dass die Prävalenzen von SF-Arzneimitteln bei den Medikamenten gegen nichtübertragbare Krankheiten signifikant höher war (25%) im Vergleich zu Antibiotika (12%; p=0,0004). Der Unterschied war in der DR Kongo besonders ausgeprägt (33% vs. 9%; p<0,0001) (siehe Abb. 2). Angesichts der steigenden Zahl an Patienten mit nichtübertragbaren Krankheiten in LMICs ist diese Zahl alarmierend. In einer Untersuchung von Herzmedikamenten in verschiedenen afrikanischen Ländern haben Antignac et al. unter anderem auch Proben aus der DR Kongo, darunter Atenolol, Furosemid, Hydrochlorothiazid und vier weitere Herzmedikamente untersucht und ähnlich hohe Prävalenzen (26,7%) an SF-Medikamenten gefunden.[20]

Um einen Beitrag zur Verbesserung der Arzneimittelqualität in LMICs zu leisten, sind verlässliche Daten zur Prävalenz von minderwertigen und gefälschten Arzneimitteln unerlässlich. Werden bei der Gehaltsbestimmung die Toleranzgrenzwerte unterschiedlicher Arzneibücher oder willkürlich gewählte Toleranzgrenzen verwendet, führt das zu sehr unterschiedlichen Prävalenzdaten. Anhand der Analysedaten der Arzneimittelproben aus Kamerun, der DR Kongo und aus Malawi konnte eindrucksvoll gezeigt werden, dass sich die berechneten Prävalenzraten bei den genau gleichen Proben um einen Faktor größer zehn (2,4% bis zu 34,3%) unterschieden, wenn unterschiedliche Toleranzgrenzen angewendet wurden (siehe Abb. 4). Anstelle willkürlicher Grenzwerte empfiehlt sich die Verwendung der USP- oder Ph. Int. Toleranzgrenzen bei zukünftigen Arzneimittelqualitätsstudien. Zur besseren Vergleichbarkeit wissenschaftlicher Studien, ist eine Harmonisierung der Toleranzgrenzen dringend erforderlich. Zudem ist es sinnvoll die tatsächlichen Ergebnisse der Gehalts- und gegebenenfalls Wirkstofffreisetzungsprüfung anzugeben, um eine bessere Bewertung von Studienergebnissen zu ermöglichen. Eine Laboranalyse kann ein Arzneimittel lediglich in „innerhalb“ und „außerhalb der Spezifikation“ einteilen. Laut WHO Definition sind „minderwertige"-Arzneimittel diejenigen, für die keine Beweise vorliegen, dass sie absichtlich bzw. betrügerisch ihre Identität, Zusammensetzung oder Quelle falsch darstellen. Dagegen liegt bei „gefälschten" Arzneimitteln ein Beweis für eine solche Täuschung vor, unabhängig davon, ob die Analyseergebnisse „in der Spezifikation" oder „außerhalb der Spezifikation" liegen.[18] Oftmals wird in Arzneimittelqualitätsstudien nicht zwischen minderwertigen und gefälschten Arzneimitteln unterschieden, obwohl diese in der

WHO Definition als unterschiedliche Kategorien definiert sind.[18] Da die Gründe für das Auftreten von minderwertigen und gefälschten Arzneimitteln ganz unterschiedlicher Natur sind, als auch die erforderlichen Maßnahmen, um auf die jeweilige Problematik zu reagieren, ist es sinnvoll, diese Kategorien zu unterscheiden. In der wissenschaftlichen Praxis ist dies jedoch oft nicht eindeutig. Fälschungen, die das echte Produkt genau nachahmen bleiben leicht unentdeckt. Zudem besteht eine Grauzone zwischen absichtlich gefälschten und unbeabsichtigten minderwertigen Arzneimitteln.[22]

Die Verpackungsanalyse und die chemische Analyse konnte drei der 601 in der DR Kongo, Kamerun und Malawi gesammelten Proben als gefälscht identifizieren, die Authentizitätsanfragen weitere sieben. Diese zeigten keine auffälligen Abweichungen bei der Gehalts- und Wirkstofffreisetzungsprüfung. Die Fälschungen wurden von den Herstellern und Vertreibern durch Unstimmigkeiten bei der Verpackung bzw. des Etiketts (z.B. Batchnummer oder verlängertes Verfallsdatum) identifiziert. Im Fall der gefälschten „CO-TRIMOXAZOLE (sulfamethoxazole & trimethoprim)" Tabletten (Abb. 6B) stimmte sowohl die Verpackung als auch die Tablettenprägung nicht mit dem Original überein. In diesem Fall wurden Tabletten und Verpackung eines Herstellers imitiert. Obwohl diese Proben den deklarierten Wirkstoff enthielten, stellen sie eine Gefahr dar, da nicht sichergestellt ist, dass diese Tabletten bei Verkauf den Qualitätsstandards entsprechen.

Authentizitätsanfragen haben sich somit als ein wirksames Instrument zur Identifizierung von Fälschungen erwiesen, sind jedoch mit einem nicht zu vernachlässigenden Arbeitsaufwand sowohl für die Durchführer der Studie als auch für die Hersteller und Vertreiber verbunden. Die Rücklaufquote lag bei 49,5% und war damit trotz der Einschränkungen durch die COVID-19 Pandemie höher als in anderen Studien berichtet.[24, 87]

Um zukünftigen Studien Anhaltspunkte zu bieten, wann eine Probe als „gefälscht“ eingestuft werden kann, auch wenn kein rechtlicher Nachweis von Vorsatz oder Betrug vorliegt, wurden anhand der Ergebnisse dieser Studie folgende Kriterien vorgeschlagen:

1) Ein Arzneimittel kann als „gefälscht“ bezeichnet werden, wenn eine zuständige nationale oder internationale Behörde erklärt, dass das Medikament, basierend auf den WHO-Definitionen, gefälscht ist.[12, 18]

2) Wenn der angegebene Hersteller erklärt hat, dass das Medikament gefälscht ist bzw. das Verfallsdatum oder andere Angaben auf dem Etikett illegal manipuliert wurden.[12]
3) Wenn die Verpackungsanalyse schlüssige Beweise liefert, dass es sich um eine Fälschung handelt, z.B. dass der angegebene Hersteller nicht existiert, oder wenn das Arzneimittel keinen Wirkstoff oder einen falschen Wirkstoff anstelle des angegebenen Wirkstoffs enthält. (Im unwahrscheinlichem Falle, dass es sich um einen nicht vorsätzlichen Produktionsfehler handelt, müsste das Arzneimittel als „minderwertig" eingestuft werden).

Ein Arzneimittel kann als „wahrscheinlich gefälscht" eingestuft werden, wenn es weniger als 50% der angegebenen Wirkstoffmenge enthält UND wenn kein Hinweis vorliegt, dass der niedrige Gehalt auf einen Wirkstoffabbau zurückzuführen ist, was in der Regel am Nachweis von Zersetzungsprodukten sichtbar wird. Beispiel dafür wären die im Kamerun gefundenen Chloroquin Tabletten, die nur 21,7% der angegebenen Wirkstoffmenge enthielten.[70, 71] Misoprostol Tabletten, die einen Wirkstoffgehalt von 13,1% der deklarierten Menge aufwiesen, aber gleichzeitig Abbauprodukten von Misoprostol zeigten, müssen demzufolge als "extrem minderwertig" und nicht als "wahrscheinlich gefälscht" eingestuft werden.[67]
Die Vorschläge und Beispiel sollen dazu dienen in der bislang noch kontrovers diskutierten Unterscheidung zwischen minderwertigen und gefälschten Arzneimitteln [22] Harmonisierungen für zukünftige Arzneimittelqualitätsstudien zu erreichen.

Die Hauptrisiken für das Auftreten von SF-Medikamenten – eingeschränkter Zugang und schwache technische Kapazitäten zur Qualitätssicherung und -kontrolle[12] – haben sich durch die COVID-19 Pandemie verschärft und zu einem starken Anstieg an SF-Medikamenten in LMICs geführt.[26] Das Fehlen bzw. die subtherapeutische Menge an Chloroquin in den fünf, im Kamerun und der DR Kongo aufgetretenen Fälschungen stellt ein ernsthaftes Gesundheitsrisiko für Patienten dar. Diese Produkte wurden zudem zu sehr viel höheren Preisen verkauft, was zu einer finanziellen Belastung von Patienten führt, die auf diese Medikamente angewiesen sind (Indikation bei *Plasmodium vivax* Malaria und Autoimmunkrankheiten). Alle beschriebenen Fälschungen konnten mithilfe des Minilabs aufgedeckt werden. Dies zeigt eindrücklich, wie mit kostengünstigen Screening-Tools ein wichtiger Beitrag zur Identifizierung von minderwertigen und gefälschten Arzneimitteln geleistet werden

kann. Auf der anderen Seite werden auch Grenzen des Minilabs aufgezeigt, wenn es um die Identifizierung von unbekannten Stoffen geht.
Die Unterbrechung der Produktions- und Lieferketten in Indien und China, den wichtigsten Herstellerländer von Generika für LMICs, hatte nicht nur Auswirkungen auf Medikamente zur Behandlung und Vorbeugung von COVID-19.[26] Seit Beginn der Pandemie wurden laut WHO bei über 20 Arzneimitteln weltweite Engpässe verzeichnet.[88] Zum ersten Mal seit über einem Jahrzehnt, ist die Zahl der Tuberkulose-Todesfälle wieder gestiegen, weil der Zugang zu Diagnose und Behandlung durch die COVID-19-Pandemie eingeschränkt war.[35] Fast die Hälfte der an Tuberkulose erkrankten Menschen hatten 2020 keinen Zugang zu einer Behandlung. Auch die Behandlung von Patienten mit arzneimittelresistenter Tuberkulose und die Tuberkuloseprävention ist 2020 deutlich zurückgegangen.[35]
Die Beschaffung von qualitätsgesicherten und kostengünstigen Antituberkulotika durch die Global Drug Facility hat sich seit nunmehr 20 Jahren bewährt. Die Verfahren der GDF können daher auch nationalen Beschaffungsbehörden, Zulassungsbehörden und NGOs als Anhaltspunkt und Maßstab bei der Qualitätssicherung dienen. Durch den Vergleich der Ergebnisse der Herstelleranalyse und der Analyse des externen QCA, konnten Auffälligkeiten im Fall der Wirkstofffreisetzung von Rifampicin und der Gehaltsbestimmung von Kanamycin Injektionen festgestellt werden. Basierend auf diesen Ergebnissen hat die GDF ein System eingeführt, um Analysenergebnisse zukünftig routinemäßig zu überwachen und auf Unstimmigkeiten zu überprüfen. In mehreren Monografien von Tuberkulose-Kombinationsprodukten ist in der Ph. Int. angegeben, dass der Test für die Wirkstofffreisetzung für Rifampicin noch ergänzt werden muss.[89] Wenn keine Arzneibuchmethoden vorliegen, sind Hersteller als auch Kontrolllabore gezwungen auf eigene Methoden auszuweichen. Insbesondere bei empfindlichen und schwerlöslichen Wirkstoffen wie Rifampicin kann das zu abweichenden Ergebnissen führen. Durch die veröffentlichte Publikation soll auch der WHO-Sachverständigenausschuss darauf hingewiesen werden, dass weitere Leitlinien und Richtlinien zum Vergleich von Analysenergebnissen nötig sind und dass Monografien der Ph. Int. ergänzt werden müssen.

Das Minilab des Global Pharma Health Fund wird seit vielen Jahren erfolgreich zur Untersuchung der Arzneimittelqualität in LMICs eingesetzt und wurde nun mit einer

neuen Technologie in Form einer Smartphone Imaging Software kombiniert. Die Ergebnisse der Validierungsstudie zeigen, dass damit eine verbesserte Probenquantifizierung der DC-Analyse möglich ist. Die entwickelte Smartphone App quantifiziert die Spots auf der DC-Platte anhand ihrer Intensität im Vergleich zu Referenzspots mit bekannter Konzentration. Basierend auf der von Yu et al. entwickelten 3D-Box[56] wurde eine einfach konstruierte Holzbox entwickelt, um die Position der DC-Platte, der UV-Lampe und der Smartphone Kamera optimal zu platzieren. Die robuste Box eignet sich gut für den Einsatz im Feld, und lässt sich anhand der Konstruktionszeichnungen vor Ort leicht nachbauen.
Eine Validierung dieses erweiterten Screening-Tools nach den Vorgaben der USP[41] konnte für 14 verschiedene Wirkstoffe erfolgreich durchgeführt werden. Die Methode erwies sich bisher als sehr robust und zeigte auch bei Modifikation verschiedener Parameter wie beispielsweise der Box, des Smartphone Models, der Position der UV-Lampe oder der Person, die die Analyse durchführt, gleichbleibend gute Ergebnisse (Differenz im Vergleich zu Standardbedingungen <4,7%). Die Handhabung der App ist weitgehend selbsterklärend und lässt sich mit geringem Schulungsaufwand zuverlässig erlernen. In einer derzeit laufenden Arzneimittelqualitätsstudie in Nigeria wird die App in Kombination mit der Box eingesetzt. Diese Studie wird weitere Informationen zur Feldtauglichkeit und praktischen Anwendbarkeit liefern.
Die Auswertung mit der entwickelten App wurde bisher für 14 verschiedene Wirkstoffe untersucht. Mit dem Minilab selbst kann ein sehr breites Spektrum unterschiedlicher APIs in unterschiedlichen Formulierungen (festen Arzneiformen sowie Injektionen) analysiert werden. Da die meisten der 102 im Minilab Handbuch enthaltenen Wirkstoffe die Fluoreszenz der DC-Platten bei 254nm löschen[45], ist die Methode potenziell für eine große Bandbreite an Wirkstoffen anwendbar. Zudem konnte am Beispiel von Cotrimoxazol gezeigt werden, dass sich auch die einzelnen Wirkstoffe von Kombinationsprodukten separat quantifizieren lassen.
Die Smartphone App und die Konstruktionszeichnung der DC-Box werden kostenlos zur Verfügung gestellt, ebenso der Algorithmus, sodass die TLCyzer-App aktualisiert und in ihren Funktionen erweitert werden kann. Aktuelle Minilab-Nutzer sollen dazu ermutigt werden, dieses Setup im Feld zu testen, um so zu einer verbesserten Arzneimittelprüfung vor Ort und einer Sicherstellung der Arzneimittelqualität in LMICs beizutragen.

Literaturverzeichnis

1. Nayyar GML, Breman JG, Herrington JE, 2015. The global pandemic of falsified medicines: Laboratory and field innovations and policy perspectives. *Am J Trop Med Hyg 92(6_Suppl)*:2-7.
2. WHO. Urgent health challenges for the next decade: World Health Organization; 2020. Available from: https://www.who.int/news-room/photo-story/photo-story-detail/urgent-health-challenges-for-the-next-decade.
3. UN. Sustainable Development Goal 3: Ensure healthy lives and promote well-being for all at all ages: United Nations; 2021 [Oktober 1, 2021]. Available from: https://sdgs.un.org/goals/goal3.
4. WHO, 2017. A study on the public health and socioeconomic impact of substandard and falsified medical products. Available at: https://apps.who.int/iris/bitstream/handle/10665/331690/9789241513432-eng.pdf?sequence=1&isAllowed=y. Accessed September 22, 2021.
5. Kaur H et al., 2016. Fake anti-malarials: start with the facts. *Malar J 15(1)*:86.
6. Khuluza F, Kigera S, Heide L, 2017. Low prevalence of substandard and falsified antimalarial and antibiotic medicines in public and faith-based health facilities of southern Malawi. *Am J Trop Med Hyg 96(5)*:1124-1135.
7. Chikowe I, Osei-Safo D, Harrison JJEK, Konadu DY, Addae-Mensah I, 2015. Post-marketing surveillance of anti-malarial medicines used in Malawi. *Malar J 14(1)*:127.
8. Peyraud N et al., 2017. An epidemic of dystonic reactions in central Africa. *Lancet Glob Health 5(2)*:e137-e138.
9. Schier JG, Rubin CS, Miller D, Barr D, McGeehin MA, 2009. Medication-associated diethylene glycol mass poisoning: A review and discussion on the origin of contamination. *J Public Health Policy 30(2)*:127-143.
10. WHO. Noncommunicable diseases 2021 [Oktober 31, 2021]. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases.
11. Do NT, Bellingham K, Newton PN, Caillet C, 2021. The quality of medical products for cardiovascular diseases: a gap in global cardiac care. *BMJ Glob Health 6(9)*:e006523.
12. WHO. WHO Global Surveillance and Monitoring System for substandard and falsified medical products. Geneva: World Health Organization; 2017 November 8, 2021]. Available from: https://apps.who.int/iris/handle/10665/326708.
13. Ozawa S, Evans DR, Bessias S, Haynie DG, Yemeke TT, Laing SK, Herrington JE, 2018. Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries: A systematic review and meta-analysis. *JAMA Netw Open 1(4)*:e181662.
14. Almuzaini T, Choonara I, Sammons H, 2013. Substandard and counterfeit medicines: a systematic review of the literature. *BMJ Open 3(8)*:e002923.
15. McManus D, Naughton BD, 2020. A systematic review of substandard, falsified, unlicensed and unregistered medicine sampling studies: a focus on context, prevalence, and quality. *BMJ Glob Health 5(8)*.
16. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Guidelines on the Conduct of Surveys of the Quality of Medicines. WHO Technical Report Series No. 996. 2016.
17. Newton PN et al., 2009. Guidelines for field surveys of the quality of medicines: A proposal. *PLOS Medicine 6(3)*:e1000052.

18. WHO, 2017. Member State mechanism on substandard/spurious/falsely labelled/falsified/ counterfeit (SSFFC) medical products. Appendix 3. Working definitions.33-36. Available at: https://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_23-en.pdf. Accessed Oktober 28, 2021.
19. Kaur H et al., 2015. Quality of artemisinin-based combination formulations for malaria treatment: Prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. *PLOS ONE 10(5)*:e0125577.
20. Antignac M et al., 2017. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa. *Int J Cardiol 243*:523-528.
21. U.S. Department of Health and Human Services Food and Drug A, Center for Drug Evaluation and Research (CDER). Guidance for Industry. Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production. 2006 [November 8, 2021]. Available from: https://www.fda.gov/media/71001/download.
22. Olliaro E, Olliaro P, Ho CWL, Ravinetto R, 2020. Legal uncertainty—the gray area around substandard medicines: where public health meets law. *Am J Trop Med Hyg 102(2)*:262-267.
23. Aka E, Legris C, Tanimoto T, Matsushita R, Kimura K, 2005. Counterfeit medicine detection by authenticity investigation. A pilot study in the street market of Côte d'Ivoire. *Jpb J Soc Pharm 24*:7-16.
24. Rahman MS et al., 2019. A cross-sectional Investigation of the quality of selected medicines for noncommunicable diseases in private community drug outlets in Cambodia during 2011-2013. *Am J Trop Med Hyg 101(5)*:1018-1026.
25. Interpol. INTERPOL warns of organized crime threat to COVID-19 vaccines 2020 [November 9, 2021]. Available from: https://www.interpol.int/News-and-Events/News/2020/INTERPOL-warns-of-organized-crime-threat-to-COVID-19-vaccines.
26. Newton PN, Bond KC, 2020. COVID-19 and risks to the supply and quality of tests, drugs, and vaccines. *Lancet Glob Health 8*:e754-e755.
27. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Model quality assurance system for procurement agencies. WHO Technical Report Series 986. Annex 3. Geneva, Switzerland: World Health Organization; 2014.
28. Moore T, Lee D, Konduri N, Kasonde L. Assuring the quality of essential medicines procured with donor funds. Health, Nutrition and Population (HNP) discussion paper. Washington, DC: World Bank; 2012 [Oktober 28, 2021]. Available from: http://hdl.handle.net/10986/13577.
29. van Valen M, Jamieson D, Parvin L, Ramirez CL, 2018. Dispelling myths about drug procurement policy. *Lancet Glob Health 6(6)*:e609-e610.
30. Management Sciences for Health. MDS-3: Managing Access to Medicines and Health Technologies. Arlington, VA; 2012 [Oktober 28, 2021]. Available from: https://www.msh.org/resources/mds-3-managing-access-to-medicines-and-health-technologies.
31. Tatay M, Torreele E, 2019. Ensuring access to life-saving medicines as countries shift from Gobal Fund support. *Bull World Health Organ 2019 (97)*:311–311A.
32. Hauk C, Schäfermann S, Martus P, Muzafarova N, Babaley M, Waning B, Heide L, 2020. Quality assurance in anti-tuberculosis drug procurement by the Stop TB Partnership—Global Drug Facility: Procedures, costs, time requirements, and

comparison of assay and dissolution results by manufacturers and by external analysis. *PLOS One 15*:e0243428.
33. Dye C, 2009. Doomsday postponed? Preventing and reversing epidemics of drug-resistant tuberculosis. *Nat Rev Microbiol 7(1)*:81-87.
34. Caminero JA, 2010. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. *Int J Tuberc Lung Dis 14(4)*:382-390.
35. WHO. Global Tuberculosis Report 2021. Genva 2021. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports.
36. Petersen A, Held N, Heide L, Difäm - EPN Minilab Survey Group, 2017. Surveillance for falsified and substandard medicines in Africa and Asia by local organizations using the low-cost GPHF Minilab. *PLOS One 12(9)*:e0184165.
37. Lalani M, Kitutu FE, Clarke SE, Kaur H, 2017. Anti-malarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings. *Malar J 16(1)*:197.
38. Vickers S, Bernier M, Zambrzycki S, Fernandez FM, Newton PN, Caillet C, 2018. Field detection devices for screening the quality of medicines: a systematic review. *BMJ Glob Health 3(4)*:e000725.
39. Chen HH, Higgins C, Laing SK, Bliese SL, Lieberman M, Ozawa S, 2021. Cost savings of paper analytical devices (PADs) to detect substandard and falsified antibiotics: Kenya case study. *Med Access Point Care 5*.
40. Roth L, Biggs KB, Bempong DK, 2019. Substandard and falsified medicine screening technologies. *AAPS Open 5(1)*:2.
41. USP. <1850> Evaluation of Screening Technologies for Assessing Medicines Quality. USP 42-NRF 38. Rockville, MD: United States Pharamcopeial Convention; 2020.
42. Kovacs S, Hawes SE, Maley SN, Mosites E, Wong L, Stergachis A, 2014. Technologies for detecting falsified and substandard drugs in low and middle-income countries. *PLOS One 9(3)*:e90601.
43. IDDO, 2018. An evaluation of portable screening devices to assess medicines quality for national Medicines Regulatory Authorities. Available at: https://www.iddo.org/external-publication/evaluation-portable-screening-devices-assess-medicines-quality-national. Accessed September 22, 2021.
44. Global Pharma Health Fund e.V. The GPHF-Minilab™ [November 10, 2021]. Available from: https://www.gphf.org/en/index.htm.
45. Jähnke R, Dwornik K. A Concise Quality Control Guide on Essential Drugs and other Medicines. Physikal Testing & Thin-Layer Chromatography. Review and Extensions 2020. 3 ed: Global Pharma Health Fund e. V. (GPHF); 2020.
46. Risha PG, Msuya Z, Clark M, Johnson K, Ndomondo-Sigonda M, Layloff T, 2008. The use of Minilabs to improve the testing capacity of regulatory authorities in resource limited settings: Tanzanian experience. *Health Policy 87(2)*:217-222.
47. Visser BJ et al., 2015. Assessing the quality of anti-malarial drugs from Gabonese pharmacies using the MiniLab(R): a field study. *Malar J 14*:273.
48. Khuluza F, Kigera S, Jahnke RW, Heide L, 2016. Use of thin-layer chromatography to detect counterfeit sulfadoxine/pyrimethamine tablets with the wrong active ingredient in Malawi. *Malar J 15*:215.
49. WHO, 2011. Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. Available at: http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. Accessed September 22, 2021.

50. Kaale E, Risha P, Layloff T, 2011. TLC for pharmaceutical analysis in resource limited countries. *J Chromatogr A 1218(19)*:2732-2736.
51. Pribluda VS et al., 2012. Implementation of basic quality control tests for malaria medicines in Amazon Basin countries: results for the 2005-2010 period. *Malar J 11*:202.
52. Risha P, Msuya Z, Ndomondo-Sigonda M, Layloff T, 2006. Proficiency testing as a tool to assess the performance of visual TLC quantitation estimates. *J AOAC Int 89(5)*:1300-1304.
53. Sherma J, Rabel F, 2019. Advances in the thin layer chromatographic analysis of counterfeit pharmaceutical products: 2008–2019. *J Liq Chromatogr Relat Technol 42(11-12)*:367-379.
54. Sherma J, 2000. Planar Chromatography. *Anal Chem 72(12)*:9-26.
55. Shewiyo DH, Kaale E, Risha PG, Dejaegher B, Smeyers-Verbeke J, Vander Heyden Y, 2012. HPTLC methods to assay active ingredients in pharmaceutical formulations: a review of the method development and validation steps. *J Pharm Biomed Anal 66*:11-23.
56. Yu H, Le HM, Kaale E, Long KD, Layloff T, Lumetta SS, Cunningham BT, 2016. Characterization of drug authenticity using thin-layer chromatography imaging with a mobile phone. *J Pharm Biomed Anal 125*:85-93.
57. Ministères de la Santé Publique Republique du Cameroun. Liste nationale des medicaments et autres produits pharmaceutiques essentiels 2017 Available from: https://dpml.cm/index.php/en/catalog/national-list-of-essential-medicines.
58. Ministère de la Sante Publique République Démocratique du Congo. Liste nationale des medicaments essentiels. Revision Mars 2010 [Oktober 27, 2021]. Available from: http://digicollection.org/hss/documents/s18817fr/s18817fr.pdf.
59. UbiPharm Togo. Annuaire Pharmacies. Available from: https://togo.ubipharm.com/AnnuairePharmacies.
60. Schäfermann S, Neci R, Ndze EN, Nyaah F, Pondo VB, Heide L, 2020. Availability, prices and affordability of selected antibiotics and medicines against non-communicable diseases in western Cameroon and northeast DR Congo. *PLOS One 15(1)*:e0227515.
61. GPHF. Manual Accompanying the GPHFMinilab™. Volume II. Thin-Layer Chromatographic Tests: Global Pharma Health Fund; 2008.
62. Pappich M. Saunders Handbook of Veterinary Drugs. Small and Large Animal, 4th edition. Amsterdam, The Netherlands: Elsevier; 2016.
63. WHO. Medical Product Alert N° 4/2017. Falsified Penicillin V Circulating in Cameroon. Ref. RHT/SAV/Alert_n4.2017 2017. Available from: https://www.who.int/medicines/publications/drugalerts/drug_alert4-2017/en/.
64. WHO. Medical product alert N° 2/2018. Falsified “Augmentin” circulating in Cameroon. Ref. RHT/SAV/Alert_n2.2018 2018. Available from: https://www.who.int/medicines/publications/drugalerts/drug_alert2-2018/en/.
65. Schäfermann S et al., 2020. Substandard and falsified antibiotics and medicines against noncommunicable diseases in western Cameroon and northeastern Democratic Republic of Congo. *Am J Trop Med Hyg 103(2)*:894-908.
66. Schäfermann S, Wemakor E, Hauk C, Heide L, 2018. Quality of medicines in southern Togo: Investigation of antibiotics and of medicines for non-communicable diseases from pharmacies and informal vendors. *PLOS One 13(11)*:e0207911.

67. Hagen N, Khuluza F, Heide L, 2020. Quality, availability and storage conditions of oxytocin and misoprostol in Malawi. *BMC Preg Childbirth 20(1)*:184-184.
68. Hauk C, Hagen N, Heide L, 2021. Identification of substandard and falsified medicines: influence of different tolerance limits and use of authenticity inquiries. *Am J Trop Med Hyg 104(5)*:1936-1945.
69. Khan MH, Okumura J, Sovannarith T, Nivanna N, Akazawa M, Kimura K, 2010. Prevalence of counterfeit anthelminthic medicines: a cross-sectional survey in Cambodia. *Trop Med Int Health 15(5)*:639-644.
70. WHO. WHO Medical Product Alert N°4/2020. Falsified Chloroquine (Update) 2020 [Oktober 31, 2021]. Available from: https://www.who.int/news/item/09-04-2020-medical-product-alert-n4-2020.
71. Gnegel G, Hauk C, Neci R, Mutombo G, Nyaah F, Wistuba D, Häfele-Abah C, Heide L, 2020. Identification of falsified chloroquine tablets in Africa at the time of the COVID-19 pandemic. *Am J Trop Med Hyg 103*:73 - 76.
72. Van Assche K, Caillet C, Newton P. Medical Product Quality Report: COVID-19 Issues. Medicine Quality Research Group, Centre of Tropical Medicine & Global Health, Nuffield Department of Medicine, University of Oxford; 2021.
73. Byaruhanga J. How Africa can manufacture to meet its own pharmaceutical needs: Africa Renewal; 2020 [November 9, 2021]. Available from: https://www.un.org/africarenewal/magazine/september-2020/how-africa-can-manufacture-meet-its-own-pharmaceutical-needs.
74. INCB. Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances. Vienna: United Nations Office at Vienna: International Narcotics Control Board (INCB); 2018 September 16, 2021.
75. UNODC. The Globalization of Crime. A Transnational Organized crime Threat Assessment.: United Nations Office on Drugs and Crimes; 2010. Available from: https://www.unodc.org/documents/data-and-analysis/tocta/TOCTA_Report_2010_low_res.pdf.
76. UNODC, 2011. Resolution 20/6. Countering fraudulent medicines, in particular their trafficking. Available at: https://www.unodc.org/documents/commissions/CCPCJ/Crime_Resolutions/2010-2019/2011/CCPCJ/Resolution_20-6.pdf. Accessed November 6, 2021.
77. Klein A, 2019. Drug problem or medicrime? Distribution and use of falsified tramadol medication in Egypt and West Africa. *JIED 1(1)*:52-62.
78. UNODC, 2021. At the crossroad of licit and illicit. Tramadol and other pharmaceutical opioids trafficking in West Africa. Available at: https://www.unodc.org/documents/nigeria/Tramadol_Trafficking_in_West_Africa.pdf. Accessed July 22, 2021.
79. WHO. WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control) 2021 [November 9, 2021]. Available from: https://extranet.who.int/pqweb/medicines.
80. Vorrath J, Voss M, 2019. The Hidden Dangers of Falsified and Substandard Medicines. SWP Comment No. 25.1-4.
81. Bland JM, Altman DG, 1986. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet 1(8476)*:307-310.
82. Ammar HO, Khalil RM, 1996. Discrepancy among dissolution rates of commercial tablets as a function of dissolution method. part 6: rifampicin. *Pharmazie 51(3)*:165-168.

83. Panchagnula R, Bhardwaj V, 2008. Effect of amorphous content on dissolution characteristics of rifampicin. *Drug Dev Ind Pharm 34(6)*:642-649.
84. Becker C, Desssman JB, Junginger HE, Kopp S, Midha K, Shah V, Barends D, 2009. Biowaiver monographs for immediate release solid oral dosage forms: rifampicin. *J Pharm Sci 98(7)*:2252-2267.
85. ICH, 2005. Validation of analytical procedures: text and methodology Q2(R1). *August 3, 2021*. Available at: http://academy.gmp-compliance.org/guidemgr/files/Q2(R1).PDF.
86. U.S. Pharmacopeial Convention. USP Technology Review: Global Pharma Health Fund (GPHF) - Minilab™. Technology Review Program Rockville, MD; 2020.
87. Islam MR et al., 2018. An Investigation into the Quality of Medicines in Yangon, Myanmar. *Pharmacy (Basel, Switzerland) 6(3)*:96.
88. INCO, UNODC, WHO, 2021. INCB, UNODC and WHO Joint Statement on Access to Controlled Medicines in Emergencies. *(September 16, 2021)*. Available at: https://www.who.int/news/item/08-09-2021-incb-unodc-and-who-joint-statement-on-access-to-controlled-medicines-in-emergencies.
89. WHO Expert Committee on Specifications for Pharmaceutical Preparation. The International Pharmacopeia, Tenth Edition 2020 [November 9, 2021]. Available from: https://digicollections.net/phint/2020/index.html#d/b.1.

Danksagungen

An erster Stelle ein herzliches Dankeschön an Prof. Dr. Lutz Heide, dass ich Teil dieser spannenden Projekte sein durfte. Vielen Dank für die kompetente Betreuung, die Motivation, Unterstützung und das Vertrauen bei der Umsetzung neuer Ideen. Bedanken möchte ich mich auch für die Ruanda-Aufenthalte, die eine sehr bereichernde Erfahrung für mich waren und mir so manchen Blick über den Tellerrand ermöglicht haben.

Ein großes Dankeschön an meinen Zweitbetreuer Prof. Dr. Harald Groß für die Tätigkeit als Prüfer, an PD Dr. Bertolt Gust für die Tätigkeit als Gutachter und Prüfer und an Prof. Dr. Rolf Daniels für die Tätigkeit als Prüfer.

Ein herzliches Dankeschön an Emmanuel Wemakor für die tatkräftige Unterstützung bei allen praktischen Tätigkeiten – vom Tabletten mörsern übers HPLC föhnen – und die tolle Zeit im Labor. Ein spezieller Dank auch an Corinna Fischer für die umfassende Unterstützung. Ein großer Dank an Kerstin Seeger und Christine Häfele-Abah für die gute Zusammenarbeit bei der Organisation des „Pharmacy in Global Health“ Kurses, der für mich immer ein alljährliches Highlight war.
Danke auch an Mark Boss für die gute Kooperation im „TLCyzer-Projekt“.

Ein herzliches Dankeschön an Nhomsai Hagen, Gesa Gnegel, Simon Schäfermann und Julia Gabel für die vielen Anregungen und Ideen, die gute Zusammenarbeit und vor allem auch für die tolle gemeinsame Zeit in Oxford, Japan, Berlin und Tübingen.

Bei allen Kolleginnen und Kollegen möchte ich mich ganz herzlich für die großartige gemeinsame Zeit bedanken. Ihr habt den 6. Stock zu einem besonderen Ort gemacht, den ich sehr vermissen werde.

Danke an die Baden-Württemberg Stiftung für die Finanzierung der Ruanda-Projekte.

Nicht zuletzt ein herzliches Dankeschön an meine Familie und Freunde und ganz besonders an meine Eltern und meinen Bruder, die mich auf meinem Weg immer unterstützt und mir den Rücken gestärkt haben.

Beteiligung

Die Abbildungen 1 und 2 wurde von Schäfermann et al. erstellt und modifiziert in diese Arbeit eingebracht. Die Abbildung 7 wurde von Gnegel et al. erstellt und modifiziert in diese Arbeit eingebracht. Die Smartphone App „TLCyzer“ wurde von Mark Boss (Fakultät für Informatik, Universität Tübingen) entwickelt.

Appendix

Hinweis: Das Manuskript des Buchartikels „**Trade in falsified and substandard medicines**“ ist im Appendix nicht enthalten, da vom Verlag noch keine Zustimmung zur Veröffentlichung vorliegt.

PLOS ONE

RESEARCH ARTICLE

Quality of medicines in southern Togo: Investigation of antibiotics and of medicines for non-communicable diseases from pharmacies and informal vendors

Simon Schäfermann, Emmanuel Wemakor, Cathrin Hauk, Lutz Heide*

Pharmaceutical Institute, Eberhard Karls University Tuebingen, Tuebingen, Germany

* heide@uni-tuebingen.de

OPEN ACCESS

Citation: Schäfermann S, Wemakor E, Hauk C, Heide L (2018) Quality of medicines in southern Togo: Investigation of antibiotics and of medicines for non-communicable diseases from pharmacies and informal vendors. PLoS ONE 13(11): e0207911. https://doi.org/10.1371/journal.pone.0207911

Editor: Godfrey Biemba, Paediatric Centre of Excellence, ZAMBIA

Received: December 22, 2017

Accepted: November 8, 2018

Published: November 29, 2018

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was funded by the Eberhard Karls University Tubingen. We furthermore acknowledge support for open access publication by Deutsche Forschungsgemeinschaft and Open Access Publishing Fund of University of Tübingen. The funders had no role in study design, data

Abstract

Substandard and falsified medicines represent a serious threat for public health and patient safety. Especially in low and middle-income countries, the prevalence of substandard and falsified medicines is reportedly high. However, reliable information on the prevalence of poor-quality medicines is scarce. In this study, 12 essential medicines, including antibiotics, antidiabetics, cardiac drugs and antiasthmatic drugs, were collected from six informal vendors and six licensed pharmacies in the southern part of Togo (regions Maritime and Plateaux). A mystery shopper approach was used in both types of outlets. In total, 64 samples were collected from licensed pharmacies and 30 from informal vendors. Both availability of medicines and prices of medicines were higher in licensed pharmacies than in informal vendors. 92 medicine samples were analyzed by visual examination, followed by chemical analysis for the content and for the dissolution of the active pharmaceutical ingredients according to the respective monographs of the United States Pharmacopoeia. 7 samples (8%) did not comply with the pharmacopoeial specifications, and one sample (1%) showed even extreme deviations. None of the samples was obviously falsified. However, one sample of amoxicillin capsules contained only 47% of the declared content of the active pharmaceutical ingredient, indicating that it may represent amoxicillin capsules 250 mg, rather than 500mg as declared on the label. Medicines stated to originate from Asia (i.e. mainly from India and China) showed a significantly higher proportion (24%) of non-compliant samples than those from Africa and Europe (4%, $p = 0.007$). High failure rates were observed in medicines both from informal vendors (13%) and from licensed pharmacies (5%), but the difference between both groups was not statistically significant ($p = 0.152$). The observed high prevalence of substandard medicines requires action from regulatory authorities and health care providers. Testing of selected samples for related substances indicated that inappropriate transport and storage conditions may have been an important cause for substandard quality.

collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Access to essential medicines has been included in the Millennium Development Goals (MDG) of the United Nations and is now included in the Sustainable Development Goals as Goal No. 3.8 [1]. It comprises access to medicines for both non-communicable diseases (NCD) and communicable diseases [2, 3]. Access to medicines in developing countries has improved in the past decades [4, 5]. However, at the same time the occurrence of substandard and falsified medicines has been reported frequently and has even been addressed as a "pandemic" by some authors [6]. A recent literature survey by the World Health Organization, estimated that in low and middle-income countries 10.5% of the medicines are substandard or falsified [7]. Several studies and reviews tried to estimate the prevalence for specific countries and regions and for different classes of therapeutics. A systematic review by Almuzaini et al. included eight studies conducted in sub-Saharan Africa which reported prevalence for substandard or counterfeit medicines ranging from 12.2 to 46% [8]. A meta-analysis of 21 surveys in sub-Saharan Africa concluded that 35% of antimalarial medicines had failed chemical analysis, and 20% had been classified as falsified [9]. However, other studies reported a much lower prevalence of falsified medicines. In several studies by the ACT Consortium Drug Quality Program (ACTcDQP), only 98 (0.97%) out of 10,079 antimalarial medicine samples from six developing countries were reported to be falsified [10]. An investigation by the World Health Organization in six countries of sub-Saharan Africa found only 2 (0.2%) out of 935 antimalarial medicine samples in which a stated active ingredient was missing entirely [11]. Several authors emphasize that there is still a severe lack of reliable data on the prevalence of substandard and falsified medicines [8]. The report of the Lancet Commission on Essential Medicines also concluded that so far, the true extent of this problem remains unknown [12]. Also the above-mentioned literature survey by the WHO discusses the problem of the strong heterogeneity of the available studies [7].

Until recently, the lack of internationally agreed definitions of substandard and falsified medicines further complicated the comparison of data on their prevalence. This situation has recently been remedied by the World Health Organization [13]. The misleading term"counterfeit medicines" as well as the provisional term "substandard/spurious/falsely labelled/falsified/counterfeit (SSFFC) medical products" have been replaced by "substandard and falsified medical products" [13, 14]. Notably, "substandard" and "falsified" are now defined as mutually exclusive classifications. Falsified medical products are "deliberately/fraudulently misrepresenting their identity, composition or source", while substandard medical products fail to meet their quality standards or specifications for other reasons than deliberate intent, e.g. due to unintentional shortcomings in the manufacturing process, or due to degradation caused by inappropriate storage conditions. Differentiation between falsified and substandard medicines therefore requires knowledge or clues of the (honest or fraudulent) intentions of the manufacturer, and is not possible on the basis of chemical analysis alone [15].

Most published studies on substandard and falsified medicines have focused on anti-malarials, some on antibiotics and antivirals, but data on medicines for non-communicable-diseases are rare [16, 17]. This is in contrast to the importance of non-communicable diseases also in developing countries. The last report published by the MDGs Gap Task Force in 2015 noted that up to 80% of the deaths from non-communicable-diseases world-wide occur in low-and middle-income countries [18, 19].

The institutional capacity and the resources to monitor the quality of the pharmaceuticals are diverse in between different African countries. Several East-African countries have successfully strengthened their regulatory authorities [20], other African countries still struggle with the implementation of a regulated supply of medicines. For this and for other reasons, the

prevalence of substandard and falsified medicines is very different in between African countries [10, 11]. Tabernero et al. noted that there is a severe lack of knowledge on the prevalence of substandard and falsified medicines in quite a number of African developing countries, including Togo [21].

Only very few studies investigated substandard and falsified medicines in the Republic of Togo so far. In 2014, an evaluation of the quality of artemisinin-based antimalarials was conducted in Ghana and Togo. It reported that 83.7% of artemisinin based combination therapies and 57.9% of the artemisinin-based monotherapies failed to comply with International Pharmacopoeia requirements due to insufficient content of the active pharmaceutical ingredient (API) [22]. The recently published quality evaluation of cardiac medicines in ten countries of Africa [17] also included 100 samples deriving from Togo. It concluded that 9% of the samples deriving from Togo where poor quality drugs. Also a study on the quality of veterinary medicines was carried out in the northern part of Togo [23].

The objective of the present study was to contribute to the knowledge about the prevalence of substandard and falsified medicine in the Republic of Togo, including both anti-infective medicines and medicines for non-communicable diseases. Medicines were sampled from the private sector, i.e. licensed pharmacies, and informal vendors, in several towns in the southern part of Togo.

Methods

Study design

Collection of the samples took place in February 2017. The study protocol was based on the guidelines on the conduct of surveys of the quality of medicines, published by the WHO in 2016 [24] and the MEDQUARG guidelines [25]. Seven antibiotics and five medicines against non-communicable diseases were included in this study, all of them contained in the list of essential medicines of the Republic of Togo [26]. These 12 medicines were solid oral dosage forms of amoxicillin, amoxicillin/ clavulanic acid, sulfamethoxazole/trimethoprim, ciprofloxacin, phenoxymethylpenicillin (penicillin V), metronidazole, doxycycline, metformin, atenolol, hydrochlorothiazide, furosemide and salbutamol (albuterol.) For each medicine, a preferred strength and dosage form (tablet or capsule) was defined which the local investigator asked for at every sampling site. If this was not available, another strength or another solid oral dosage form was collected.

The samples were collected in the southern part of Togo, in the regions Maritime and Plateaux. In Lomé the local investigator asked several citizens for well stocked informal drug vendors in the south of Togo. Five such vendors were named in the region Maritime located in Lomé Centre, in the suburbs Agoe-nyvie and Agoe-laogope, as well as in the towns Tsévié and Tabligbo, 30 km north and 75 km northeast of Lomé, respectively. Furthermore, one vendor was named located in the town of Kpalimé, 120km northwest of Lomé and close to the border to Ghana, in the region Plateaux. S1 Fig (Supporting Information) shows a map of these locations. The informal vendors operated in small shops located away from the main shopping roads. Such non-accredited medicine stores in Togo and neighboring countries have been described already in earlier studies [22, 23]. While visiting each of the six chosen informal drug outlets, the investigator identified the geographically nearest licensed pharmacy. A list of licensed pharmacies in Togo is available in the internet [27], and indeed all six pharmacies named by the local citizens were found in this list, but none of the informal vendors. Licensed pharmacies operated in premises with good professional appearance, located at major shopping roads. In both types of sampling sites the investigator acted as a customer and purchased a quantity of 100 tablets or capsules for each of the 12 medicines, if available. If the vendor

asked for the purpose of the purchase, the investigator stated that these medicines were intended for use in a local medical facility operated by a relative. If the quantity of 100 tablets or capsules per medicine was not available, a smaller quantity was purchased, but not less than 30 tablets or capsules to ensure a sufficient amount for chemical analysis. At each of the twelve sampling sites, prices and quantities of purchased medicines were recorded. Each sample was collected and stored in the original primary and secondary packaging if possible. If no primary or secondary packaging was available, the samples were stored in light protective screw-cap bottles. An adhesive label with a unique sample number was attached to the primary or secondary packaging of each sample. The samples were stored at a cool and dry place and transported to the University of Tuebingen, Germany, within three weeks after collection. There, all medicines were stored at 21˚C in an air-conditioned room until analysis.

Sample size calculation

The sample size calculation was based on the hypothesis that the proportion of out-of-specification medicines would be higher in medicines from informal vendors than in medicines from licensed pharmacies. Estimating the proportions to be 10% in medicines from licensed pharmacies and 40% in medicines from informal vendors, the sample size required to observe a significant difference between these group with 95% confidence and a power of 80% resulted as 29 samples per group, using the following formula:

$$n = (Z_{\alpha/2} + Z_{\beta})^2 * (p_1(1 - p_1) + p_2(1 - p_2))/(p_1 - p_2)^2,$$

where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84) and p_1 and p_2 are the expected sample proportions of the two groups [28].

We decided to attempt the collection of 12 medicines from 6 facilities, i.e. 72 samples, from each group, in order to allow for a contingency since not all medicines were expected to be available in each of the sampling sites.

Medicine quality analysis

Analysis was performed at the Pharmaceutical Institute of Tuebingen University. Prior to chemical analysis, the packaging of each sample was visually examined. Sample number, brand name, type of medicine (originator, branded generic or generic), batch number, manufacturing date, expiry date, name of marketing authorization holder (MAH), name of manufacturer, international non-proprietary names (INN) of the active pharmaceutical ingredients (APIs), dosage form, strength, type of packaging material or container (primary and/or secondary packaging), presence of a leaflet for patients, and price per dosage form were recorded on a standardized form. Digital photos showing the tablets or capsules, the primary packaging, the leaflet, the secondary packaging and the sample number were taken and archived.

Chemical analysis was carried out according to the methods specified in the monographs of the United States Pharmacopoeia 2016 (USP 39) for the respective dosage forms for each of the 12 medicines. The chemical quality assessment included the determination of identity, assay (content of API) and dissolution (proportion of API dissolved from the dosage form over time). Following the respective monographs of the USP 39, the assay (quantification of the content of the API) was carried out by HPLC for all investigated medicines, and dissolution of the API was quantified by HPLC for all investigated medicines except metformin, which was quantified by UV spectroscopy.

Validation of the assay procedures according to USP using medicines purchased in Germany showed good reproducibility of the results. In contrast we initially noticed high variability of the assay results from some of the samples collected in Africa, e.g. of amoxicillin/ clavulanic acid tablets. Further investigation showed that a more thorough mechanical disintegration of these tablets was required in the sample preparation, to yield complete and reproducible detection of the API content. USP specifies these mechanical disintegration procedures only in general terms. ("dissolve not less than 10 tablets in water with the aid of mechanical stirring"). According to our observations, tablets which have been stored under tropical climates require thorough mechanical disintegration in order to achieve correct assay results, and the same observation has recently been reported by Mufusama *et al.* [29].

One sample of amoxicillin (QEW067) was found to contain only 47% of the declared API content; it was tested for content uniformity according to the method for of USP 39, determining the contents of 10 tablets individually. Furthermore, for two samples of amoxicillin/ clavulanic acid and one sample of hydrochlorothiazide tablets, content uniformity was investigated by analyzing 10 tablets individually, after sample preparation with a Branson 250 Sonifier (Emerson Industrial Automation, St. Louis, MO, USA) pulsing at 70% power, in an interval of 10 seconds with 10 seconds intermission for a total duration of three minutes using the same solvent as stated in the USP39 monograph. HPLC analysis according to USP showed a high uniformity of the content (QEW002, amoxicillin SD = 0.70%, clavulanic acid SD = 2.46%; QEW041, amoxicillin SD = 2.63%; clavulanic acid SD = 2.44%; QEW074, hydrochlorothiazide SD = 1.70%, respectively). The assay value reported in this study for these three samples is therefore the average of the 10 individual measurements for each sample.

All methods were validated according to USP instructions for system suitability and the Q2 Guideline of the International Council for Harmonization [30]. HPLC analysis was carried out using an Agilent 1100 HPLC (Agilent Technologies, Santa Clara, CA, USA) and the columns, mobile phases and UV-detection wavelengths specified in the USP 39. UV spectroscopy was carried out using a Perkin-Elmer Lambda 125 UV spectrophotometer (Perkin-Elmer, Waltham, Massachusetts, USA). Dissolution testing was performed using a PTWS 610 Dissolution Testing apparatus (Pharma Test Apparatebau AG, Hainburg, Germany).

Definition of compliance of samples with specifications

The USP 39 criteria of the respective monographs were followed in assessing compliance or non-compliance of the investigated samples. The limits for compliance stated by the USP 39 are different for different APIs and are summarized in Table 1. Samples falling outside of these limits were considered as non-compliant.

As proposed by a study published by the WHO in 2011 [11], the non-compliant samples were further divided into those showing only moderate deviations from the USP 39 criteria, and those showing extreme deviations. As suggested by the mentioned WHO study, extreme deviation was defined as the content of API deviating more than 20% from the declared content and/or the average dissolution of the tested units falling more than 25% below the pharmacopoeial limit (i.e. below the pharmacopoeial Q-value minus 25%).

For the combined results, a sample was rated as "non-compliant" if either assay or dissolution or both tests had failed.

Testing for related substances

Selected samples containing amoxicillin were tested for related substances following the method stated in the USP 39 monograph for amoxicillin trihydrate. HPLC peaks of possible degradation products observed in these samples were compared to peaks appearing in

Table 1. Limits for compliance according to United States Pharmacopoeia 39 [% of declared content].

API	assay	dissolution
Amoxicillin	90–120	75
Amoxicillin / clavulanic acid	90–120	85/80
Penicillin V	90–120	75
Ciprofloxacin	90–110	80
Sulfmethoxazole / trimethoprim	93–107	70/70
Metronidazole	90–110	85
Doxycycline	90–120	80
Metformin	95–105	70
Atenolol	90–110	80
Hydrochlorothiazide	90–110	60
Furosemid	90–110	80
Salbutamol	90–110	80

https://doi.org/10.1371/journal.pone.0207911.t001

reference tablets that had been subjected to forced degradation at 80˚C in a drying oven for 4 days [31]. As explained above, in this study, the classification as compliant or non-compliant was based only on identity, assay and dissolution without considering the absence or presence of related substances, since only few samples were tested for related substances.

Calculation of medicine prices

The prices of all samples were recorded in local currency (CFA francs). The price per dosage form was calculated in US $ with the exchange rate [CFA] to [US $] of 01.02.2017 (1 CFA = 0.00163428 $). As suggested by the WHO/HAI manual on measuring medicines prices [32] a Median Price Ratio (MPR) was calculated, i.e. the ratio of the observed median price of a medicine to an international reference price. As recommended by the WHO/HAI manual, the median supplier price from the MSH 2015 international medical products price guide [33] was chosen as international reference price. If medicines of different strengths were collected, median prices and MPRs were calculated individually for each strength.

Statistical analysis

Statistical analyses were performed using MedCalc (MedCalc Software, Ostend, Belgium) [34, 35].Comparisons of proportions were evaluated by the "N-1" Chi-squared test as recommended by Campbell (2007) and Richardson (2011) [36, 37]. Confidence intervals were calculated as the "exact" Clopper-Pearson confidence interval for the observed proportion [38, 39]. Prices of medicines were compared to an international reference price (see above), and differences of the resulting price ratios were evaluated using the Kruskal-Wallis test.

Results

Overview of collected samples

In this study 12 different medicines were collected from six licensed pharmacies and six informal vendors, resulting in a theoretical total of 144 samples. Because not all sampling sites had all medicines in stock, we were able to purchase a total of 89 samples. Visual examination showed that two samples contained blisters from two different manufacturers and one sample even from three different manufacturers, sold together in one secondary packaging. One further sample contained blisters from the same manufacturer but with two different batch

Table 2. Overview of medicine samples collected and analyzed.

Active pharmaceutical ingredient of the sample	Licensed pharmacies	Informal vendors	Total	No. of commercial preparations (brands)	No. of batches
Amoxicillin	6	6	12	6	11
Amoxicillin / clavulanic acid	7	0	7	5	7
Phenoxymethylpenicillin	2	1	3	2	2
Ciprofloxacin	7	6	13	8	11
Doxycycline	8	3	11	5	7
Sulfamethoxazole / trimethoprim	5	1	6	3	5
Metronidazole	6	6	12	4	6
Atenolol	6	1	7	1	3
Furosemide	6	4	10	5	6
Hydrochlorothiazide	3	1	4	3	4
Metformin	6	1	7	1	5
Salbutamol	2	0	2	1	1
Total	64	30	94	44	68

https://doi.org/10.1371/journal.pone.0207911.t002

numbers. All these four samples had been obtained from licensed pharmacies. The different blisters of these four purchases were separated and analyzed as separate samples. Thereby, the total numbers of samples of this study increased from 89 to 94. For two of these samples the number of tablets was insufficient for analysis according to USP 39. These two samples were analyzed, but their results were excluded from overall data evaluation and statistical analysis.

In one case, hydrochlorothiazide was requested, but actually a combination product containing hydrochlorothiazide 25 mg and captopril 50mg (Ecazide, BristolMyers Squibb) was obtained. This sample was analyzed according to the methods for hydrochlorothiazide tablets (and found to be compliant with the specifications), but it was excluded from the analysis of prices.

As shown in Table 2, the 94 samples represented 44 different commercial preparations (brands) and a total of 68 different batches. According to the information given on the labels, they were produced by 26 different manufacturers in 12 different countries. Table 3 shows that most of the medicines sold in private pharmacies were from European countries, while most of the medicines sold by informal vendors were produced in African countries. Most of the

Table 3. Comparison of medicine samples from licensed pharmacies and informal vendors.

	Licensed pharmacies	Informal vendors
Stated origin of medicines		
- Africa	8 (13%)	19 (63%)
- Asia	11 (17%)	7 (23%)
- Europe	45 (70%)	4 (13%)
Type of medicine		
- generic	44 (69%)	25 (83%)
- branded generic	13 (20%)	5 (17%)
- originator	7 (11%)	0 (0%)
Packaging of purchased sample		
- primary and secondary packaging (blister strips and cardboard boxes)	55 (86%)	11 (37%)
- only primary packaging (blister strips)	9 (14%)	18 (60%)
- no original packaging (sold in plastic bag)	0 (0%)	1 (3%)

https://doi.org/10.1371/journal.pone.0207911.t003

samples (69 out of 94, i.e. 73%) were generic medicines sold under the international nonproprietary name of their active pharmaceutical ingredient, while 19% were so called branded generics, and only 7 samples (7%) were originator products. All seven originator medicines were obtained in licensed pharmacies. A complete list of all 94 samples, including the results of chemical analysis is shown in S1 Table (Supporting Information).

In the six visited pharmacies, on average 10 of the 12 investigated medicines were available (range 8–12 medicines). In the six informal vendors, on average only five medicines were available (range 3–8 medicines). The highest availability was observed for amoxicillin, ciprofloxacin and metronidazole.

S2 Table (Supporting Information) compares the prices of the medicines in licensed pharmacies and informal vendors. Overall, the prices in licensed pharmacies were very similar to those observed previously in the private health care sector in low- and middle- income countries [40]. Prices in informal vendors were cheaper than those in licensed pharmacies by 41%. Further details are given in the legend of S2 Table.

As shown in Table 3, the majority (86%) of samples obtained in private pharmacies were sold with their primary or secondary packaging, i.e. blister stripes and cardboard box. However, the informal vendors sold most of the samples (60%) without secondary packaging. One sample was even dispensed without primary and secondary packaging, i.e. in a plastic bag. Since this sample represented furosemide tablets which are light sensitive, this packaging is in contrast to the requirements specified in the USP 39 monograph. Notably, four further samples of furosemide tablets (two from licensed pharmacies, two from informal vendors) were sold without secondary packaging in clear transparent blisters without light protection, also violating USP39 requirements.

Expiry dates

None of the samples were expired at the time of purchase. The remaining shelf life of the medicines ranged from 1 to 53 months, with a median of 26 months. 11 samples, produced by Denk Pharma (Germany), Aldo Union (Spain) and Roche (France), had remaining shelf lives of more than 36 months, showing that the manufacturers had decided to state quite long shelf lives for these products.

Packaging analysis and visual inspection

Inspection of the primary and secondary packaging, of package leaflets and of batch numbers and expiry dates showed no mistakes or inconsistencies which are frequently found in falsified medicines [15, 41]. Therefore, packaging analysis did not indicate the presence of any obviously falsified medicines. Visual inspection of the dosage forms showed a strong discoloration in one sample of doxycycline tablets, depicted in S2 Fig. This sample had contained blisters with two different batch numbers in one secondary packaging, as mentioned above. While the blisters with uniformly colored tablets (exp. date 05.2019) were found to comply with the USP39 specifications, the blister with ten darkened, spotted tablets (exp. date 12.2017) showed extreme deviations from the USP39 specifications (55% of stated content of doxycycline).

Chemical analysis

As explained above, four samples consisted of blisters of more than one batch and therefore the blisters were analyzed as distinctive samples. For two of the resulting samples (including the ten darkened, spotted doxycycline tablets mentioned above) the number of tablets was too small to perform a complete chemical analysis according to the USP 39. The results of these

Table 4. Compliance of medicine samples with the criteria of the United States Pharmacopoeia 39.

API of sample		Non-compliant in assay (number of samples)		Non-compliant in dissolution (number of samples)		Non-compliant, total	
	Total number	Moderate deviation	Extreme deviation	Moderate deviation	Extreme deviation	Number of samples	%
Amoxicillin	12	2	1	1	1	3	25%
Hydrochlorothiazide	4	1	0	0	0	1	25%
Ciprofloxacin	13	3	0	0	0	3	23%
Amoxicillin/clavulanic acid	6	0	0	0	0	0	0%
Doxycycline	10	0	0	0	0	0	0%
Metronidazole	12	0	0	0	0	0	0%
Phenoxymethylpenicillin	3	0	0	0	0	0	0%
Sulfamethoxazole/ Trimethoprim	6	0	0	0	0	0	0%
Atenolol	7	0	0	0	0	0	0%
Furosemide	10	0	0	0	0	0	0%
Metformin	7	0	0	0	0	0	0%
Salbutamol	2	0	0	0	0	0	0%
Total	**92**	**6**	**1**	**1**	**1**	**7**	**8%**

The limits for compliance of the USP39, and for extreme deviation according to a WHO publication [11], are explained in the methods section.

https://doi.org/10.1371/journal.pone.0207911.t004

two samples were therefore excluded from the evaluation of the results, leaving 92 samples for overall data evaluation.

Notably, in none of the 92 samples the stated API was absent, and in only one sample the content of API was lower than 80% of the declared content. Out of the total of 92 samples, 85 (92%, 95%CI = 85–97%) complied with the specifications of USP 39 for both, assay (= content of API) and dissolution. However, 6 samples (7%, 95%CI = 2–14%) showed moderate deviations and 1 samples (1%, 95%CI = 0.03–6%) showed extreme deviations. Table 4 summarizes the results for the 12 tested medicines. Non-compliant samples were observed for amoxicillin, hydrochlorothiazide and ciprofloxacin, but not for any of the other nine investigated medicines. Of the 7 non-compliant samples, 5 failed only in assay, while 2 failed in both criteria. The data summarized in Table 4 are shown in detail in Figs 1 and 2.

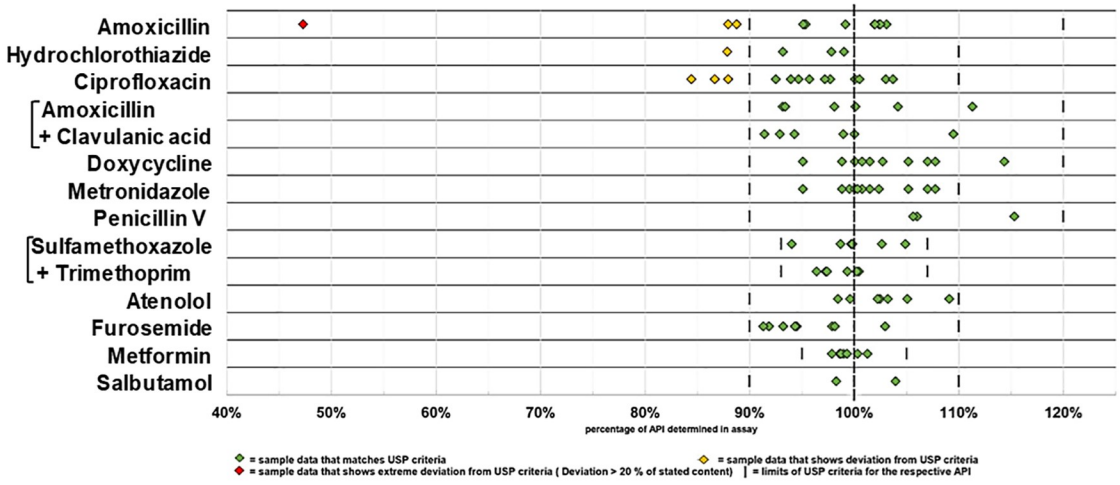


Fig 1. Content of the active pharmaceutical ingredient determined for each sample.

https://doi.org/10.1371/journal.pone.0207911.g001

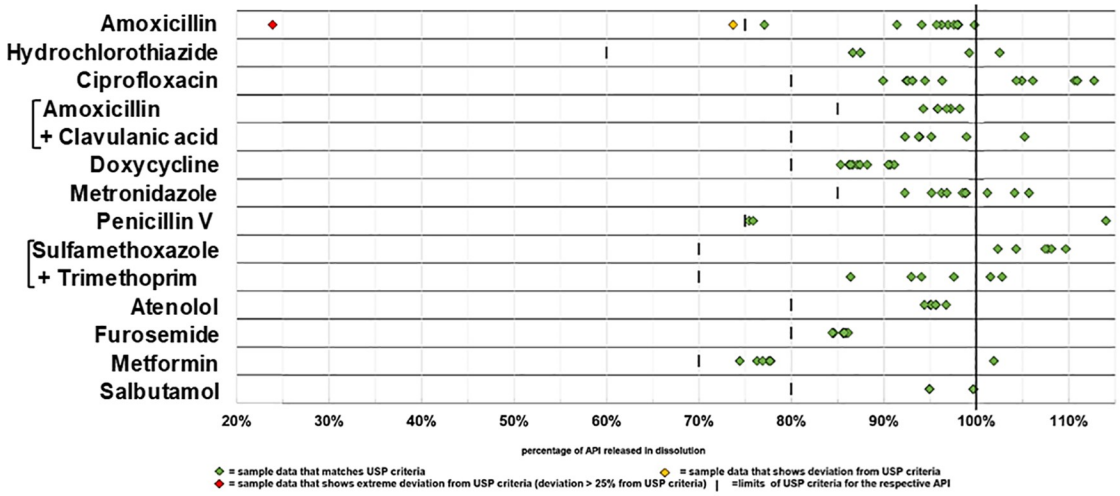


Fig 2. Dissolution of the active pharmaceutical ingredient determined for each sample.

https://doi.org/10.1371/journal.pone.0207911.g002

Table 5 lists the results of the chemical analysis for each of the 26 stated manufacturers located in 12 countries on three continents. Notably, the highest failure rate was observed in samples deriving from Asia (24% non-compliant). This is markedly higher than the failure rate of the other samples of this study (average 4%) and this difference is statistically significant ($p = 0.007$). 18 samples had been produced in Togo itself, including 15 from a single Togolese manufacturer. All of the samples produced by that company complied with the USP specifications. This shows an encouraging achievement of international quality standards by this local manufacturer.

As mentioned above, this study included 7 originator medicines, all of them obtained in licensed pharmacies and (according to the label information) produced by multinational pharmaceutical companies. One of these seven products failed USP 39 specifications (87.9% of the stated API content determined in assay), while another sample of the same brand with the same expiry date passed all pharmacopoeial tests. We speculate that the poor quality may be the result of inappropriate transport and storage conditions of the individual sample. Fig 3 shows the prevalence of non-compliant medicines, grouped according to different criteria. Generic medicines showed a lower percentage of non-compliant and extremely deviant samples than branded generic medicines or originator products. Medicines obtained from licensed pharmacies showed a lower failure rate than those from informal vendors (5% *versus* 13% non-compliant). However, the difference between the failure rates in licensed pharmacies and informal vendors did not reach statistical significance ($p = 0.152$).

Quality problems were found both in antibiotics and in medicines for non-communicable diseases (10% and 3% non-compliant, respectively), but the difference between both groups was not statistically significant ($p = 0.285$).

The frequency of non-compliant samples was not significantly related to the selling price of the medicines (Fig 3). Non-compliant medicines were found in two of the six investigated pharmacies, and in three of the six investigated informal vendors.

Testing for thermal degradation products of amoxicillin

In order to provide some first evidence whether inappropriate storage and/or transport conditions may have contributed to the substandard quality of some of the investigated medicines, we analyzed several amoxicillin samples for the presence of thermal degradation products of

Table 5. Stated origin and manufacturers of medicines, and compliance with USP 39 criteria.

Stated origin	Stated manufacturer	Total samples	Non-compliant samples	% non-compliant	Extreme deviation	% extreme deviation
Togo	Tongmei	15	0		0	
	Sprukfield	3	1		0	
	total	**18**	**1**		**0**	
Benin	Pharmaquick	**5**	**0**		**0**	
Ghana	Letap	**3**	**0**		**0**	
Nigeria	Nuel Pharma	**1**	**1**		**0**	
Africa		**27**	**2**	**7%**	**0**	**0%**
India	Lincoln Pharma	6	1		0	
	Alice	1	0		0	
	Cian	1	1		0	
	CIPLA	1	0		0	
	Fourrts	1	0		0	
	Medopharm	1	0		0	
	total	**11**	**2**		**0**	
China	Greenfield	1	0		0	
	North China Pharmaceutical	3	1		0	
	Yangzhou NO.3	1	1		1	
	total	**5**	**2**		**1**	
Turkey	Billim	**1**	**0**		**0**	
Asia		**17**	**4**	**24%**	**1**	**6%**
France	Baily-Creat	13	0		0	
	GSK-France	3	0		0	
	Roche	1	0		0	
	total	**17**	**0**		**0**	
Germany	Denk Pharma	16	0		0	
	Philco Pharma	1	0		0	
	total	**17**	**0**		**0**	
Austria	Sandoz GmbH	**8**	**0**		**0**	
Spain	Aldo-Union	2	0		0	
	Novartis	2	1		0	
	total	**4**	**1**		**0**	
Italy	Bristol Myers Squibb	1	0		0	
	F.I.R.M.A S.p.A	1	0		0	
	total	**2**	**0**		**0**	
Europe		**48**	**1**	**2%**	**0**	**0%**
Total		**92**	**10**	**11%**	**1**	**1%**

https://doi.org/10.1371/journal.pone.0207911.t005

the API. First, reference tablets of amoxicillin were subjected to a forced degradation (four days in a drying oven at 80˚C). HPLC analysis according to the method for "related substances" of the USP 39 monograph for amoxicillin trihydrate showed that this treatment led to a reduction of the HPLC peak corresponding to amoxicillin (retention time 7.5 min) by 23%, with the concomitant appearance of a new peak at 48 min (peak area a 230 nm: 2.0% of amoxicillin peak).

Three compliant samples of amoxicillin, and one non-compliant sample showing an insufficient amount of the API, were investigated for the presence of this peak at 48 min. The peak was clearly detected in the non-compliant sample, amounting to 2.0% of the peak area of amoxicillin. The amount of this specific impurity in the non-compliant sample indicates that

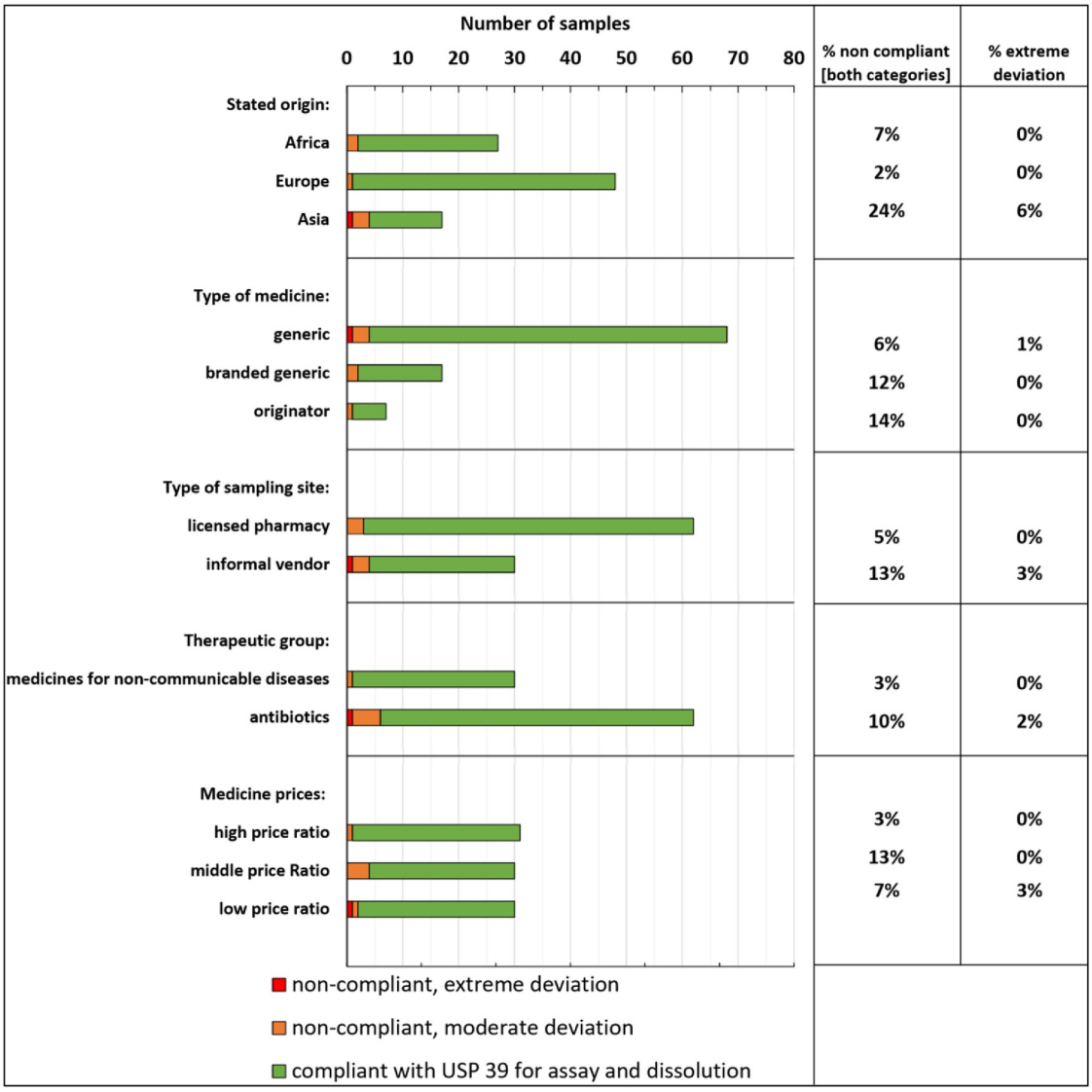


Fig 3. The prevalence of non-compliant medicines grouped according to different criteria.

https://doi.org/10.1371/journal.pone.0207911.g003

amoxicillin had undergone some thermal degradation either before or (more likely) after manufacturing of the tablets.

In contrast two compliant samples showed only traces of this peak (< 0.1% of the peak area of amoxicillin), while the third compliant sample did show the peak of the decomposition product (1.8% of the peak area of amoxicillin).

Discussion

None of the 94 medicine samples collected in this study was obviously falsified, as judged from packaging analysis. All samples contained the declared active pharmaceutical ingredient(s), though in one case less than 50% of the declared amount (Fig 1). A low prevalence of falsified medicines is indeed consistent with results from the current scientific literature [7, 10, 11, 15]. Usually the highest rate of falsified medicines in developing countries is found in antimalarial medicines [15]. In contrast, the present study in Togo focused on antibiotics and medicines

for non-communicable diseases. Therefore, the finding that the relatively small number of 94 samples in the present study did not include an obviously falsified sample is not a surprise. This finding does not, however, prove that falsified medicines are absent in Togo. Higher sample numbers and e.g. the inclusion of antimalarials, would most likely show the presence of such medicines [7, 15].

As mentioned above, one sample of amoxicillin capsules contained only 47% of the decared content of the active pharmaceutical ingredient, and the analysis of 10 individual capsules showed a high uniformity of this individual content (SD = 1.72%). This indicates that this sample may have been manufactured as 250mg amoxicillin trihydrate capsules, rather than 500mg as declared on the label. This may represent a deliberate misrepresentation of its composition, i.e. a falsified medicine.

In this study, 8% of the investigated samples did not comply to USP 39 specifications (in assay, dissolution, or both), and 1% showed even an extreme deviation from the pharmacopoeial limits. This prevalence is consistent with recent review published by the WHO which estimated the prevalence of substandard and falsified medicines in low and middle income countries to be 10.5% [7].

It should be noted that a meaningful comparison of failure rates in between different medicine quality surveys in the literature is very difficult. As correctly stated in the recent literature survey by the WHO [7], different studies use different sampling approaches, different analytical techniques, they include or ignore different pharmacopoeial criteria (e.g. dissolution of API) and they use different thresholds for the percentage of the API in order to classify a sample as "within specification" or "out of specification". In the present study, we investigated the identity, the quantity and dissolution of the API, and followed the analytical methods and the thresholds specified in by the United States Pharmacopoeia 39 (USP 39). The limits for compliance given by the USP 39 are similar to those specified in the International Pharmacopoeia and usually wider than the limits specified by the British Pharmacopoeia.

As noted in the recent literature survey by the WHO [7], most publications of substandard and falsified medicines only state a pass or fail for a chosen threshold, rather than giving actual percentage of the API determined. For the present study, we depicted the actual percentage of the content of API, and of the percentage of the API dissolved in the dissolution test, for all 92 samples in Figs 1 and 2 as well as in the S1 Table. As strikingly obvious from these figures, the results for assay and dissolution are distributed over a wide range, and the percentage of "substandard medicines" depends on the threshold applied in the respective study. In order to improve the comparability of different studies on the quality of medicines, a general reporting of the percentages of the API detected in the individual samples, e.g. as shown in Figs 1 and 2, may be useful.

As mentioned in a previous publication by the World Health Organization [11], the observed quality failure rates of medicines cannot always be directly related to therapeutic failures of these medicines. Following that WHO publication, however, we used thresholds for extreme deviations which may be associated with health implications. Within our study, one sample (1%) showed such extreme deviations.

In accordance with our expectations, the failure rate observed in medicines from licensed pharmacies was lower than that from informal vendors, but the difference was smaller than expected and did not reach statistical significance. Notably, the sample showing extreme deviations had been obtained from an informal vendor.

Medicines stated to originate from Asia (i.e. mainly from India and China) showed a significantly higher failure rate than those from Africa and Europe. India certainly has excellent pharmaceutical manufacturers and plays an important role in providing quality generic medicines at low prices to developing countries [41, 42]. However, our study indicates that some

manufacturers in India and China supply medicines to Africa which turn out to be substandard. It should be in the interest of regulatory authorities and professional organizations of Asian and African countries to minimize such problems by appropriate regulations and procurement practices, including supplier prequalification schemes.

Several findings reported in the Results section indicate that degradation, possibly due to inappropriate storage and transport conditions, may have contributed to the substandard quality of some of the samples. Notably, the labels of 43 of the 94 samples in this study stated that the products should be stored below 25˚C. Yet, none of the investigated licensed pharmacies and informal vendors used an air condition. According to the ICH Quality Guidelines [43], Togo is assigned to climatic zone IV, and long term stability of medicines for use in Togo should be demonstrated at 30˚C and 65% relative humidity by the manufacturer. Improvements in regulation and in procurement practice should ensure that only medicines which are compliant in such stability tests are imported to Togo. Health care providers need to pay attention to storage requirements stated on the medicine packages, and either improve the storage conditions in their premises or restrict their selection of medicines to those which do not require storage below 25˚C.

Notably, all antibiotics could be purchased without prescription from licensed pharmacies and informal vendors with equal ease. The high availability of antibiotics from informal vendors is worrisome due to the potential of antimicrobial resistance arising from the inappropriate use of antibiotics.

Limitations of this study

The small size (n = 94 samples) presents a principal limitation of this study which was funded exclusively by intramural funds of Tuebingen University. This study was powered to prove an expected difference of 30 percent in the prevalence of poor quality medicines between pharmacies and informal vendors and was insufficiently powered to prove smaller differences in other sub-group analyses. Alternative approaches within the limits of the available budget may have been a concentration on fewer types of medicines (e.g. just two to four rather than 12 types), or the omission of the time-consuming and expensive dissolution testing in the chemical analysis. However, also these alternatives would have had obvious and strong disadvantages. Another principal limitation of this study is the non-random selection of sampling sites which implies that the results cannot be regarded a representative. In any medicine quality study which includes informal vendors, random sampling of these sites is impossible as there is no reliable list of such illegal facilities. We purposefully identified informal vendors which were reported to be well-stocked, in order to ensure that sufficient numbers of samples of the 12 different medicines could be collected. This may introduce a bias since medicine quality may be different between large and small informal vendors. A list of licensed pharmacies in Togo is published on the internet [27] by a private medicine wholesaler; therefore, an alternative approach would have been a random selection of licensed pharmacies from that (unofficial) list, followed by identification of the nearest informal vendor to that pharmacy. On the other hand, this may have introduced other biases, e.g. in favor of more affluent regions where most licensed pharmacies are located. An additional limitation is that this study sampled medicines only from licensed pharmacies and informal vendors, not from other sectors of the pharmaceutical supply system. And while this study included testing for identity, content and dissolution of the APIs, it did not comprehensively include other criteria such as testing for related substances or content uniformity. As emphasized in a recent WHO publication [7], further studies are required which can provide reliable estimates of the prevalence of substandard and falsified medical products, by product type, geographical distribution and severity of

deviation from the pharmacopoeial standards, in Togo as well as in other low- and middle-income countries.

Supporting information

S1 Table. Complete list of all 94 samples.
(XLSX)

S2 Table. Prices of the medicines in licensed pharmacies and informal vendors.
(DOCX)

S1 Fig. Map of the sampling sites in the regions Maritime and Plateaux of the Republic of Togo.
(DOCX)

S2 Fig. Discoloration discovered upon visual inspection of a sample of doxycycline tablets.
(DOCX)

Acknowledgments

The authors are grateful to the University of Tuebingen (management, faculty and staff) for support of research and training on pharmaceutical challenges in developing countries. Furthermore, they are grateful to Pharma Test Apparatebau AG, Hainburg, Germany, for the provision of a PTWS 610 Dissolution Testing apparatus at special conditions in support of efforts to improve medicine quality in Africa.

Author Contributions

Data curation: Simon Schäfermann.

Investigation: Simon Schäfermann, Emmanuel Wemakor, Cathrin Hauk.

Methodology: Simon Schäfermann.

Supervision: Lutz Heide.

Visualization: Simon Schäfermann.

Writing – original draft: Simon Schäfermann, Lutz Heide.

Writing – review & editing: Lutz Heide.

References

1. UN-DESA. Sustainable Development Goal 3. Progress of goal 3 in 2017. 2017 https://sustainabledevelopment.un.org/sdg3.
2. WHO. Global action plan for the prevention and control of noncommunicable diseases. 2013 http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf?ua=1.
3. Hogerzeil HV, Liberman J, Wirtz VJ, Kishore SP, Selvaraj S, Kiddell-Monroe R, et al. Promotion of access to essential medicines for non-communicable diseases: practical implications of the UN political declaration. Lancet. 2013; 381(9867):680–9. https://doi.org/10.1016/S0140-6736(12)62128-X PMID: 23410612
4. WHO. The world medicines situation 2011. medicines prices, availability and affordability Geneva, Switzerland, 2011 http://apps.who.int/medicinedocs/documents/s18065en/s18065en.pdf.
5. Wilsdon TL, l.;. The evolution of access to essential medicines for the treatment of HIV/AIDS -evidence from 2000 to 2015, London UK: Charles River Associates, 2016 https://www.ifpma.org/wp-content/uploads/2016/06/2016-The-Evolution-of-Access-to-Essential-Medicines-CRA.pdf.

6. Nayyar GM, Attaran A, Clark JP, Culzoni MJ, Fernandez FM, Herrington JE, et al. Responding to the pandemic of falsified medicines. Am J Trop Med Hyg. 2015; 92(6 Suppl):113–8. https://doi.org/10.4269/ajtmh.14-0393 PMID: 25897060
7. WHO. A study on the public health and socioeconomic impact of substandard and falsified medical products, Geneva, Switzerland, 2017 http://www.who.int/medicines/regulation/ssffc/publications/se-study-sf/en/.
8. Almuzaini T, Choonara I, Sammons H. Substandard and counterfeit medicines: a systematic review of the literature. BMJ Open. 2013; 3(8):e002923. https://doi.org/10.1136/bmjopen-2013-002923 PMID: 23955188
9. Nayyar GM, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. Lancet Infect Dis. 2012; 12(6):488–96. https://doi.org/10.1016/S1473-3099(12)70064-6 PMID: 22632187
10. Kaur H, Clarke S, Lalani M, Phanouvong S, Guerin P, McLoughlin A, et al. Fake anti-malarials: start with the facts. Malar J. 2016; 15:86. https://doi.org/10.1186/s12936-016-1096-x PMID: 26873700
11. WHO. Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa, 2011. http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf.
12. Wirtz VJ, Hogerzeil HV, Gray AL, Bigdeli M, de Joncheere CP, Ewen MA, et al. Essential medicines for universal health coverage. Lancet. 2017; 389(10067):403–76. https://doi.org/10.1016/S0140-6736(16)31599-9 PMID: 27832874
13. WHO. Report of the informal technical working group on draft working definitions of substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products 2016. http://apps.who.int/gb/ssffc/pdf_files/MSM5/A_MSM5_7-en.pdf.
14. Seventieth World Health Assembly update M, Geneva. 29 May 2017, Geneva, Switzerland, 2017. http://www.who.int/en/news-room/detail/29-05-2017-seventieth-world-health-assembly-update-29-may-2017.
15. Petersen A, Held N, Heide L, Difam. EPN Minilab Survey Group. Surveillance for falsified and substandard medicines in Africa and Asia by local organizations using the low-cost GPHF Minilab. PLoS One. 2017; 12(9):e0184165. https://doi.org/10.1371/journal.pone.0184165 PMID: 28877208
16. Twagirumukiza M, Cosijns A, Pringels E, Remon JP, Vervaet C, Van Bortel L. Influence of tropical climate conditions on the quality of antihypertensive drugs from Rwandan pharmacies. Am J Trop Med Hyg. 2009; 81(5):776–81. https://doi.org/10.4269/ajtmh.2009.09-0109 PMID: 19861610
17. Antignac M, Diop BI, Macquart de Terline D, Bernard M, Do B, Ikama SM, et al. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa. Int J Cardiol. 2017. Volume 243, p 523–528.
18. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med. 2014; 371(9):818–27. https://doi.org/10.1056/NEJMoa1311890 PMID: 25162888
19. United Nations. MDG Gap Task Force Report 2015. 2015 http://www.un.org/millenniumgoals/pdf/MDG_Gap_2015_E_web.pdf.
20. Mawangi JM. Towards African medicines regulatory harmonization: The case of the East African Community. Pharmaceuticals Policy and Law. 2016; 18(1–4):91–8.
21. Tabernero P, Fernandez FM, Green M, Guerin PJ, Newton PN. Mind the gaps—The epidemiology of poor-quality anti-malarials in the malarious world—analysis of the WorldWide Antimalarial Resistance Network database. Malar J. 2014; 13:139. https://doi.org/10.1186/1475-2875-13-139 PMID: 24712972
22. Osei-Safo D, Agbonon A, Konadu DY, Harrison JJ, Edoh M, Gordon A, et al. Evaluation of the quality of artemisinin-based antimalarial medicines distributed in Ghana and Togo. Malar Res Treat. 2014; 2014:806416. https://doi.org/10.1155/2014/806416 PMID: 25400975
23. Tchamdja E, Kulo AE, Akoda K, Teko-Agbo A, Assoumy AM, Niang EM, et al. Drug quality analysis through high performance liquid chromatography of isometamidium chloride hydrochloride and diminazene diaceturate purchased from official and unofficial sources in Northern Togo. Prev Vet Med. 2016; 126:151–8. https://doi.org/10.1016/j.prevetmed.2016.02.001 PMID: 26907208
24. WHO. Guidelines on the conduct of surveys of the quality of medicines. WHO Expert Comittee on specifications for pharmaceutical preparations (fiftieth report) WHO Technical Report Series no 996 Annex 7 WHO, Geneva, Switzerland2016.
25. Newton PN, Lee SJ, Goodman C, Fernandez FM, Yeung S, Phanouvong S, et al. Guidelines for field surveys of the quality of medicines: a proposal. PLoS Med. 2009; 6(3):e52. https://doi.org/10.1371/journal.pmed.1000052 PMID: 19320538
26. WHO. Liste nationale des medicament essentielles sous dci pour les adultes 2012 http://www.who.int/selection_medicines/country_lists/Togo_LNME_adulte_2012.pdf?ua=1.
27. Annuaire Pharmacies: Ubipharm Togo; http://www.ubipharm-togo.com/AnnuairePharmacies.

28. MEDCALC easy-to-use statistical software, Comparison of proportions. https://www.medcalc.org/calc/comparison_of_proportions.php.
29. Mufusama JP, Ndjoko Ioset K, Feineis D, Hoellein L, Holzgrabe U, Bringmann G. Quality of the antimalarial medicine artemether—lumefantrine in 8 cities of the Democratic Republic of the Congo. Drug Test Anal. 2018; 10(10):1599–606. https://doi.org/10.1002/dta.2420 PMID: 29896850
30. ICH. ICH Guideline validation of analytical procedures: text and methodology Q2(R1) 2014 http://academy.gmp-compliance.org/guidemgr/files/Q2(R1).PDF.
31. Raju CBVN, Sharma HK, Rao CS, Rao GN. RP-HPLC Method for Analysis of Related Substances in Amoxicillin Drug Substance. Acta Chromatogr. 2009; 21(1):57–70.
32. WHO HAI. Measuring medicines prices, availability, affordability and price components.2008. http://www.who.int/medicines/areas/access/OMS_Medicine_prices.pdf.
33. MSH. The International Medical Products Price Guide 2015 http://mshpriceguide.org/en/home/.
34. MedCalc. Comparison of proportions calculator 2018 https://www.medcalc.org/calc/comparison_of_proportions.php.
35. MedCalc. Test for one proportion calculator 2018 www.medcalc.org/calc/test_one_proportion.php.
36. Campbell I. Chi-squared and Fisher-Irwin tests of two-by-two tables with small sample recommendations. Stat Med. 2007; 26(19):3661–75. https://doi.org/10.1002/sim.2832 PMID: 17315184
37. Richardson JT. The analysis of 2 x 2 contingency tables–yet again. Stat Med. 2011; 30(8):890; author reply 1–2. https://doi.org/10.1002/sim.4116 PMID: 21432882
38. Clopper C P E. the use of confidence of fiducial limits illustrated in the case of the binomial. Biometrika. 1934(26):404–13.
39. Fleiss JL L B, Paik MC. Statistical methods for rates and proportions. 3rd ed: John Wiley & Sons; 2003.
40. United Nations. Millenium Development Goal 8. The Global Partnership for Development. Making Rhetoric a Reality. MDG Gap Task Force Report 2012. New York, 2012. http://www.un.org/millenniumgoals/2012_Gap_Report/MDG_2012Gap_Task_Force_report.pdf.
41. Khuluza F, Kigera S, Heide L. Low Prevalence of Substandard and Falsified Antimalarial and Antibiotic Medicines in Public and Faith-Based Health Facilities of Southern Malawi. Am J Trop Med Hyg. 2017.
42. Waning B, Diedrichsen E, Moon S. A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries. J Int AIDS Soc. 2010; 13:35. https://doi.org/10.1186/1758-2652-13-35 PMID: 20840741
43. ICH. ICH Harmonised Tripartite Guideline, stability testing of new drug substances and products Q1A (R2) 2003 http://www.ich.org/products/guidelines/quality/quality-single/article/stability-testing-of-new-drug-substances-and-products.html.

S1 Table **Overview of all samples**

Sample ID	Name of product	Stated API	Therapeutic class *1*	Stated amount of API [mg]	Dosage Form	Sample site	Site Type	Region of sample site	Obtained quantity [tabs./caps.]	Stated manufacturer	Stated country of origin	Batch number	Manufacturing date	Expiry Date	Shelf life remaining at collection [months]	Stated storage requirements
QEW001	Amoxycillin Sandoz	Amoxicillin	Antibiotic	500	Tablets	Pharmacy Lome 2	formal	Lomè	100	Sandoz GmbH	Austria	GB7776	n.a	February 2020	36	below 25 °
QEW012	Amoxycillin Sandoz	Amoxicillin	Antibiotic	500	Tablets	Pharmacy Kpalime	formal	Lomè	100	Sandoz GmbH	Austria	GB7777	n.a	February 2020	36	below 25 °
QEW020	Amoxycillin Sandoz	Amoxicillin	Antibiotic	500	Tablets	Pharmacy Lome 3	formal	Lomè	60	Sandoz GmbH	Austria	GB7775	n.a	February 2020	36	not stated
QEW032	Amoxycillin Sandoz	Amoxicillin	Antibiotic	500	Tablets	Pharmacie Tsevie	formal	Tsevie	100	Sandoz GmbH	Austria	GB7776	n.a	February 2020	36	below 25 °
QEW040	Amoxycillin Sandoz	Amoxicillin	Antibiotic	500	Tablets	Pharmacy Lome 3	formal	Taligbo	100	Sandoz GmbH	Austria	FW2563	n.a	November 2019	33	below 25 °
QEW049	Amoxicillin Ubithera	Amoxicillin	Antibiotic	500	Capsules	Pharmacy Lome 1	formal	Kpalime	120	Lincoln Pharma	India	163131088	n.a	January 2019	23	not stated
QEW060	Amoxycillin Sandoz	Amoxicillin	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Sandoz GmbH	Austria	FW2561	n.a	November 2019	33	below 25 °
QEW067	Derm's Amoxicillin	Amoxicillin	Antibiotic	500	Capsules	Pharmacy Lome 1	formal	Tsevie	100	Yangzhou NO.3	China	160439	April 2016	April 2019	26	cool and dry
QEW070	Amoxicillin	Amoxicillin	Antibiotic	500	Capsules	Informal Vendor Agoe laogope	informal	Lomè	50	Sprukfield	Togo	15061	n.a	July 2018	17	not stated
QEW075 B	Amoxicillin TM	Amoxicillin	Antibiotic	500	Tablets	Pharmacy Lome 1	formal	Taligbo	120	Tongmei	Togo	807	n.a	June 2019	28	not stated
QEW078	Amoxicillin	Amoxicillin	Antibiotic	500	Capsules	Informal Vendor Agoe laogope	informal	Lomè	100	Letap	Ghana	1230196	n.a	July 2018	17	not stated
QEW080 B	Amoxicillin TM	Amoxicillin	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Kpalime	120	Tongmei	Togo	407	n.a	June 2019	28	not stated
QEW002	Augmentin Adults	Amoxicillin and Clavulanic acid	Antibiotic	500 / 62,5	Tablets	Pharmacy Kpalime	formal	Lomè	32	GSK france	France	2387	n.a	November 2017	9	below 25 °
QEW021 A*	Fleming	Amoxicillin and Clavulanic acid	Antibiotic	500 / 62,5	Tablets	Pharmacy Lome 3	formal	Lomè	16	Medreich	India	160004	n.a	December 2017	10	below 25 °
QEW021 B	Augmentin Adults	Amoxicillin and Clavulanic acid	Antibiotic	500 / 62,5	Tablets	Pharmacy Lome 3	formal	Lomè	16	GSK france	France	2386	n.a	November 2017	9	below 25 °
QEW021 C	AmoxiClav Denk	Amoxicillin and Clavulanic acid	Antibiotic	500 / 62,5	Tablets	Pharmacy Lome 3	formal	Lomè	32	Denk Pharma	Germany	19284	n.a	April 2018	14	below 25 °
QEW033	Clavumoccid	Amoxicillin and Clavulanic acid	Antibiotic	500 / 62,5	Tablets	Pharmacie Tsevie	formal	Tsevie	24	Medopharm	India	16213001	July 2017	April 2018	14	below 25 °
QEW041	Ticasse	Amoxicillin and Clavulanic acid	Antibiotic	500 / 125	Tablets	Pharmacy Lome 3	formal	Taligbo	60	Billim	Turkey	5181058A	n.a	July 2019	29	below 25 °
QEW050	Augmentin Adults	Amoxicillin and Clavulanic acid	Antibiotic	500 / 62,5	Tablets	Pharmacy Lome 1	formal	Kpalime	8	GSK france	France	2388	n.a	November 2017	9	below 25 °
QEW004	Ciprofloxacine Ubigen	Ciprofloxacin	Antibiotic	750	Tablets	Pharmacy Lome 2	formal	Lomè	100	Lincoln Pharma	India	GK6006	n.a	March 2019	25	below 30°
QEW014 A	CI Cian	Ciprofloxacin	Antibiotic	500	Tablets	Pharmacy Kpalime	formal	Lomè	50	Cian	India	CTE6024	n.a	February 2019	24	below 30°
QEW014 B	Ciprofloxacine TM	Ciprofloxacin	Antibiotic	250	Tablets	Pharmacy Kpalime	formal	Lomè	10	Tongmei	Togo	108	June 2016	July 2019	29	below 25 °
QEW023	Ciprofloxacine TM	Ciprofloxacin	Antibiotic	500	Tablets	Pharmacy Lome 3	formal	Lomè	60	Tongmei	Togo	101	November 2015	December 2018	22	not stated
QEW034	Ciprofloxacine TM	Ciprofloxacin	Antibiotic	500	Tablets	Pharmacie Tsevie	formal	Tsevie	80	Tongmei	Togo	205	May 2016	April 2019	26	not stated
QEW043	Ciplox-500	Ciprofloxacin	Antibiotic	500	Tablets	Pharmacy Lome 3	formal	Taligbo	60	CIPLA	India	61512	n.a	March 2019	25	below 30°
QEW052	Ciprofloxacine Ubigen	Ciprofloxacin	Antibiotic	750	Tablets	Pharmacy Lome 1	formal	Kpalime	100	Lincoln Pharma	India	GK6006	n.a	March 2019	25	below 30°
QEW061	Ciprofloxacine	Ciprofloxacin	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	North China pharmaceuti	China	160910	n.a	September 2019	31	not stated
QEW068	CIPRO-500	Ciprofloxacin	Antibiotic	500	Tablets	Pharmacy Lome 1	formal	Tsevie	100	Nuel Pharma	Nigeria	NCP-02	August 2016	July 2019	29	below 30°
QEW071	Cipromax Fort	Ciprofloxacin	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Lomè	50	Greenfield	China	16090112	n.a	August 2019	30	cool and dry
QEW076	Cipro 500	Ciprofloxacin	Antibiotic	500	Tablets	Pharmacy Lome 1	formal	Taligbo	100	Sprukfield	Togo	AR15003	n.a	January 2018	11	not stated
QEW079	Cipro 500	Ciprofloxacin	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Sprukfield	Togo	AR15004	n.a	January 2018	11	not stated
QEW081	Ciprofloxacine	Ciprofloxacin	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Kpalime	100	North China pharmaceut	China	160910	n.a	September 2019	31	not stated
QEW007 *	Doxycycline	Doxycycline	Antibiotic	100	Tablets	Pharmacy Lome 2	formal	Lomè	10	Bailly-Creat	France	40	n.a	December 2017	10	below 25 °
QEW007X	Doxycycline	Doxycycline	Antibiotic	100	Tablets	Pharmacy Lome 2	formal	Lomè	90	Bailly-Creat	France	45	n.a	May 2019	27	below 25 °
QEW016	Doxynor 100	Doxycycline	Antibiotic	100	Tablets	Pharmacy Kpalime	formal	Lomè	20	F.I.R.M.A S.p.A	Italy	20	n.a	March 2019	25	not stated
QEW016 B	Doxycycline	Doxycycline	Antibiotic	100	Tablets	Pharmacy Kpalime	formal	Lomè	40	Bailly-Creat	France	45	n.a	May 2019	27	below 25 °
QEW026	Doxycycline	Doxycycline	Antibiotic	100	Tablets	Pharmacy Lome 3	formal	Lomè	60	Bailly-Creat	France	45	n.a	May 2019	27	not stated
QEW036	Doxycycline	Doxycycline	Antibiotic	100	Tablets	Pharmacie Tsevie	formal	Tsevie	90	Bailly-Creat	France	45	n.a	May 2019	27	below 25 °
QEW045	Philco-Doxy	Doxycycline	Antibiotic	100	Tablets	Pharmacy Lome 3	formal	Taligbo	60	Philco Pharma	Germany	1404055-2	n.a	March 2017	1	below 25 °
QEW054	Doxycycline	Doxycycline	Antibiotic	100	Tablets	Pharmacy Lome 1	formal	Kpalime	100	Bailly-Creat	France	45	n.a	May 2019	27	below 25 °
QEW063	Doxycycline	Doxycycline	Antibiotic	100	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Pharmaquick	Benin	992600	n.a	November 2017	9	not stated
QEW073	Doxefil	Doxycycline	Antibiotic	100	Capsules	Informal Vendor Agoe laogope	informal	Lomè	50	Fourrts	India	B3034A	n.a	January 2018	11	not stated
QEW084	Doxycycline	Doxycycline	Antibiotic	100	Tablets	Informal Vendor Agoe laogope	informal	Kpalime	100	Pharmaquick	Benin	99280	n.a	November 2017	9	not stated
QEW006	Metronidazole Creazol	Metronidazole	Antibiotic	500	Tablets	Pharmacy Lome 2	formal	Lomè	100	Bailly-Creat	France	114	n.a	September 2019	31	below 25 °
QEW015	Metronidazole Creazol	Metronidazole	Antibiotic	500	Tablets	Pharmacy Kpalime	formal	Lomè	100	Bailly-Creat	France	116	n.a	September 2019	31	below 25 °
QEW025	Metronidazole TM	Metronidazole	Antibiotic	500	Tablets	Pharmacy Lome 3	formal	Lomè	60	Tongmei	Togo	604	n.a	March 2019	25	not stated
QEW035	UbiThera Metronidazole	Metronidazole	Antibiotic	250	Tablets	Pharmacie Tsevie	formal	Tsevie	100	Lincoln Pharma	India	GP5001	n.a	April 2018	14	not stated
QEW044	Metronidazole TM	Metronidazole	Antibiotic	500	Tablets	Pharmacy Lome 3	formal	Taligbo	60	Tongmei	Togo	604	n.a	March 2019	25	not stated
QEW053	Metronidazole Creazol	Metronidazole	Antibiotic	500	Tablets	Pharmacy Lome 1	formal	Kpalime	60	Bailly-Creat	France	118	n.a	September 2019	31	below 25 °
QEW062	Metronidazole	Metronidazole	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	North China pharmaceut	China	160904	n.a	September 2019	31	not stated
QEW069	Metronidazole TM	Metronidazole	Antibiotic	500	Tablets	Pharmacy Lome 1	formal	Tsevie	100	Tongmei	Togo	604	n.a	March 2019	25	not stated
QEW072	Metronidazole TM	Metronidazole	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Tongmei	Togo	604	n.a	March 2019	25	not stated
QEW077	Metronidazole TM	Metronidazole	Antibiotic	500	Tablets	Pharmacy Lome 1	formal	Taligbo	100	Tongmei	Togo	604	n.a	March 2019	25	not stated
QEW080 A	Metronidazole TM	Metronidazole	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Tongmei	Togo	604	n.a	March 2019	25	not stated
QEW083	Metronidazole TM	Metronidazole	Antibiotic	500	Tablets	Informal Vendor Agoe laogope	informal	Kpalime	100	Tongmei	Togo	604	n.a	March 2019	25	not stated
QEW005	Starpen 1000	Penicillin v	Antibiotic	1000	Tablets	Pharmacy Kpalime	formal	Lomè	60	Sandoz GmbH	Austria	GE6581	n.a	March 2018	13	below 25 °
QEW024	Starpen 1000	Penicillin v	Antibiotic	1000	Tablets	Pharmacy Lome 3	formal	Lomè	60	Sandoz GmbH	Austria	GE6581	March 2016	March 2018	13	below 25 °
QEW082	Penicillin V	Penicillin v	Antibiotic	125	Tablets	Informal Vendor Agoe laogope	informal	Kpalime	100	Letap	Ghana	3909	n.a	August 2017	6	not stated
QEW003	Bactrim Adultes comprime	Sulfamethoxazole and Trimethoprim	Antibiotic	400 / 80	Tablets	Pharmacy Lome 2	formal	Lomè	60	Roche	France	F1067F02	n.a	January 2021	47	below 30°
QEW013	Co-Trimoxazole Ubigen	Sulfamethoxazole and Trimethoprim	Antibiotic	400 / 80	Tablets	Pharmacy Kpalime	formal	Lomè	100	Lincoln Pharma	India	GM6005	June 2015	May 2019	27	not stated
QEW022	Cotrimoxazole TM	Sulfamethoxazole and Trimethoprim	Antibiotic	400 / 80	Tablets	Pharmacy Lome 3	formal	Lomè	60	Tongmei	Togo	206	n.a	May 2019	27	not stated
QEW042	Cotrimoxazole TM	Sulfamethoxazole and Trimethoprim	Antibiotic	400 / 80	Tablets	Pharmacy Lome 3	formal	Taligbo	100	Tongmei	Togo	103	n.a	February 2019	24	not stated
QEW051	Co-Trimoxazole Ubigen	Sulfamethoxazole and Trimethoprim	Antibiotic	400 / 80	Tablets	Pharmacy Lome 1	formal	Kpalime	100	Lincoln Pharma	India	GM6005	June 2015	May 2019	27	below 25 °
QEW085	Cotrimoxazole TM	Sulfamethoxazole and Trimethoprim	Antibiotic	400 / 80	Tablets	Informal Vendor Agoe laogope	informal	Kpalime	90	Tongmei	Togo	211	n.a	January 2019	23	not stated
QEW009	Atenolol Denk	Atenolol	MANCD	50	Tablets	Pharmacy Lome 2	formal	Lomè	100	Denk Pharma	Germany	3089	n.a	May 2019	27	below 25 °
QEW018	Atenolol Denk	Atenolol	MANCD	50	Tablets	Pharmacy Kpalime	formal	Lomè	100	Denk Pharma	Germany	3089	n.a	May 2019	27	below 25 °
QEW028	Atenolol Denk	Atenolol	MANCD	50	Tablets	Pharmacy Lome 3	formal	Lomè	60	Denk Pharma	Germany	3090	n.a	May 2019	27	not stated
QEW038	Atenolol Denk	Atenolol	MANCD	50	Tablets	Pharmacie Tsevie	formal	Tsevie	100	Denk Pharma	Germany	3089	n.a	May 2019	27	below 25 °
QEW047	Atenolol Denk	Atenolol	MANCD	50	Tablets	Pharmacy Lome 3	formal	Taligbo	60	Denk Pharma	Germany	3089	n.a	May 2019	27	below 25 °
QEW056	Atenolol Denk	Atenolol	MANCD	50	Tablets	Pharmacy Lome 1	formal	Kpalime	100	Denk Pharma	Germany	3125	n.a	July 2019	29	below 25 °

Sample ID	Name of product	Stated API	Therapeutic class *1*	Stated amount of API [mg]	Dosage Form	Sample site	Site Type	Region of sample site	Obtained quantity [tabs./caps.]	Stated manufacturer	Stated country of origin	Batch number	Manufacturing date	Expiry Date	Shelf life remaining at collection [months]	Stated storage requirements
QEW065	Atenolol Denk	Atenolol	MANCD	50	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Denk Pharma	Germany	3089	n.a	May 2019	27	below 25 °
QEW011	Furo Denk	Furosemide	MANCD	40	Tablets	Pharmacy Lome 2	formal	Lomè	100	Denk Pharma	Germany	92X	n.a	September 2020	43	below 25 °
QEW019	Furosemide	Furosemide	MANCD	40	Tablets	Pharmacy Kpalime	formal	Lomè	60	Bailly-Creat	France	42	n.a	March 2019	25	not stated
QEW030	Furosemide	Furosemide	MANCD	40	Tablets	Pharmacy Lome 3	formal	Lomè	60	Bailly-Creat	France	42	n.a	March 2019	25	not stated
QEW039	Furosemide	Furosemide	MANCD	40	Tablets	Pharmacie Tsevie	formal	Tsevie	100	Bailly-Creat	France	42	n.a	March 2019	25	below 25 °
QEW048	Furosemide	Furosemide	MANCD	40	Tablets	Pharmacy Lome 3	formal	Taligbo	120	Pharmaquick	Benin	9913	n.a	May 2018	15	not stated
QEW058	Furosemide	Furosemide	MANCD	40	Tablets	Pharmacy Lome 1	formal	Kpalime	100	Bailly-Creat	France	42	n.a	March 2019	25	below 25 °
QEW066	Furosemide	Furosemide	MANCD	40	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Bailly-Creat	France	42	n.a	March 2019	25	below 25 °
QEW075 A	Furosemide	Furosemide	MANCD	40	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Pharmaquick	Benin	9546	n.a	May 2017	3	not stated
QEW086	Furosemide	Furosemide	MANCD	40	Tablets	Informal Vendor Agoe laogope	informal	Kpalime	100	Alice	India	TE6280	n.a	June 2019	28	not stated
QEW087	Furosemide	Furosemide	MANCD	n.n	Tablets	Informal Vendor Agoe laogope	informal	Kpalime	40	Letap	Ghana	n.n	n.a	n.n		not stated
QEW010	Esidrex 25mg	Hydrochlorothiazide	MANCD	25	Tablets	Pharmacy Kpalime	formal	Lomè	100	Novartis	Spain	BC920	n.a	December 2018	22	cool and dry
QEW029	Esidrex 25mg	Hydrochlorothiazide	MANCD	25	Tablets	Pharmacy Lome 3	formal	Lomè	60	Novartis	Spain	BC919	n.a	December 2018	22	cool and dry
QEW074	Hydrochlorothiazide	Hydrochlorothiazide	MANCD	50	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Pharmaquick	Benin	9928	n.a	April 2019	26	not stated
QEW057	Ecazide	Hydrochlorothiazide + Captopril	MANCD	25	Tablets	Pharmacy Lome 1	formal	Kpalime	60	Bristol Myers Squibb	Italy	AAK6882	n.a	May 2019	27	below 25 °
QEW008	Metformin Denk	Metformin	MANCD	500	Tablets	Pharmacy Lome 2	formal	Lomè	100	Denk Pharma	Germany	954	n.a	January 2021	47	below 25 °
QEW017	Metformin Denk	Metformin	MANCD	500	Tablets	Pharmacy Kpalime	formal	Lomè	100	Denk Pharma	Germany	959	n.a	March 2021	49	below 25 °
QEW027	Metformin Denk	Metformin	MANCD	500	Tablets	Pharmacy Lome 3	formal	Lomè	60	Denk Pharma	Germany	989	n.a	March 2021	49	below 25 °
QEW037	Metformin Denk	Metformin	MANCD	500	Tablets	Pharmacie Tsevie	formal	Tsevie	100	Denk Pharma	Germany	954	n.a	January 2021	47	below 25 °
QEW046	Metformin Denk	Metformin	MANCD	500	Tablets	Pharmacy Lome 3	formal	Taligbo	60	Denk Pharma	Germany	8ZY	n.a	May 2020	39	below 25 °
QEW055	Metformin Denk	Metformin	MANCD	500	Tablets	Pharmacy Lome 1	formal	Kpalime	100	Denk Pharma	Germany	957	n.a	March 2021	49	below 25 °
QEW064	Metformin Denk	Metformin	MANCD	500	Tablets	Informal Vendor Agoe laogope	informal	Lomè	100	Denk Pharma	Germany	954	n.a	January 2021	47	below 25 °
QEW031	Buto-Asma	Salbutamol	MANCD	2	Tablets	Pharmacy Lome 3	formal	Lomè	80	Aldo-Union	Spain	0619K002	n.a	July 2021	53	below 30°
QEW059	Buto-Asma	Salbutamol	MANCD	2	Tablets	Pharmacy Lome 1	formal	Kpalime	40	Aldo-Union	Spain	0619K002	n.a	July 2021	53	below 30°

MANCD = medicine against non-communicable disease

n.a. = not available

* = Results were excluded

S2 Table: Prices of the medicines in licensed pharmacies and informal vendors

API	Median price per dosage form [$]		median price ratio	
	formal	Informal	formal	Informal
Amoxicillin 500 mg	0.09	0.07	3.36	2.63
Amoxicillin / Clavulanicacid 500/125mg	0.47		4.96	
Phenoxymethylpenicillin 1000mg	0.28	0.02 (125mg)	7.57	1.36
Ciprofloxacin 500mg	0.18	0.06	4.74	1.53
Doxycycline 100mg	0.07	0.04	5.04	3.07
Sulfamethoxazole / Trimethoprim 400/80mg	0.04	0.14	3.30	12.50
Metronidazole 500mg	0.06	0.05	6.63	3.88
Atenolol 50mg	0.13	0.13	11.99	12.22
Furosemide 40mg	0.07	0.04	10.72	6.70
Hydrochlorothiazide 25 / 50mg	0.06	0.03 (50mg)	14.44	6.67
Metformin 500mg	0.08	0.08	5.28	5.25
Salbutamol 2mg	0.12		49.27	
Overall median price ratio			5.28[a]	3.18[a]

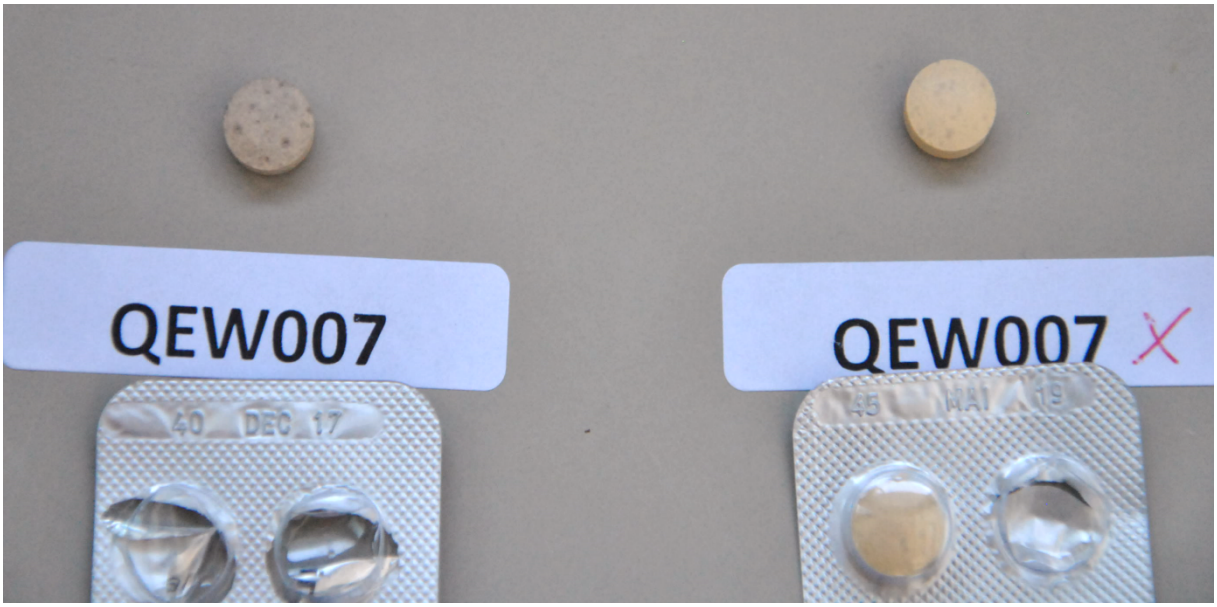
[a] median price ratio of all medicines collected

The table shows the median prices per tablet or capsule. Following a standardized method developed by WHO and Health Action International,[1] those prices were compared to an international reference price, i.e to the median supplier price given in the MSH International Medical Products Price Guide of 2015.[2] Overall, the resulting median price ratio (MPR) was 5.3 in licensed pharmacies, compared to 3.2 in informal vendors. Therefore, as expected, medicines are more expensive in pharmacies. A United Nations report of 2012[3] stated that in low and middle income countries the median price ratio in the (formal) private sector was on average 5.3, identical to the figure found for pharmacies in Togo. As expected, the MPR for generic medicines and branded generics (average MPR = 4.1) was lower than that for originator medicines (average MPR= 13.5). Medicines from Africa and Asia (in both cases average MPR = 3.0) were more affordable than those from Europe (average MPR= 7.2). Notably, medicines for non-communicable diseases were sold at much more unfavorable prices (average MPR=10.7) than antibiotics (average MPR=3.1). For the two samples of salbutamol 2mg tablets, sold as branded generics in private pharmacies, the MPR even reached 49.3.

[1] WHO HAI. Measuring medicines prices, availability, affordability and price components.2008. Available from: http://www.who.int/medicines/areas/access/OMS_Medicine_prices.pdf

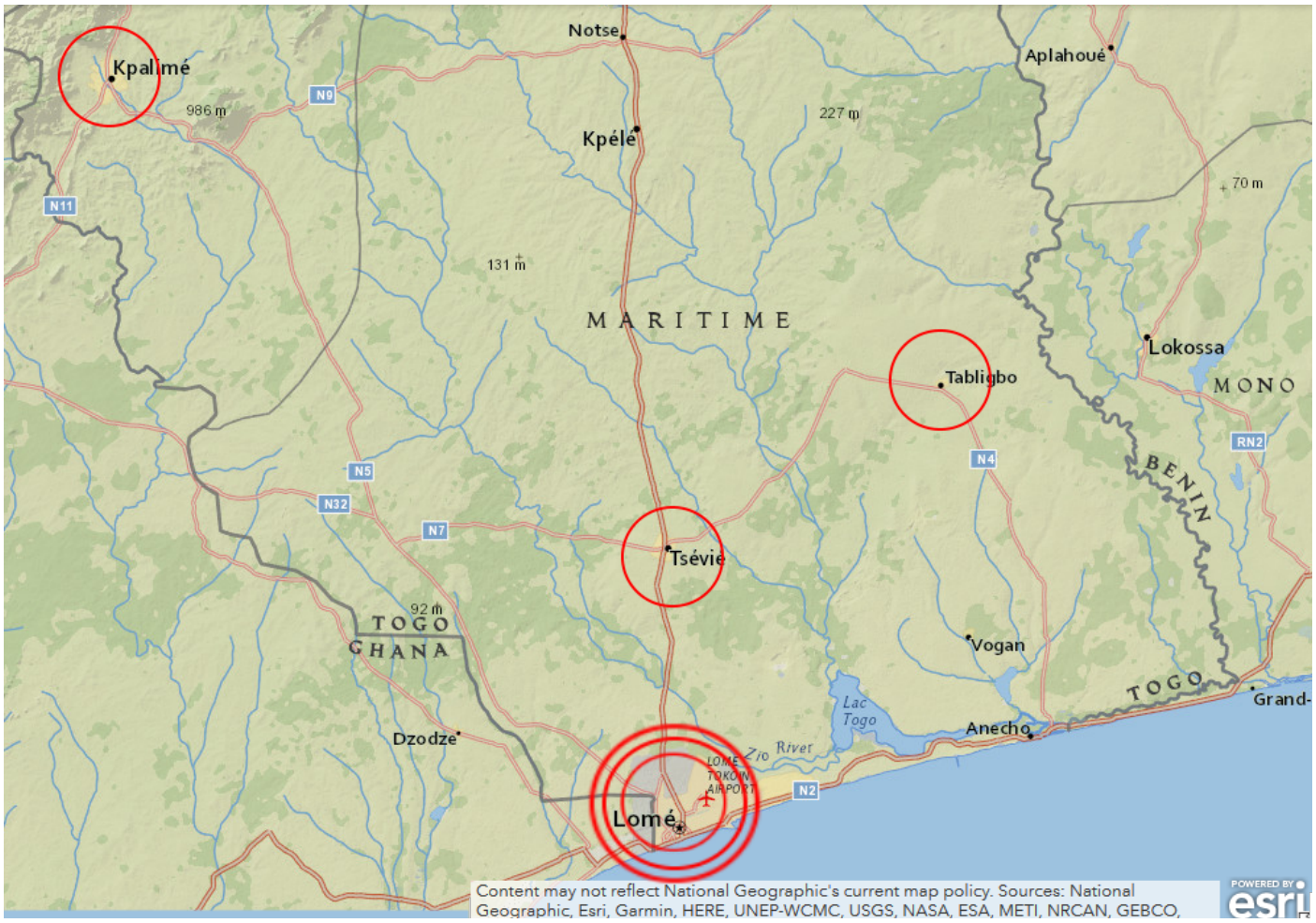
[2] MSH. The International Medical Products Price Guide 2015. Available from: http://mshpriceguide.org/en/home/

[3] United Nations. Millenium Development Goal 8. The Global Partnership for Development. Making Rhetoric a Reality. MDG Gap Task Force Report 2012. New York. 2012. Available from: http://www.un.org/millenniumgoals/2012_Gap_Report/MDG_2012Gap_Task_Force_report.pdf



S2 Figure: Discoloration discovered upon visual inspection of a sample of doxycycline tablets

This sample of doxycycline 100mg tablets (Bailly-Creat, France) contained blisters with two different batch numbers in one secondary packaging. While the blisters with the uniformly colored tablets (batch no. 45; exp. date 05.2019) depicted on the right side (QEW007X) were found to comply with the USP39 specifications, the blisters with the darkened, spotted tablets (batch no. 40; exp. date 12.2017) depicted on the left side (QEW007) showed extreme deviations from the USP39 specifications both in the assay (58% of stated content of doxycycline) and in dissolution. Since QEW007 consisted of only one blister of 10 tablets, which was lower than the amount required by the USP 39 monographs, the results for this sample were excluded from the overall data analysis.



S 1 Figure: **Map of the sampling sites in the regions Maritime and Plateaux of the Republic of Togo** (*https://viewer.nationalmap.gov/advanced-viewer/*)

In Lomé samples were collected in Lomé Centre and in the suburbs Agoe-nyvie and Agoe-laogope. Furthermore, samples were collected in the towns Tsévié and Tabligbo, 30 km north and 75 km northeast of Lomé, respectively, and in the town of Kpalimé, 120km northwest of Lomé and close to the border to Ghana.

Am. J. Trop. Med. Hyg., 103(2), 2020, pp. 894–908
doi:10.4269/ajtmh.20-0184

Substandard and Falsified Antibiotics and Medicines against Noncommunicable Diseases in Western Cameroon and Northeastern Democratic Republic of Congo

Simon Schäfermann,[1] Cathrin Hauk,[1] Emmanuel Wemakor,[1] Richard Neci,[2] Georges Mutombo,[2] Edward Ngah Ndze,[3] Tambo Cletus,[3] Fidelis Nyaah,[4] Manyi Pattinora,[4] Dorothee Wistuba,[5] Irina Helmle,[1] Christine Häfele-Abah,[6] Harald Gross,[1] and Lutz Heide[1]*

[1]*Pharmaceutical Institute, Eberhard Karls University Tuebingen, Tuebingen, Germany;* [2]*Le Dépôt Central Médico-Pharmaceutique de la 8e CEPAC (DCMP), Bukavu, Democratic Republic of Congo;* [3]*Cameroon Baptist Convention (CBC), Central Pharmacy, Mutengene, Cameroon;* [4]*Presbyterian Church in Cameroon (PCC), Central Pharmacy, Limbe, Cameroon;* [5]*Institute of Organic Chemistry, Eberhard Karls University Tuebingen, Tuebingen, Germany;* [6]*German Institute for Medical Mission (Difaem), Tuebingen, Germany*

Abstract. Falsified and substandard medicines may undermine the progress toward the Sustainable Development Goals. The present study investigated the quality of 13 essential medicines in Cameroon and the Democratic Republic of Congo (DR Congo). Five hundred six medicine samples were collected from the government and faith-based health facilities, private pharmacies, and informal vendors (total 60 facilities). Collected samples were analyzed according to the U.S. Pharmacopeia (USP) for identity, content, and dissolution of their active pharmaceutical ingredients (APIs) and for uniformity of dosage units. Three samples (0.6%) were identified as falsified. Overall, 8.5% of the samples failed USP specifications for the content of the API and 11.7% failed dissolution testing. Medicines from informal vendors showed a higher out-of-specification rate (28.2%) than other types of drug outlets (12.3%; $P < 0.0001$). All three falsified medicines had been sold by informal vendors. The failure rate of medicines stated to be produced in Europe (5.1%) was lower than that for medicines from Asia (17.7%; $P = 0.0049$) and Africa (22.2%; $P = 0.0042$). Medicines against noncommunicable diseases showed a higher failure rate than antibiotics (25.3% versus 12.1%; $P = 0.0004$). Four hundred fifty-one of the samples were analyzed in Cameroon and the DR Congo with the Global Pharma Health Fund Minilab (thin-layer chromatography and disintegration testing). The three falsified medicines were readily detected in Minilab analysis. However, substandard samples were detected with low sensitivity. A well-enforced ban of medicine sales by informal vendors and increased attention to supplier qualification in the procurement process may reduce the prevalence of substandard and falsified medicines.

INTRODUCTION

In the past decades, access to medicines in low- and middle-income countries (LMICs) has improved,[1,2] but the occurrence of substandard and falsified (SF) medicines has been reported frequently and was even described as a "pandemic" by some authors.[3] Substandard and falsified medicines pose a serious risk to global health, and therefore, access to safe, quality, and affordable medicines has been included in the Sustainable Development Goals of the United Nations as Goal No. 3.8.[4] Substandard and falsified medicines may cause prolonged illness and treatment failures and can also directly harm patients through toxic effects or adverse reactions.[5,6] Yet, reliable data about their prevalence are sparse.[7–9] Following the first international conference on Medicine Quality and Public Health in 2018, researchers from all over the world called for investment, policy change, and action to eliminate SF medical products, and they formulated a research agenda stressing the urgent need for epidemiological evidence on the prevalence of SF medical products in different countries, in different sectors of the health system, and for different categories of medicines.[10]

Although medicine quality problems have been reported to occur worldwide, the burden of SF medicines is heavily concentrated in LMICs.[8] A review article by the WHO calculated an average prevalence of 10.5% SF medicines in these countries.[7] A review and meta-analysis by Ozawa et al.[11] estimated their prevalence in Africa to be 18.7%. Both these reviews emphasized the problem of strong heterogeneity of methods and results across different surveys on SF medicines.[7,11] The lack of a common terminology further hampered the comparison of data from different studies, until finally the 2017 World Health Assembly agreed on common definitions for "substandard" and "falsified" medicines.[12] Substandard medicines are now defined as "authorized medical products that fail to meet either their quality standards or specifications or both." They may result from poor manufacturing, or from inappropriate transport or storage conditions. Falsified medicines are defined as "medical products that deliberately or fraudulently misrepresent their identity, composition, or source."[12]

In the Democratic Republic of Congo (DR Congo) and in Cameroon, so far only few medicine quality studies have been conducted, mostly focusing on antimalarials, antiretrovirals, and antibiotics. The Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa (QAMSA) study conducted by the WHO in six African countries reported that in Cameroon, 37% of the 41 tested antimalarial samples failed quality testing.[13] Petersen et al.[14] investigated 869 medicines from seven African and Asian countries using the Minilab of the Global Pharma Health Fund (GPHF, Giessen, Germany).[15] For those samples which failed Minilab testing, confirmatory analysis was carried out using high-performance liquid chromatography (HPLC). In Cameroon and in the DR Congo, 7.1% and 2.7% of the samples collected were found to be falsified or substandard, respectively, although the authors noted that a number of substandard medicines may have escaped detection because of the limited sensitivity of the GPHF Minilab.[14] In 2018, Mufusama et al.[16] reported the quality of artemether/lumefantrine combination products collected in eight cities of the DR Congo. When analyzed using thin-layer chromatography (TLC) with the GPHF Minilab, four of the 150 investigated samples (2.7%)

*Address correspondence to Lutz Heide, Pharmaceutical Institute, Eberhard Karls University Tuebingen, Auf der Morgenstelle 8, Tuebingen 72076, Germany. E-mail: heide@uni-tuebingen.de

were found not to contain the declared active pharmaceutical ingredients (APIs), and this was confirmed by HPLC analysis. The failure rate reportedly increased to 46.7% when also quantitative deviations from the declared amount of the APIs were considered. The authors noted that this failure rate was quite high compared with other medicine quality surveys. Schiavetti et al.[17] investigated the quality of medicines used in children, supplied by private wholesalers in Kinshasa in the DR Congo in 2018. Of the 239 tested samples, representing artemether/lumefantrine and amoxicillin powders for suspension and paracetamol tablets, 27% were of poor quality. By contrast, 35 antiretroviral medicine samples collected in different regions of Cameroon all showed good quality.[18]

As emphasized in the WHO Global Status Report on noncommunicable diseases (NCDs) of 2014,[19] the burden of death and disease resulting from NCDs is heavily concentrated in LMICs. Hunter-Adams et al.[20] expected that the burden of diabetes in Africa will be more than double in the next decade. Nevertheless, so far, the quality of medicines against NCDs has only been evaluated in few studies. The SEVEN study investigated the quality of seven cardiac medicines from 10 different countries, including the DR Congo,[21] and 26.7% of the 90 samples collected in the DR Congo were reported to be of poor quality.

Following the aforementioned call for research on the prevalence of SF medicines in different countries, in different sectors of the health system, and for different categories of medicines,[10] the present study investigated the prevalence of SF medicines among selected medicines against NCDs and antibiotics in government and faith-based health facilities, private pharmacies, and informal vendors of Cameroon and of the DR Congo. Samples were first tested with the GPHF Minilab. Subsequently, all samples, irrespective of the results obtained in the GPHF Minilab analysis, were also tested with the methods of the U.S. Pharmacopeia (USP) for identity, content, and dissolution of the APIs and for uniformity of the dosage units. The use of both Minilab and compendial analysis in the present study allows an evaluation of the sensitivity and specificity of the screening with the GPHF Minilab. Data on the availability, prices, and affordability of the medicines were collected additionally and have been published elsewhere.[22]

To the best of our knowledge, this is the largest and most comprehensive study on medicine quality conducted in Cameroon and the DR Congo so far, and at the same time, the largest investigation of the dissolution of the APIs of medicines on the African market published until now.

MATERIALS AND METHODS

Study design and included medicines. This study was designed observing the recommendations contained in the WHO guidelines on the conduct of surveys of the quality of medicines[23] and the Medicine Quality Assessment Reporting Guidelines (MEDQUARG guidelines).[24] Thirteen medicines, that is, seven antibiotics and six medicines against NCDs were included, in dosages for adults. They are listed in Table 1. All of them were selected from the essential medicines lists of the Republic of Cameroon[25] and the DR Congo.[26] Medicines were selected for which both a USP-finished pharmaceutical product monograph and a GPHF Minilab method were available for medicine quality analysis. The included medicines were identical in both countries with one exception: in the DR Congo, atenolol tablets were included, but in Cameroon, the local partners and Jingi et al.[27] reported that atenolol was not frequently used. On request by the local partners, glibenclamide (=glyburide) was included instead of atenolol in Cameroon.

Ethical approval. This study was approved by the Ministry of Health of the DR Congo (Ref. CAB/Min-Prov/SGFEAHRAP/SK/01/2017) and by the Ministry of Public Health of the Republic of Cameroon, Comité National d' Ethique de la Recherche pour la Santé Humain (Ref. 243674339).

Sampling sites. This study was conducted in the northeast of the DR Congo in the provinces Ituri, North Kivu, South Kivu, and Tanganyika, and in western Cameroon, in the regions Adamawa, Centre, Littoral, Northwest, Southwest, and West (Figure 1) because these were the provinces/regions where the local partners worked. The selection of the sampling sites has been described in the evaluation of the availability and

TABLE 1
Limits for compliance/noncompliance, and for moderate and extreme deviations from pharmacopoeial specifications, used in this study.

International nonproprietary names	Dosage form	Content of the API (=assay) (% of declared content)			Dissolution of the API (% of declared content)		
		Complies	Moderate deviation	Extreme deviation	Complies	Moderate deviation	Extreme deviation
Amoxicillin	Tablets	90–120	80 to < 90	< 80 or > 120	≥ 85	< 85 to 60	< 60
Clavulanic acid		90–120	80 to < 90	< 80 or > 120	≥ 80	< 80 to 55	< 55
Amoxicillin	Tablets	90–120	80 to < 90	< 80 or > 120	≥ 75	< 75 to 50	< 50
Amoxicillin	Capsules	90–120	80 to < 90	< 80 or > 120	≥ 80	< 80 to 55	< 55
Ciprofloxacin	Tablets	90–110	80 to < 90 or > 110 to 120	< 80 or > 120	≥ 80	< 80 to 55	< 55
Doxycycline	Tablets/capsules	90–120	80 to < 90	< 80 or > 120	≥ 85	< 85 to 60	< 60
Doxycycline hyclate	Tablets	90–120	80 to < 90	< 80 or > 120	≥ 85	< 85 to 60	< 60
Doxycycline hyclate	Capsules	90–120	80 to < 90	< 80 or > 120	≥ 80	< 80 to 55	< 55
Penicillin V	Tablets	90–120	80 to < 90	< 80 or > 120	≥ 75	< 75 to 50	< 50
Metronidazole	Tablets	90–110	80 to < 90 or > 110 to 120	< 80 or > 120	≥ 85	< 85 to 60	< 60
Sulfamethoxazole	Tablets	93–107	80 to < 93 or > 107 to 120	< 80 or > 120	≥ 70	< 70 to 45	< 45
Trimethoprim		93–107	80 to < 93 or > 107 to 120	< 80 or > 120	≥ 70	< 70 to 45	< 45
Atenolol	Tablets	90–110	80 to < 90 or >110 to 120	< 80 or > 120	≥ 80	< 80 to 55	< 55
Furosemide	Tablets	90–110	80 to < 90 or > 110 to 120	< 80 or > 120	≥ 80	< 80 to 55	< 55
Glibenclamide (glyburide)	Tablets	90–110	80 to < 90 or > 110 to 120	< 80 or > 120	≥ 70	< 70 to 45	< 45
Hydrochlorothiazide	Tablets	90–110	80 to < 90 or > 110 to 120	< 80 or > 120	≥ 60	< 60 to 35	< 35
Metformin	Tablets	95–105	80 to < 95 or > 105 to 120	< 80 or > 120	≥ 70	< 70 to 45	< 45
Salbutamol (albuterol)	Tablets	90–110	80 to < 90 or > 110 to 120	< 80 or > 120	≥ 80	< 80 to 55	< 55

API = active pharmaceutical ingredients. United States Pharmacopeia 41 specifications were used for compliance/non-compliance. Following the suggestion of the QAMSA study by WHO,[13] extreme deviation was defined as an API content deviating by more than 20% from the declared amount, and/or an average dissolution of the API of the tested units falling more than 25% below the pharmacopoeial Q-value. In this study, all observed assay failures were due to insufficient API content, no sample failed due to excessive API content (see Results section).

prices of the included medicines.[22] For the four provinces in the northeast DR Congo, a complete list of the health zones (total 116 zones) was obtained. On consultation with the local partners, 70 of these zones were identified as unsafe for travel by the study personnel and, therefore, had to be excluded from the study. Of the remaining 46 health zones, two from each of the four provinces were randomly selected using the return random number (RAND) function of Microsoft Excel. In addition, Kadutu Health Zone in Bukavu, South Kivu, was added on request by the local partners because it comprised the biggest unlicensed market for medicines and was considered important in the assessment of medicine quality problems in that region. In the DR Congo, the health zone is a set of health centers linked to a hospital.[28] In each of the selected health zones, the samples were collected first from the main hospital of that zone. When this was a government-operated general referral hospital, medicines were sampled also from the nearest church health center, private pharmacy, and informal vendor of medicines. Correspondingly, if the main hospital was a church-operated centre hospitalier, medicines were sampled also from the nearest governmental health center, private pharmacy, and informal vendor. In Ituri Province, no informal medicine vendors could be found because tight control was enforced by the authorities in that province following a major medicine scandal.[5] Therefore, in the DR Congo, samples for this study were collected from 34 medicine outlets, located in nine health zones in four provinces.

The structure of the health system of Cameroon has been described in two recent documents.[29,30] For the present study, a complete list of the 45 church health facilities in the six included regions was obtained. For each region, one church health facility was randomly selected. Samples were collected from this church health facility and from the geographically nearest governmental health facility, private pharmacy, and informal vendor in that region. By chance, the random selection had not included any church health facility operated by the catholic church, and the local partners requested that of the 10 catholic health facilities existing in the six regions, two were randomly selected and included as well. Therefore, in Cameroon, samples were collected from 26 medicine outlets, located in six of Cameroon's 10 regions.

Sample collection. Samples were collected between August 2017 and November 2018. An overt sampling approach was used in public and church health facilities, that is, the investigators identified themselves and explained the purpose of the study. By contrast, a mystery shopper approach was used in informal vendors and private pharmacies, that is, the local investigators acted as customers, stating that they own a small informal medicine outlet. If the medicine outlets had more than one brand of the included medicines in stock, the cheapest brand was collected. For each sample, an amount of 100 dosage units (capsules or tablets) was purchased if available, otherwise less, but samples were only collected if at least 30 dosage units could be obtained. In government and church health facilities, replacements for the sampled medicines were offered by the sample collectors to avoid that stock-outs would result from this study. Replacement medicines were obtained from the medical stores of the local partner organizations. If the visited facilities preferred, the sampled medicines were paid for.

Samples were purchased in their original containers if possible. Preprinted labels with a unique sample number were attached to each sample on collection. Brand name, batch number, manufacturing date, expiry date, name of manufacturer, international nonproprietary names of the APIs, strength, dosage form, package size, and price were recorded as stated on the labels. All samples were transported from the collection sites to the medical stores of the local partner organizations as fast as possible. Shipment to Tuebingen University, Germany, was done by commercial courier services. At Tuebingen University, the samples were stored in an air-conditioned storage room at 21°C until analysis.

Chemical analysis. Of all samples consisting of more than 50 units (=tablets or capsules), 25 units were retained by the local partners for GPHF Minilab analysis in the respective country and the remaining units were shipped to Tuebingen University, Germany, for compendial analysis. For three samples, less than 50 units had been collected, and in these cases, all units were sent to Germany.

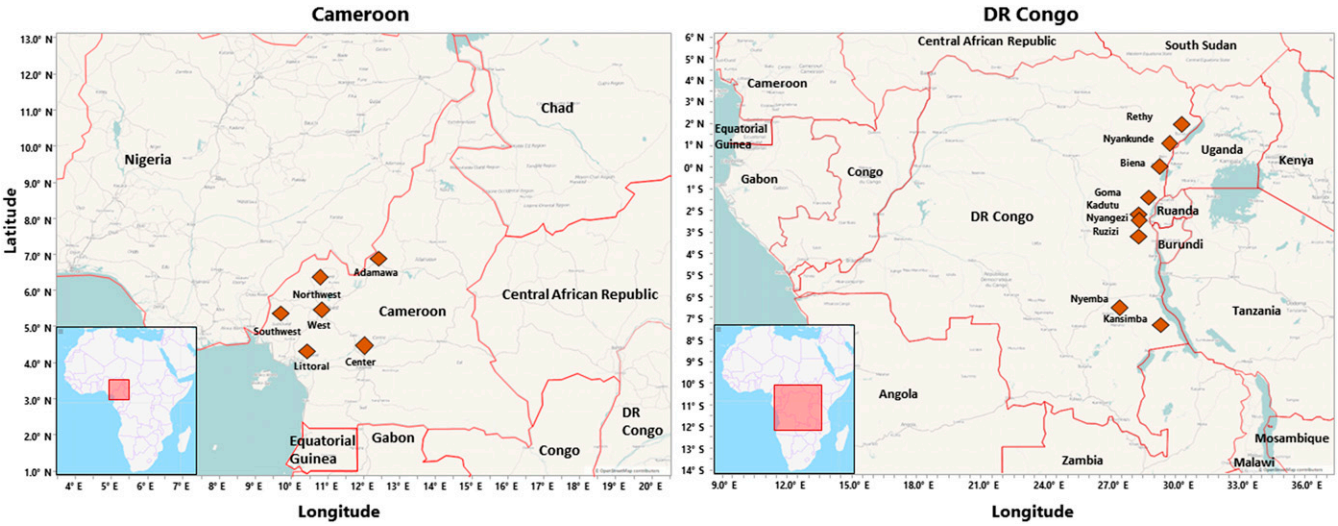


FIGURE 1. Map of the locations from which samples were collected in Cameroon and the Democratic Republic of Congo (DR Congo). This figure appears in color at www.ajtmh.org.

Global Pharma Health Fund Minilab analysis comprised visual inspection, TLC, and disintegration testing according to the Minilab manual[15] and was carried out by the local partners in Cameroon and the DR Congo. Results of TLC analysis were recorded by photographs of the developed TLC plates.

Compendial analysis was carried out at the Pharmaceutical Institute of Tuebingen University according to the monographs of the USP 2018 (USP 41) for the respective finished pharmaceutical products. It comprised identification of the declared API by HPLC in comparison with certified reference standards, and quantification of the API (=assay), dissolution testing, and testing for uniformity of dosage units. Certified pharmaceutical secondary reference standards were purchased from Sigma-Aldrich (St. Louis, MO). Using the columns and solvent systems specified by USP 41, HPLC-UV analysis was carried out using an Agilent 1100 HPLC or an Agilent 1260 Infinity II HPLC (Agilent Technologies, Santa Clara, CA). Dissolution tests were performed with a PTWS 610 Dissolution Testing Instrument (Pharma Test Apparatebau AG, Hainburg, Germany) and an Agilent 708-DS Dissolution Apparatus (Agilent Technologies). Uniformity of dosage units was determined using the test for weight variation which, according to USP 41, is applicable if one unit contains at least 25 mg of the API, and the API comprises 25% or more of the whole tablet or the capsule content weight. In this study, this was applicable for the samples containing amoxicillin, ciprofloxacin, doxycycline, penicillin V, metronidazole, sulfamethoxazole, atenolol, furosemide, and metformin, and thereby for 425 of the 506 investigated samples.

Samples that showed unknown substances in LC-UV analysis were further analyzed using LC-HR-MS/MS and, in case of sample QMC266, nuclear magnetic resonance (NMR) analysis was performed for identification of these unknown substances. LC-HR-MS/MS analysis was conducted in the Institute of Organic Chemistry, Tuebingen University, on a Thermo Scientific UltiMate 3000 HPLC System coupled with an ESI-TOF Bruker maXis 4G (Bruker Daltonics, Billerica, MA) in the positive mode and using high resolution. For NMR analysis of sample QMC266, the tablets were ground and the API was dissolved in methanol. The resulting solution was filtered and evaporated to dryness, and the residue was redissolved in d_4-MeOH. One-dimensional and 2D NMR spectra were recorded at the Pharmaceutical Institute, Tuebingen University, with a Bruker Avance III HD 400 MHz NMR spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany). NMR spectra were calibrated to the residual solvent signals (d_4-MeOH resonances at $\delta_H = 3.31$ and $\delta_C = 49.0$ ppm) or the internal offset for[15] N assigned by the instrument manufacturer.

Definitions of medicine quality. For the compendial tests, the limits for compliance described in the respective USP 41 monograph were used. As proposed in the QAMSA study by the WHO[13] and also applied in our previous study in southern Togo,[31] samples deviating from USP 41 specifications for assay and/or dissolution were further divided into those showing only moderate deviations from the pharmacopoeial limits and those showing extreme deviations. Extreme deviation was defined as an API content deviating by more than 20% from the declared amount and/or an average dissolution of the API of the tested units falling more than 25% below the pharmacopoeial limit (i.e., below the pharmacopoeial Q value minus 25%).[13] Table 1 shows the limits for compliance given by USP 41 for all investigated types of medicines and the limits for extreme deviations.

For the definition of falsified medicines, the current WHO definitions were used.[12] Results of GPHF Minilab TLC and disintegration testing were classified as pass/fail following the instructions of the GPHF Minilab manual.[15]

Statistical calculations. Statistical evaluations were performed using JMP 14.2 (SAS GmbH, Heidelberg, Germany). The prevalence of SF medicines and the corresponding CIs were determined by distribution analysis. Significance of differences in the prevalence of SF medicines between different groups was calculated using Fisher's exact test or Pearson's chi-squared test. Comparisons of Minilab testing results to compendial testing results were calculated with contingency analysis.

Information of national authorities and stakeholders. The Laboratoire National de Contrôle de Qualitè de Médicaments de d'Expertise (LANACOME), Cameroon, and the WHO Rapid Alert System were informed immediately about falsified medicines detected in this study. The complete survey results were shared with the national authorities, that is, the Directeur Général de la Santé, Ministère de la Santé Publique, DR Congo; the Direction de la Pharmacie et du Médicament de la Republique du Congo; the Direction de la Pharmacie du Médicament et des Laboratoires, Ministère de la Santé Publique, Cameroon; and the LANACOME, Cameroon; and with the WHO Rapid Alert System. In addition, the findings of this study were presented to representatives of the African national medicine quality control laboratories at the third African Medicines Quality Forum in Abuja, Nigeria, in February 2020.

RESULTS

Overview of collected medicine samples. A total of 502 medicine samples were purchased from 26 sampling sites in Cameroon and 34 sampling sites in the DR Congo. Visual inspection showed that four samples included packages with two different batch numbers instead of representing a uniform sample. These different batches were subsequently treated as separate samples and analyzed for their quality individually. Therefore, the total sample size was 506.

The total number of samples collected per type of medicine is depicted in Figure 2A. Obviously, not all medicines were available at all of the 60 sampling sites; therefore, the theoretical number of 60 samples was not reached for any of the included medicines, although ciprofloxacin and metronidazole tablets came close with 57 samples each. A detailed analysis of the availability as well as of prices and affordability of the included medicines has been published in a separate article.[22]

As shown in Figure 2B, originator medicines represented only 6% of the collected samples. The vast majority were generic medicines, either sold under their international nonproprietary name ("unbranded generic products") or under a brand name decided by the marketing authorization holder ("branded generic products").

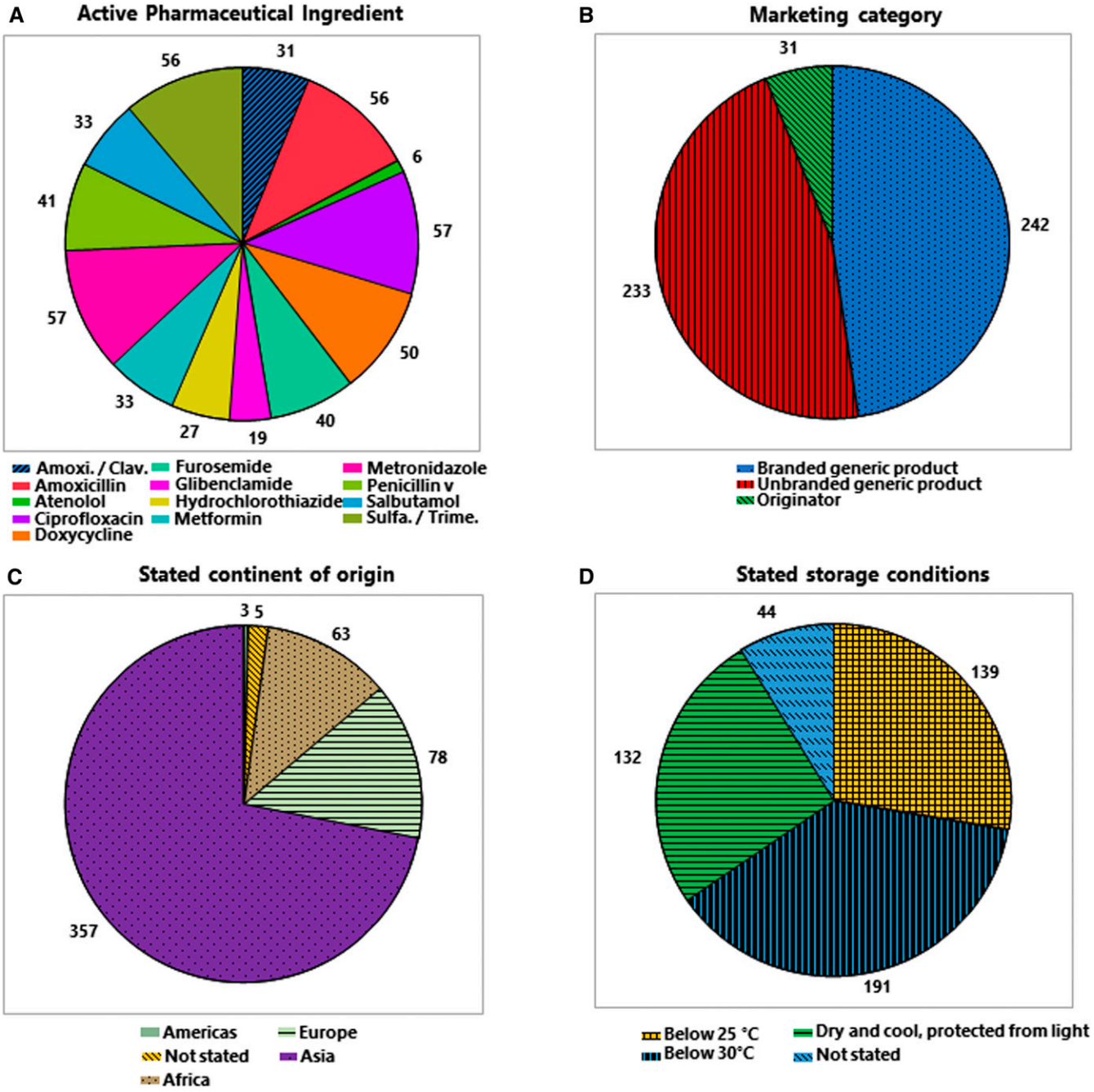


FIGURE 2. Distribution of all collected samples (n = 506) over different categories. In the pie chart in (**A**), the different active pharmaceutical ingredients (APIs) are arranged in clockwise orientation. This figure appears in color at www.ajtmh.org.

Figure 2C shows the dominance of Asian countries as medicine suppliers to Cameroon and the DR Congo. According to the information stated on the packaging, 357 (71%) of the samples collected were manufactured in Asia, of these 231 in India, 121 in China, and five in other Asian countries. Seventy-eight samples (15%) were stated to be manufactured in Europe and 63 samples (12%) in Africa. With only three samples, the Americas played no significant role in the supply of the investigated medicines.

According to the information stated on the packaging, the collected samples represented 260 different brands (414 different batches), produced by 119 different manufacturers in 26 different countries. A complete list of these manufacturers and countries is given in Supplemental Table S1. The most frequently encountered manufacturer was Medopharm, Chennai, India, representing 42 samples. However, most manufacturers were only represented with very small number of samples (mean = four samples and median = three samples).

According to current stability testing guidelines for pharmaceuticals,[32–34] the DR Congo is regarded as climatic zone IVa (hot and humid) and Cameroon as climatic zone IVb (hot and very humid). Medicines intended to be marketed in these two countries should be tested for long-term stability at 30°C/65% relative humidity (DR Congo) or at 30°C/75%

relative humidity (Cameroon), respectively. Medicines for which stability has been demonstrated under either of these two conditions should carry the WHO-recommended labeling statement "Do not store above 30°C."[32–35] As shown in Figure 2D, however, only 38% of the collected samples indeed showed this statement. Twenty-eight percent of the samples were labeled "Do not store above 25°C," indicating that they may not have been tested for stability under the appropriate conditions for medicines to be marketed in the DR Congo or in Cameroon. Twenty-six percent of the samples carried less precise, with not WHO-recommended labeling statements such as "Store in a cool and dry place, protected from light," and 9% had no storage recommendation at all printed on the packaging or leaflet. However, there was a marked difference between the medicines from the two countries (Figure 3). In the DR Congo, 53% of the medicine samples showed the correct labeling statement "Do not store above 30°C," and only 1% carried no storage recommendation at all. By contrast, in Cameroon, only 21% of the medicine samples showed the correct labeling statement "Do not store above 30°C," and 17% carried no storage recommendation at all.

Figure 3 furthermore shows the distribution of the samples collected across different marketing categories, stated continents of origin, and types of sampling sites, separately for Cameroon and the DR Congo.

In total, 10 of the 506 samples (2%) were already expired at the time of collection. Although these 10 samples were already expired, they were sold at the point of care to be used in patient treatment. Therefore, also these samples were analyzed for their quality, and the results were included into the overall data analysis. Of these 10 expired samples, two (both representing the same product and batch) were found to deviate from USP specifications in the analysis described in the following paragraphs. They are marked in Supplemental Tables S1 and S3.

Visual inspection showed only a single sample which appeared to be falsified based on its incorrect labeling (penicillin V tablets, described in the next paragraph).

Falsified medicines. Among the 506 medicine samples, three (0.6%) were found not to contain their declared API, and two of these even contained a different, non-declared API. These three samples are shown in Figure 4. Notably, all three of them were sold by informal vendors.

One sample (sample no. QMCA241, Figure 4A), collected in Cameroon, was labeled as "Augmentin® SmithKline Beecham (amoxicillin 500 mg/clavulanic acid 125 mg tablets)" and carried a registration number used for Augmentin by the Nigerian National Agency for Food and Drug Administration and Control. Packaging and tablets appeared to be of excellent quality and gave no immediate indication of falsification. However, both Minilab TLC analysis and HPLC analysis according to USP readily showed complete absence of both stated APIs. The WHO Rapid Alert System was informed and thereupon published a Medical Product Alert about this falsification.[36] On request by the WHO, the authors of the present article forwarded this sample to the stated manufacturer, who confirmed that this was a falsified medicine not produced by their company.

Another sample (sample no. QMCA035, Figure 4B), also collected in Cameroon, was labeled as "Penicillin-V Tablets, Oxford Pharma Co. Ltd., Belgium." On the label, the active ingredient was incorrectly spelled as "phenoxymetgyl" rather than phenoxymethyl penicillin (Figure 4). The stated manufacturer "Oxford Pharma, Belgium" does not exist.

		Cameroon							DR Congo						
			non-compliant total			both tests	only assay	only dissolution		non-compliant total			both tests	only assay	only dissolution
		N total	N	[%]	95% CI	N	N	N	N total	N	[%]	95% CI	N	N	N
brand	Unbranded generic products	118	22	19%	[12.6-26.6]	12	6	4	115	12	10%	[6.1-17.4]	1	6	5
	Branded generic products	108	19	18%	[11.6-25.8]	2	5	12	134	28	21%	[14.9-28.5]	4	6	18
	Originator	18	1	6%	[1.0-25.8]	1	0	0	13	0	0%		0	0	0
continent of origin	Africa	23	6	26%	[12.5-46.5]	1	0	5	40	8	20%	[11.1-36.3]	4	2	2
	Americas	3	0	0%		0	0	0							
	Asia	156	31	20%	[14.8-27.5]	12	8	11	201	32	16%	[11.4-21.4]	1	10	21
	Europe	57	4	7%	[2.8-16.7]	2	2	0	21	0	0%		0	0	0
	Not stated	5	1	20%	[2.0-43.5]	0	1	0							
site type	Government health facilities	36	9	25%	[13.8-41.1]	2	2	5	42	3	7%	[24.6-19.0]	1	1	1
	Church health facilities	71	10	14%	[7.8-24.0]	3	4	3	72	4	6%	[2.2-13.4]	1	1	2
	Pharmacies	70	4	6%	[2.2-13.8]	1	2	1	91	17	19%	[12.0-27.9]	1	7	9
	Informal Vendors	67	19	28%	[19.0-40.1]	9	3	7	57	16	28%	[18.1-40.8]	2	3	11
indication	Antibiotics	152	24	16%	[10.9-22.4]	8	6	10	196	18	9%	[5.9-14.0]	2	7	9
	Medicines against non-communicable diseases	92	18	20%	[12.8-28.8]	7	5	6	66	22	33%	[23.2-45.3]	3	5	14
store at	Below 25 °C	89	8	9%	[4.6-16.7]	4	3	1	50	11	22%	[12.8-35.2]	2	1	8
	Below 30 °C	51	5	10%	[4.3-21.0]	1	0	4	140	10	7%	[3.9-12.6]	2	2	6
	Dry and cool, protected from light	62	18	29%	[19.2-41.3]	7	6	5	70	19	27%	[18.1-38.5]	1	9	9
	Not stated	42	11	26%	[15.3-41.1]	3	2	6	2	0	0%		0	0	0
active pharmaceutical ingredient	Amoxicillin and Clavulanic acid	19	5	26%	[11.8-48.8]	1	3	1	12	2	17%	[4.7-44.8]	0	0	2
	Amoxicillin	24	2	8%	[2.3-25.8]	0	0	2	32	2	6%	[1.7-20.1]	0	0	2
	Ciprofloxacin	25	2	8%	[2.2-25.0]	0	2	0	32	4	13%	[5.0-28.1]	0	3	1
	Doxycycline	22	1	5%	[0.8-21.8]	0	0	1	28	1	4%	[0.6-17.7]	0	0	1
	Metronidazole	25	3	12%	[4.2-30.0]	0	0	3	32	5	16%	[6.9-31.8]	1	2	2
	Penicillin V	14	7	50%	[26.8-73.2]	6	1	0	27	3	11%	[3.9-28.1]	1	2	0
	Sulfamethoxazole and Trimethoprim	23	4	17%	[7.0-37.1]	1	0	3	33	1	3%	[0.5-15.3]	0	0	1
	Atenolol								6	1	17%	[3.0-56.4]	0	0	1
	Furosemide	17	1	6%	[1.0-27.0]	0	0	1	23	15	65%	[44.9-81.2]	1	1	13
	Glibenclamide	19	6	32%	[15.4-54.0]	0	2	4							
	Hydrochlorothiazide	21	0	0%		0	0	0	6	0	0%		0	0	0
	Metformin	20	1	5%	[0.9-23.6]	0	0	1	13	1	8%	[1.3-33.3]	1	0	0
	Salbutamol	15	10	67%	[41.7-84.8]	7	3	0	18	5	28%	[12.5-50.9]	1	4	0
	Overall	**244**	**42**	**17%**	**[13.0-22.4]**	**15**	**11**	**16**	**262**	**40**	**15%**	**[11.4-20.1]**	**5**	**12**	**23**

FIGURE 3. Frequency of noncompliance with pharmacopoeial specifications for assay and dissolution in different subgroups of medicines. This figure appears in color at www.ajtmh.org.

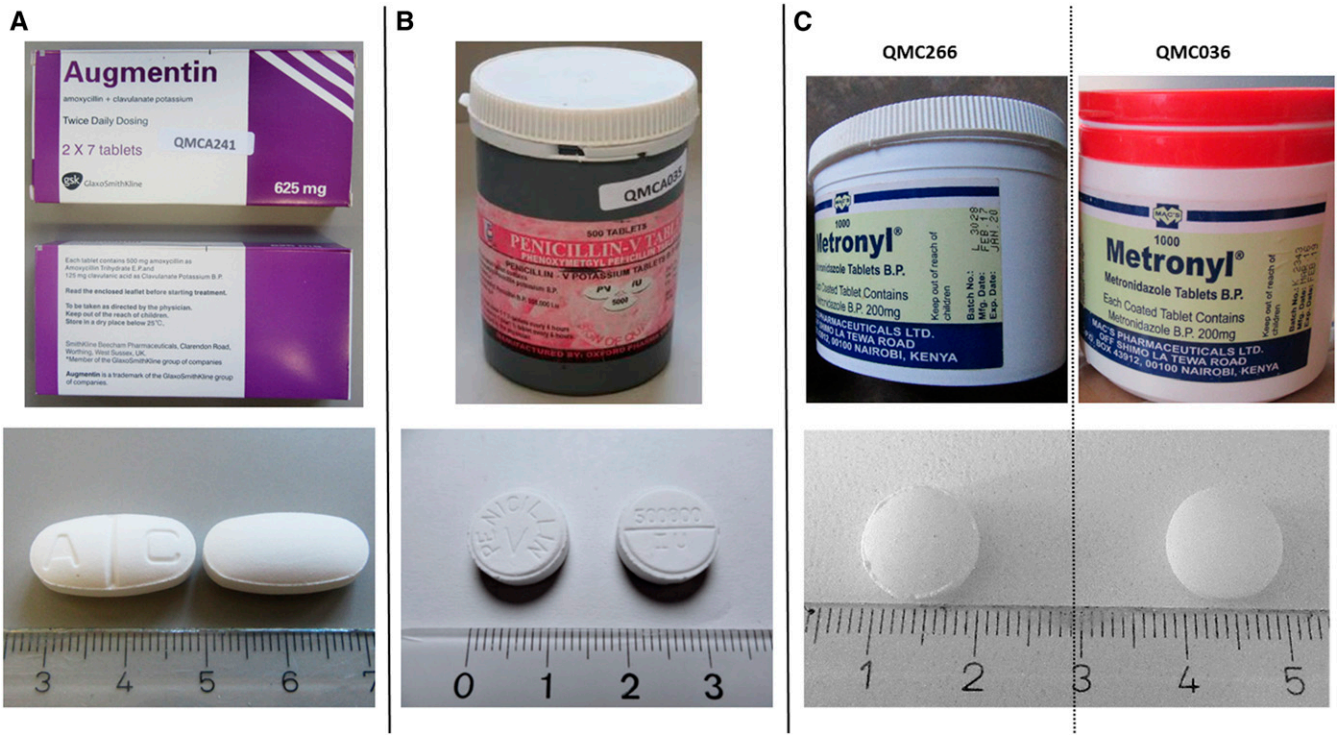


FIGURE 4. Pictures of the three samples identified as falsified medicines. (**A**) Falsified Augmentin (sample no. QMCA241), containing no detectable active pharmaceutical ingredient (API). (**B**) Falsified penicillin V tablets (sample no. QMCA035), containing 50 mg paracetamol. Note that the API is misspelled on the label. (**C**) Left: falsified Metronyl (sample no. QMC266); manufactured date: February 2017, batch no: L3028, containing 93 mg metronidazole benzoate. Right: Metronyl (sample no. QMC036); manufactured date: March 2016, batch no: K2343, complying with U.S. Pharmacopeia 41 specifications for metronidazole tablets. This figure appears in color at www.ajtmh.org.

Although the tablets appeared to have been professionally pressed and embossed, the labels and packaging were of poor quality. Both Minilab TLC analysis and HPLC analysis readily showed complete absence of the stated API but indicated the presence of another, unknown compound, and LC-HR-MS/MS analysis proved that the unknown compound was paracetamol (Supplemental Figure S1). The paracetamol content was found to be only 50 mg per tablet, clearly lower than the content of paracetamol tablets listed in the current WHO Essential Medicines List (100–500 mg).[37] Again, the WHO Rapid Alert System was informed and published a Medical Product Alert about this falsification.[38]

A third sample (sample no. QMC266; Figure 4C) was labeled as "Metronyl® Metronidazole Tablets B.P., Mac's Pharmaceuticals Ltd., Nairobi, Kenya." It was sold in an already opened plastic container by an informal vendor in the DR Congo. Visual inspection gave no obvious indication of falsification. However, both Minilab TLC analysis and HPLC analysis readily showed complete absence of the stated API and the presence of another, unknown compound, and LC-HR-MS/MS (Supplemental Figure S2) suggested that this compound might represent metronidazole benzoate. Subsequently, 1D and 2D NMR spectra were recorded, and a de novo structure elucidation was carried out (Supplemental Figures S3–S11). This confirmed unambiguously that the unknown compound indeed was the benzoic acid ester of metronidazole. ^{1}H and ^{13}C NMR spectra of the unknown compound and of a metronidazole benzoate standard were perfectly superimposable (Supplemental Figures S9 and S10). Metronidazole has a bitter taste, and the benzoic acid ester of metronidazole is sometimes used as a prodrug with more acceptable taste, both in pediatric formulations and in veterinary medicine.[39] The metronidazole benzoate content of sample QMC266 was determined as 93 mg per tablet, in clear contrast to the labeling claim of 200 mg free metronidazole. Another batch of the same Metronyl brand had been collected in a government health facility of the DR Congo. That sample (QMC036; Figure 4C) showed an exactly identical label as QMC266, except for the different batch number and expiry date, and was found to be fully compliant with USP specifications in identity, assay, dissolution, and uniformity of dosage units. As shown in Figure 4C, the tablets of falsified sample QMC266 had the same diameter and shape (and also the same weight) as the good-quality sample of Metronyl tablets but showed ridges at the edges, indicating poor manufacturing. Possibly, the plastic container in which sample QMC266 was sold may have originally contained authentic, good-quality Metronyl tablets and may have later been filled with the falsified medicine by the informal vendor. However, this cannot be ascertained from the available information. Attempts of the local partners to find further Metronyl packages remained unsuccessful. Both the stated manufacturer and the WHO Rapid Alert System were informed about this falsified medicine. So far, no answer was received from the stated manufacturer.

All remaining 503 samples were found to contain the declared APIs. Several samples of salbutamol and glibenclamide tablets were found to contain an additional substance which was identified by LC-HR-MS/MS as the preservative methyl 4-hydroxybenzoate (methylparaben). This preservative is

considered safe and acceptable, although in most countries, the presence of such a preservative must be stated in the package leaflet.

Analysis of the quantity of the APIs. All collected samples were analyzed for the amount of the API ("assay"). Figure 5 shows the API content determined in each of the 506 samples. Different limits for compliance are specified by USP for different APIs (Table 1), for example, 95–105% of the declared content for metformin tablets or 90–120% of the declared content for penicillin V tablets (Figure 5). Four hundred sixty-three samples (91.5%) complied with the USP specifications for assay and are depicted in Figure 5 as green symbols. Twenty-eight samples (5.5%) showed moderate deviations from the pharmacopoeial limits (i.e., deviations not exceeding 20% of the stated content) and are depicted as yellow symbols. Fifteen samples (3.0%) showed extreme deviations (i.e., deviations of more than 20% of the stated content) and are depicted as red symbols; these include the three falsified medicines described earlier (marked with black circles in Figure 5).

The highest proportions of substandard samples in the assay were observed for salbutamol tablets (24% moderate and 21% extreme deviations) and for penicillin V tablets (10% moderate and 15% extreme deviations). None of the samples with other APIs showed extreme deviations in the assay (except the two falsified products of Metronyl and Augmentin described earlier).

In total, 43 samples (8.5%) were noncompliant in the assay. Figure 3 shows the numbers of noncompliant samples separately for Cameroon and the DR Congo. Supplemental Figure S12 shows the API content determined in each of the 506 samples, analyzed by similar subgroups as used in Figure 3.

Analysis of the dissolution of the APIs. All collected samples were analyzed for the dissolution of the API according to USP 41. Figure 6 shows the dissolution results determined for each of the 506 samples. Again, USP specifies different limits for compliance ("Q values") for different APIs. For example, USP demands for metronidazole tablets that not less than 85% of the declared API content must dissolve under the specified conditions and for hydrochlorothiazide tablets not less than 60%. In total, 447 samples (88.3%) complied with the USP specifications for dissolution and are depicted in Figure 6 as green symbols. Forty-four samples (8.7%) showed moderate deviations from the pharmacopoeial limits (i.e., an amount of dissolved API lower than, but not more than 25% lower than the pharmacopoeial limit) and are depicted as yellow symbols. Fifteen samples (3.0%) showed extreme deviations (i.e., an amount of dissolved API more than 25% lower than the pharmacopoeial limit) and are depicted as red symbols; these included the three falsified medicines described earlier. In total, 59 samples (11.7%) resulted as noncompliant in dissolution by USP 41 criteria. However, it has to be considered that 12 of these samples (including the three falsified medicines)

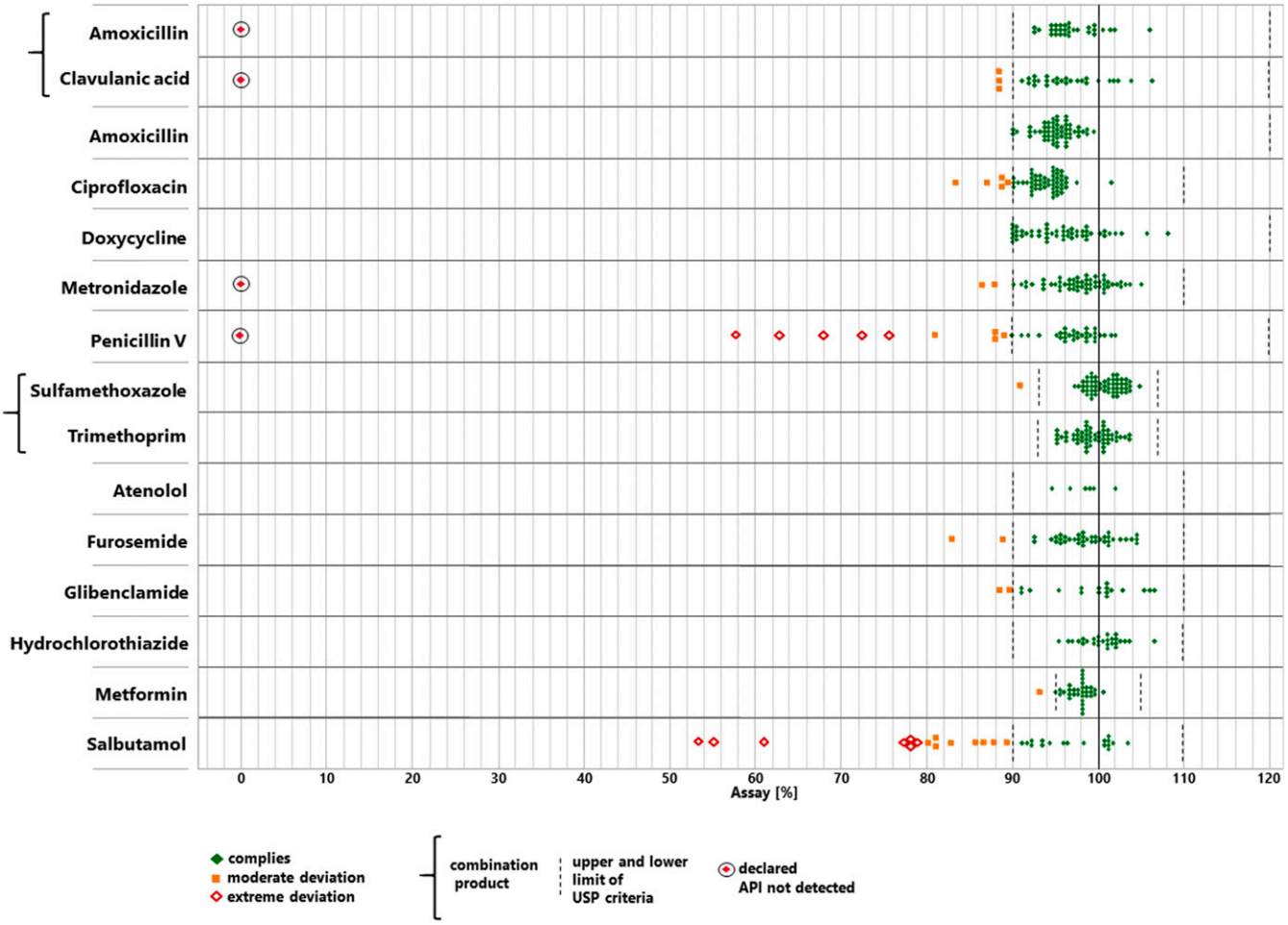


FIGURE 5. Content of the active pharmaceutical ingredient (API) determined for each sample. This figure appears in color at www.ajtmh.org.

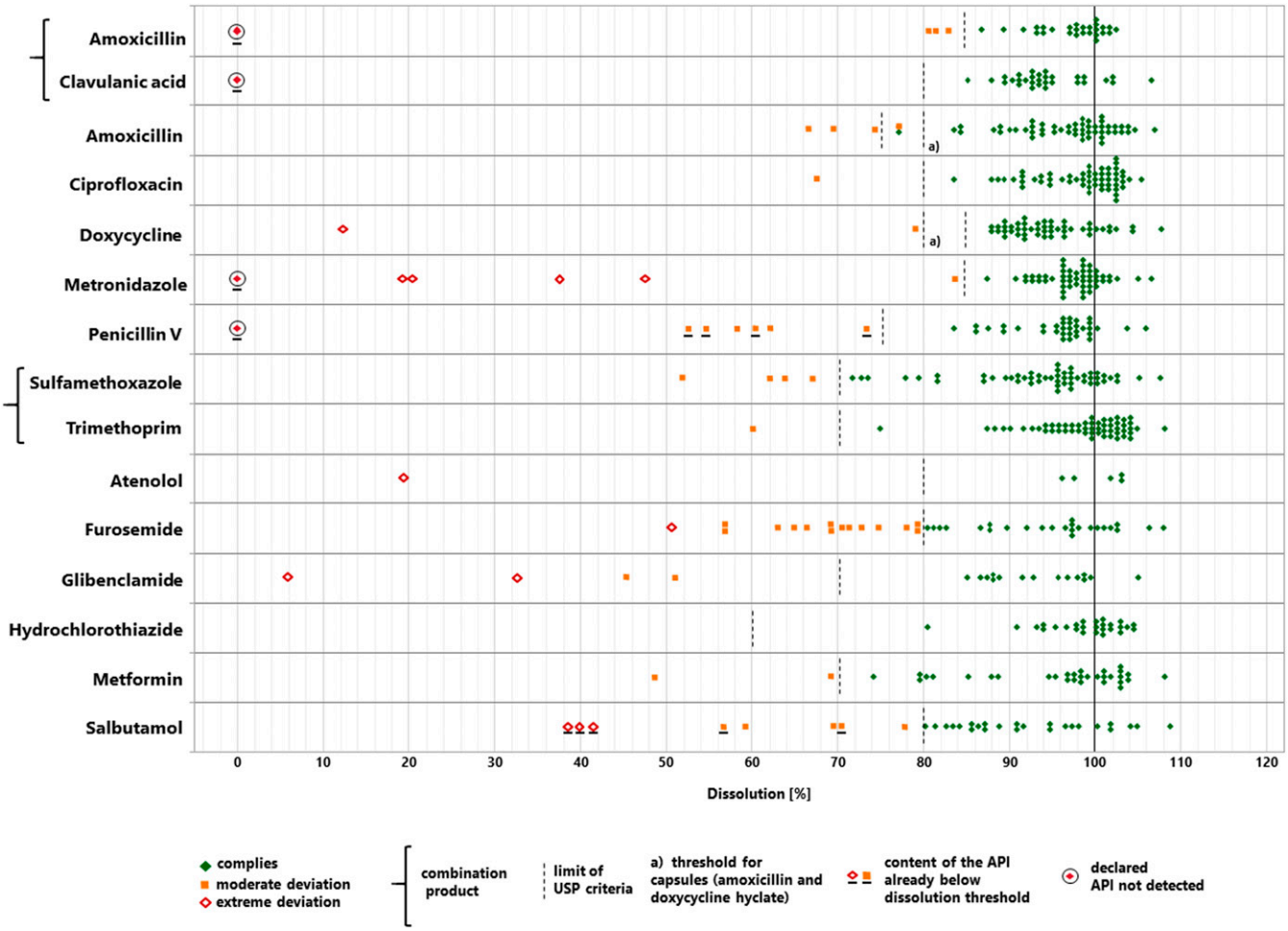


FIGURE 6. Dissolution of the active pharmaceutical ingredient (API) determined for each sample. This figure appears in color at www.ajtmh.org.

had already been shown in assay testing to contain an API amount which was lower than the pharmacopoeial limit for dissolution. These samples are marked in Figure 6.

Dissolution failures were observed most frequently for furosemide tablets (n = 15), salbutamol tablets (n = 8), and glibenclamide tablets (n = 4). However, extreme deviations in dissolution were also found for doxycycline, metronidazole, atenolol, and metformin, and of course for the three falsified products described earlier. Figure 6, therefore, illustrates that noncompliance with dissolution specifications is a frequent and serious problem in many of the investigated types of medicines, even more so than noncompliance with assay specifications shown in Figure 5.

Figure 3 shows the numbers of noncompliant samples in different categories of medicines, separately for Cameroon and the DR Congo. Supplemental Figure S13 shows the dissolution results determined for each of the 506 samples, analyzed by similar subgroups as used in Figure 3.

Uniformity of dosage units. As explained in the Methods section, uniformity of dosage units was investigated using the test for weight variation which, according to USP 41, was applicable for 425 of the 506 samples. Of the 425 tested samples, 26 (6.1%) failed the test for uniformity (including the three falsified samples). Sixteen (3.8%) of these simultaneously failed in assay and/or dissolution, whereas 10 (2.4%) failed in uniformity testing alone.

Combined results of compendial analyses. From the analyzed samples, 8.5% failed in assay testing, 11.7% in dissolution testing, and 6.1% in testing for uniformity of dosage units. Obviously, a number of samples failed in more than one of the mentioned criteria. Therefore, the observed out-of-specification rate calculated from assay testing alone (i.e., 8.5%) increased to 16.2% (i.e., nearly doubled) when also dissolution was considered and to 18.6% when the uniformity of the dosage unit was considered as well.

As correctly stated in an authoritative review by the WHO,[7] if the goal is to assess the health effects of a medicine, API content and dissolution (which affects bioavailability) are the most important quality criteria. Therefore, hereafter, we focus on assay and dissolution results.

The only API for which no sample was found to be out of specification was hydrochlorothiazide (Figure 3). Notably, of the 27 samples investigated for this API, 14 represented the originator medicine and were sold for very high prices.[22]

Especially high failure rates were observed for penicillin V, furosemide, and salbutamol (Figure 3). For penicillin V tablets, the failure rate was 50% in Cameroon. This was especially due to the four penicillin V samples stated to be produced by a certain manufacturer in China (Shandong Shenglu Pharmaceutical Co. Ltd., Sishui, China, see Supplemental Tables S1 and S3). All four of these samples showed extreme deviations in the assay. No samples from this manufacturer were found in the DR Congo.

Furosemide tablets showed a failure rate of 65% in the DR Congo. This was mainly caused by samples stated to be manufactured by Arco Pharma Pvt. Ltd., Vasai, India, and Prashi Pharma Pvt. Ltd., Mumbai, India (see Supplemental Tables S1 and S3). Eleven of the 12 furosemide samples stated to be manufactured by these two companies from India failed dissolution testing. No samples of these two manufacturers were found in Cameroon.

Salbutamol tablets showed a 66% failure rate in Cameroon largely because of the five salbutamol samples stated to be produced by a certain company in India (Medico Remedies Pvt. Ltd., Maharashtra, India, see Supplemental Tables S1 and S3), four of them even failing with extreme deviations. No medicines of this manufacturer were found in the DR Congo.

A complete list of the manufacturers stated on the labels of the investigated medicines and a summary of the analytical results obtained for the individual (stated) manufacturers are given in Supplemental Table S1. Furthermore, a complete list of all batches and brands investigated, with their stated manufacturers and the analytical results, is given in Supplemental Table S3.

Analysis using the GPHF Minilab. Of the 506 collected samples, 451 were analyzed by the local researchers in Cameroon and the DR Congo using the thin-layer chromatographic test and the disintegration test of the GPHF Minilab.[15] No Minilab analysis was performed for the 49 samples from the Ituri Province in the northeast of the DR Congo because the local researcher left for another position during the time of this study, and no trained replacement could be found in time. For three samples, the small number of tablets collected allowed only for compendial analysis but not for an additional Minilab analysis. For three further samples, the required reagents for Minilab analysis had become unavailable at the local laboratory.

Notably, all three falsified medicines shown in Figure 4 were correctly reported as failing Minilab TLC analysis. These three samples were immediately reported by the local researchers and sent to Tuebingen University for confirmatory analysis, allowing a timely publication of the WHO Medical Product Alerts mentioned earlier.[36,38]

Twelve further samples were reported to fail TLC analysis. Three of these were reported to show insufficient intensity of the TLC spots, indicating an insufficient amount of the API. Two were reported to show additional spots in TLC, and for seven samples, it was not stated in which aspects the TLC test had failed.

Fifteen samples were reported to fail disintegration testing, that is, they did not disintegrate within 30 minutes in water of 37°C, following the procedure described in the GPHF Minilab manual.[15]

In total, 30 of 451 samples (6.7%) were reported to fail Minilab analysis, 15 in the TLC test and 15 in disintegration testing. No sample was reported to fail in both tests. Supplemental Figure S14 summarizes the results of the Minilab tests in the same way as Figure 3 summarizes the results of the compendial analysis.

Comparison of the results of GPHF Minilab and compendial analysis. Tables 2–4 compare the results of GPHF Minilab testing with those of compendial analysis according to USP 41. Minilab testing correctly identified all three samples which did not contain the stated API, resulting in 100% sensitivity and specificity for the Minilab in the identification of such falsified medicines in this study.

According to the GPHF Minilab manual,[15] semiquantitative evaluation of TLC analysis is carried out by visual comparison of the spots of the sample with two spots of an authentic reference, representing 100% and 80% of the declared amount of the API, respectively. If the sample spot is considered weaker than the 80% reference spot, the sample is classified as failing and should be forwarded to confirmatory compendial analysis. Minilab testing is, therefore, not designed to detect moderate deviations from the declared API amount, that is, deviations by less than 20%. Indeed, as shown in Table 3, of 26 samples showing moderate deviations in compendial assay testing, only two had been reported to fail Minilab TLC testing. By contrast, of the 14 samples which showed extreme deviations in USP assay testing, six had been reported to fail Minilab TLC testing, resulting in 43% sensitivity of the Minilab in the detection of such medicines. Supplemental Table S2 lists all 15 samples reported to fail Minilab TLC analysis and the eight samples with extreme deviations which still were reported to pass Minilab TLC analysis, with their respective analytical results.

Testing for disintegration is a routine part of compendial medicine quality testing for solid oral dosage forms (e.g., tablets and capsules) and is performed using precisely defined equipment and conditions. The Minilab protocol includes a simplified testing method for disintegration which can be conducted without sophisticated equipment. Notably, disintegration testing measures a different endpoint than dissolution testing according to the USP. Therefore, a comparison of the results of Minilab disintegration testing with those of compendial dissolution testing is not possible in a strict sense. Nevertheless, it may still be of interest how well Minilab disintegration testing can predict the results of compendial dissolution testing. As was to be expected, the sensitivity of the Minilab in this comparison was low, that is, 9% (Table 4). The sensitivity increased to 36% if only extreme dissolution failures were considered.

In Tables 2–4, the values for specificity show the proportion of USP-compliant samples which were correctly predicted by the Minilab test as being compliant. Specificity resulted as 98% for assay and 97% for dissolution because the numbers of good-quality samples which were reported to fail Minilab

TABLE 2

Sensitivity and specificity of Global Pharma Health Fund Minilab testing for the prediction of the outcome of the compendial analysis according to U.S. Pharmacopeia 41: identity

		Compendial result			
		Fail	Complies	Total	
Minilab result	Fail	3	0	3	Sensitivity = $\frac{3}{3+0}$ = 100%
	Pass	0	448	448	Specificity = $\frac{448}{448+0}$ = 100%
	Total	3	448	451	

TABLE 3

Sensitivity and specificity of Global Pharma Health Fund Minilab testing for the prediction of the outcome of the compendial analysis according to U.S. Pharmacopeia 41: assay (= content of active pharmaceutical ingredient)

		Compendial result					
		Extreme deviation	Moderate deviation	Complies	Total	Detection of any deviation (moderate or extreme)	Detection of extreme deviation
Minilab result	Fail	6*	2	7	15*	Sensitivity = $\frac{6+2}{(6+2)+(8+24)} = 20\%$	Sensitivity = $\frac{6}{6+8} = 43\%$
	Pass	8	24	404	436	Specificity = $\frac{404}{404+7} = 98\%$	
	Total	14*	26	411	451*		

See text for definitions of moderate and extreme deviations.
* Includes the three falsified samples mentioned in Table 2.

analysis were low (seven samples in TLC testing and 10 samples in disintegration testing).

DISCUSSION

Prevalence of falsified and substandard medicines. Of a total of 506 medicine samples collected in government and church health facilities, pharmacies, and informal vendors in Cameroon and the DR Congo, three samples (0.6%) were falsified, as evidenced by the absence of the stated API and, in two of these cases, by the presence of undeclared APIs (Figure 4). All other samples did contain the stated APIs, and visual inspection gave no indication of falsification. Obviously, a complete absence of falsified medicines must be aimed for. Nevertheless, the percentage of falsified medicines observed in this study is clearly lower than often portrayed in alarmist media reports about medicine quality in Africa. Our finding is in good accordance with the results of three large medicine quality studies in Africa, conducted by the WHO (QAMSA study),[13] U.S. Pharmacopeial Convention,[40] and ACT Consortium Drug Quality Program,[41] which reported 0.2%, 0.3%, and 1.0% prevalence of falsified medicines, respectively. Two smaller studies conducted in Malawi and Togo by authors of the present article found 0.6%[42] and 0.0%[31] falsified medicines, respectively.

As noted in earlier studies, substandard medicines are much more frequently encountered than falsified medicines. In the present study, the percentage of medicines failing USP specifications for the assay (=content of API), for the dissolution of the API, and for the uniformity of the dosage units was 8.5%, 11.7%, and 6.1%, respectively. This is similar to the result of the WHO QAMSA study,[13] which investigated antimalarial medicines in six African countries and reported failure rates in assay, dissolution, and uniformity of 10.9%, 15.0%, and 6.4%, respectively.

Overall, 18.6% of the medicine samples investigated in the present study did not comply with USP 41 specifications in one or several of the aforementioned three criteria, whereas 16.2% failed in the assay and/or the dissolution. This failure rate is in good agreement with the 18.7% estimate for the prevalence of SF medicines reported by Ozawa et al.[11] from a meta-analysis of more than 40 medicine quality studies conducted in Africa. It is furthermore in reasonable agreement with the results of an authoritative review by the WHO[7] which analyzed the results of 100 medicine quality studies, purposefully selected for their scientific quality. For studies which had used HPLC analysis (as also the present study did), that review reported an aggregated failure rate of 15.6% for medicine samples from LMICs. That review clearly stated that the included studies did not systematically test for dissolution, and our study showed that the failure rate almost doubles when dissolution is considered in addition to assay. Therefore, the reported rate of 15.6%[7] estimated by the WHO must be expected to increase when dissolution is systematically included into the testing procedures.

As clearly visible from Figure 5, many samples which failed assay testing missed the pharmacopoeial limits only by a narrow margin. Although complete compliance of all medicines with the relevant specifications must be demanded, the public health risk posed by small deviations in the assay and/or the dissolution is probably low. Following the classification suggested by the WHO QAMSA study,[13] we, therefore, differentiated between "moderate" and "extreme" deviations in assay and dissolution testing (see the Methods section for definitions). As depicted in Figures 5 and 6, and Supplemental Figures S12 and S13, overall 4.7% of the samples showed extreme deviations from the pharmacopoeial specifications (1.8% only in assay testing, 1.8% only in dissolution testing, and 1.2% simultaneously in assay and dissolution testing).

Figure 5 shows that except for the three falsified medicines, no sample was found to contain less than 50% of the declared content in assay testing. However, 13 of the 506 samples (2.6%) showed less than 50% dissolution of the API (in addition to the three falsified medicines). Also this observation emphasizes the importance of dissolution testing in medicine quality analysis.

Subgroup analysis of the prevalence of SF medicines. As explained in the Results section, we subsequently focus on

TABLE 4

Sensitivity and specificity of Global Pharma Health Fund Minilab testing for the prediction of the outcome of the compendial analysis according to U.S. Pharmacopeia 41: Minilab disintegration testing versus compendial dissolution testing

		Compendial dissolution result					
		Extreme deviation	Moderate deviation	Complies	Total	Detection of any deviation (moderate or extreme)	Detection of extreme deviation
Minilab disintegration result	Fail	5	0	10	15	Sensitivity = $\frac{5+0}{(5+0)+(9+40)} = 9\%$	Sensitivity = $\frac{5}{5+9} = 36\%$
	Pass	9*	40	387	436*	Specificity = $\frac{387}{387+10} = 97\%$	
	Total	14*	40	397	451*		

See text for definitions of moderate and extreme deviations.
* Includes the three falsified samples mentioned in Table 2.

the assay and dissolution results, that is, the most important criteria for the health effects of a medicine.[7] Overall, the proportion of medicines which were out-of-specification in assay and/or dissolution was similar in Cameroon (17.2%) and the DR Congo (15.3%; $P = 0.629$) (Figure 3). However, as shown in Supplemental Figures S12 and S13, the number of samples with extreme deviations was clearly higher in Cameroon (7.8%) than in the DR Congo (1.9%; $P = 0.0026$). It is remarkable that in the northeast of the DR Congo, despite extreme poverty, political unrest, and disruptions by the Ebola epidemic, medicine quality is not worse but rather better than in the more affluent Cameroon.

As expected, medicine quality problems were most pronounced in informal vendors, with an out-of-specification rate of 28.2%. This rate was nearly identical in both countries and was significantly higher than in the three other types of outlets combined (12.3%; $P < 0.0001$). Notably, all three falsified medicines encountered in this study were sold by informal vendors, and also the rate of medicines with extreme deviations was significantly higher in informal vendors (11.3%) than in the three other categories of outlets (2.6%; $P = 0.0003$). Therefore, a well-enforced ban of medicine sales by informal vendors, as already implemented successfully in several East African countries, may represent a key intervention to reduce the problem of SF medicines.

In the DR Congo, the rate of out-of-specification medicines was similar in church health facilities (5.6%) and in government facilities (7.1%), and both values were significantly lower than that in informal vendors (28.1%; $P = 0.0005$ and $P = 0.0099$, respectively). None of the medicines in government or church health facilities showed extreme deviations. By contrast, private pharmacies showed an 18.7% failure rate, including 3.3% of medicines with extreme deviations. This indicates a lack of regulatory control of private pharmacies and their supply chains in the DR Congo.

In significant contrast to the high failure rate in medicines from private pharmacies in the DR Congo, Cameroon private pharmacies showed only a 5.7% failure rate ($P = 0.018$). Notably, of the 70 samples investigated from pharmacies in Cameroon, 47 were stated to be manufactured in Europe. As shown in our analysis of availability and prices,[22] medicine prices in pharmacies in Cameroon were considerably higher than in other types of health facilities/outlets, and also much higher than in pharmacies in the DR Congo.

Medicines from church health facilities in Cameroon showed a 14.1% out-of-specification rate. Government health facilities in Cameroon showed an out-of-specification rate of 25.0%, similar to that found in medicines from informal vendors (28.4%). This indicates a need for improvements in medicine procurement and supply chain practices, especially of the government health services.

All authentic originator medicines investigated in this study were found to be within specifications. Of the 31 samples stated to be originator medicines, only the falsified Augmentin depicted in Figure 4 failed specifications. The failure rate of samples stated to be originator medicines was, therefore, 3%, significantly lower than the rate for (unbranded or branded) generic products (17.1%; $p = 0.0431$). Of the 506 samples investigated in this study, 78 were stated to be produced in Europe, including 30 originator medicines and 48 generic products. Of these, the falsified Augmentin and the falsified penicillin V depicted in Figure 4 failed specifications, and two branded generic products of amoxicillin/clavulanic acid which showed 88.6% of the declared amount of clavulanic acid and thereby narrowly missed the pharmacopoeial limit of 90%. The failure rate of medicines stated to be produced in Europe was, therefore, 5.1%, significantly lower than that of medicines stated to be produced in Asia (17.7%; $P = 0.0049$) and for medicines stated to be produced in Africa (22.2%; $P = 0.0042$). The difference between the medicines from Asia and Africa was not statistically significant ($P = 0.385$).

It must be emphasized that for many manufacturers from Asia and Africa, this study found most or all investigated samples to be in specifications (Supplemental Table S1). Notably, there were large manufacturers from India (e.g., Medopharm) or from China (e.g., CSPC Ouyi Pharmaceutical Co. Ltd., Shijiazhuang, China), represented by high numbers of samples in this study, whose out-of-specification rates were as low as those of the samples stated to be produced in Europe. On the other hand, there were some manufacturers, mostly represented by smaller numbers of samples in this study, with very high out-of-specification rates (see the Results section and Supplemental Table S1).

As noted in our analysis of the prices of medicines investigated in this study,[22] medicines produced in Europe were much more expensive for the patients than medicines from Asia and Africa (i.e., nearly three times as expensive in Cameroon and nearly seven times as expensive in the DR Congo). Given the financial constraints in LMICs such as Cameroon and the DR Congo, restriction of procurement to medicines from countries with stringent regulatory authorities (i.e., mostly countries from Europe, North America, and Japan)[35] may not be an affordable option. Rather, careful supplier qualification, that is, selection of manufacturers with a proven track record of providing good medicine quality is a key measure for quality assurance in medicine procurement. The WHO has established the Prequalification of Medicines Program to assist procurement agencies in the selection of good-quality products.[43,44] Of the 13 types of medicines investigated in this study, three are included in the WHO Prequalification Program (ciprofloxacin, cotrimoxazole, and doxycycline). However, of 506 samples collected, only a single one (Ciplox-500®, Cipla, Mumbai, India) represented a WHO-prequalified product (and this was found to comply with USP specifications). To achieve a larger impact of the WHO Prequalification of Medicines Program on medicine quality in Cameroon and the DR Congo, a wider range of products may have to be included into the program, and in the procurement processes, more attention may have to be given to the selection of WHO-prequalified products.

Medicines against NCDs showed a 25% failure rate in assay and dissolution testing, significantly higher than that of antibiotics (12%; $P = 0.0004$). This difference was especially pronounced in the DR Congo (33% versus 9%; $P < 0.0001$) (Figure 3). This is alarming in view of the increasing burden of NCDs in LMICs.[45,46] In an evaluation of cardiac drugs in different African countries, Antignac et al.[21] also analyzed samples from the DR Congo, including atenolol, furosemide, hydrochlorothiazide, and four other cardiac medicines. They reported a prevalence of 26.7% poor-quality samples in the DR Congo, similar to the prevalence of 33.3% determined for NCD medicines in that country in the present study. Both the present survey and study by Antignac et al.[21] found

hydrochlorothiazide samples to be of good quality. As mentioned earlier, more than half of the hydrochlorothiazide samples found in the present survey represented the originator medicine Esidrex® (Novartis), which were sold for very high prices in the DR Congo and Cameroon.[22]

Comparing the different storage recommendations on the packaging, medicines that carried a precise, WHO-recommended labeling statement, that is, either "Do not store above 30°C" or "Do not store above 25°C" showed a failure rate of 10%, significantly lower than those carrying a less precise recommendation or none at all (failure rate 27%; $P < 0.0001$). Possibly, suppliers giving attention to precise storage recommendations also give attention to other aspects of good manufacturing practice. However, medicines labeled "Do not store above 30°C" were not found to be better than those labeled "Do not store above 25°C" (8% versus 14% failure rate; $P = 0.0999$; not significant), indicating that this difference in labeling was not correlated with a relevant difference in quality and/or stability in the samples investigated in the present study.

The GPHF Minilab as a screening tool for SF medicines. Compendial (=pharmacopoeial) medicine analysis requires sophisticated equipment (usually HPLC) and highly trained personnel and, therefore, is expensive. In LMICs, the overall capacity for such analyses is limited. As a result, there is increasing worldwide interest in simple, inexpensive screening methods that will help in conducting larger post-marketing surveillance studies at an affordable cost.

So far, the most widely applied screening method in LMICs is the GPHF Minilab. The aforementioned review by the WHO,[7] summarizing the result of 100 medicine quality studies, aggregated results for 48,218 samples. Of these, 20,010 had been investigated with the GPHF Minilab, and 5.0% of these had been reported to fail Minilab testing. By contrast, 19,809 samples had been investigated by HPLC, and 15.6% of these had been reported to fail this testing. These percentages are similar to the results of the present study, which found 6.7% of the investigated samples to fail Minilab analysis (which was carried out by local faith-based organizations in Cameroon and the DR Congo), compared with an overall 16.2% which failed the assay and/or dissolution testing according to USP41 (carried out at Tuebingen University, Tuebingen, Germany). Whereas the studies reviewed by the WHO[7] mostly used only Minilab or only HPLC for analysis, the present study investigated 451 samples by both Minilab and HPLC, allowing a direct comparison of the results.

Minilab testing readily and reliably identified all three falsified medicines (Table 2). However, as mentioned in the Results section, Minilab is not designed to detect moderate deviations from the declared API amount, and this is clearly visible in the results shown in Table 3. Extreme deviations in API content were detected with a sensitivity of 43%.

As also explained in the Results section, disintegration and dissolution are different endpoints, and therefore, it is no surprise that samples failing USP dissolution testing were detected in the simple Minilab disintegration test with only 9% sensitivity. However, samples showing extreme dissolution failures in USP testing were detected by Minilab disintegration testing with 36% sensitivity (Table 4).

The sensitivity and specificity values determined in the present study should not be regarded as a final assessment of the analytical capacity of the Minilab because further improvements are certainly possible. For example, among the seven samples which Minilab TLC testing incorrectly reported as "failing" (Supplemental Table S2), three were cotrimoxazole samples reported to show a too weak spot of trimethoprim. Trimethoprim is the minor component of cotrimoxazole, besides the major component sulfamethoxazole. It is difficult to optimize TLC conditions in a way that allows a reliable estimation of the quantity of both components. Our study suggests that, if the trimethoprim spot appears too weak, the analysis should be repeated, applying a larger amount of both sample and reference. This, as well as a routine repetition of all "failed" Minilab analyses by another person or laboratory,[14] is likely to further improve specificity. In addition, both sensitivity and specificity may be improved by quantification of TLC spot intensity with imaging software, for example, using a mobile phone app.[47]

Nevertheless, the results in Tables 2–4 show, besides the power of the Minilab in the detection of falsified medicines which do not contain the declared API, the limitations of the Minilab in the detection of quantitative deviations. This has also been noted in the WHO QAMSA study.[13] The present study confirmed the well-known fact that Minilab testing cannot detect moderate deviations in medicine quality and observed that Minilab testing also missed a considerable number of samples with extreme deviations. As stated by the distributors of the Minilab,[48] Minilab testing, therefore, should not be considered as a replacement for HPLC in the formal evaluation of pharmaceuticals. Rather, when compliance or noncompliance with compendial specifications is to be determined, compendial methods must be used. The value of screening methods, such as the Minilab, is primarily in studies in a low-resource environment, attempting to identify and eliminate as many falsified and grossly substandard medicines as possible with a limited budget. Samples failing Minilab analyses in such studies must subsequently be analyzed with compendial methods for confirmation. The rather high specificity of Minilab testing (Tables 2–4) ensures that the number of expensive compendial analyses to be performed remains limited. The costs of Minilab analyses and of compendial analyses have been estimated in two previous publications.[14,42]

Other simple and (more or less) inexpensive screening methods for medicine quality have recently been reviewed.[49] As stated by the authors of that review, unfortunately, there is a lack of independent evaluations of most of these methods, particularly in field settings. Spectroscopic devices, especially using NIR and Raman spectroscopy, are attractive because of the ease and speed of handling. However, they require a complete library of spectra of all brands to be investigated. In the present study, which investigated only 13 medicines in only two countries, 260 different brands produced by 119 different manufacturers in 26 different countries were found. Creating and maintaining a complete library of reference spectra from such an assortment of brands and manufacturers is a formidable task, and its feasibility has yet to be demonstrated.

Limitations of this study. Although the sample size of our study is quite large in comparison with previous similar studies,[7,11] the selection of medicines was limited to a small number of antibiotics and medicines against NCDs. Therefore, the results are not representative for other types of medicines, and further studies with other types of medicines, especially

against NCDs, are required. In this study, two different sampling approaches had to be used: an overt approach in government and faith-based health facilities because these cannot sell a basket of prescription medicines to persons who are not patients in their facilities; and a mystery shopper approach in informal vendors (and in private pharmacies) because informal vendors would not be expected to agree to participate in a medicine quality study. Using an overt approach in government and faith-based health facilities may have potentially created a bias because staff may have preferably offered those medicines for collection which they considered to be of good quality. However, a meta-analysis by Ozawa et al.[11] did not find evidence for a significant bias in studies with overt approaches as compared with studies with mystery shopper approaches. The selection of sampling sites was not strictly random, especially in the northeast of the DR Congo where only health zones could be included which were safe enough for travel by the study personnel. This may have led to an exclusion of health zones with potentially higher rates of SF medicines because political instability may restrict regulatory activities in these health zones.

Received March 11, 2020. Accepted for publication March 31, 2020.

Published online May 11, 2020.

Note: Supplemental tables and figures appear at www.ajtmh.org.

Acknowledgments: We want to thank Albert Petersen for advice and support in the inception and execution of this study. We are grateful to the management and staff of CBC and PCC (Cameroon) and of DCMP and CADIMEBU (DR Congo), especially to Valentin Basolanduma Pondo of CADIMEBU, to the management and staff of Difaem (Germany), and to the management, faculty, and staff of Tuebingen University for their active support to this study.

Financial support: This study was funded by the Eberhard Karls University Tuebingen.

Disclaimer: The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' addresses: Simon Schäfermann, Cathrin Hauk, Emmanuel Wemakor, Harald Gross, Irina Helmle and Lutz Heide, Pharmaceutical Institute, Eberhard Karls University, Tuebingen, Germany, E-mails: simon.schaefermann@uni-tuebingen.de, cathrin.hauk@uni-tuebingen.de, emmanuel.wemakor@uni-tuebingen.de, harald.gross@uni-tuebingen.de, irina.helmle@uni-tuebingen.de, and heide@uni-tuebingen.de. Richard Neci and Georges Mutombo, Le Dépôt Central Médico-Pharmaceutique de la 8e CEPAC (DCMP), Bukavu, Democratic Republic of Congo, E-mails: richardneci@dcmp8ecepac.org and assurqualit@dcmp8ecepac.org. Edward Ngah Ndze and Tambo Cletus, Cameroon Baptist Convention (CBC), Central Pharmacy, Mutengene, Cameroon, E-mails: ndzedward@gmail.com and tambocle@yahoo.com. Fidelis Nyah and Manyi Pattinora, Presbyterian Church in Cameroon (PCC), Central Pharmacy, Limbe, Cameroon, E-mails: nyaahngoh@gmail.com and patt_nora@yahoo.com. Dorothee Wistuba, Institute for Organic Chemistry, Eberhard Karls University, Tuebingen, Germany, E-mail: dorothee.wistuba@uni-tuebingen.de. Christine Häfele-Abah, Deutsches Institut fuer Aerztliche Mission (Difaem), Tuebingen, Germany, E-mail: haefele@difaem.de.

REFERENCES

1. WHO, 2011. *The World Medicines Situation 2011. Medicines Prices, Availability and Affordability*. Geneva, Switzerland: World Health Organization. Available at: http://apps.who.int/medicinedocs/documents/s18065en/s18065en.pdf. Accessed February 14, 2020.
2. Wilsdon T, Li I, 2016. *The Evolution of Access to Essential Medicines for the Treatment of HIV/AIDS -Evidence From 2000 to 2015*. Available at: https://www.ifpma.org/wp-content/uploads/2016/06/2016-The-Evolution-of-Access-to-Essential-Medicines-CRA.pdf. Accessed February 14, 2020.
3. Nayyar GM, Attaran A, Clark JP, Culzoni MJ, Fernandez FM, Herrington JE, Kendall M, Newton PN, Breman JG, 2015. Responding to the pandemic of falsified medicines. *Am J Trop Med Hyg 92 (Suppl 6):* 113–118.
4. UN-DESA, 2017. *Sustainable Development Goal 3. Progress of Goal 3 in 2017*. (E/2017/66). Available at: https://sustainabledevelopment.un.org/sdg3. Accessed February 14, 2020.
5. Peyraud N et al., 2017. An epidemic of dystonic reactions in central Africa. *Lancet Glob Health 5:* e137–e138.
6. Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ Jr., Bennish ML, 1995. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. *BMJ 311:* 88–91.
7. WHO, 2017. *A Study on the Public Health and Socioeconomic Impact of Substandard and Falsified Medical Products*. Available at: http://www.who.int/medicines/regulation/ssffc/publications/se-study-sf/en/. Accessed February 14, 2020.
8. WHO, 2017. *WHO Global Surveilance and Monitoring System for Substandard and Falsified Medical Products*. Available at: http://www.who.int/medicines/regulation/ssffc/publications/gsms-report-sf/en/. Accessed February 14, 2020.
9. Wirtz VJ et al., 2017. Essential medicines for universal health coverage. *Lancet 389:* 403–476.
10. Newton PN, Bond KC; Oxford Statement Signatories, 2019. Global access to quality-assured medical products: the Oxford Statement and call to action. *Lancet Glob Health 7:* e1609–e1611.
11. Ozawa S, Evans DR, Bessias S, Haynie DG, Yemeke TT, Laing SK, Herrington JE, 2018. Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries: a systematic review and meta-analysis. *JAMA Netw Open 1:* e181662.
12. WHO, 2017. *Seventieth World Health Assembly update*. Available at: http://www.who.int/en/news-room/detail/29-05-2017-seventieth-world-health-assembly-update-29-may-2017. Accessed February 14, 2020.
13. WHO, 2011. *Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa*. Available at: http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. Accessed February 14, 2020.
14. Petersen A, Held N, Heide L, Difäm EPN Minilab Survey Group, 2017. Surveillance for falsified and substandard medicines in Africa and Asia by local organizations using the low-cost GPHF Minilab. *PLoS One 12:* e0184165.
15. Global Pharma Health Fund, 2008. *Manual Accompanying the GPHF Minilab™. Volume II. Thin-Layer Chromatographic Tests*. Darmstadt, Germany: Global Pharma Health Fund.
16. Mufusama JP, Ndjoko Ioset K, Feineis D, Hoellein L, Holzgrabe U, Bringmann G, 2018. Quality of the antimalarial medicine artemether–lumefantrine in 8 cities of the Democratic Republic of the Congo. *Drug Test Anal 10:* 1599–1606.
17. Schiavetti B et al., 2018. The quality of medicines used in children and supplied by private pharmaceutical wholesalers in Kinshasa, Democratic Republic of Congo: a prospective survey. *Am J Trop Med Hyg 98:* 894–903.
18. Djobet MP, Singhe D, Lohoue J, Kuaban C, Ngogang J, Tambo E, 2017. Antiretroviral therapy supply chain quality control and assurance in improving people living with HIV therapeutic outcomes in Cameroon. *AIDS Res Ther 14:* 19.
19. WHO, 2014. *Global Status Report on Noncommunicable Diseases 2014*. Geneva, Switzerland: World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/148114/9789241564854_eng.pdf;jsessionid=8345CF691DD47D27C879E5B13E2E8228?sequence=1. Accessed February 14, 2020.
20. Hunter-Adams J, Yongsi BN, Dzasi K, Parnell S, Boufford JI, Pieterse E, Oni T, 2017. How to address non-communicable diseases in urban Africa. *Lancet Diabetes Endocrinol 5:* 932–934.
21. Antignac M et al., 2017. Fighting fake medicines: first quality evaluation of cardiac drugs in Africa. *Int J Cardiol 243:* 523–528.

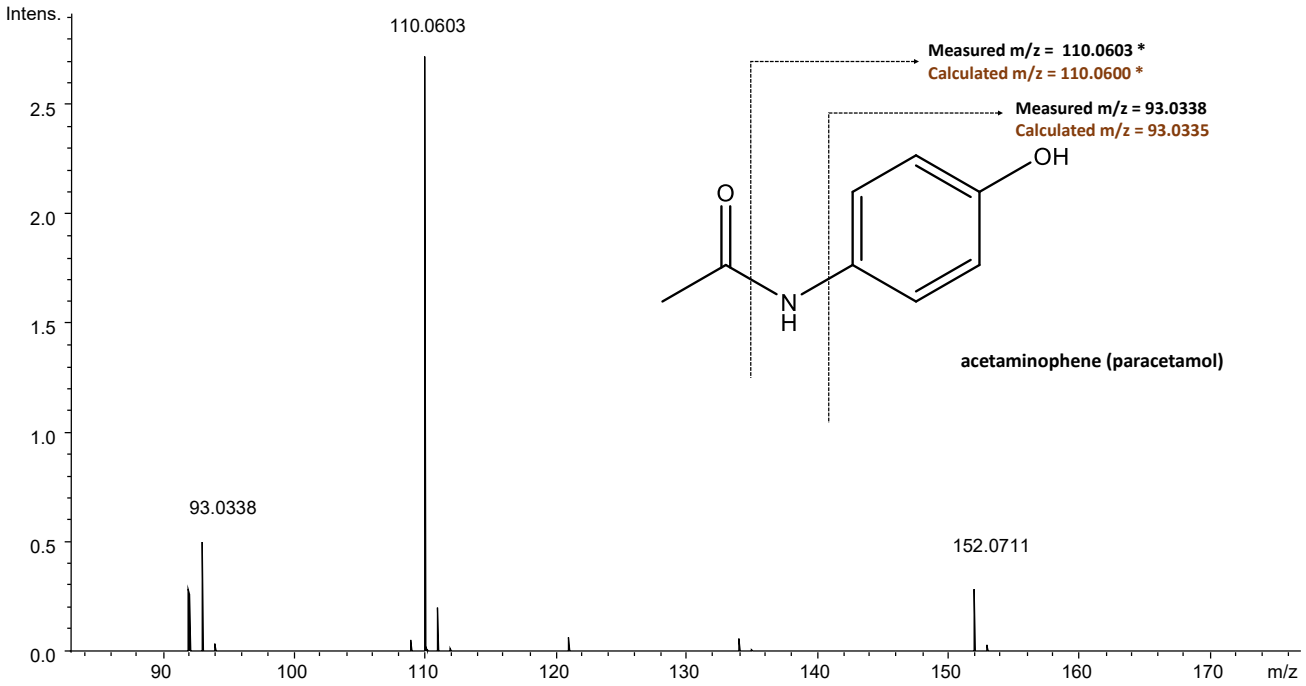
22. Schäfermann S, Neci R, Ndze EN, Nyaah F, Pondo VB, Heide L, 2020. Availability, prices and affordability of selected antibiotics and medicines against non-communicable diseases in western Cameroon and northeast DR Congo. *PLoS One 15:* e0227515.
23. WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2016. *Guidelines on the Conduct of Surveys of the Quality of Medicines. WHO Technical Report Series No. 996. 2016*. Available at: http://apps.who.int/medicinedocs/documents/s22404en/s22404en.pdf. Accessed February 14, 2020.
24. Newton PN et al., 2009. Guidelines for field surveys of the quality of medicines: a proposal. *PLoS Med 6:* e52.
25. Ministeres de la Sante Publique Republique du Cameroun, 2017. *Liste nationale des medicaments et autres produit pharmaceutiques essentiels 2017*. Available at: https://dpml.cm/index.php/en/catalog/national-list-of-essential-medicines. Accessed February 14, 2020.
26. Ministere de la Sante Publique Republique Democratique du Congo, 2010. *Liste nationale des medicaments essentiels. Revision Mars 2010*. Available at: http://apps.who.int/medicinedocs/en/m/abstract/Js18817fr/. Accessed February 14, 2020.
27. Jingi AM, Noubiap JJ, Ewane Onana A, Nansseu JR, Wang B, Kingue S, Kengne AP, 2014. Access to diagnostic tests and essential medicines for cardiovascular diseases and diabetes care: cost, availability and affordability in the West Region of Cameroon. *PLoS One 9:* e111812.
28. Karemere H, Ribesse N, Marchal B, Macq J, 2015. Analyzing Katana referral hospital as a complex adaptive system: agents, interactions and adaptation to a changing environment. *Confl Health 9:* 17.
29. Ongolo-Zogo P, Yondo D, Ndongo JS, Moustapha N, Evina CD, 2017. *Primary Health Care Systems (PRIMASYS). Comprehensive Case Study From Cameroon*. Geneva, Switzerland: World Health Organization. WHO/HIS/HSR/17.43. Available at: https://www.who.int/alliance-hpsr/projects/AHPSR-PRIMASYS-Cameroon-comprehensive.pdf. Accessed February 14, 2020.
30. WHO, 2017. *Health Analytical profile: Cameroon–2016*. Available at: https://www.afro.who.int/publications/health-analytical-profilecameroon-2016. Accessed February 14, 2020.
31. Schäfermann S, Wemakor E, Hauk C, Heide L, 2018. Quality of medicines in southern Togo: investigation of antibiotics and of medicines for non-communicable diseases from pharmacies and informal vendors. *PLoS One 13:* e0207911.
32. WHO, 2009. *Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. WHO Technical Report Series, No. 953, 2009, Annex 2*. Available at: https://www.who.int/medicines/publications/pharmprep/pdf_trs953.pdf?ua=1. Accessed February 14, 2020.
33. Dietz R, Feilner K, Gerst F, 1993. *Drugs Made in Germany. Drug Stability Testing Classification of Countries According to Climatic Zone*. Available at: https://niniguaia.files.wordpress.com/2013/07/climate-zones.pdf. Accessed February 14, 2020.
34. WHO, 2015. *Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. WHO Technical Report Series, No. 953, 2015, Annex 2*. Available at: https://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityConditionsTable2UupdatedMarch2015.pdf?ua=1. Accessed February 14, 2020.
35. WHO, 2018. *WHO Expert Committee on Specifications for Pharmaceutical Preparations Fifty-Second Report. WHO Technical Report Series No. 1010*. Available at: https://apps.who.int/iris/bitstream/handle/10665/272452/9789241210195-eng.pdf?ua=1. Accessed February 14, 2020.
36. WHO, 2018. *Medical Product Alert N° 2/2018. Falsified "Augmentin" Circulating in Cameroon*. Ref. RHT/SAV/Alert_n2.2018. Available at: https://www.who.int/medicines/publications/drugalerts/drug_alert2-2018/en/. Accessed February 14, 2020.
37. WHO, 2019. *World Health Organization. Model List of Essential Medicines. 21st List. 2019*. Geneva, Switzerland: World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1. Accessed February 14, 2020.
38. WHO, 2017. *Medical Product Alert N° 4/2017. Falsified Penicillin V Circulating in Cameroon*. Ref. RHT/SAV/Alert_n4.2017. Available at: https://www.who.int/medicines/publications/drugalerts/drug_alert4-2017/en/. Accessed February 14, 2020.
39. Pappich MG, 2016. *Saunders Handbook of Veterinary Drugs. Small and Large Animal*, 4th edition. Amsterdam, The Netherlands: Elsevier.
40. Hajjou M et al., 2015. Monitoring the quality of medicines: results from Africa, Asia, and South America. *Am J Trop Med Hyg 92 (Suppl 6):* 68–74.
41. Kaur H et al., 2016. Fake anti-malarials: start with the facts. *Malar J 15:* 86.
42. Khuluza F, Kigera S, Heide L, 2017. Low prevalence of substandard and falsified antimalarial and antibiotic medicines in public and faith-based health facilities of southern Malawi. *Am J Trop Med Hyg 96:* 1124–1135.
43. WHO, 2020. *WHO List of Prequalified Medicinal Products, Medicines and Finished Pharmaceutical Products*. Available at: https://extranet.who.int/prequal/content/prequalified-lists/medicines. Accessed February 14, 2020.
44. t Hoen EF, Hogerzeil HV, Quick JD, Sillo HB, 2014. A quiet revolution in global public health: the World Health Organization's prequalification of medicines programme. *J Public Health Policy 35:* 137–161.
45. Tsabang N, Fongnzossie E, Donfack D, Yedjou CG, Tchounwou PB, Minkande JZ, Nouedou C, Van PD, Sonwa, 2016. Comparative study of epidemiological and anthropological aspects of diabetes and hypertension in Cameroon. *J For Res 5:* 165.
46. Nyirenda MJ, 2016. Non-communicable diseases in sub-Saharan Africa: understanding the drivers of the epidemic to inform intervention strategies. *Int Health 8:* 157–158.
47. Yu H, Le HM, Kaale E, Long KD, Layloff T, Lumetta SS, Cunningham BT, 2016. Characterization of drug authenticity using thin-layer chromatography imaging with a mobile phone. *J Pharm Biomed Anal 125:* 85–93.
48. Jähnke R, 2018. Letter to the editor on previously published GPHF-minilab assessment. *Am J Trop Med Hyg 98:* 1880.
49. Vickers S, Bernier M, Zambrzycki S, Fernandez FM, Newton PN, Caillet C, 2018. Field detection devices for screening the quality of medicines: a systematic review. *BMJ Glob Health 3:* e000725.

Supplementary PDF I:

Contents

Figure S1: HR - MS/MS Fragmentation pattern measured for the falsified penicillin V tablets QMCA035

HR - MS/MS Fragmentation pattern measured from the falsified penicillin V samples (QMCA035) collected in the Republic of Cameroon, actually containing acetaminophen (paracetamol) The exact *m/z* of the paracetamol parent ion measured was 152.0711 (calculated 152.0706).



*the fragment ion with a *m/z* of 110, results from the protonated 4-aminophenol ($[H_2N\text{-}C_6H_4OH+H]^+$) formed by loss of ethone ($H_2C{=}C{=}O$).

Figure S2: HR - MS/MS Fragmentation pattern measured for the falsified metronidazole tablets QMC266

HR - MS/MS Fragmentation pattern measured from the falsified metronidazole tablets (QMC266) collected in the DR Congo, actually containing metronidazole benzoate.

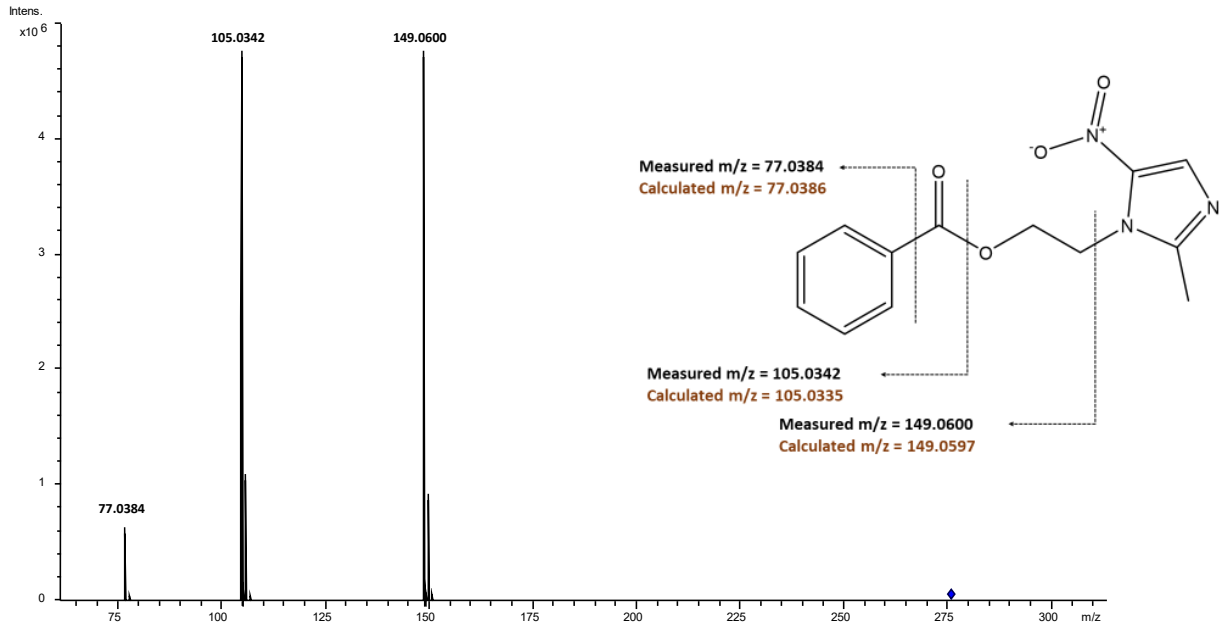


Figure S3: ^{1}H NMR spectrum (400 MHz, d_4-MeOH) of the sample QMC266

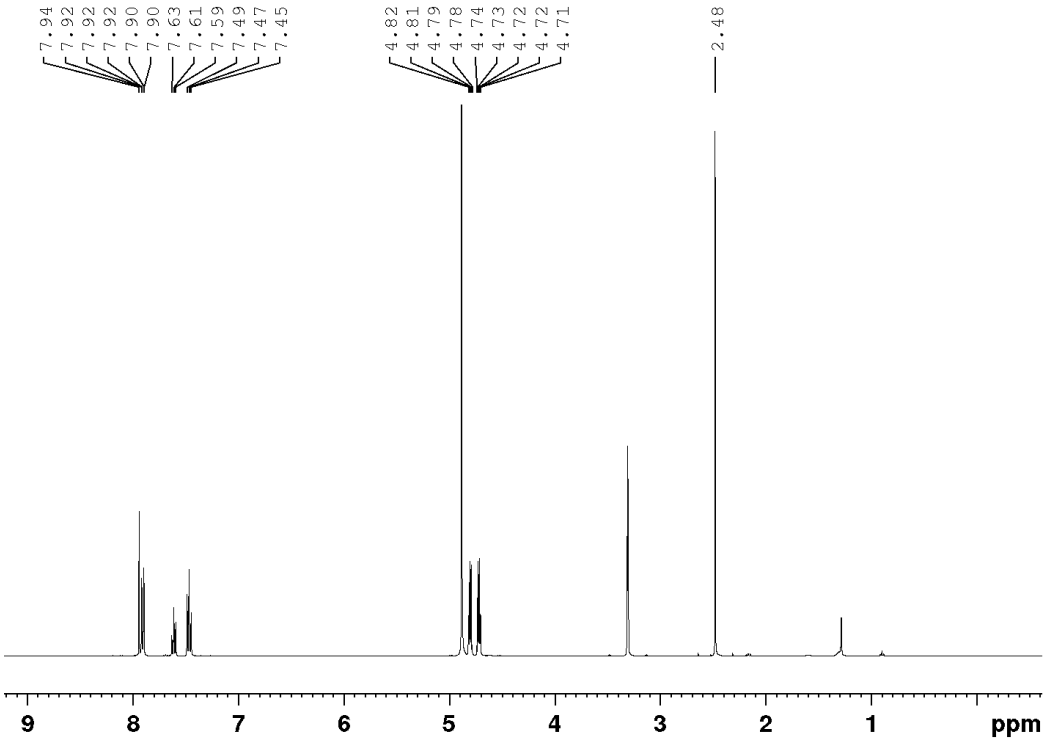


Figure S4: ^{13}C NMR spectrum (101 MHz, d_4-MeOH) of the sample QMC266

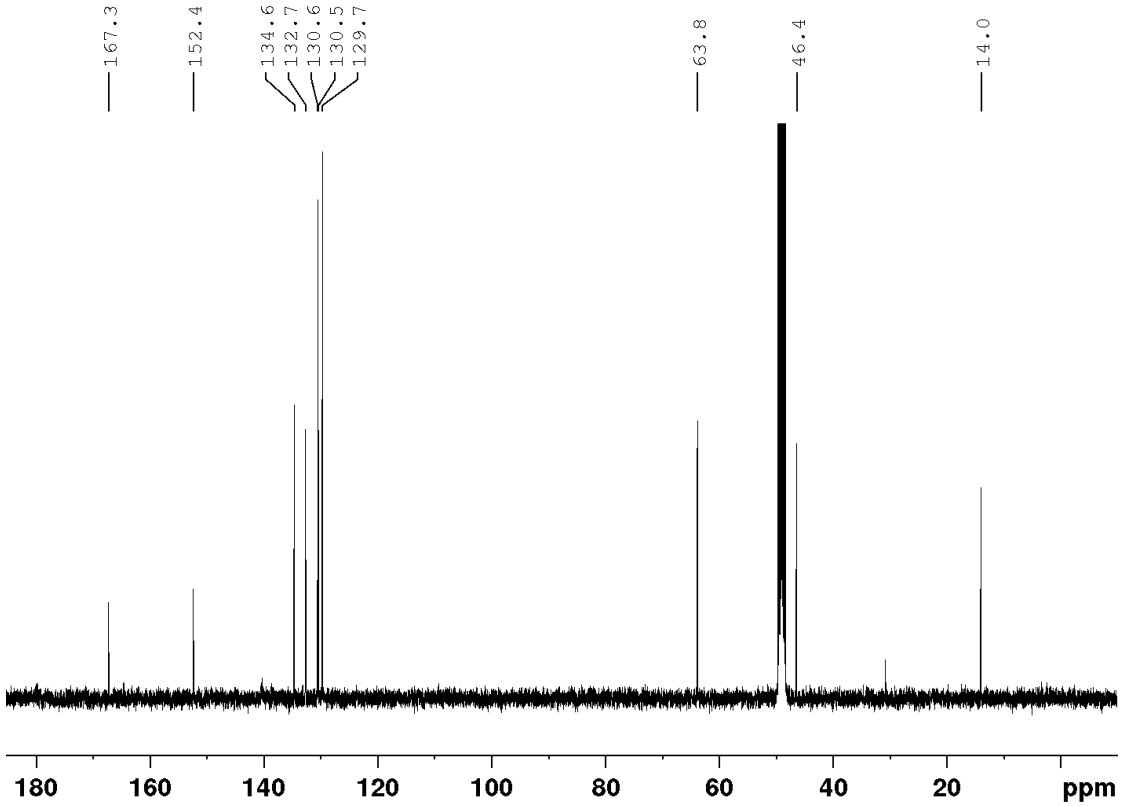


Figure S5: Edited ^{1}H-^{13}C HSQC NMR spectrum (400 MHz, d_4-MeOH) of the sample QMC266

This experiment reveals which proton is directly bond to which carbon. Blue cross peaks indicate CH and CH_3 moieties, while red cross-peaks indicate CH_2-groups.

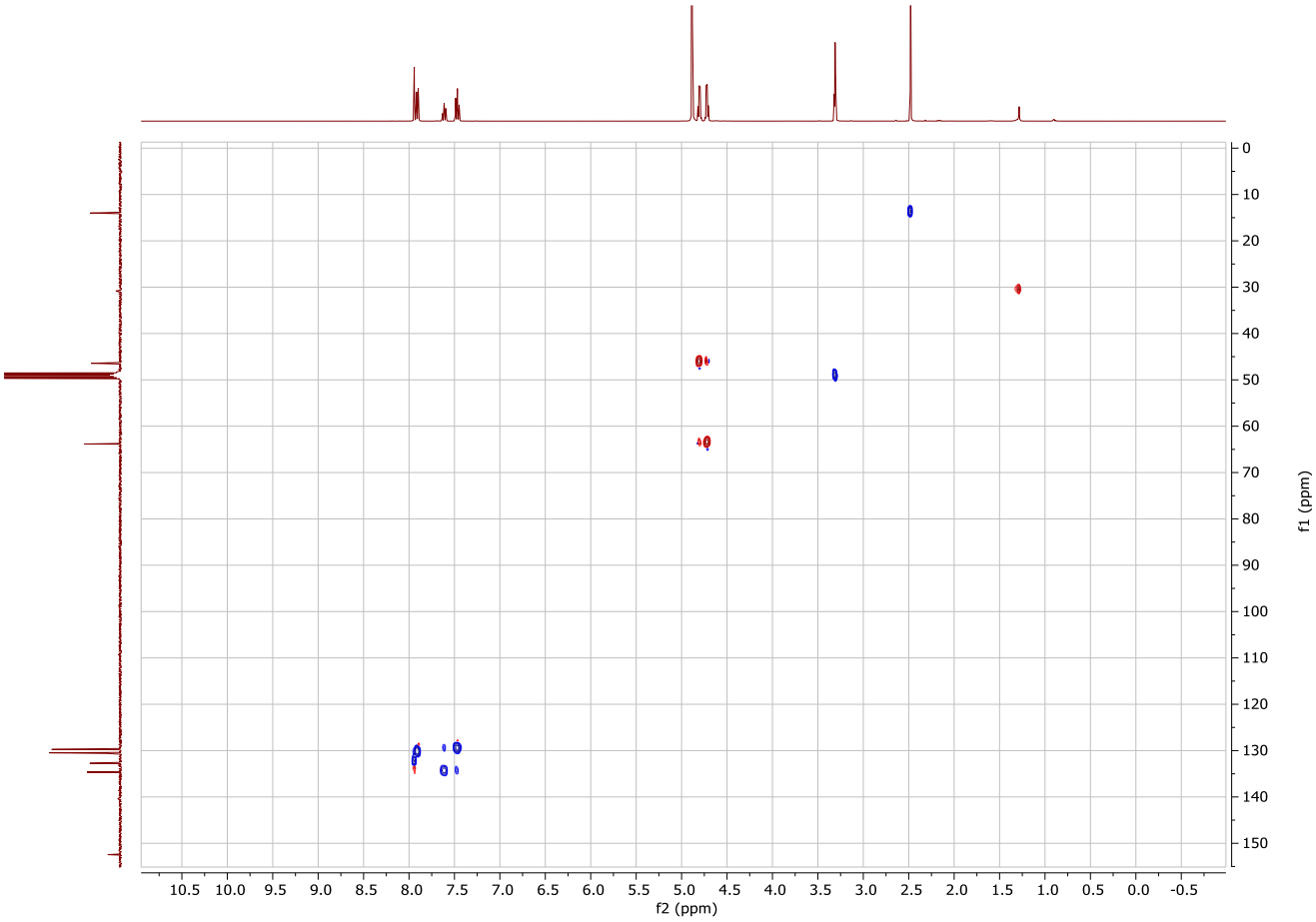


Figure S6: ^{1}H-^{1}H-COSY NMR spectrum (400 MHz, d_4-MeOH) of the sample QMC266

Bold lines in the depicted chemical formula visualize the observed COSY-correlations.

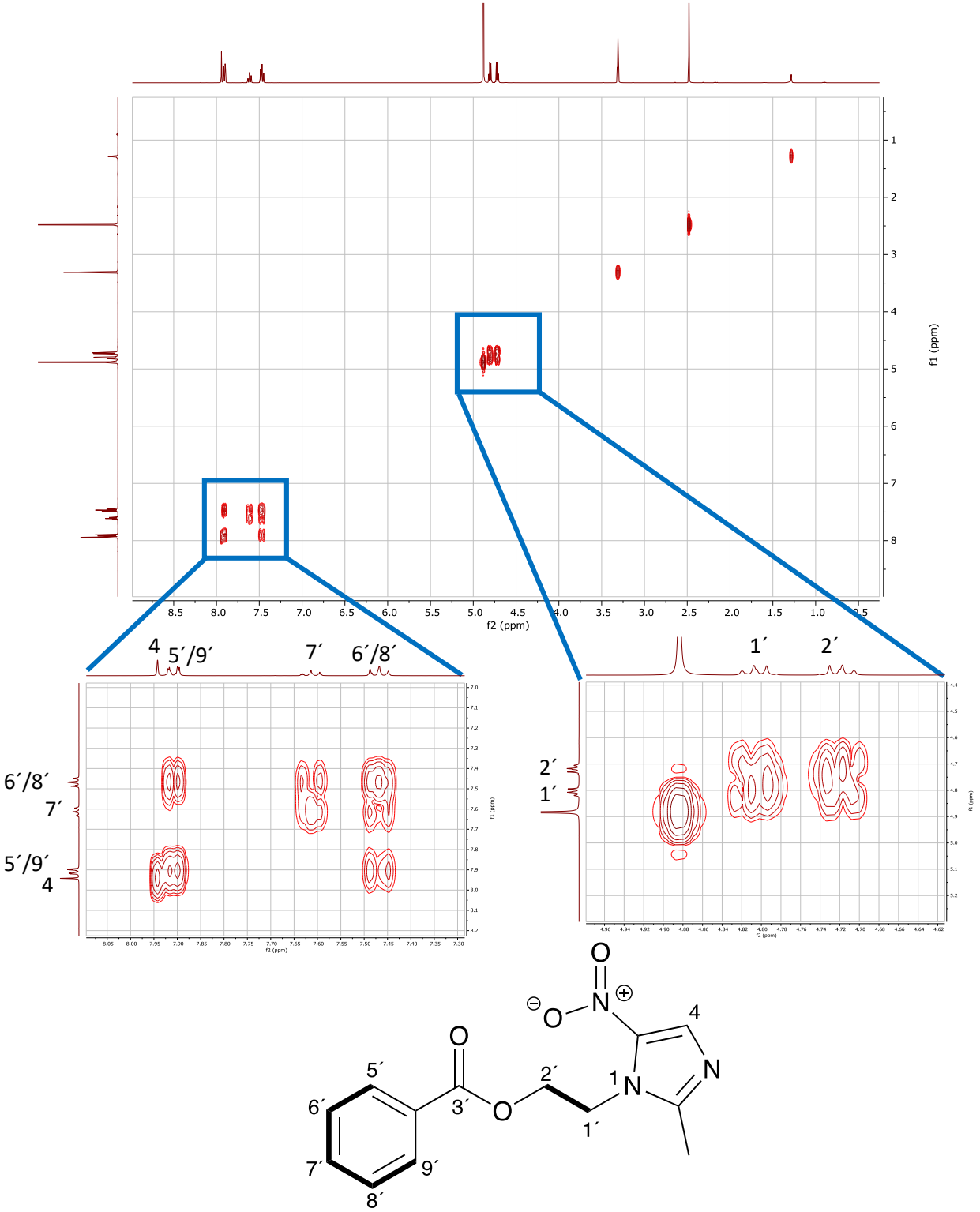
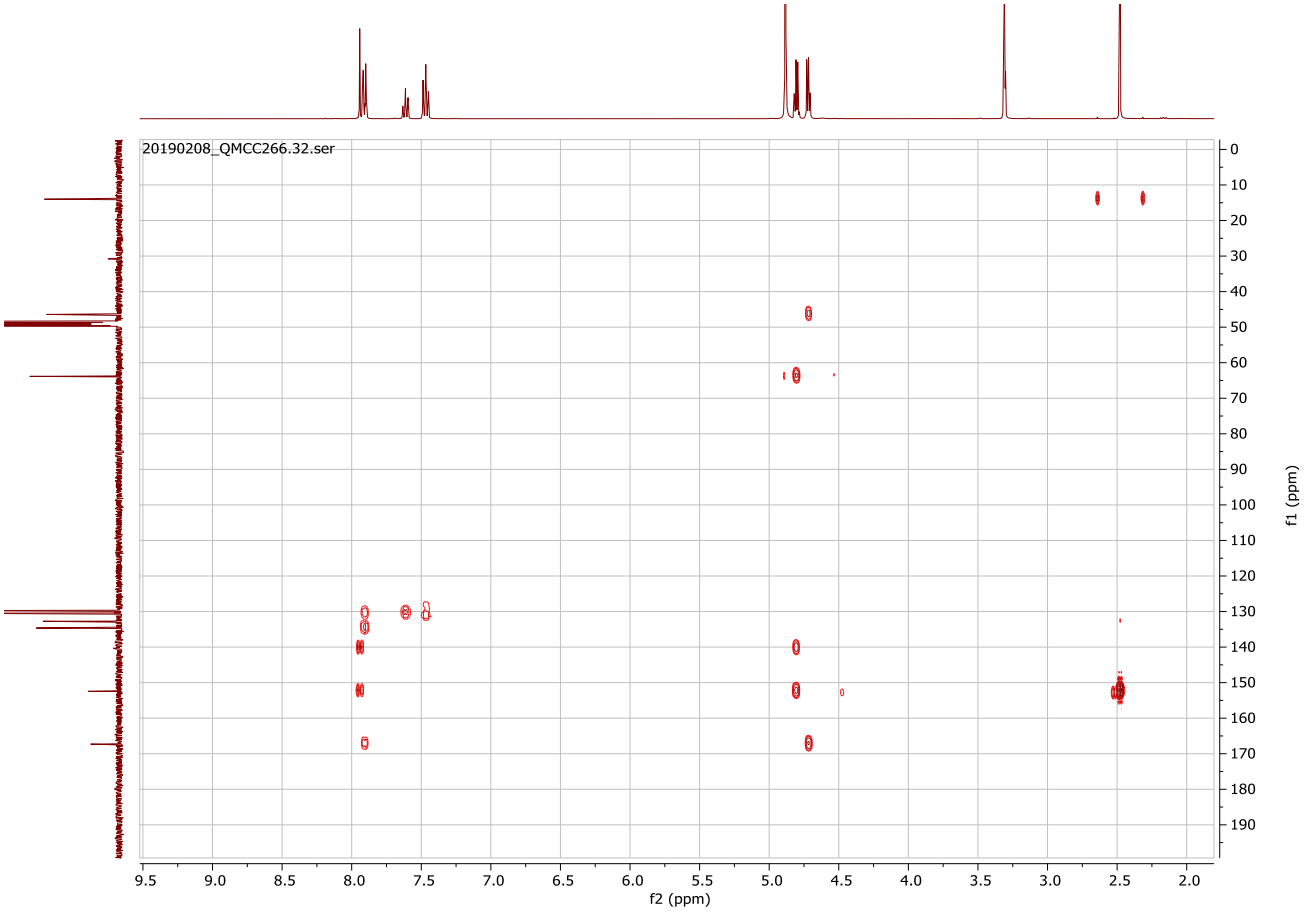


Figure S7: ^{1}H-^{13}C-HMBC NMR spectrum (400 MHz, d_4-MeOH) of the sample QMC266

Red arrows in the depicted chemical structure visualize the observed 2- and 3-bond HMBC long range correlations.



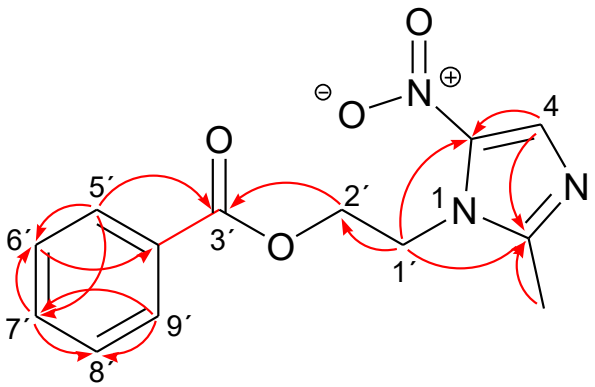
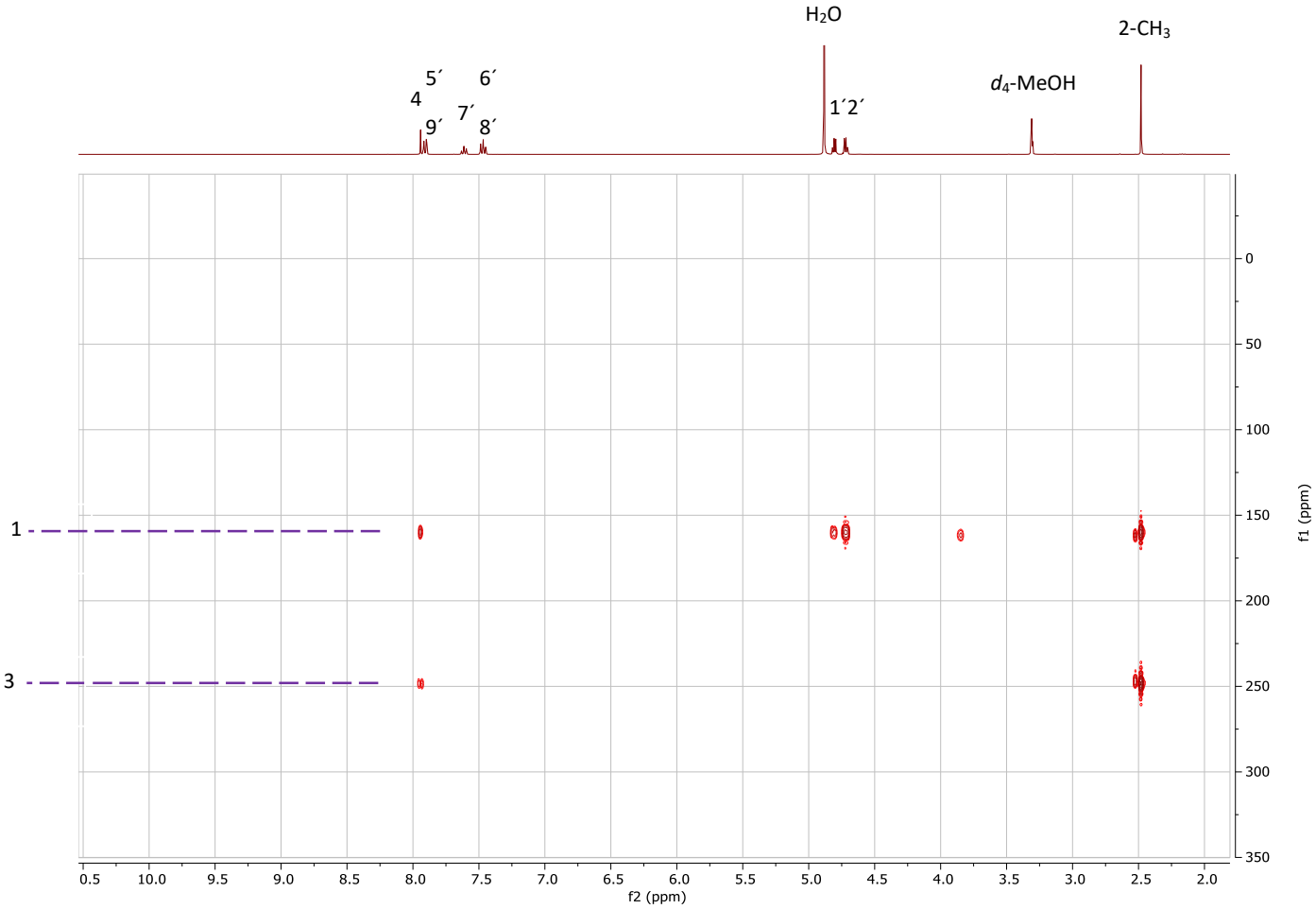


Figure S8: ^{1}H-^{15}N-HMBC NMR spectrum (400 MHz, d_4-MeOH) of the sample QMC266

Red arrows in the depicted chemical structure visualize the observed HMBC long range correlations.



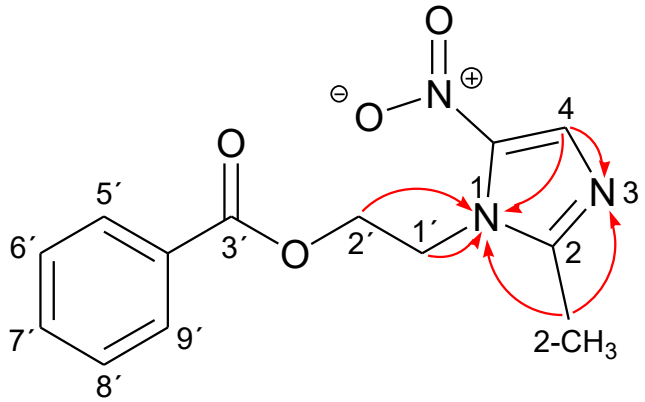


Figure S9: Superimposed ^{1}H NMR spectra (400 MHz, d_4-MeOH) of a metronidazole benzoate standard and the sample QMC266

metronidazole benzoate standard depicted in red (above) and the sample QMC266 depicted in blue (below).

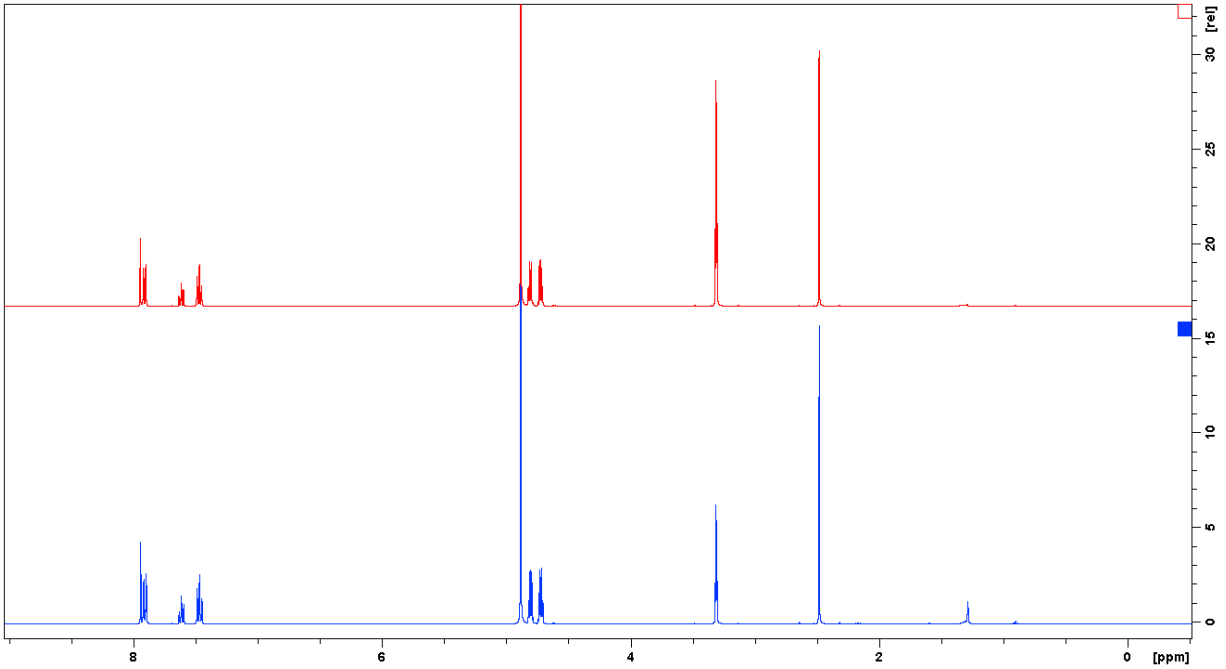


Figure S10: Superimposed ^{13}C NMR spectra (101 MHz, d_4-MeOH) of a metronidazole benzoate standard and the sample QMC266

metronidazole benzoate standard depicted in red (above) and the sample QMC266 depicted in blue (below).

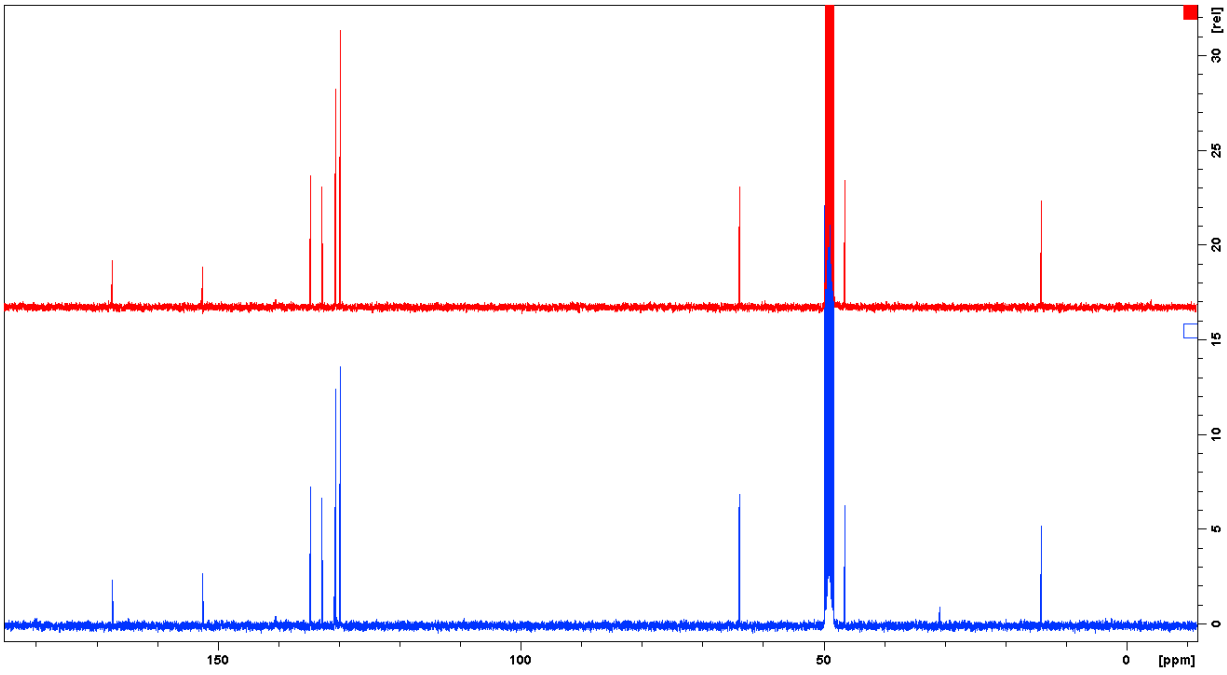
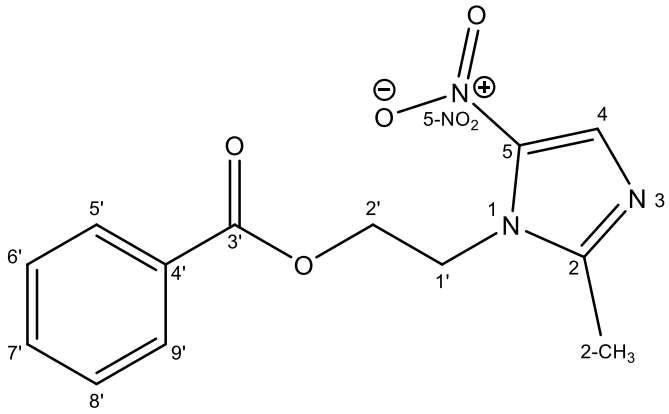


Figure S11: NMR Results for metronidazole benzoate in sample QMC266 collected in the DR Congo

Position	$\delta_{C/N}$[a]	δ_H (integral, multiplicity)[b]	COSY	HMBC[c]
1	160.0 N_t			
2	152.4 C_q			
2-CH_3	14.0 CH_3	2.48 (3H, s)		1, 2, 3
3	248.3 N_t			
4	132.7 CH	7.94 (1H, s)		1, 2, 3, 5
5	140.5 C_q[d]			
5-NO_2	n.o.[e]			
1'	46.4 CH_2	4.81 (2H, m)	2'	1, 2', 2, 5
2'	63.8 CH_2	4.72 (2H, m)	1'	1, 1', 3'
3'	167.3 CO			
4'	130.6 C_q			
5'/9'	130.5 CH	7.90+7.92 (2H, m)	6', 8'	3', 7', 5', 9'
6'/8'	129.7 CH	7.47 (2H, m)	5', 7', 9'	4', 6', 8'
7'	134.6 CH	7.61 (1H, m)	6', 8'	6´, 8'



2'-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl benzoate

[a] Recorded at 101 MHz for ^{13}C. ^{15}N NMR values were extracted from the corresponding ^{1}H-^{15}N HMBC NMR spectrum.

Multiplicity determined by an edited ^{1}H-^{13}C HSQC and a DEPT135 NMR experiment.

[b] Recorded at 400 MHz.

[c] Protons showing long-range correlation with indicated carbon or nitrogen.

[d] ^{13}C NMR value was extracted from a ^{1}H-^{13}C HMBC NMR spectrum.

[e] Not observed.

Figure S12: Content of the active pharmaceutical ingredient determined for each sample, sorted by different categories

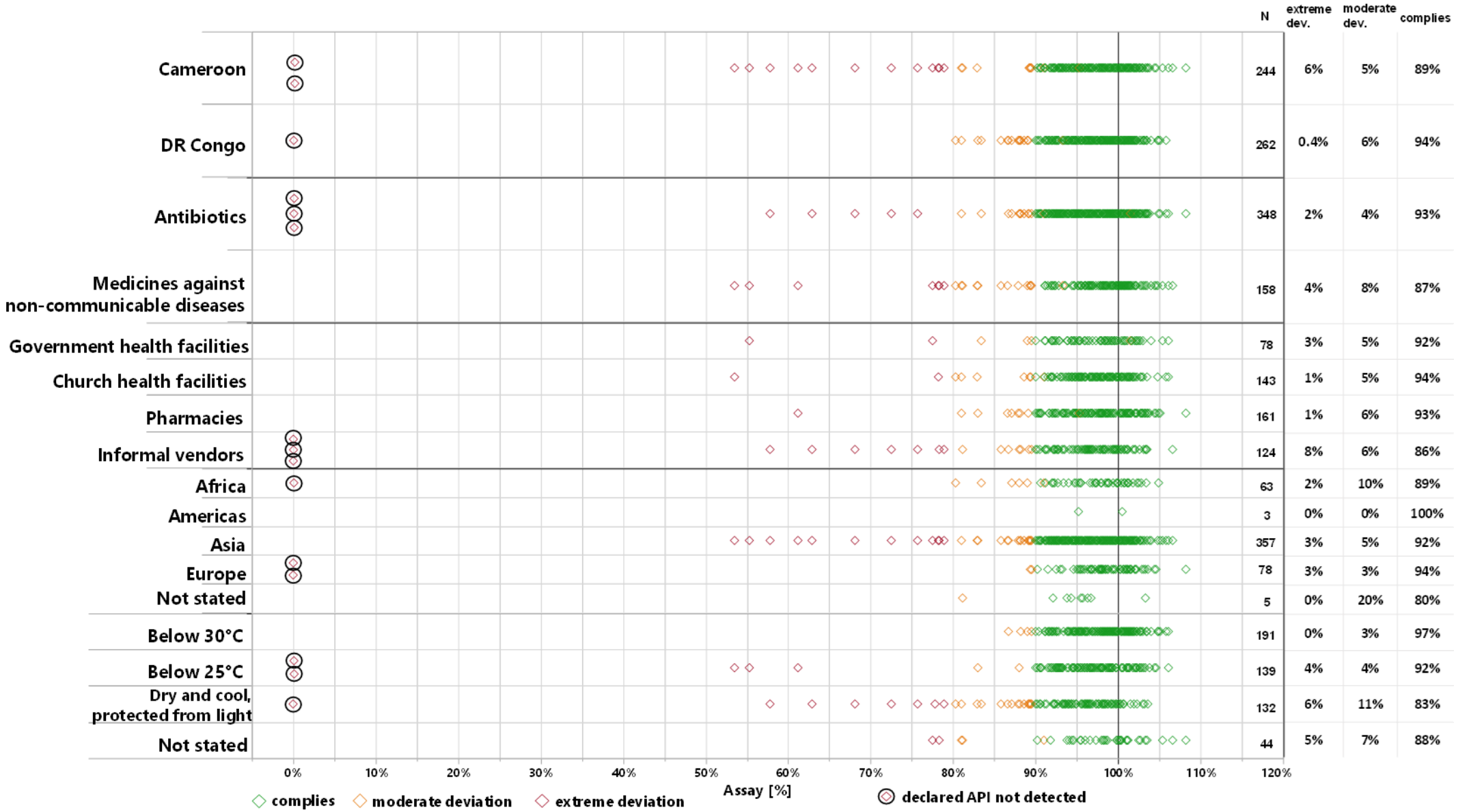


Figure S13: Dissolution of the active pharmaceutical ingredient determined for each sample, sorted by different categories

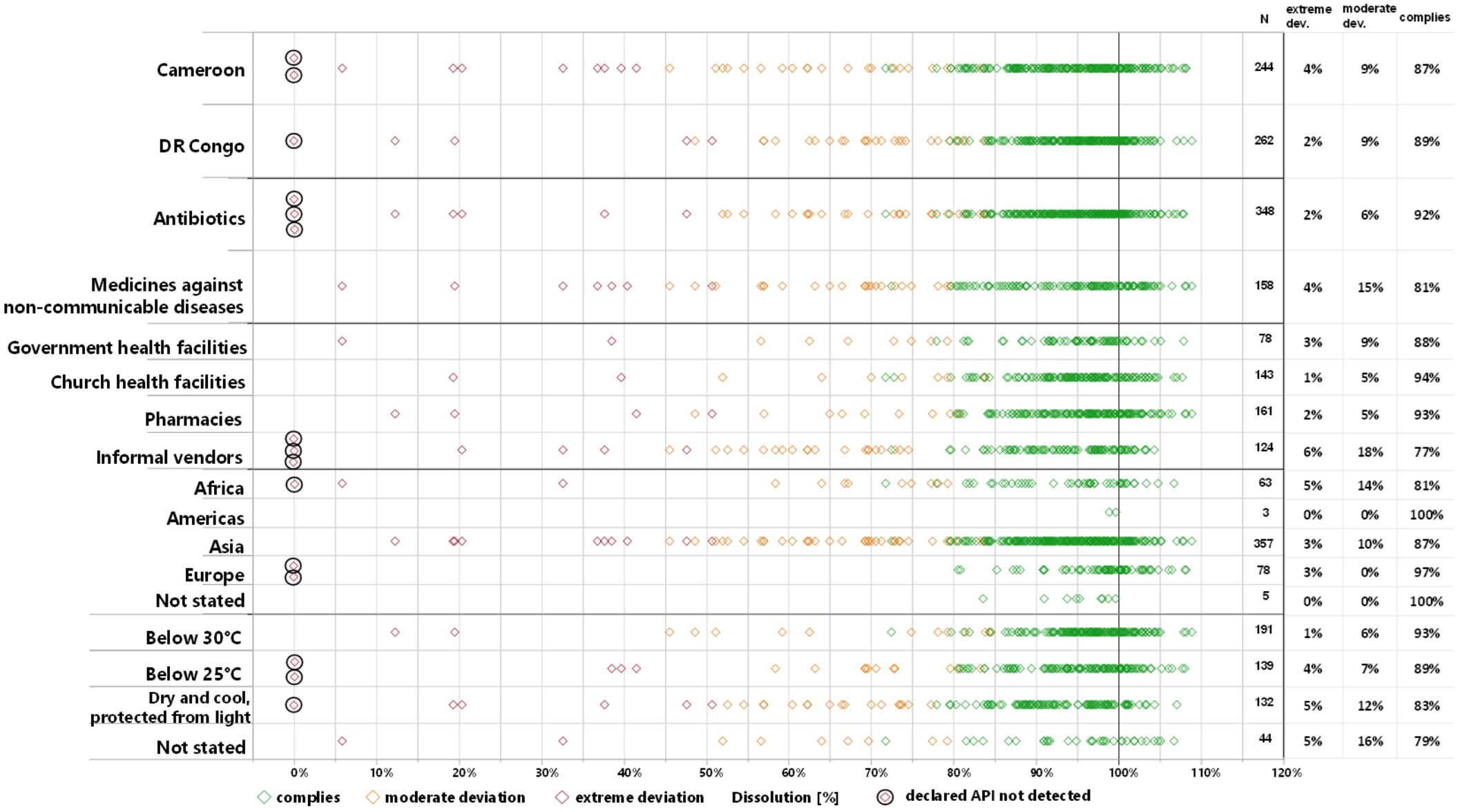
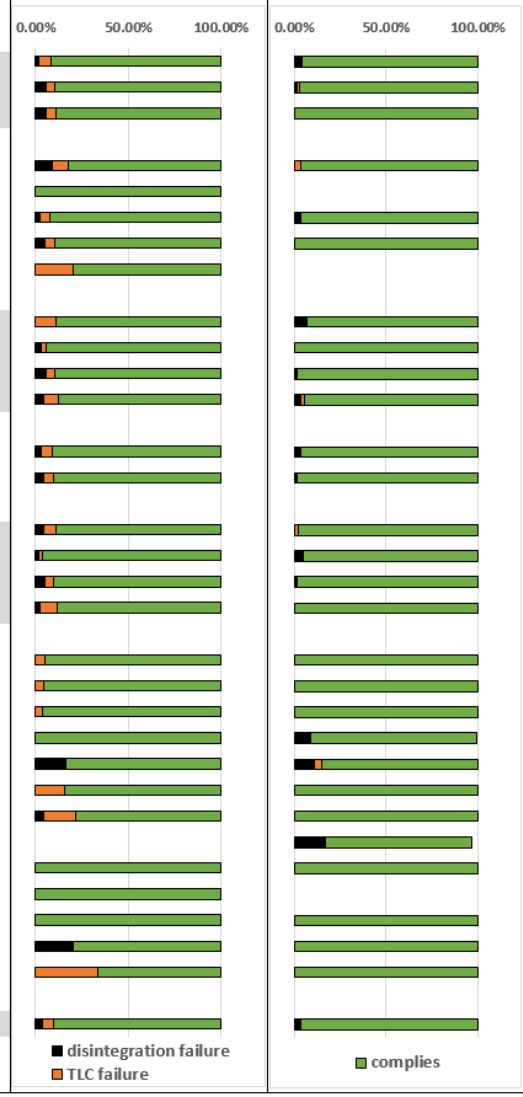


Figure S14: Frequency of non-compliance in Minilab TLC and disintegration testing in different subgroups of medicines

		Cameroon						DR Congo					
			non-compliant total			only disintegration	only TLC		non-compliant total			only disintegration	only TLC
		N total	N	[%]	95% CI	N	N	N total	N	[%]	95% CI	N	N
brand	Generics	117	10	9%	[5-15]	2	8	96	4	4%	[2-10]	4	0
	Branded	108	11	10%	[6-17]	6	5	102	3	3%	[1-8]	2	1
	Originator	18	2	11%	[3-33]	1	1	10	0	0%		0	0
continent of origin	Africa	23	4	17%	[8-42]	2	2	30	1	3%	[1-16]	0	1
	Americas	3	0	0%		0	0						
	Asia	155	12	8%	[4-13]	4	8	162	6	4%	[2-8]	6	0
	Europe	57	6	11%	[6-23]	3	3	16	0	0%		0	0
	Not stated	5	1	20%	[2-44]	0	1						
site type	Government health facilities	36	4	11%	[4-25]	0	4	42	3	7%	[3-19]	3	0
	Church health facilities	71	4	6%	[2-14]	2	2	40	0	0%		0	0
	Pharmacies	70	7	10%	[5-19]	4	3	70	1	1%	[0-8]	1	0
	Informal vendors	66	8	12%	[6-22]	3	5	56	3	5%	[2-15]	2	1
indication	Antibiotics	151	14	9%	[6-15]	5	9	157	6	4%	[2-8]	5	1
	MANCD	92	9	10%	[5-18]	4	5	51	1	2%	[0-10]	1	0
store at	Below 25 °C	89	10	11%	[6-20]	4	6	43	1	2%	[0-12]	0	1
	Below 30°C	51	2	4%	[1-13]	1	1	102	5	5%	[2-11]	5	0
	Dry and cool, protected from light	61	6	10%	[5-20]	3	3	61	1	2%	[0-9]	1	0
	Not stated	42	5	12%	[5-25]	1	4	2	0	0%		0	0
active pharmaceutical ingredient	Amoxicillin and Clavulanic acid	19	1	5%	[1-25]	0	1	11	0	0%		0	0
	Amoxicillin	24	1	4%	[1-20]	0	1	25	0	0%		0	0
	Ciprofloxacin	25	1	4%	[1-20]	0	1	26	0	0%		0	0
	Doxycycline	22	0	0%		0	0	20	2	10%	[2.8-30]	2	0
	Metronidazole	25	4	16%	[6-35]	4	0	27	4	15%	[6-33]	3	1
	Penicillin V	13	2	15%	[4-42]	0	2	21	0	0%		0	0
	Sulfamethoxazole and Trimethoprim	23	5	22%		1	4	27	0	0%		0	0
	Atenolol	0	0	0%		0	0	5	1	20%	[4-62]	1	0
	Furosemide	17	0	0%		0	0	18	0	0%		0	0
	Glibenclamide	19	0	0%		0	0	0	0	0%		0	0
	Hydrochlorothiazide	21	0	0%		0	0	4	0	0%		0	0
	Metformin	20	4	20%	[8-42]	4	0	10	0	0%		0	0
	Salbutamol	15	5	33%	[15-58]	0	5	14	0	0%		0	0
	Overall	**243**	**23**	**9%**	**[6.4-13.8]**	**9**	**14**	**208**	**7**	**3%**	**[1.6-6.8]**	**6**	**1**



TLC= thin-layer chromatography

Table S1: List of stated manufacturers of samples investigated in this study, and results for USP 41 assay and dissolution testing

Stated Continent of Origin	Stated Country of Origin	Stated Manufacturer	N	complies	moderate deviation	extreme deviation
Africa	Benin	Pharmaquick	7	5	0	2
	Burundi	Société industrielle Pharmaceutique (SIPHAR)	1	1	0	0
	Cameroon	Africure Pharmaceuticals Cameroon S.A.	2	1	1	0
		Cinpharm **	3	2	1	0
	DR Congo	Phatkin B.P.	5	2	3	0
		Zenufa Laboratoire	4	3	1	0
	Ghana	Entrance Pharmaceuticals & Research Centre	5	3	2	0
	Kenya	Cosmos Limited	1	1	0	0
		DAWA Limited	7	6	1	0
		Elys Chemical Industries Ltd.	3	2	1	0
		Laboratory & Allied Ltd.	2	2	0	0
		MAC'S Pharmaceuticals Ltd.	2	1	0	1 §
		Pharmaceutical Manufacturing Co. Ltd.	1	0	1	0
		Regal Pharmaceuticals Ltd.	5	5	0	0
	Nigeria	New Divine Favour Pharmaceutical Industries Ltd.	1	1	0	0
	Senegal	Wintrop Pharma Sénégal Group SANOFI	1	1	0	0
	Togo	Sprukfield	4	4	0	0
	Uganda	Kampala Pharmaceutical Industries	7	7	0	0
	Uganda	Rene Industries Ltd.	2	2	0	0
	subtotal		**63**	**49**	**11**	**3**
Americas	British West Indies	Prost Pharma (France)	2	2	0	0
	USA	Sandoz	1	1	0	0
	subtotal		**3**	**3**	**0**	**0**

Stated Continent of Origin	Stated Country of Origin	Stated Manufacturer	N	complies	moderate deviation	extreme deviation
Asia	China	Anhui Chengshi Pharmaceutical Co. Ltd	1	1	0	0
		Anhui Medipharm Co. Ltd.	1	0	1	0
		Chifeng Wanze Pharmaceutical Co. Ltd.	1	1	0	0
		CSPC Ouyi Pharmaceutical Co. Ltd.	22	21	1	0
		CSPC Zhongnuo Pharmaceuticals Co. Ltd.	10	10	0	0
		Farmasino Pharmaceutical Co. Ltd	6	5	1	0
		Greenfield Pharmaceuticals (Jiang Su) Co. Ltd.	1	1	0	0
		Guilin Pharmaceutical Co. Ltd.	4	4	0	0
		Jiangsu Pengyao Pharmaceutical Co. Ltd.	2	2	0	0
		Jiangsu Ruinian Qianjin Pharm. Co.Ltd	4	4	0	0
		Jiangxi Xier Kangtai Pharmaceutical Co. Ltd.	5	3	2	0
		Jinzhou Jiuyang Pharmaceutical Co. Ltd	3	2	0	1
		JSPY Pharmaceutical Co. Ltd.	3	3	0	0
		Nanjing Baijingyu Pharmaceutical Co. Ltd.	3	3	0	0
		Nanjing Sino Pharmaceutical Ltd.	1	1	0	0
		Ningbo Shuangwei Pharmaceutical Co. Ltd	6	6	0	0
		North China Pharmaceutical Co. Ltd. ***	8	8	0	0
		Reyoung Pharmaceutical Co. Ltd.	9	9	0	0
		Shandong Shenglu Pharmaceutical Co. Ltd	4	0	0	4
		Shandong Xier Kangtai Pharm Co. Ltd	1	1	0	0
		Shandong Yikang Pharmaceutical Co. Ltd.	2	1	1	0
		Shanghai Juchen Import and Exports Co. Ltd.	4	4	0	0
		Shanxi Lianbang Pharmaceutical Co. Ltd.	2	2	0	0

Stated Continent of Origin	Stated Country of Origin	Stated Manufacturer	N	complies	moderate deviation	extreme deviation
		Sinochem Jiangsu Co. Ltd	14	8	3	3
		Sishui xier Kang Pharmaceutical Co. Ltd	1	0	0	1
		Yanzhou Xierkangtai pharmaceutical Co. Ltd.	3	2	1	0
	Hong Kong	Hongkong Prost Medicines and Health Products Co. Ltd	3	3	0	0
	India	Agog Pharma Ltd.	4	4	0	0
		Alkem Laboratories Ltd.	1	0	1	0
		Arco Pharma Pvt. Ltd	7	1	6	0
		Asence Pharma Pvt. Ltd.	6	4	2	0
		Astra Lifecare Pvt. Ltd.	11	9	0	2
		Aura pharmaceuticals Pvt. Ltd	9	5	4	0
		Aurobindo Pharma Ltd.	1	0	1	0
		Axon Drugs Pvt. Ltd.	1	1	0	0
		Bliss GVS Pharma Ltd.	1	0	1	0
		Cadila Healthcare Ltd.	1	1	0	0
		Cipla Ltd.	1	1	0	0
		Ciron Drugs and Pharmaceuticals Ltd.	2	2	0	0
		Combitic Global Caplet Pvt. Ltd.	1	1	0	0
		Fourrts	3	3	0	0
		Global Pharma Healthcare Pvt. Ltd.	4	4	0	0
		Holden Medical Laboratories Pvt. Ltd.	3	3	0	0
		Intermed	1	1	0	0
		Ipca Laboratories Ltd.	1	1	0	0
		J. B. Chemicals and Pharmaceuticals Ltd.	1	1	0	0
		Kopran Limited	2	2	0	0
		Leben Laboratories Pvt. Ltd	1	1	0	0
		Lincoln Pharmaceuticals Ltd.	8	8	0	0
		Lord Lifescience Pvt. Ltd.	1	0	1	0
		Macleods Pharmaceuticals Ltd.	4	4	0	0
		Mancare pharmaceutical Ltd	4	4	0	0

Stated Continent of Origin	Stated Country of Origin	Stated Manufacturer	N	complies	moderate deviation	extreme deviation
		Maneesh Pharmaceuticals Ltd	1	1	0	0
		Maxheal Laboratories Pvt. Ltd.	2	1	1	0
		Maxtar Bio-Genics	14	9	2	3 *
		Medicamen Biotech Ltd.	8	7	1	0
		Medicef Pharma	4	4	0	0
		Medico Remedies Pvt. Ltd.	5	0	1	4
		Medley Pharmaceuticals Ltd.	5	5	0	0
		Medopharm Pvt. Ltd.	41	39	2	0
		Mepro Pharmaceuticals Pvt. Ltd.	2	2	0	0
		Micro Labs Ltd.	4	4	0	0
		Milan Laboratories (India) Pvt. Ltd	6	5	1	0
		Nem Laboratories Pvt. Ltd.	1	1	0	0
		not stated	1	1	0	0
		Osaka Pharmaceuticals Pvt. Ltd.	3	1	2	0
		PIL Pharmaceuticals Pvt. Ltd.	1	1	0	0
		Prashi Pharma Pvt. Ltd	6	1	4	1
		Shalina Laboratories Pvt. Ltd.	1	1	0	0
		Sparsh Bio-Tech Pvt. Ltd.	7	7	0	0
		Strides Arcolab Limited	23	21	2	0
		Strides Shasun Limited	11	9	2	0
		Triveni Formulations Limited	1	1	0	0
		Ultra Care International	2	2	0	0
		UMEDICA Laboratories	1	1	0	0
		Zee Laboratories	1	1	0	0
		ZIM Laboratories Ltd.	1	1	0	0
	Sultanat of Oman	National pharmaceutical industries	1	1	0	0
	Turkey	Bilim Pharmaceuticals	1	1	0	0
	subtotal		**357**	**294**	**44**	**19**
Europe	Austria	Sandoz	10	10	0	0
	Belgium	Merck	3	3	0	0
		Oxford Pharma	1	0	0	1 §
	Cyprus	Medochemie Ltd.	2	2	0	0

Stated Continent of Origin	Stated Country of Origin	Stated Manufacturer	N	complies	moderate deviation	extreme deviation
		Remedica Ltd	2	2	0	0
	France	Famar Lyon	1	1	0	0
		Glaxo Welcome Production	3	3	0	0
		Laboratoires Bailleul	1	1	0	0
		Laboratoire Bailly-Creat	6	6	0	0
		Sanofi-Winthrop Industrie	6	6	0	0
	Germany	Aspen Bad Oldesloe GmbH	1	1	0	0
		Berlin Chemie	1	1	0	0
		Denk Pharma GmbH & Co. KG	12	10	2	0
		Salutas Pharma GmbH	2	2	0	0
	Italy	Errekappa Euroterapici S.p.A	1	1	0	0
		Laboratori Guidotti S.p.A	1	1	0	0
	Spain	Ferrer Internacional S.A.	3	3	0	0
		Novartis Farmacéutica S.A.	14	14	0	0
	Sweden	Bluefish Pharmaceuticals AD	1	1	0	0
	United Kingdom	SmithKline Beecham Pharmaceuticals	1	0	0	1 §
		Sonmart Pharma (UK)	6	6	0	0
	subtotal		**78**	**74**	**2**	**2**
not stated	not stated	Cinpharm **	3	3	0	0
		not stated	2	1	1	0
	subtotal		**6**	**5**	**1**	**0**
total			**506**	**424**	**58**	**24**

* Two of these three samples had been expired at the date of collection.

** Cinpharm recently became a Cameroonian company. However, three samples did not state the country of manufacture, therefore these three samples were listed in the category “not stated”.

*** The name of this manufacturer was given on different samples as "North China Pharmaceutical Co. Ltd.", or as "NCPC, PRC", or as "NCPC North Best". Since all of them appear to have the same contact address, they were considered in this study as a single manufacturer.

§ Falsified medicine; poor quality can not be attributed to the stated manufacturer.

Table S2: List of samples reported to fail GPHF Minilab TLC analysis, and of samples reported to pass GPHF Minilab TLC analysis but showing extreme deviations in USP assay testing, with their respective USP assay results

Sample ID	API	USP assay classification	USP assay result [%]
1) Samples reported to <u>fail</u> GPHF Minilab TLC analysis:			
QMCA241	Amoxicillin / clavulanic acid	extreme deviation	0% / 0%
QMC266	Metronidazole	extreme deviation	0%
QMCA035	Penicillin V	extreme deviation	0%
QMCA001	Salbutamol	extreme deviation	54%
QMCA025	Salbutamol	extreme deviation	55%
QMCA215	Salbutamol	extreme deviation	61%
QMCA072	Salbutamol	deviation	81%
QMCA074	Sulfamethoxazole / Trimethoprim	deviation	91% / 95%
QMCA019	Sulfamethoxazole / Trimethoprim	complies	99% / 98%
QMCA212	Sulfamethoxazole / Trimethoprim	complies	102% / 100%
QMCA082	Sulfamethoxazole / Trimethoprim	complies	103% / 100%
QMCA032	Amoxicillin	complies	92%
QMCA210	Penicillin V	complies	93%
QMCA084	Salbutamol	complies	94%
QMCA184	Ciprofloxacin	complies	95%
2) Samples reported to <u>pass</u> GPHF Minilab TLC analysis but showing extreme deviations in USP assay testing:			
QMCA253	Penicillin V	extreme deviation	58%
QMCA107	Penicillin V	extreme deviation	68%
QMCA244	Penicillin V	extreme deviation	73%
QMCA177	Penicillin V	extreme deviation	76%
QMCA168	Salbutamol	extreme deviation	78%
QMCA179	Salbutamol	extreme deviation	78%
QMCA191	Salbutamol	extreme deviation	78%
QMCA239	Salbutamol	extreme deviation	79%

Table S3: Compendial quality results for the different products and batches as stated on the packaging

See separate pdf file

Table S3: List of all batches and brands investigated in this study, with their stated manufacturers and analytical results for assay and dissolution

Note: Medicines were collected in health facilities, i.e. at the point of care, and it is unknown whether the manufacturers' storage recommendation have been complied with from the time of manufacture until the time of sample collection. Changes in medicines quality may have occurred due to inappropriate transport and storage conditions, and non-compliance with USP specifications is therefore not necessarily due to substandard manufacturing or packaging. However, the quality results listed below reflect what patients receive in the investigated health facilities.

* Two of these three samples had been expired at the date of collection.

** Cinpharm recently became a Cameroonian company. However, three samples did not state the country of manufacture, therefore these three samples were listed in the category "not stated".

*** The name of this manufacturer was given on different samples as "North China Pharmaceutical Co. Ltd.", or as "NCPC, PRC", or as "NCPC North Best". Since all of them appear to have the same contact address, they were considered in this study as a single manufacturer.

§ Falsified medicine; poor quality can not be attributed to the stated manufacturer.

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	**Stated country of origin**	**Stated manufacturer**	**INN**	**Stated product name**	**Batchnumber**	**N**	**complies**	**deviation**	**extreme deviation**	**complies 2**	**deviation2**	**extreme deviation 2**	**complies 3**	**deviation 3**	**extreme deviation 3**
Africa	Benin	Pharmaquick	Furosemide	Furosemide Pharmaquick	991300	1	1	0	0	1	0	0	1	0	0
Africa	Benin	Pharmaquick	Glibenclamide	Glibenclamid Pharmaquick	965500	2	2	0	0	0	0	2	0	0	2
Africa	Benin	Pharmaquick	Hydrochlorothiazide	Hydrochlorothiazide Pharmaquick	992701	2	2	0	0	2	0	0	2	0	0
Africa	Benin	Pharmaquick	Hydrochlorothiazide	Hydrochlorothiazide Pharmaquick	992801	2	2	0	0	2	0	0	2	0	0
Africa	Burundi	Société industrielle Pharmaceutique (SIPHAR)	Doxycycline	Siphadox 100	SDC-001	1	1	0	0	1	0	0	1	0	0
Africa	Cameroon	Africure Pharmaceuticals Cameroon S.A.	Doxycycline	Doxycycline Capsules BP	4517001	2	2	0	0	1	1	0	1	1	0
Africa	Cameroon	Cinpharm **	Amoxicillin	Cinamox	18026	1	1	0	0	0	1	0	0	1	0
Africa	Cameroon	Cinpharm **	Sulfa/Trimet	Cincotrim	16001	1	1	0	0	1	0	0	1	0	0
Africa	Cameroon	Cinpharm **	Ciprofloxacin	Proloxcin	16001	1	1	0	0	1	0	0	1	0	0
Africa	DRC	Phatkin B.P.	Amoxicillin	Amoxin 250	02-16	1	1	0	0	1	0	0	1	0	0
Africa	DRC	Phatkin B.P.	Amoxicillin	Amoxin 500	09-16	1	1	0	0	0	1	0	0	1	0
Africa	DRC	Phatkin B.P.	Ciprofloxacin	Ciprokin-500	03-17	1	1	0	0	1	0	0	1	0	0
Africa	DRC	Phatkin B.P.	Ciprofloxacin	Ciprokin-500	17-17	1	0	1	0	1	0	0	0	1	0
Africa	DRC	Phatkin B.P.	Penicillin V	Peni-V	04-17	1	0	1	0	0	1	0	0	1	0
Africa	DRC	Zenufa Laboratoire	Ciprofloxacin	Ciproz 500	16T-141	1	0	1	0	1	0	0	0	1	0
Africa	DRC	Zenufa Laboratoire	Furosemide	Zenamide	14T-35	1	1	0	0	1	0	0	1	0	0
Africa	DRC	Zenufa Laboratoire	Furosemide	Zenamide	15T-75	1	1	0	0	1	0	0	1	0	0
Africa	DRC	Zenufa Laboratoire	Metronidazole	Zenogyl 250	16T-98	1	1	0	0	1	0	0	1	0	0
Africa	Ghana	Entrance Pharmaceuticals & Research Centre	Sulfa/Trimet	Co-Trimoxazole	NT17127	1	0	1	0	0	1	0	0	1	0
Africa	Ghana	Entrance Pharmaceuticals & Research Centre	Sulfa/Trimet	Co-Trimoxazole	NT17208	1	1	0	0	0	1	0	0	1	0
Africa	Ghana	Entrance Pharmaceuticals & Research Centre	Glibenclamide	Glibenclamide	NT17149	1	1	0	0	1	0	0	1	0	0
Africa	Ghana	Entrance Pharmaceuticals & Research Centre	Metronidazole	Metronidazole	NT17122	1	1	0	0	1	0	0	1	0	0
Africa	Ghana	Entrance Pharmaceuticals & Research Centre	Metronidazole	Metronidazole	NT17145	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	Cosmos Limited	Sulfa/Trimet	Cosatrim	60446	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	DAWA Limited	Metronidazole	Eflaron 250	1607130	2	2	0	0	2	0	0	2	0	0
Africa	Kenya	DAWA Limited	Furosemide	Frusemide	1605057	1	0	1	0	0	1	0	0	1	0
Africa	Kenya	DAWA Limited	Amoxicillin	Moxacil-250	1707321	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	DAWA Limited	Amoxicillin	Moxacil-500	1706107	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	**Stated country of origin**	**Stated manufacturer**	**INN**	**Stated product name**	**Batchnumber**	**N**	**complies**	**deviation**	**extreme deviation**	**complies 2**	**deviation2**	**extreme deviation 2**	**complies 3**	**deviation 3**	**extreme deviation 3**
Africa	Kenya	DAWA Limited	Salbutamol	Sabulin	1504062	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	DAWA Limited	Salbutamol	Sabulin	1608101	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	Elys Chemical Industries Ltd.	Sulfa/Trimet	CO-TRI	4E46	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	Elys Chemical Industries Ltd.	Furosemide	Frusemide	4G68	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	Elys Chemical Industries Ltd.	Furosemide	Frusemide	5H102	1	1	0	0	0	1	0	0	1	0
Africa	Kenya	Laboratory & Allied Ltd.	Amoxicillin	Kemoxyl 250	66735	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	Laboratory & Allied Ltd.	Sulfa/Trimet	Lecotrim	67056	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	MAC'S Pharmaceuticals Ltd.	Metronidazole	Metronyl	K2343	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	MAC'S Pharmaceuticals Ltd.	Metronidazole	Metronyl	L3028	1	0	0	1 [§]	0	0	1 [§]	0	0	1 [§]
Africa	Kenya	Pharmaceutical Manufacturing Co. Ltd.	Salbutamol	Astalin	15-02040	1	0	1	0	0	1	0	0	1	0
Africa	Kenya	Regal Pharmaceuticals Ltd.	Penicillin V	Unipen	151876	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	Regal Pharmaceuticals Ltd.	Penicillin V	Unipen 250	170093	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	Regal Pharmaceuticals Ltd.	Penicillin V	Unipen 250	170888	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	Regal Pharmaceuticals Ltd.	Penicillin V	Unipen 250	170890	1	1	0	0	1	0	0	1	0	0
Africa	Kenya	Regal Pharmaceuticals Ltd.	Sulfa/Trimet	Unitrim	160732	1	1	0	0	1	0	0	1	0	0
Africa	Nigeria	New Divine Favour Pharmaceutical Industries Ltd.	Doxycycline	New Divine Doxycycline Capsules	17	1	1	0	0	1	0	0	1	0	0
Africa	Senegal	Wintrop Pharma Sénégal Group SANOFI	Metronidazole	Flagyl 500	9705	1	1	0	0	1	0	0	1	0	0
Africa	Togo	Sprukfield	Sulfa/Trimet	Co-Trimoxazole	AT15001	2	2	0	0	2	0	0	2	0	0
Africa	Togo	Sprukfield	Sulfa/Trimet	Co-Trimoxazole	AT15007	1	1	0	0	1	0	0	1	0	0
Africa	Togo	Sprukfield	Sulfa/Trimet	Co-Trimoxazole	I3617	1	1	0	0	1	0	0	1	0	0
Africa	Uganda	Kampala Pharmaceutical Industries	Doxycycline	Azudox	2517	1	1	0	0	1	0	0	1	0	0
Africa	Uganda	Kampala Pharmaceutical Industries	Amoxicillin	Kam Amoxy Capsules	2417	1	1	0	0	1	0	0	1	0	0
Africa	Uganda	Kampala Pharmaceutical Industries	Sulfa/Trimet	Kam Cotri	1816	1	1	0	0	1	0	0	1	0	0
Africa	Uganda	Kampala Pharmaceutical Industries	Salbutamol	Kam Vent	0217	1	1	0	0	1	0	0	1	0	0
Africa	Uganda	Kampala Pharmaceutical Industries	Salbutamol	Kam Vent	0417	1	1	0	0	1	0	0	1	0	0
Africa	Uganda	Kampala Pharmaceutical Industries	Salbutamol	Kam Vent	0617	1	1	0	0	1	0	0	1	0	0
Africa	Uganda	Kampala Pharmaceutical Industries	Salbutamol	Kam Vent	0716	1	1	0	0	1	0	0	1	0	0
Africa	Uganda	Rene Industries Ltd.	Doxycycline	Doxyren	00217	1	1	0	0	1	0	0	1	0	0
Africa	Uganda	Rene Industries Ltd.	Sulfa/Trimet	Renetrim	04617	1	1	0	0	1	0	0	1	0	0
Americas	British West Indies	Prost Pharma (France)	Amoxicillin	Amoxdels-500	160952	1	1	0	0	1	0	0	1	0	0
Americas	British West Indies	Prost Pharma (France)	Sulfa/Trimet	Cotrimo-480mg	170610	1	1	0	0	1	0	0	1	0	0
Americas	USA	Sandoz	Furosemide	Furosemide	FT4986	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	Stated country of origin	Stated manufacturer	INN	Stated product name	Batchnumber	N	complies	deviation	extreme deviation	complies 2	deviation2	extreme deviation 2	complies 3	deviation 3	extreme deviation 3
Asia	China	Anhui Chengshi Pharmaceutical Co. Ltd	Metronidazole	Metronidazole Tablets	170627	1	1	0	0	1	0	0	1	0	0
Asia	China	Anhui Medipharm Co. Ltd.	Ciprofloxacin	Cipro 500	1704581	1	0	1	0	1	0	0	0	1	0
Asia	China	Chifeng Wanze Pharmaceutical Co. Ltd.	Metronidazole	Metazol	X6021	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP 500 mg	527160901	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP 500 mg	527170206	1	1	0	0	0	1	0	0	1	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP 500 mg	527170207	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP 500 mg	784150901	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP 500 mg	784150902	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP 500 mg	784150904	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP 500 mg	784160201	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP 500 mg	784160501	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP 500 mg	784161002	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Sulfa/Trimet	Cotrimoxazole Tablets B.P	541141102	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Sulfa/Trimet	Cotrimoxazole Tablets B.P	541150603	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Sulfa/Trimet	Cotrimoxazole Tablets B.P	541161201	2	2	0	0	2	0	0	2	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Doxycycline	Doxycycline Hyclate tablets USP	503150911	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Doxycycline	Doxycycline Hyclate tablets USP	6140911	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Metronidazole	Metronidazole 250 mg tables BP	825151102	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Metronidazole	Metronidazole 250 mg tables BP	825160701	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Metronidazole	Metronidazole 250 mg tables BP	825160702	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Metronidazole	Metronidazole 250 mg tables BP	82516202	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Metronidazole	Metronidazole 250 mg tables BP	825170302	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Metronidazole	Metronidazole 250 mg tables BP	825170306	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	Stated country of origin	Stated manufacturer	INN	Stated product name	Batchnumber	N	complies	deviation	extreme deviation	complies 2	deviation2	extreme deviation 2	complies 3	deviation 3	extreme deviation 3
Asia	China	CSPC Ouyi Pharmaceutical Co. Ltd.	Doxycycline	Unidoxy	160820	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	Amoxicillin	Amoxicillin Capsules BP	706170381	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	Amoxicillin	Amoxicillin Tablets USP	677150802	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	Amoxicillin	Amoxicillin Tablets USP	678150103	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	Amoxicillin	Amoxicillin Tablets for Oral Suspension	797160904	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	Amoxicillin	Amoxicillin Tablets for Oral Suspension	797160908	2	2	0	0	2	0	0	2	0	0
Asia	China	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	Amoxicillin	Amoxy-500	B6011	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	Amoxicillin	Amoxy-500	B6012	1	1	0	0	1	0	0	1	0	0
Asia	China	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	Penicillin V	Phenoxymethylpenicillin Tablets BP	688151109	2	2	0	0	2	0	0	2	0	0
Asia	China	Farmasino Pharmaceutical Co. Ltd	Amoxicillin	Amoxyn-500	160777	1	1	0	0	0	1	0	0	1	0
Asia	China	Farmasino Pharmaceutical Co. Ltd	Doxycycline	Doxiciclina	W160507	3	3	0	0	3	0	0	3	0	0
Asia	China	Farmasino Pharmaceutical Co. Ltd	Metronidazole	Mefagyl	SU20110076	1	1	0	0	1	0	0	1	0	0
Asia	China	Farmasino Pharmaceutical Co. Ltd	Penicillin V	Peni-V	W160939	1	1	0	0	1	0	0	1	0	0
Asia	China	Greenfield Pharmaceuticals (Jiang Su) Co. Ltd.	Ciprofloxacin	Cipromax Fort 500	173121091	1	1	0	0	1	0	0	1	0	0
Asia	China	Guilin Pharmaceutical Co. Ltd.	Sulfa/Trimet	Co-Trimoxazole USP	XN150764	1	1	0	0	1	0	0	1	0	0
Asia	China	Guilin Pharmaceutical Co. Ltd.	Sulfa/Trimet	Co-Trimoxazole USP	XN150766	1	1	0	0	1	0	0	1	0	0
Asia	China	Guilin Pharmaceutical Co. Ltd.	Sulfa/Trimet	Sulfamethoxazole and trimethoprim	XN150932	1	1	0	0	1	0	0	1	0	0
Asia	China	Jiangsu Pengyao Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacine Tablets USP	1510241	1	1	0	0	1	0	0	1	0	0
Asia	China	Jiangsu Pengyao Pharmaceutical Co. Ltd.	Metronidazole	Metronidazole Tablets BP	1608262	1	1	0	0	1	0	0	1	0	0
Asia	China	Jiangsu Ruinian Qianjin Pharm. Co.Ltd	Doxycycline	Doxycycline Sprukfield	141110	2	2	0	0	2	0	0	2	0	0
Asia	China	Jiangsu Ruinian Qianjin Pharm. Co.Ltd	Ciprofloxacin	Zeprox-500	170116	2	2	0	0	2	0	0	2	0	0
Asia	China	Jiangxi Xier Kangtai Pharmaceutical Co. Ltd.	Amoxicillin	Amoxycillin Capsules	150866	1	1	0	0	1	0	0	1	0	0
Asia	China	Jiangxi Xier Kangtai Pharmaceutical Co. Ltd.	Glibenclamide	Deominal	170303	2	2	0	0	0	2	0	0	2	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	**Stated country of origin**	**Stated manufacturer**	**INN**	**Stated product name**	**Batchnumber**	**N**	**complies**	**deviation**	**extreme deviation**	**complies 2**	**deviation2**	**extreme deviation 2**	**complies 3**	**deviation 3**	**extreme deviation 3**
Asia	China	Jiangxi Xier Kangtai Pharmaceutical Co. Ltd.	Doxycycline	Surelife Doxycyline	161109	2	2	0	0	2	0	0	2	0	0
Asia	China	Jinzhou Jiuyang Pharmaceutical Co. Ltd	Metronidazole	Metronidazole Tablets	T20160801	2	2	0	0	2	0	0	2	0	0
Asia	China	Jinzhou Jiuyang Pharmaceutical Co. Ltd	Metronidazole	Metronidazole Tablets B.P. 250mg	T21	1	1	0	0	0	0	1	0	0	1
Asia	China	JSPY Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciproin - 750	160422	1	1	0	0	1	0	0	1	0	0
Asia	China	JSPY Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciproinh - 500	160713	1	1	0	0	1	0	0	1	0	0
Asia	China	JSPY Pharmaceutical Co. Ltd.	Metronidazole	Metrole-500	150205	1	1	0	0	1	0	0	1	0	0
Asia	China	Nanjing Baijingyu Pharmaceutical Co. Ltd.	Doxycycline	Doxycycline Hyclate Tablets USP	DHA15007	1	1	0	0	1	0	0	1	0	0
Asia	China	Nanjing Baijingyu Pharmaceutical Co. Ltd.	Doxycycline	Doxycycline Hyclate Tablets USP	DHA17001	1	1	0	0	1	0	0	1	0	0
Asia	China	Nanjing Baijingyu Pharmaceutical Co. Ltd.	Sulfa/Trimet	Sulfamethoxazole and Trimethoprim Tablets USP	TSH15051	1	1	0	0	1	0	0	1	0	0
Asia	China	Nanjing Sino Pharmaceutical Ltd.	Amoxicillin	Amoxicillin	160103	1	1	0	0	1	0	0	1	0	0
Asia	China	Ningbo Shuangwei Pharmaceutical Co. Ltd	Amoxicillin	Amoxzem	161025	1	1	0	0	1	0	0	1	0	0
Asia	China	Ningbo Shuangwei Pharmaceutical Co. Ltd	Amoxicillin	Amoxzem	161212	1	1	0	0	1	0	0	1	0	0
Asia	China	Ningbo Shuangwei Pharmaceutical Co. Ltd	Amoxicillin	Amoxzem Tab.	151121	2	2	0	0	2	0	0	2	0	0
Asia	China	Ningbo Shuangwei Pharmaceutical Co. Ltd	Amoxicillin	Amoxzem Tab.	170617	1	1	0	0	1	0	0	1	0	0
Asia	China	Ningbo Shuangwei Pharmaceutical Co. Ltd	Metronidazole	Metrozem-500	171034	1	1	0	0	1	0	0	1	0	0
Asia	China	North China Pharmaceutical Co. Ltd.***	Penicillin V	Phenoxymethylpencillin 250mg BP	150923	1	1	0	0	1	0	0	1	0	0
Asia	China	North China Pharmaceutical Co. Ltd.***	Penicillin V	Phenoxymethylpenicillin Tablets 250mg	160334	2	2	0	0	2	0	0	2	0	0
Asia	China	North China Pharmaceutical Co. Ltd.***	Penicillin V	Phenoxymethylpenicillin Tablets BP	160405	1	1	0	0	1	0	0	1	0	0
Asia	China	North China Pharmaceutical Co. Ltd.***	Penicillin V	Phenoxymethylpenicillin Tablets BP	160906	1	1	0	0	1	0	0	1	0	0
Asia	China	North China Pharmaceutical Co. Ltd.***	Penicillin V	Phenoxymethylpenicillin Tablets BP	160907	2	2	0	0	2	0	0	2	0	0
Asia	China	North China Pharmaceutical Co. Ltd.***	Penicillin V	Phenoxymethylpenicilline	C6007	1	1	0	0	1	0	0	1	0	0
Asia	China	Reyoung Pharmaceutical Co. Ltd.	Amoxicillin	Amoxiciline Ubigen	163131260	1	1	0	0	1	0	0	1	0	0
Asia	China	Reyoung Pharmaceutical Co. Ltd.	Amoxicillin	Amoxiciline Ubigen	173132202	1	1	0	0	1	0	0	1	0	0
Asia	China	Reyoung Pharmaceutical Co. Ltd.	Amoxicillin	Amoxicillin Capsules BP	153132033	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	Stated country of origin	Stated manufacturer	INN	Stated product name	Batchnumber	N	complies	deviation	extreme deviation	complies 2	deviation2	extreme deviation 2	complies 3	deviation 3	extreme deviation 3
Asia	China	Reyoung Pharmaceutical Co. Ltd.	Amoxicillin	Amoxicillin Capsules BP	163132143	1	1	0	0	1	0	0	1	0	0
Asia	China	Reyoung Pharmaceutical Co. Ltd.	Amoxicillin	Amoxyn-500	160863	1	1	0	0	1	0	0	1	0	0
Asia	China	Reyoung Pharmaceutical Co. Ltd.	Amoxicillin	Amoxyn-500	P6064	1	1	0	0	1	0	0	1	0	0
Asia	China	Reyoung Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacin Tablets	163121042	1	1	0	0	1	0	0	1	0	0
Asia	China	Reyoung Pharmaceutical Co. Ltd.	Ciprofloxacin	Ciprofloxacin Tablets	163121044	2	2	0	0	2	0	0	2	0	0
Asia	China	Shandong Shenglu Pharmaceutical Co. Ltd	Penicillin V	Penicillin V	20160919	3	0	0	3	0	3	0	0	0	3
Asia	China	Shandong Shenglu Pharmaceutical Co. Ltd	Penicillin V	Transglobe Pen Tabs	170310	1	0	0	1	0	1	0	0	0	1
Asia	China	Shandong Xier Kangtai Pharm Co. Ltd	Metformin	Jeo-Phage Tablets	1610110	1	1	0	0	1	0	0	1	0	0
Asia	China	Shandong Yikang Pharmaceutical Co. Ltd.	Penicillin V	Penicillin V Potassium 250mg	170322	2	1	1	0	2	0	0	1	1	0
Asia	China	Shanghai Juchen Import and Exports Co. Ltd.	Amoxicillin	Konmoxy Capsules	173131530	1	1	0	0	1	0	0	1	0	0
Asia	China	Shanghai Juchen Import and Exports Co. Ltd.	Amoxicillin	Konmoxy Capsules	173131532	1	1	0	0	1	0	0	1	0	0
Asia	China	Shanghai Juchen Import and Exports Co. Ltd.	Amoxicillin	Konmoxy Capsules	173131533	1	1	0	0	1	0	0	1	0	0
Asia	China	Shanghai Juchen Import and Exports Co. Ltd.	Metronidazole	Metronidazole Tablets	171287	1	1	0	0	1	0	0	1	0	0
Asia	China	Shanxi Lianbang Pharmaceutical Co. Ltd.	Doxycycline	Doxycycline Capsules	160565	2	2	0	0	2	0	0	2	0	0
Asia	China	Sinochem Jiangsu Co. Ltd	Amoxicillin	Amoxicillin 500mg	170710	1	1	0	0	0	1	0	0	1	0
Asia	China	Sinochem Jiangsu Co. Ltd	Amoxicillin	Amoxicillin Capsules B.P	161011	2	2	0	0	2	0	0	2	0	0
Asia	China	Sinochem Jiangsu Co. Ltd	Ciprofloxacin	Ciprofloxacine Tablets USP	160283	1	1	0	0	1	0	0	1	0	0
Asia	China	Sinochem Jiangsu Co. Ltd	Ciprofloxacin	Ciprofloxacine Tablets USP	1605603	4	3	1	0	4	0	0	3	1	0
Asia	China	Sinochem Jiangsu Co. Ltd	Ciprofloxacin	Ciprolif-500	170751	2	1	1	0	2	0	0	1	1	0
Asia	China	Sinochem Jiangsu Co. Ltd	Metronidazole	Metronidazole GP	170717	1	1	0	0	0	0	1	0	0	1
Asia	China	Sinochem Jiangsu Co. Ltd	Metronidazole	Metronidazole GP	171201	2	2	0	0	0	0	2	0	0	2
Asia	China	Sinochem Jiangsu Co. Ltd	Penicillin V	Peni-V	170504	1	1	0	0	1	0	0	1	0	0
Asia	China	Sishui xier Kang Pharmaceutical Co.Ltd	Penicillin V	Penicillin V Potassium - 5000,000	160718	1	0	0	1	0	1	0	0	0	1
Asia	China	Yanzhou Xierkangtai pharmaceutical Co. Ltd.	Amoxicillin	Amoxicillin	S37	1	1	0	0	1	0	0	1	0	0
Asia	China	Yanzhou Xierkangtai pharmaceutical Co. Ltd.	Doxycycline	Doxycycline	S06	1	1	0	0	1	0	0	1	0	0
Asia	China	Yanzhou Xierkangtai pharmaceutical Co. Ltd.	Penicillin V	Penicillin VK Tablets	S20170329	1	0	1	0	1	0	0	0	1	0
Asia	Hong Kong	Hongkong Prost Medicines And Health Products Co. Ltd.	Hydrochlorothiazide	Hydrochlorothiazide	160815	3	3	0	0	3	0	0	3	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	**Stated country of origin**	**Stated manufacturer**	**INN**	**Stated product name**	**Batchnumber**	**N**	**complies**	**deviation**	**extreme deviation**	**complies 2**	**deviation2**	**extreme deviation 2**	**complies 3**	**deviation 3**	**extreme deviation 3**
Asia	India	Agog Pharma Ltd.	Doxycycline	Agodox	C55016	1	1	0	0	1	0	0	1	0	0
Asia	India	Agog Pharma Ltd.	Doxycycline	Agodox	C73018	1	1	0	0	1	0	0	1	0	0
Asia	India	Agog Pharma Ltd.	Sulfa/Trimet	Co-Trimoxazole Tablets BP Trimago	T64108	1	1	0	0	1	0	0	1	0	0
Asia	India	Agog Pharma Ltd.	Sulfa/Trimet	Co-Trimoxazole Tablets BP Trimago	T71155	1	1	0	0	1	0	0	1	0	0
Asia	India	Alkem Laboratories Ltd.	Amoxi/Clav	Acinet	6150096	1	1	0	0	0	1	0	0	1	0
Asia	India	Arco Pharma Pvt. Ltd	Furosemide	Frusema	562E	1	1	0	0	0	1	0	0	1	0
Asia	India	Arco Pharma Pvt. Ltd	Furosemide	Frusema	618E	3	3	0	0	1	2	0	1	2	0
Asia	India	Arco Pharma Pvt. Ltd	Furosemide	Frusema	619E	3	3	0	0	0	3	0	0	3	0
Asia	India	Asence Pharma Pvt. Ltd.	Furosemide	Furosemide Tabrad	T-799002	2	2	0	0	2	0	0	2	0	0
Asia	India	Asence Pharma Pvt. Ltd.	Metronidazole	Metronidazole 500	T-800003	1	1	0	0	1	0	0	1	0	0
Asia	India	Asence Pharma Pvt. Ltd.	Furosemide	Tafuros 40	AC25701	2	2	0	0	1	1	0	1	1	0
Asia	India	Asence Pharma Pvt. Ltd.	Amoxi/Clav	Tamclav 1G	PT7088	1	1	0	0	0	1	0	0	1	0
Asia	India	Astra Lifecare Pvt. Ltd.	Salbutamol	Asbutol-P4	023	1	1	0	0	1	0	0	1	0	0
Asia	India	Astra Lifecare Pvt. Ltd.	Doxycycline	Asdoxin	617	1	1	0	0	0	0	1	0	0	1
Asia	India	Astra Lifecare Pvt. Ltd.	Ciprofloxacin	Asflox-500	463	3	3	0	0	3	0	0	3	0	0
Asia	India	Astra Lifecare Pvt. Ltd.	Furosemide	Asix	028	1	1	0	0	1	0	0	1	0	0
Asia	India	Astra Lifecare Pvt. Ltd.	Furosemide	Asix	031	1	1	0	0	1	0	0	1	0	0
Asia	India	Astra Lifecare Pvt. Ltd.	Metronidazole	Astrogyl	497	1	1	0	0	1	0	0	1	0	0
Asia	India	Astra Lifecare Pvt. Ltd.	Penicillin V	As-V	185	1	1	0	0	1	0	0	1	0	0
Asia	India	Astra Lifecare Pvt. Ltd.	Penicillin V	As-V	187	1	1	0	0	1	0	0	1	0	0
Asia	India	Astra Lifecare Pvt. Ltd.	Atenolol	Hyperlok-100	025	1	1	0	0	0	0	1	0	0	1
Asia	India	Aura pharmaceuticals Pvt. Ltd	Sulfa/Trimet	Cotrimex-480	01	1	1	0	0	0	1	0	0	1	0
Asia	India	Aura pharmaceuticals Pvt. Ltd	Metronidazole	Megyl	006	2	2	0	0	2	0	0	2	0	0
Asia	India	Aura pharmaceuticals Pvt. Ltd	Metronidazole	Megyl	009	1	1	0	0	1	0	0	1	0	0
Asia	India	Aura pharmaceuticals Pvt. Ltd	Salbutamol	Salbutamol Tablets BP	001	5	2	3	0	5	0	0	2	3	0
Asia	India	Aurobindo Pharma Ltd.	Amoxi/Clav	Koact 625	EL5016026-D	1	1	0	0	0	1	0	0	1	0
Asia	India	Axon Drugs Pvt. Ltd.	Metformin	Asur-850	16ASU01	1	1	0	0	1	0	0	1	0	0
Asia	India	Bliss GVS Pharma Ltd.	Metformin	BGMET 850	BMT004	1	0	1	0	0	1	0	0	1	0
Asia	India	Cadila Healthcare Ltd.	Atenolol	Catenol 100	GR2742	1	1	0	0	1	0	0	1	0	0
Asia	India	Cipla Ltd.	Ciprofloxacin	Ciplox-500	ID55812	1	1	0	0	1	0	0	1	0	0
Asia	India	Ciron Drugs and Pharmaceuticals Ltd.	Metformin	Shalformin	5E01015	2	2	0	0	2	0	0	2	0	0
Asia	India	Combitic Global Caplet Pvt. Ltd.	Doxycycline	Doxynol 200	CDY-13	1	1	0	0	1	0	0	1	0	0
Asia	India	Fourrts	Sulfa/Trimet	Co-Trimoxazole Tablets BP Megatrim	C1796	1	1	0	0	1	0	0	1	0	0
Asia	India	Fourrts	Doxycycline	Doxycycline Hyclate Tablets USP	E1193	1	1	0	0	1	0	0	1	0	0
Asia	India	Fourrts	Metformin	METFIL	C0335	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	Stated country of origin	Stated manufacturer	INN	Stated product name	Batchnumber	N	complies	deviation	extreme deviation	complies 2	deviation2	extreme deviation 2	complies 3	deviation 3	extreme deviation 3
Asia	India	Global Pharma Healthcare Pvt. Ltd.	Hydrochlorothiazide	Hydrochlorothiazide comprimes BP	TE399	4	4	0	0	4	0	0	4	0	0
Asia	India	Holden Medical Laboratories Pvt. Ltd.	Atenolol	Atenolol Tablets BP	HE15C28	1	1	0	0	1	0	0	1	0	0
Asia	India	Holden Medical Laboratories Pvt. Ltd.	Ciprofloxacin	Ciprofloxacin Tablets USP	HE16D39	1	1	0	0	1	0	0	1	0	0
Asia	India	Holden Medical Laboratories Pvt. Ltd.	Glibenclamide	Glibenclamide Tablets B.P	HE15L66	1	1	0	0	1	0	0	1	0	0
Asia	India	Intermed	Amoxi/Clav	Amoxicillin and Clavulanate Potassium Tablets	QTN02	1	1	0	0	1	0	0	1	0	0
Asia	India	Ipca Laboratories Ltd.	Amoxi/Clav	Rapiclav-1g	CIJ177040	1	1	0	0	1	0	0	1	0	0
Asia	India	J. B. Chemicals and Pharmaceuticals Ltd.	Metronidazole	Unique's Metrogyl 200	AM56004	1	1	0	0	1	0	0	1	0	0
Asia	India	Kopran Limited	Amoxicillin	AMYN-250	S3646054	1	1	0	0	1	0	0	1	0	0
Asia	India	Kopran Limited	Sulfa/Trimet	Trim - 480	K3806011	1	1	0	0	1	0	0	1	0	0
Asia	India	Leben Laboratories Pvt. Ltd	Doxycycline	Doxyleb	C137	1	1	0	0	1	0	0	1	0	0
Asia	India	Lincoln Pharmaceuticals Ltd.	Doxycycline	Alldox	AA5006	1	1	0	0	1	0	0	1	0	0
Asia	India	Lincoln Pharmaceuticals Ltd.	Doxycycline	Alldox	AA7001	1	1	0	0	1	0	0	1	0	0
Asia	India	Lincoln Pharmaceuticals Ltd.	Ciprofloxacin	CEEPRO-500	DY6028	1	1	0	0	1	0	0	1	0	0
Asia	India	Lincoln Pharmaceuticals Ltd.	Ciprofloxacin	Ciprofloxacine Ubigen	GK6007	1	1	0	0	1	0	0	1	0	0
Asia	India	Lincoln Pharmaceuticals Ltd.	Ciprofloxacin	Ciprofloxacine Ubigen	GK7010	1	1	0	0	1	0	0	1	0	0
Asia	India	Lincoln Pharmaceuticals Ltd.	Sulfa/Trimet	Cotrimoxazole Ubigen	GM6006	2	2	0	0	2	0	0	2	0	0
Asia	India	Lincoln Pharmaceuticals Ltd.	Sulfa/Trimet	Sulphatrim	NE6004	1	1	0	0	1	0	0	1	0	0
Asia	India	Lord Lifescience Pvt. Ltd.	Salbutamol	Salbesone	HONO	1	0	1	0	1	0	0	0	1	0
Asia	India	Macleods Pharmaceuticals Ltd.	Ciprofloxacin	Coflox-500	FCF657A	1	1	0	0	1	0	0	1	0	0
Asia	India	Macleods Pharmaceuticals Ltd.	Ciprofloxacin	Coflox-500	FCF659A	1	1	0	0	1	0	0	1	0	0
Asia	India	Macleods Pharmaceuticals Ltd.	Sulfa/Trimet	Co-trimoxazole Tablets BP 480mg	1708	1	1	0	0	1	0	0	1	0	0
Asia	India	Macleods Pharmaceuticals Ltd.	Sulfa/Trimet	Co-trimoxazole Tablets BP 480mg	HTF713A	1	1	0	0	1	0	0	1	0	0
Asia	India	Mancare pharmaceutical Ltd	Furosemide	Frunmide	TPF03	1	1	0	0	1	0	0	1	0	0
Asia	India	Mancare pharmaceutical Ltd	Furosemide	Frunmide	TRI18	1	1	0	0	1	0	0	1	0	0
Asia	India	Mancare pharmaceutical Ltd	Furosemide	Lancize	TRF28	1	1	0	0	1	0	0	1	0	0
Asia	India	Mancare pharmaceutical Ltd	Furosemide	Lancize	TRF32	1	1	0	0	1	0	0	1	0	0
Asia	India	Maneesh Pharmaceuticals Ltd	Doxycycline	Doxycycline Tablets	S01	1	1	0	0	1	0	0	1	0	0
Asia	India	Maxheal Laboratories Pvt. Ltd.	Salbutamol	Salbutamol	SW7003	1	0	1	0	0	1	0	0	1	0
Asia	India	Maxheal Laboratories Pvt. Ltd.	Ciprofloxacin	Wincip-500	WC6001	1	1	0	0	1	0	0	1	0	0
Asia	India	Maxtar Bio-Genics	Sulfa/Trimet	Cotrimoxazole Pextran_SS	MT4T-1601	2	2	0	0	0	2	0	0	2	0
Asia	India	Maxtar Bio-Genics	Metformin	Maxformin-500	MT3M-1602	1	1	0	0	1	0	0	1	0	0
Asia	India	Maxtar Bio-Genics	Metformin	Maxformin-500	MT3M-1607	1	1	0	0	1	0	0	1	0	0
Asia	India	Maxtar Bio-Genics	Metformin	Maxformin-500	MXTEJ1701	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	Stated country of origin	Stated manufacturer	INN	Stated product name	Batchnumber	N	complies	deviation	extreme deviation	complies 2	deviation2	extreme deviation 2	complies 3	deviation 3	extreme deviation 3
Asia	India	Maxtar Bio-Genics	Metronidazole	Metzole-500	MT7T-1601	2	2	0	0	2	0	0	2	0	0
Asia	India	Maxtar Bio-Genics	Salbutamol	Salbutamol Comprimes BP	MTSA-1402	3*	0	0	3*	0	0	3*	0	0	3*
Asia	India	Maxtar Bio-Genics	Salbutamol	Salbutamol Comprimes BP	MTSA-1602	4	4	0	0	4	0	0	4	0	0
Asia	India	Medicamen Biotech Ltd.	Ciprofloxacin	Ciprofloxacine USP 500 mg	NT6698	1	1	0	0	1	0	0	1	0	0
Asia	India	Medicamen Biotech Ltd.	Doxycycline	Doxycycline Hyclate	NT7540	1	1	0	0	1	0	0	1	0	0
Asia	India	Medicamen Biotech Ltd.	Glibenclamide	Glibenclamide	NT5047	1	1	0	0	1	0	0	1	0	0
Asia	India	Medicamen Biotech Ltd.	Glibenclamide	Glibenclamide	NT5048	2	2	0	0	2	0	0	2	0	0
Asia	India	Medicamen Biotech Ltd.	Metformin	Metformin	NT5524	1	1	0	0	1	0	0	1	0	0
Asia	India	Medicamen Biotech Ltd.	Metformin	Metformin	NT5525	1	1	0	0	0	1	0	0	1	0
Asia	India	Medicamen Biotech Ltd.	Metronidazole	Metronidazole	NT5371	1	1	0	0	1	0	0	1	0	0
Asia	India	Medicef Pharma	Amoxi/Clav	Arauclav	ET16G014	1	1	0	0	1	0	0	1	0	0
Asia	India	Medicef Pharma	Amoxi/Clav	Moxyclav	ET16E008	1	1	0	0	1	0	0	1	0	0
Asia	India	Medicef Pharma	Amoxi/Clav	Moxyclav	ET16G010	1	1	0	0	1	0	0	1	0	0
Asia	India	Medicef Pharma	Amoxi/Clav	Moxyclav	ET16G020	1	1	0	0	1	0	0	1	0	0
Asia	India	Medico Remedies Pvt. Ltd.	Salbutamol	Salbutamol Tablets BP	SAU513	2	0	0	2	0	2	0	0	0	2
Asia	India	Medico Remedies Pvt. Ltd.	Salbutamol	Salbutamol Tablets BP	SAU537	1	0	0	1	1	0	0	0	0	1
Asia	India	Medico Remedies Pvt. Ltd.	Salbutamol	Salbutamol Tablets BP	SAU602	1	0	1	0	0	1	0	0	1	0
Asia	India	Medico Remedies Pvt. Ltd.	Salbutamol	Salbutamol Tablets BP	SAU630	1	0	0	1	1	0	0	0	0	1
Asia	India	Medley Pharmaceuticals Ltd.	Ciprofloxacin	Ecoflox-500	D60130	1	1	0	0	1	0	0	1	0	0
Asia	India	Medley Pharmaceuticals Ltd.	Ciprofloxacin	Ecoflox-500	D60184	1	1	0	0	1	0	0	1	0	0
Asia	India	Medley Pharmaceuticals Ltd.	Ciprofloxacin	Ecoflox-500	D60246	1	1	0	0	1	0	0	1	0	0
Asia	India	Medley Pharmaceuticals Ltd.	Ciprofloxacin	Ecoflox-500	D60263	1	1	0	0	1	0	0	1	0	0
Asia	India	Medley Pharmaceuticals Ltd.	Ciprofloxacin	Ecoflox-500	D60445	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Amoxi/Clav	Amoxicillin 500mg + Clavulanic acid 125mg BP	F456733	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Amoxicillin	Amoxicillin Gelules	1475017	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Amoxicillin	Amoxicillin Tablets USP 250	15329002	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Amoxicillin	Amoxicillin Tablets USP 500	16144002	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Amoxicillin	Amoxicillin Tablets USP 500	16363002	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Ciprofloxacin	Ciprofloxacine 500 mg USP	5E 101	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Ciprofloxacin	Ciprofloxacine Comprimes USP	217090001	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Ciprofloxacin	Ciprofloxacine Comprimes USP	6C66	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Ciprofloxacin	Ciprofloxacine Comprimes USP	6C67	2	2	0	0	2	0	0	2	0	0
Asia	India	Medopharm Pvt. Ltd.	Amoxi/Clav	Clavumoccid	16213003	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Amoxi/Clav	Cledomox 562.5	17361003	1	0	1	0	1	0	0	0	1	0
Asia	India	Medopharm Pvt. Ltd.	Amoxi/Clav	Co-amoxiclav	1680002	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Sulfa/Trimet	Co-trimoxazole BP	4J32	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Sulfa/Trimet	Co-trimoxazole BP	4J34	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Sulfa/Trimet	Co-trimoxazole BP	4MB107	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Sulfa/Trimet	Co-trimoxazole BP	6MD354	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Sulfa/Trimet	Co-trimoxazole BP	6MD360	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Sulfa/Trimet	Co-trimoxazole BP	6MD364	2	2	0	0	2	0	0	2	0	0
Asia	India	Medopharm Pvt. Ltd.	Sulfa/Trimet	Co-trimoxazole BP	6MG195	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	Stated country of origin	Stated manufacturer	INN	Stated product name	Batchnumber	N	complies	deviation	extreme deviation	complies 2	deviation2	extreme deviation 2	complies 3	deviation 3	extreme deviation 3
Asia	India	Medopharm Pvt. Ltd.	Sulfa/Trimet	Co-trimoxazole BP	6MG198	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Sulfa/Trimet	Co-trimoxazole USP	XN150772	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Doxycycline	Doxycycline Hyclate USP	4MJ124	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Doxycycline	Doxycycline Hyclate USP	5MH47	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Doxycycline	Doxycycline Hyclate USP	5MJ146	2	2	0	0	2	0	0	2	0	0
Asia	India	Medopharm Pvt. Ltd.	Penicillin V	Fenoximetilpenicilina	1208524	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Furosemide	Furosemid BP	4MJ129	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Doxycycline	Generic Plus Doxycycline Hyclate 100mg USP	6MF123	2	2	0	0	2	0	0	2	0	0
Asia	India	Medopharm Pvt. Ltd.	Metformin	Metformin Tablets 500 mg BP	7MA42	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Metronidazole	Metronidazole	4MJ164	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Metronidazole	Metronidazole 250 mg BP	5B07	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Metronidazole	Metronidazole 250 mg BP	5F42	1	1	0	0	0	1	0	0	1	0
Asia	India	Medopharm Pvt. Ltd.	Metronidazole	Metronidazole 250 mg BP	5MA91	2	2	0	0	2	0	0	2	0	0
Asia	India	Medopharm Pvt. Ltd.	Metronidazole	Metronidazole 250 mg BP	5ME187	1	1	0	0	1	0	0	1	0	0
Asia	India	Medopharm Pvt. Ltd.	Salbutamol	Salbutamol Tablets BP	6MF93	2	2	0	0	2	0	0	2	0	0
Asia	India	Medopharm Pvt. Ltd.	Salbutamol	Salbutamol Tablets BP	6MF94	2	2	0	0	2	0	0	2	0	0
Asia	India	Mepro Pharmaceuticals Pvt. Ltd.	Ciprofloxacin	Ciprofloxacin	UCP224	1	1	0	0	1	0	0	1	0	0
Asia	India	Mepro Pharmaceuticals Pvt. Ltd.	Doxycycline	Doxycycline	UDH220	1	1	0	0	1	0	0	1	0	0
Asia	India	Micro Labs Ltd.	Furosemide	Furosemide 40mg BP	FRIH0077	4	4	0	0	4	0	0	4	0	0
Asia	India	Milan Laboratories (India) Pvt. Ltd	Sulfa/Trimet	Co-Trimoxazole	MG16041	1	1	0	0	1	0	0	1	0	0
Asia	India	Milan Laboratories (India) Pvt. Ltd	Amoxicillin	Miloxy 250	MP17005	1	1	0	0	1	0	0	1	0	0
Asia	India	Milan Laboratories (India) Pvt. Ltd	Amoxicillin	Miloxy 250	MP17069	1	1	0	0	1	0	0	1	0	0
Asia	India	Milan Laboratories (India) Pvt. Ltd	Amoxicillin	Miloxy 250	MP17210	1	1	0	0	1	0	0	1	0	0
Asia	India	Milan Laboratories (India) Pvt. Ltd	Amoxicillin	Miloxy 250	MP17258	1	1	0	0	1	0	0	1	0	0
Asia	India	Milan Laboratories (India) Pvt. Ltd	Penicillin V	Penicillin-Tablets	MP0268	1	0	1	0	1	0	0	0	1	0
Asia	India	Nem Laboratories Pvt. Ltd.	Furosemide	Frusemide	FRS615	1	1	0	0	1	0	0	1	0	0
Asia	India	not stated	Amoxi/Clav	Oxynic	B1730	1	1	0	0	1	0	0	1	0	0
Asia	India	Osaka Pharmaceuticals Pvt. Ltd.	Glibenclamide	Transglobe glibenclamide	6A038	3	1	2	0	3	0	0	1	2	0
Asia	India	PIL Pharmaceuticals Pvt. Ltd.	Amoxi/Clav	Co-amoxiclav Tablets BP 625mg	AAGB6027	1	1	0	0	1	0	0	1	0	0
Asia	India	Prashi Pharma Pvt. Ltd	Furosemide	Frusemide	FR-01	2	2	0	0	0	1	1	0	1	1
Asia	India	Prashi Pharma Pvt. Ltd	Furosemide	Frusemide	FR-02	2	2	0	0	0	2	0	0	2	0
Asia	India	Prashi Pharma Pvt. Ltd	Furosemide	Frusemide	FR-03	1	1	0	0	0	1	0	0	1	0
Asia	India	Prashi Pharma Pvt. Ltd	Metronidazole	Metro 250	MT-133	1	1	0	0	1	0	0	1	0	0
Asia	India	Shalina Laboratories Pvt. Ltd.	Sulfa/Trimet	Sulfatrim	J7007	1	1	0	0	1	0	0	1	0	0
Asia	India	Sparsh Bio-Tech Pvt. Ltd.	Amoxicillin	HIPEN	HC225	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	Stated country of origin	Stated manufacturer	INN	Stated product name	Batchnumber	N	complies	deviation	extreme deviation	complies 2	deviation2	extreme deviation 2	complies 3	deviation 3	extreme deviation 3
Asia	India	Sparsh Bio-Tech Pvt. Ltd.	Amoxicillin	HIPEN	HC232	1	1	0	0	1	0	0	1	0	0
Asia	India	Sparsh Bio-Tech Pvt. Ltd.	Penicillin V	Speniv Tablets 250	PT448	1	1	0	0	1	0	0	1	0	0
Asia	India	Sparsh Bio-Tech Pvt. Ltd.	Penicillin V	Speniv Tablets 250	PT457	1	1	0	0	1	0	0	1	0	0
Asia	India	Sparsh Bio-Tech Pvt. Ltd.	Penicillin V	Speniv Tablets 250	PT460	1	1	0	0	1	0	0	1	0	0
Asia	India	Sparsh Bio-Tech Pvt. Ltd.	Penicillin V	Speniv Tablets 250	PT467	2	2	0	0	2	0	0	2	0	0
Asia	India	Strides Arcolab Limited	Amoxicillin	Amoxicillin Tablets	AG-044	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Amoxicillin	Amoxicillin Tablets	AG-064	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Ciprofloxacin	Ciprofloxacine Tablets USP	7750797	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Ciprofloxacin	Ciprofloxacine Tablets USP	7750816	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Sulfa/Trimet	Co-trimoxazole Tablets BP	7750175	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Sulfa/Trimet	Co-trimoxazole Tablets BP	7750676	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Sulfa/Trimet	Co-trimoxazole Tablets BP	7750677	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Sulfa/Trimet	Co-trimoxazole Tablets BP	7750714	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Sulfa/Trimet	Co-trimoxazole Tablets BP	7750718	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Sulfa/Trimet	Co-trimoxazole Tablets BP	7750719	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Furosemide	Frusemide BP	7351588	2	1	1	0	1	1	0	0	2	0
Asia	India	Strides Arcolab Limited	Metformin	Metformin Tablets BP	7351219	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Metformin	Metformin Tablets BP	7351823	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Metformin	Metformin Tablets BP	7351824	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Metronidazole	Metronidazole Comprimes BP	7750163	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Metronidazole	Metronidazole Comprimes BP	7750581	2	2	0	0	2	0	0	2	0	0
Asia	India	Strides Arcolab Limited	Metronidazole	Metronidazole Comprimes BP	7750973	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Metronidazole	Metronidazole Comprimes BP	7751013	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Metronidazole	Metronidazole Comprimes BP	7751017	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Metronidazole	Metronidazole Comprimes BP	7751018	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Arcolab Limited	Metronidazole	Metronidazole Comprimes BP	7751038	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Shasun Limited	Ciprofloxacin	Ciprofloxacine	7352249	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Shasun Limited	Doxycycline	Doxycycline Gelules BP	7750636	4	4	0	0	4	0	0	4	0	0
Asia	India	Strides Shasun Limited	Metformin	Metformin	7352132	2	2	0	0	2	0	0	2	0	0
Asia	India	Strides Shasun Limited	Metronidazole	Metrosim-200	7351898	1	0	1	0	1	0	0	0	1	0
Asia	India	Strides Shasun Limited	Metronidazole	Metrosim-200	7352023	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Shasun Limited	Metronidazole	Metrosim-200	7352053	1	1	0	0	1	0	0	1	0	0
Asia	India	Strides Shasun Limited	Metronidazole	Metrosim-200	7352173	1	0	1	0	1	0	0	0	1	0
Asia	India	Triveni Formulations Limited	Doxycycline	Doxycycline Capsules B.P	WF607	1	1	0	0	1	0	0	1	0	0
Asia	India	Ultra Care International	Sulfa/Trimet	Cotrimoxazole Tablets B.P	UT035	2	2	0	0	2	0	0	2	0	0
Asia	India	UMEDICA Laboratories	Glibenclamide	Glibenclamide	NB502	1	1	0	0	1	0	0	1	0	0
Asia	India	Zee Laboratories	Amoxicillin	Monamox-250 DT	416-170	1	1	0	0	1	0	0	1	0	0
Asia	India	ZIM Laboratories Ltd.	Atenolol	Atenolol Tablets BP	FO38J601	1	1	0	0	1	0	0	1	0	0
Asia	Sultanat of Oman	National Pharmaceutical Industries Co. (SAOG)	Ciprofloxacin	Omacip 500	2016312	1	1	0	0	1	0	0	1	0	0
Asia	Turkey	Bilim Pharmaceuticals	Amoxi/Clav	Klacin BID	16256320A	1	1	0	0	1	0	0	1	0	0
Europe	Austria	Sandoz	Amoxicillin	Amoxycillin Sandoz	GM3744	1	1	0	0	1	0	0	1	0	0
Europe	Austria	Sandoz	Amoxicillin	Amoxycillin Sandoz	HD4437	1	1	0	0	1	0	0	1	0	0
Europe	Austria	Sandoz	Amoxicillin	Amoxycillin Sandoz	HD4445	1	1	0	0	1	0	0	1	0	0
Europe	Austria	Sandoz	Amoxi/Clav	Curam 625	FL5158	1	1	0	0	1	0	0	1	0	0
Europe	Austria	Sandoz	Penicillin V	Ospen	GM5718	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	**Stated country of origin**	**Stated manufacturer**	**INN**	**Stated product name**	**Batchnumber**	**N**	**complies**	**deviation**	**extreme deviation**	**complies 2**	**deviation2**	**extreme deviation 2**	**complies 3**	**deviation 3**	**extreme deviation 3**
Europe	Austria	Sandoz	Penicillin V	Ospen	GY5549	2	2	0	0	2	0	0	2	0	0
Europe	Austria	Sandoz	Penicillin V	Ospen	HC8534	1	1	0	0	1	0	0	1	0	0
Europe	Austria	Sandoz	Penicillin V	Ospen	HK8732	1	1	0	0	1	0	0	1	0	0
Europe	Austria	Sandoz	Penicillin V	Starpen	GH3937	1	1	0	0	1	0	0	1	0	0
Europe	Belgium	Merck	Metformin	Glucophage	18664	1	1	0	0	1	0	0	1	0	0
Europe	Belgium	Merck	Metformin	Glucophage	18670	1	1	0	0	1	0	0	1	0	0
Europe	Belgium	Merck	Metformin	Glucophage	F0471	1	1	0	0	1	0	0	1	0	0
Europe	Belgium	Oxford Pharma	Penicillin V	Penicillin-V Tablets	190	1	0	0	1 [§]	0	0	1 [§]	0	0	1 [§]
Europe	Cyprus	Medochemie Ltd.	Amoxi/Clav	Moxiclav 1g	PE042	1	1	0	0	1	0	0	1	0	0
Europe	Cyprus	Medochemie Ltd.	Amoxi/Clav	Moxiclav 625mg	P9H020	1	1	0	0	1	0	0	1	0	0
Europe	Cyprus	Remedica Ltd	Metformin	Glyformin 500	67721	1	1	0	0	1	0	0	1	0	0
Europe	Cyprus	Remedica Ltd	Metformin	Glyformin 500	68397	1	1	0	0	1	0	0	1	0	0
Europe	France	Famar Lyon	Metformin	Glucophage 500 mg	F0554	1	1	0	0	1	0	0	1	0	0
Europe	France	Glaxo Welcome Production	Amoxi/Clav	Augmentin Adultes	2478	1	1	0	0	1	0	0	1	0	0
Europe	France	Glaxo Welcome Production	Amoxi/Clav	Augmentin Adultes	HN8F	2	2	0	0	2	0	0	2	0	0
Europe	France	Laboratoire Bailly-Creat	Sulfa/Trimet	Cotrim Fort	CR479	1	1	0	0	1	0	0	1	0	0
Europe	France	Laboratoire Bailly-Creat	Metronidazole	Creazol	124	1	1	0	0	1	0	0	1	0	0
Europe	France	Laboratoire Bailly-Creat	Doxycycline	Doxycreat	45	1	1	0	0	1	0	0	1	0	0
Europe	France	Laboratoire Bailly-Creat	Doxycycline	Doxycreat	47	1	1	0	0	1	0	0	1	0	0
Europe	France	Laboratoire Bailly-Creat	Doxycycline	Doxycreat	50	1	1	0	0	1	0	0	1	0	0
Europe	France	Laboratoire Bailly-Creat	Doxycycline	Doxycreat	51	1	1	0	0	1	0	0	1	0	0
Europe	France	Laboratoires Bailleul	Doxycycline	Tolexine Ge	T1701500	1	1	0	0	1	0	0	1	0	0
Europe	France	Sanofi-Winthrop Industrie	Glibenclamide	Daonil	6LP5A	1	1	0	0	1	0	0	1	0	0
Europe	France	Sanofi-Winthrop Industrie	Glibenclamide	Daonil	7M74A	1	1	0	0	1	0	0	1	0	0
Europe	France	Sanofi-Winthrop Industrie	Glibenclamide	Daonil	7M74E	1	1	0	0	1	0	0	1	0	0
Europe	France	Sanofi-Winthrop Industrie	Furosemide	Lasilix 40 mg	6NV5A	1	1	0	0	1	0	0	1	0	0
Europe	France	Sanofi-Winthrop Industrie	Furosemide	Lasilix 40 mg	7KF7A	1	1	0	0	1	0	0	1	0	0
Europe	France	Sanofi-Winthrop Industrie	Furosemide	Lasilix 40 mg	7M33F	1	1	0	0	1	0	0	1	0	0
Europe	Germany	Aspen Bad Oldesloe GmbH	Salbutamol	Ventoline	G3415	1	1	0	0	1	0	0	1	0	0
Europe	Germany	Berlin Chemie	Sulfa/Trimet	Berlocid	61001	1	1	0	0	1	0	0	1	0	0
Europe	Germany	Denk Pharma GmbH & Co. KG	Amoxi/Clav	AmoxiClav-Denk	19694	1	1	0	0	1	0	0	1	0	0
Europe	Germany	Denk Pharma GmbH & Co. KG	Amoxi/Clav	AmoxiClav-Denk	20014	1	1	0	0	1	0	0	1	0	0
Europe	Germany	Denk Pharma GmbH & Co. KG	Amoxi/Clav	AmoxiClav-Denk	20517	1	0	1	0	1	0	0	0	1	0
Europe	Germany	Denk Pharma GmbH & Co. KG	Amoxi/Clav	AmoxiClav-Denk	20518	2	1	1	0	2	0	0	1	1	0
Europe	Germany	Denk Pharma GmbH & Co. KG	Atenolol	Atenolol Denk	3231	1	1	0	0	1	0	0	1	0	0
Europe	Germany	Denk Pharma GmbH & Co. KG	Metformin	Metformin Denk	19965	1	1	0	0	1	0	0	1	0	0
Europe	Germany	Denk Pharma GmbH & Co. KG	Metformin	Metformin Denk	20384	1	1	0	0	1	0	0	1	0	0
Europe	Germany	Denk Pharma GmbH & Co. KG	Metformin	Metformin Denk	95H	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	**Stated country of origin**	**Stated manufacturer**	**INN**	**Stated product name**	**Batchnumber**	**N**	**complies**	**deviation**	**extreme deviation**	**complies 2**	**deviation2**	**extreme deviation 2**	**complies 3**	**deviation 3**	**extreme deviation 3**
Europe	Germany	Denk Pharma GmbH & Co. KG	Metformin	Metformin Denk	9C7	2	2	0	0	2	0	0	2	0	0
Europe	Germany	Denk Pharma GmbH & Co. KG	Metformin	Metformin Denk	9DE	1	1	0	0	1	0	0	1	0	0
Europe	Germany	Salutas Pharma GmbH	Hydrochlorothiazide	Novartis Access Hydrochlorothiazide	GN5244	2	2	0	0	2	0	0	2	0	0
Europe	Italy	Errekappa Euroterapici S.p.A	Atenolol	Atenol	0008639	1	1	0	0	1	0	0	1	0	0
Europe	Italy	Laboratori Guidotti S.p.A	Metformin	Metforal	58042	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Ferrer Internacional S.A.	Glibenclamide	Glidiabet	J010	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Ferrer Internacional S.A.	Glibenclamide	Glidiabet	J011	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Ferrer Internacional S.A.	Glibenclamide	Glidiabet	J012	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	B1789	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BA453	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BJ475	2	2	0	0	2	0	0	2	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BL800	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BL801	2	2	0	0	2	0	0	2	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BR630	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BR631	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BT359	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BT900	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BV229	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BV384	1	1	0	0	1	0	0	1	0	0
Europe	Spain	Novartis Farmacéutica S.A.	Hydrochlorothiazide	Esidrex	BV831	1	1	0	0	1	0	0	1	0	0
Europe	Sweden	Bluefish Pharmaceuticals AD	Metformin	Metformina Bluefish	5150657	1	1	0	0	1	0	0	1	0	0
Europe	United Kingdom	SmithKline Beecham Pharmaceuticals	Amoxi/Clav	Augmentin	562626	1	0	0	1 [§]	0	0	1 [§]	0	0	1 [§]
Europe	United Kingdom	Sonmart Pharma (UK)	Doxycycline	Doxycycline Capsules	170821	2	2	0	0	2	0	0	2	0	0
Europe	United Kingdom	Sonmart Pharma (UK)	Metformin	Metformin Tablets	170820	2	2	0	0	2	0	0	2	0	0
Europe	United Kingdom	Sonmart Pharma (UK)	Metronidazole	Metronidazole Tablets 250mg	170832	1	1	0	0	1	0	0	1	0	0
Europe	United Kingdom	Sonmart Pharma (UK)	Amoxicillin	Sonmamox Amoxicilline 500mg	170801	1	1	0	0	1	0	0	1	0	0

							USP assay			USP dissolution			USP assay and dissolution combined		
Stated continent of origin	**Stated country of origin**	**Stated manufacturer**	**INN**	**Stated product name**	**Batchnumber**	**N**	**complies**	**deviation**	**extreme deviation**	**complies 2**	**deviation2**	**extreme deviation 2**	**complies 3**	**deviation 3**	**extreme deviation 3**
not stated	not stated	Cinpharm **	Amoxi/Clav	Cinclamox	DW3311	2	2	0	0	2	0	0	2	0	0
not stated	not stated	Cinpharm **	Amoxi/Clav	Cinclamox	DW3312	1	1	0	0	1	0	0	1	0	0
not stated	not stated	not stated	Amoxicillin	Filmox 500	SAECB002	1	1	0	0	1	0	0	1	0	0
not stated	not stated	not stated	Salbutamol	not stated	not stated	1	0	1	0	1	0	0	0	1	0

Am. J. Trop. Med. Hyg., 103(1), 2020, pp. 73–76
doi:10.4269/ajtmh.20-0363

Identification of Falsified Chloroquine Tablets in Africa at the Time of the COVID-19 Pandemic

Gesa Gnegel,[1,2] Cathrin Hauk,[1] Richard Neci,[3,4] Georges Mutombo,[4] Fidelis Nyaah,[5] Dorothee Wistuba,[6] Christine Häfele-Abah,[2] and Lutz Heide[1]*

[1]*Pharmaceutical Institute, Eberhard Karls University Tuebingen, Tuebingen, Germany;* [2]*German Institute for Medical Mission (Difaem), Tuebingen, Germany;* [3]*Ecumenical Pharmaceutical Network, Nairobi, Kenya;* [4]*Le Dépôt Central Médico-Pharmaceutique de La 8e CEPAC (DCMP), Bukavu, Democratic Republic of Congo;* [5]*Presbyterian Church in Cameroon (PCC), Central Pharmacy, Limbe, Cameroon;* [6]*Institute of Organic Chemistry, Eberhard Karls University Tuebingen, Tuebingen, Germany*

Abstract. Reports that chloroquine and hydroxychloroquine may be effective against COVID-19 have received worldwide attention, increasing the risk of the introduction of falsified versions of these medicines. Five different types of falsified chloroquine tablets were discovered between March 31, 2020 and April 4, 2020, in Cameroon and the Democratic Republic of Congo by locally conducted thin layer chromatographic analysis. Subsequent investigation by liquid chromatography and mass spectrometry in Germany proved the absence of detectable amounts of chloroquine and the presence of undeclared active pharmaceutical ingredients, that is, paracetamol and metronidazole, in four of the samples. The fifth sample contained chloroquine, but only 22% of the declared amount. Such products represent a serious risk to patients. Their occurrence exemplifies that once medicines or vaccines against COVID-19 may be developed, falsified products will enter the market immediately, especially in low- and middle-income countries (LMICs). Timely preparations for the detection of such products are required, including the establishment of appropriate screening technologies in LMICs.

In February 2020 and March 2020, reports that chloroquine (CQ) and hydroxychloroquine (HCQ) may be effective against COVID-19[1–4] received massive political and media attention worldwide, despite limited evidence.[5,6] Concerns have been raised that the premature off-label use of CQ and HCQ in COVID-19 may result in shortages of these medicines in their established, approved indications (i.e., against autoimmune diseases and, in case of CQ, *Plasmodium vivax* malaria).[7,8] The demand for CQ and HCQ quickly outstripped the supply, exacerbating the risk of falsified medicines entering the market.[8] We here report the recent occurrence of falsified CQ, detected in Cameroon and the Democratic Republic (DR) of Congo.

The Ecumenical Pharmaceutical Network (EPN), among other tasks, monitors medicine quality using the Global Pharma Health Fund (GPHF) Minilab,[9] a screening methodology based on thin layer chromatography (TLC) which is easy to conduct in resource-limited environments.[10] In March 2020, local member organizations of the EPN reported that both in private pharmacies and in informal markets, several types of falsified CQ tablets were appearing which, in local GPHF Minilab analysis,[11] were found not to contain CQ. Through the German Institute for Medical Mission (Difaem), the member organization of EPN which coordinates the Minilab network, the WHO Rapid Alert System, was informed, and the WHO published an international Medical Product Alert about falsified CQ tablets.[12]

In the following days, further falsified CQ samples were identified in Cameroon. Five samples were forwarded by commercial courier from Cameroon and the DR Congo to Tuebingen University, Germany. They are depicted in Figure 1, together with photos of their TLC analysis, according to the GPHF Minilab procedure.[11] Details of the samples are listed in Table 1.

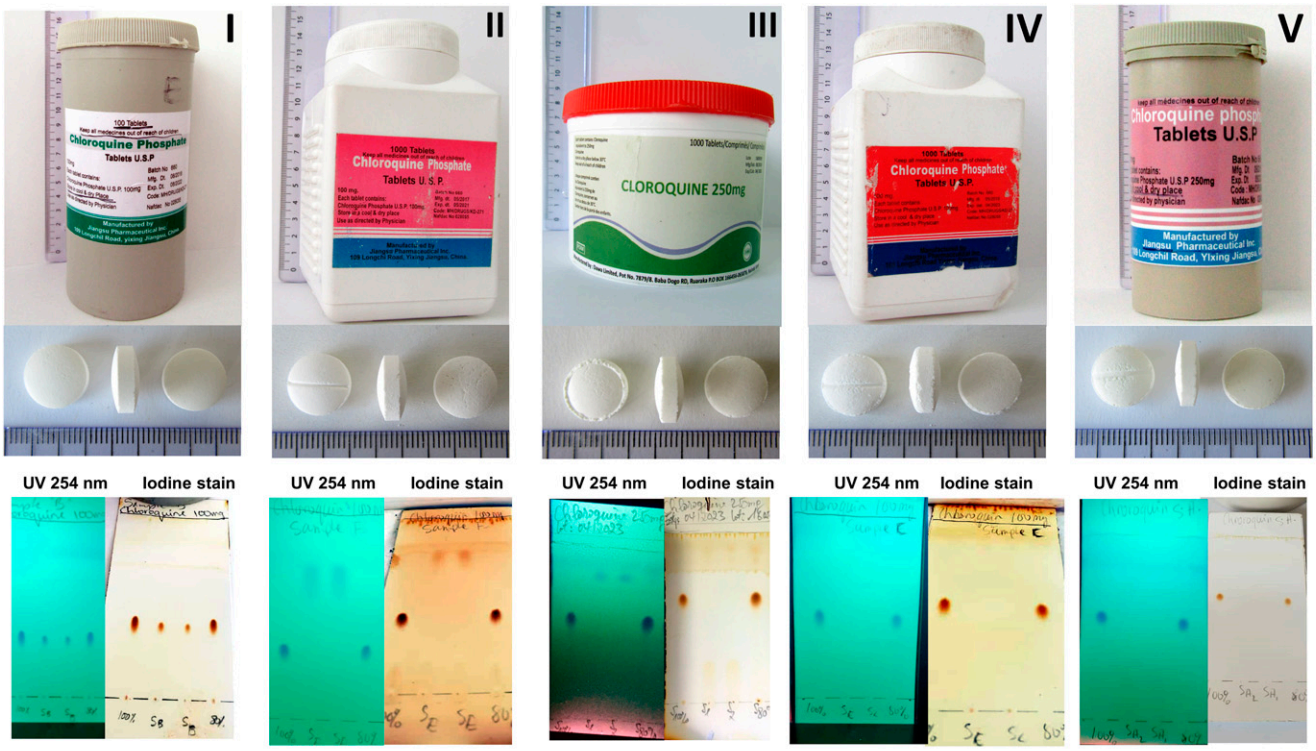
Thin layer chromatography readily showed the presence of CQ in the reference solutions, visible both under UV light and in subsequent detection with iodine vapor. By contrast, CQ was not detectable in four of the investigated samples. The fifth sample showed a spot of CQ, but the compound was apparently present only in a low amount (Figure 1, sample I). For samples II and III (Figure 1), TLC analysis with UV detection showed the presence of further, undeclared compounds with a higher retention factor than CQ. The undeclared compound in sample II was also detectable by iodine staining, but the compound in sample III was not (Figure 1), indicating that these two compounds were chemically different.

These observations were confirmed at Tübingen University by high-performance liquid chromatography (HPLC) according to the U.S. Pharmacopeia.[13] As shown in Figure 2, no CQ was detected in four of the samples. By contrast, in sample I, CQ was present in an amount corresponding to 21.7 mg CQ phosphate, that is, only 21.7% of the amount stated on the label. Samples II and V showed an unknown compound with a retention time of 4.7 minutes in HPLC, and samples III, IV, and V showed a further unknown compound with a retention time of 4.5 minutes.

Liquid chromatography (LC) coupled with high-resolution mass spectrometry (HR-MS) showed that the two unknown compounds had exact molecular masses of 152.0709 and 172.0719, consistent with the masses of paracetamol and of metronidazole, respectively. Their identity was confirmed in comparison with authentic reference compounds of paracetamol and of metronidazole, showing identical retention times, molecular masses, and mass spectrometric fragmentation as the references (Supplemental Table S4, Supplemental Figures S2 and S3, Supplemental Information). The quantities of these compounds were determined as 35.7 mg paracetamol per tablet for sample II and as 126.5 mg metronidazole per tablet for sample III. Samples IV and V were found to contain smaller amounts of metronidazole, that is, 14.1 mg and 14.6 mg per tablet, respectively. Sample V additionally contained traces of paracetamol (1.6 mg per tablet).

The labeling of the five samples showed mistakes and spelling errors (Table 1), suggesting that they were produced not by established manufacturers but by criminals. The stated manufacturer of sample III, Dawa Limited, Kenya, was contacted by the local partners in the DR Congo and confirmed

*Address correspondence to Lutz Heide, Pharmaceutical Institute, Eberhard Karls University Tuebingen, Auf der Morgenstelle 8, Tuebingen 72076, Germany. E-mail: heide@uni-tuebingen.de



Chloroquine (CQ) amount declared:

100 mg CQ phosphate	100 mg CQ phosphate	250 mg CQ	100 mg CQ phosphate	250 mg CQ phosphate

Active principles detected:

21.7 mg CQ phosphate	no CQ 35.7 mg paracetamol	no CQ 126.5 mg metronidazole	no CQ 14.1 mg metronidazole	no CQ 1.6 mg paracetamol 14.6 mg metronidazole

FIGURE 1. Falsified samples of chloroquine (CQ) tablets identified in Cameroon and the Democratic Republic Congo, and their thin layer chromatographic (TLC) analysis[11]; see Supplemental Information for details of the analytical procedure. Each TLC plate shows two spots of the respective sample in the middle and two spots of authentic CQ (corresponding to 100% and 80% of the declared amount of the sample) on the left and the right, respectively. Thin layer chromatography plates were photographed in Cameroon and the Democratic Republic Congo with locally available equipment; therefore, the angle of photography is not uniform. The active principles listed at the bottom were identified by high-performance liquid chromatography according to the U.S. Pharmacopeiea and by liquid chromatography–high-resolution mass spectrometry analysis (see text). The CQ amount in sample I was calculated as CQ phosphate; the identity of the counterion (phosphate or sulfate) was not determined. (Photos: packaging, © G. G., C. H., and L. H.; TLC analysis, © F. N. and G. M.)

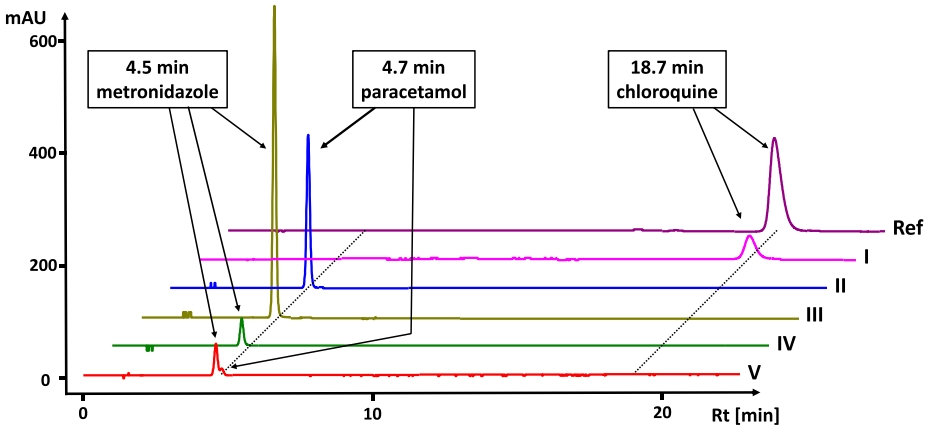


FIGURE 2. High-performance liquid chromatography analysis of falsified samples of chloroquine (CQ) tablets. Analysis was carried out according to the U.S. Pharmacopeia[13]; see Supplementary Information for details of the analytical procedure. Ref = CQ authentic reference substance; I, II, III, IV, and V = falsified samples of CQ tablets (see Figure 1, Table 1).

TABLE 1
Falsified samples of chloroquine tablets identified in Cameroon and the DR Congo

Sample code (Figures 1 and 2)	I	II	III	IV	V
Stated product name	Chloroquine phosphate tablets U.S.P	Chloroquine phosphate tablets U.S.P.	Cloroquine [*sic*] 250 mg	Chloroquine phosphate tablets U.S.P.	Chloroquine phosphate tablets U.S.P
Stated strength	100 mg	100 mg	250 mg	100 mg	250 mg
Stated manufacturer	Jiangsu Pharmaceutical Inc., China	Jiangsu Pharmaceutical Inc., China	Dawa Limited, Kenya	Jiangsu Pharmaceutical Inc., China	Jlangsu [*sic*] Pharmaceutical Inc., China
Batch number, mfg date, exp date	660, August 2018, August 2022	660, May 2017, May 2021	1605059, May 2019, April 2023	660, May 2019, April 2023	660, September 2018, September 2022
Found in	Limbe, Cameroon	Douala, Cameroon	Bukavu, DR Congo	Douala, Cameroon	Douala, Cameroon
Type of facility found in	Private pharmacy	Private pharmacy	Informal vendor	Private pharmacy	Informal vendor
Date of discovery	April 3, 2020	March 31, 2020	April 4, 2020	April 4, 2020	March 31, 2020
Labeling inconsistencies					
Spelling errors	+	–	+	–	+
Invalid NAFDAC registration number	+	+	–	+	+
Same batch number for different products	+	+	–	+	+

DR = Democratic Republic; NAFDAC = National Agency for Food and Drug Administration and Control, Nigeria. NAFDAC registration numbers were checked using the NAFDAC Registered Products Database available at www.nafdac.gov.ng/our-services/registered-products/.

that this sample had not been produced by them. Samples I, II, IV, and V were stated to be produced by "Jiangsu Pharmaceutical Inc., China," but no company with that name, or with the address stated on the labels, could be identified on the internet.

Notably, while this report was in preparation, Cameroon customs authorities reported the seizure of 210 cartons of falsified CQ tablets.[14]

The low amount of CQ in sample I is likely to reflect the attempt by the criminal producers to save costs in the purchase of the active pharmaceutical ingredient. The inclusion of paracetamol, as in sample II, has been reported previously in a falsified medicine from Cameroon, also identified by members of EPN.[10,15] Both in sample II and in that previous case, the amount of paracetamol was too low to achieve a relevant therapeutic effect. Metronidazole is very bitter and was included in samples III, IV, and V probably to mimic the bitter taste of CQ. The antibacterial and antiprotozoal compound metronidazole is usually formulated in tablets of 200–500 mg each. Therefore, samples III, IV, and V contain a subtherapeutic dose, which may contribute to the emergence of antimicrobial resistance. The additional presence of traces of paracetamol in sample V may represent a contamination from a prior production batch, reflecting poor manufacturing standards.

The absence of CQ in four of the five investigated samples, the subtherapeutic amount of CQ in the fifth sample, and the presence of undeclared active pharmaceutical ingredients in four of these samples represent serious health risks for the patients in Cameroon and the DR Congo. The authorities in Cameroon and the DR Congo, and the WHO Rapid Alert System were informed about these findings.

Such products may furthermore cause financial hardships to the patients: sample III was sold in the DR Congo for US$200 for a package of 1,000 tablets, that is, 15 times more expensive than the international procurement price.[16] In Cameroon, the EPN partner organization even reported the occurrence of a further package of 100 CQ tablets with a stated price of 250,000 CFA, that is, US$413 (Supplemental Figure S1, Supplemental Information).

The occurrence of such falsified CQ samples at this time of the COVID-19 pandemic also has wider implications. For any medicine or vaccine which may be reported to be effective against this disease, a frantic demand is to be expected, resulting in a serious danger of the appearance of falsified medicines. Low- and middle-income countries (LMICs) will be especially vulnerable: with their constrained access to essential medicines, their often weak technical capacity for medicine quality assurance and control, and their challenges in the maintenance of appropriate standards of governance in healthcare facilities and national medicines regulatory authorities, they show exactly those conditions which the WHO has identified as favoring the occurrence of substandard and falsified medicines.[17] Because of the recent disruption of the production and supply chains in India and China, which are the most important producer countries of generic medicines for LMICs, this problem will not remain restricted to medicines for the treatment and prevention of COVID-19 but encompass many types of medicines.

The rapid installation of simple, inexpensive screening technologies which can detect substandard and falsified medicines, such as TLC or near infrared or Raman spectroscopy,[8,9,18] may represent an important part of the response to the COVID-19 pandemic in LMICs. The data displayed in Figure 1 are a good example for the possibilities and limitations of the GPHF Minilab[11] in the identification of falsified medicines in future screening programs.

Received April 26, 2020. Accepted for publication May 5, 2020.

Published online May 12, 2020.

Note: Supplemental tables and figures appear at www.ajtmh.org.

Acknowledgments: Publication charges for this article were waived due to the ongoing pandemic of COVID-19.

Financial support: This study was funded by the University of Tuebingen.

Authors' addresses: Gesa Gnegel, Cathrin Hauk, and Lutz Heide, Pharmaceutical Institute, Eberhard Karls University Tuebingen, Tuebingen, Germany, E-mails: gesa.gnegel@uni-tuebingen.de, cathrin.hauk@uni-tuebingen.de, and heide@uni-tuebingen.de. Richard Neci, Ecumenical

Pharmaceutical Network, Nairobi, Kenya, E-mail: richard.neci@epnetwork.org. Georges Mutombo, Le Dépôt Central Médico-Pharmaceutique de la 8e CEPAC (DCMP), Bukavu, Democratic Republic of Congo, E-mail: georgesmutombo@dcmp8ecepac.org. Fidelis Nyaah, Presbyterian Church in Cameroon (PCC), Central Pharmacy, Limbe, Cameroon, E-mail: nyaahngoh@gmail.com. Dorothee Wistuba, Institute of Organic Chemistry, Eberhard Karls University Tuebingen, Tuebingen, Germany, E-mail: dorothee.wistuba@uni-tuebingen.de. Christine Häfele-Abah, German Institute for Medical Mission (Difaem), Tuebingen, Germany, E-mail: haefele@difaem.de.

REFERENCES

1. Yao X et al., 2020. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* ciaa237 [Epub ahead of print]. Available at: https://doi.org/10.1093/cid/ciaa237.
2. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G, 2020. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res 30:* 269–271.
3. Gautret P et al., 2020. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 105949 [Epub ahead of print]. Available at: https://doi.org/10.1016/j.ijantimicag.2020.105949.
4. Gao J, Tian Z, Yang X, 2020. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends 14:* 72–73.
5. Keshtkar-Jahromi M, Bavari S, 2020. A call for randomized controlled trials to test the efficacy of chloroquine and hydroxychloroquine as therapeutics against novel coronavirus disease (COVID-19). *Am J Trop Med Hyg 102:* 932–933.
6. Ferner RE, Aronson JK, 2020. Chloroquine and hydroxychloroquine in covid-19. *BMJ 369:* m1432.
7. Jakhar D, Kaur I, 2020. Potential of chloroquine and hydroxychloroquine to treat COVID-19 causes fears of shortages among people with systemic lupus erythematosus. *Nat Med* [Epub ahead of print]. Available at: https://doi.org/10.1038/s41591-020-0853-0.
8. Newton PN et al., 2020. COVID-19 and risks to the supply and quality of tests, drugs, and vaccines. *Lancet Glob Health* [Epub ahead of print]. Available at: https://doi.org/10.1016/S2214-109X(20)30136-4.
9. Petersen A, Held N, Heide L, on behalf of the Difaem EPN Minilab Survey Group, 2017. Surveillance for falsified and substandard medicines in Africa and Asia by local organizations using the low-cost GPHF Minilab. *PLoS One 12:* e0184165.
10. Schäfermann S et al., 2020. Substandard and falsified antibiotics and medicines against non-communicable diseases in western Cameroon and north-eastern Democratic Republic of Congo. *Am J Trop Med Hyg*. [Epub ahead of print]. doi: 10.4269/ajtmh.20-0184.
11. Jähnke WO, Dwornik K, 2020. *Manual Accompanying the GPHF Minilab™. Physical Testing and Thin-Layer Chromatography*. Giessen, Germany: Global Pharma Health Fund.
12. WHO, 2020. *Medical Product Alert N°4/2020. Falsified Chloroquine Products Circulating in the WHO Region of Africa*. Available at: https://www.who.int/news-room/detail/09-04-2020-medical-product-alert-n4-2020. Accessed April 20, 2020.
13. United States Pharmacopeia 42 NF 37, 2019. *Monograph: Chloroquine Phosphate Tablets*. Rockville, MD: USP.
14. Xinhua, 2020. *Cameroon Customs Seizes 210 Cartons of Fake Chloroquine*. Available at: http://www.xinhuanet.com/english/2020-04/22/c_138998967.htm. Accessed April 24, 2020.
15. WHO, 2017. *Medical Product Alert N° 4/2017. Falsified Penicillin V Circulating in Cameroon*. Available at: https://www.who.int/medicines/publications/drugalerts/drug_alert4-2017/en/. Accessed April 20, 2020.
16. Management Sciences for Health, 2015. *The International Medical Products Price Guide 2015*. Available at: http://mshpriceguide.org/en/home/. Accessed April 20, 2020.
17. World Health Organization, 2017. *Global Surveillance and Monitoring System for Substandard and Falsified Medical Products*. Available at: https://www.who.int/medicines/regulation/ssffc/publications/gsms-report-sf/en/. Accessed April 20, 2020.
18. Vickers S, Bernier M, Zambrzycki S, Fernandez FM, Newton PN, Caillet C, 2018. Field detection devices for screening the quality of medicines: a systematic review. *BMJ Glob Health 3:* e000725.

Supplemental Information for

The identification of falsified chloroquine tablets in Africa at the time of the COVID-19 pandemic

Figure S1: *Package of 100 chloroquine phosphate tablets 100 mg found in Yaoundé, Cameroon, on April 9, 2020, with a stated price of 250,000 CFA, i.e. 414 US $ (Photo: © F. Nyaah). Due to the exorbitant price, this sample was not purchased and not analyzed.*

Methods of thin-layer chromatography and quantitative HPLC analysis

Method	Chloroquine phosphate and sulfate (GPHF Minilab Manual 2020)[1]
Stationary phase	Merck TLC aluminium plates pre-coated with silica gel 60 F_{254}, 5x10 cm
Mobile phase	Ethyl acetate/methanol/25% aqueous ammonia solution 1:4:0.1 (v/v)
Applied volume of sample and standard	2 µl
Detection	1) UV light, 254 nm; 2) Exposure to iodine vapor and visual evaluation in daylight
Standards	Chloroquine phosphate in water, 2.5 and 2.0 mg/ml
Sample preparation	Tablets with a declared content of 100 mg chloroquine phosphate: one tablet was finely ground with a pestle and suspended in 20 ml of water. (Tablets with a declared content 250 mg chloroquine phosphate: one tablet was finely ground with a pestle and suspended in 50 ml of water.) After three minutes of shaking, the solution was allowed to sit for additional five minutes. 2 ml of the supernatant were removed and diluted with 2 ml of water.

Table S1: *Method for thin-layer chromatography*

Method	Chloroquine Phosphate Tablets (USP 42 monograph, 2019)[2]
Instrument	HPLC (Agilent 1100 Series)
Column/stationary phase	Reprospher 100 C18, 250 x 4 mm, 5µm (Dr. Maisch GmbH, Ammerbuch, Germany)
Mobile phase	Methanol/aqueous buffer 22:78 (v/v) (aqueous buffer contained 6.8 g monobasic potassium phosphate and 1 ml perchloric acid per liter water; pH 2.5)
Flow rate	1.2 ml/min
Oven temperature	30 °C
Injection volume	10 µl
Detector	UV, 224 nm
Standard	0.15 mg/ml chloroquine phosphate Pharmaceutical Secondary Standard (Sigma-Aldrich LOT #LRAB3715) in water.
Sample preparation	One tablet was finely ground in a mortar. An aliquot of approx. 100 mg was weighed into a 100 ml volumetric flask. 50 ml of water were added. The flask was sonicated for 15 minutes and then filled up with water to 100 ml. For each sample, two independent experiments were carried out.

Table S2: *Method for quantitative HPLC analysis of chloroquine and paracetamol*

Method	Metronidazole Tablets (USP 42 monograph 2019)[3]
Instrument	HPLC (Agilent 1100 Series)
Column/stationary phase	Reprospher 100 C8, 150 x 4.6 mm, 5µm (Dr. Maisch GmbH, Ammerbuch, Germany)
Mobile phase	Methanol/water 20:80 (v/v)
Flow rate	1.0 ml/min
Oven temperature	30 °C
Injection volume	5 µl
Detector	UV, 254 nm
Standard	0.56 mg/ml Metronidazole Analytical Standard (Sigma-Aldrich LOT #MKBZ3056V) in methanol/water 20:80 (v/v).
Sample preparation	Three tablets were finely ground in a mortar. An aliquot of approx. 100 mg was weighed into a 100 ml volumetric flask. 50 ml of methanol were added. The flask was sonicated for 10 minutes and then filled up to 100 ml with mobile phase. For each sample, two aliquots were weighted and analyzed.

Table S3: *Method for quantitative HPLC analysis of metronidazole*

High resolution liquid chromatography-mass spectrometry

HR-HPLC/MS(/MS) was carried out using a Thermofisher UltiMate 3000 HPLC with a Phenomenex Luna 3µm Polar C18 100 Å column 150 x 2 mm, column temperature 30°C. Eluent A: 0.1% formic acid in water; eluent B: 0.1% formic acid in methanol. Gradient 5-100% B over 20 min followed by 100% B isocratic for 10 min; flow rate 0.3 ml/min. UV detection with a diode array detector. HR mass spectrometry: ESI-TOF Bruker MaXis 4G. The sample solutions were investigated in comparison to authentic paracetamol and metronidazole reference in H_2O/methanol 2:1. In samples III, IV and V, peaks at 5.0 min (metronidazole) were detected. In samples II and V, peaks at 5.4 min (paracetamol) were detected. UV spectra of the samples and the respective references were identical. The molecular ion of the respective samples showed the same exact mass as the molecular ion from paracetamol and/or metronidazole (Table S4). These were consistent with the molecular formula $C_8H_9NO_2$ of paracetamol and $C_6H_9N_3O_3$ of metronidazole.

Sample	Retention time	$[M+H]^+_{theoretical}$	$[M+H]^+_{measured}$	relative mass accuracy
Metronidazole reference	5.0 min	172.0717	172.0719	1.3 ppm
Paracetamol reference	5.4 min	152.0706	152.0709	2.0 ppm
Sample II	5.4 min	152.0706	152.0709	1.8 ppm
Sample III	5.0 min	172.0717	172.0721	2.3 ppm
Sample IV	5.0 min	172.0717	172.0720	1.9 ppm
Sample V	5.0 min	172.0717	172.0718	1.0 ppm
	5.4 min	152.0706	152.0708	1.2 ppm

Table S4: *Retention times, and theoretical and measured exact masses, for the investigated samples and for metronidazole and paracetamol reference substances. HPLC conditions for HPLC-MS are different from those for quantitative analysis according to USP, therefore retention times are different from those shown in Figure 2.*

MS/MS analysis showed the presence of the characteristic fragments of metronidazole (Fig. S2) in samples III, IV and V, and the presence of the characteristic fragments of paracetamol (Fig. S3) in samples II and V. The observed fragmentation of the samples and the respective references were identical.

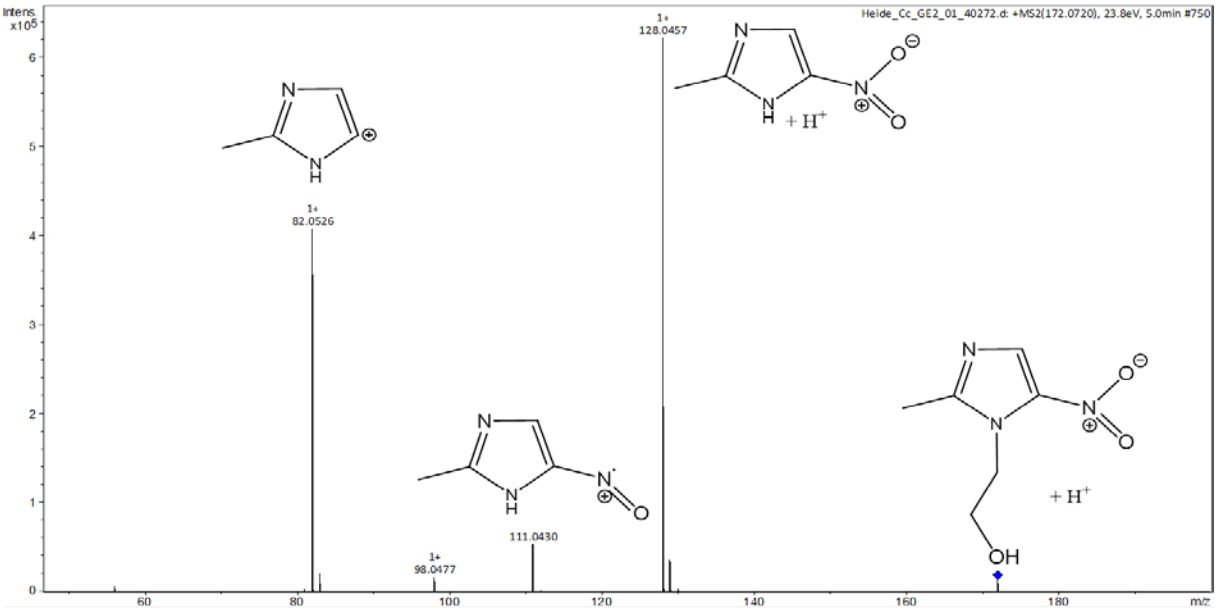


Figure S2: *MS/MS fragmentation of metronidazole in sample IV.*

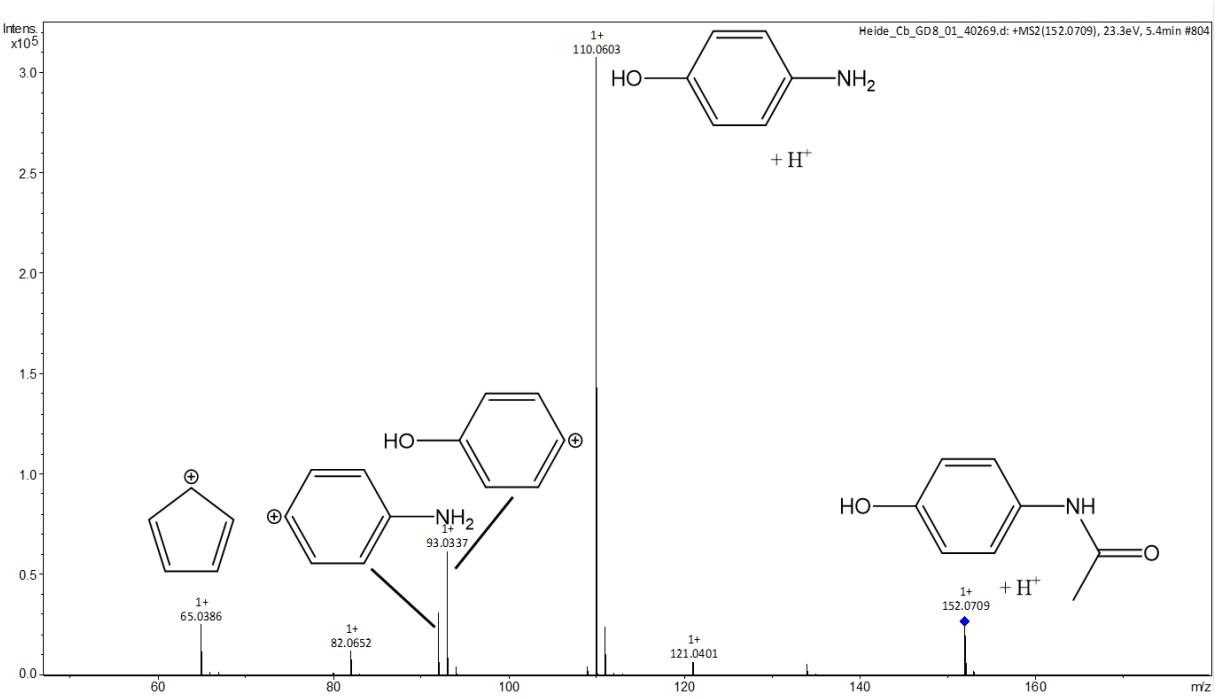


Figure S3: *MS/MS fragmentation of paracetamol in sample II.*

References:

1. Jähnke WO, Dwornik K, 2020. Manual accompanying the GPHF Minilab™. Physical testing and thin-layer chromatography. Giessen, Germany: Global Pharma Health Fund.
2. United States Pharmacopeia 42 NF 37, 2019. Monograph: Chloroquine Phosphate Tablets. USP, Rockville, USA.
3. United States Pharmacopeia 42 NF 37, 2019. Monograph: Metronidazole Tablets. USP, Rockville, USA.

PLOS ONE

RESEARCH ARTICLE

Quality assurance in anti-tuberculosis drug procurement by the Stop TB Partnership—Global Drug Facility: Procedures, costs, time requirements, and comparison of assay and dissolution results by manufacturers and by external analysis

Cathrin Hauk[1], Simon Schäfermann[1], Peter Martus[2], Nigorsulton Muzafarova[3], Magali Babaley[3], Brenda Waning[3], Lutz Heide[1]*

1 Pharmaceutical Institute, Eberhard Karls University Tübingen, Tübingen, Germany, **2** Institute for Clinical Epidemiology and Applied Biometry, Eberhard Karls University Tübingen, Tübingen, Germany, **3** Global Drug Facility, Stop TB Partnership, Geneva, Switzerland

* heide@uni-tuebingen.de

Citation: Hauk C, Schäfermann S, Martus P, Muzafarova N, Babaley M, Waning B, et al. (2020) Quality assurance in anti-tuberculosis drug procurement by the Stop TB Partnership—Global Drug Facility: Procedures, costs, time requirements, and comparison of assay and dissolution results by manufacturers and by external analysis. PLoS ONE 15(12): e0243428. https://doi.org/10.1371/journal.pone.0243428

Editor: Seyed Ehtesham Hasnain, Jamia Hamdard, INDIA

Received: October 2, 2020

Accepted: November 22, 2020

Published: December 3, 2020

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: This work was supported by Stop TB Partnership / UNOPS grant number STBP/USAID/GSA/92954/2017-40 (to LH, Eberhard Karls University Tübingen). The principal design of this study was part of the grant support agreement.

Abstract

Background

Quality-assured medicines are a principal means of achieving health-related Sustainable Development Goals. An example of quality assurance/quality control (QA/QC) procedures in drug procurement is provided by the operation of the Global Drug Facility (GDF) of the Stop TB Partnership, the largest provider of tuberculosis (TB) medicines to the public sector worldwide.

Methods

Procedures and results of GDF's quality assurance/quality control (QA/QC) over the five-year period 2013–2017 were analysed retrospectively. 13,999 batches of 51 different medicines had been procured and reviewed within this period. 1,388 of these batches had been analysed in the laboratories of GDF's external quality control agent (QCA). Assay and dissolution results determined by the manufacturers and by the external QCA were compared using Bland-Altman analysis.

Results

All investigated batches of medicines were in specifications at the time of shipment. The costs for QA/QC were 0.8% of purchase costs. The median time required for chemical analysis was 10 working days. Comparison of the medicine quality analysis results showed for the poorly water-soluble compound rifampicin a bias of 4.4%, with the manufacturers reporting higher values than the external QCA, most likely due to different methods employed for the analysis. Overall 95% limits of agreement (LOAs) were -6.7 to +8.0% for assay, and

Competing interests: NM, MB and BW are employees of the Global Drug Facility at the Stop TB Partnership. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

-10.1 to +11.8% for dissolution. In case of kanamycin injections, 95% LOAs for assay reached -14.5 to +13.2%, largely attributable to samples from one manufacturer who had used a microbiological assay while the external QCA had used an HPLC assay.

Conclusions

GDF's procedures represent a useful benchmark when evaluating QA/QC procedures of other medicine procurement operations. Inter-laboratory comparison using Bland-Altman plots allows to investigate bias and variability in medicine quality control and should be considered as a routine procedure by drug procurement agencies, to identify priorities for further improvements.

Introduction

Improving access to quality-assured medicines is a principal means of achieving health-related Sustainable Development Goals and Universal Health Coverage [1]. However, according to a recent WHO literature survey, poor-quality medicines constitute approximately 10% of all medicines in low- and middle-income countries [2]. The number of deaths resulting annually from the use of poor-quality anti-infective medicines is estimated as 72,000–169,000 for childhood pneumonia, and 31,000–116,000 for malaria [2]. Arguably, the most effective intervention to counter the problem of substandard and falsified medicines is to strengthen quality assurance in drug procurement. General recommendation for quality assurance in medicine procurement agencies are available [3–6]. However, the scientific literature is virtually devoid of detailed empirical data on procedures, costs and time requirements of quality assurance/quality control (QA/QC) in drug procurement. Such data are needed especially at present, since stagnating donor health funding forces many countries to expand their national procurement processes, including medicine procurement for AIDS, tuberculosis (TB) and malaria [7]. This can introduce the risk of purchasing medicines of unknown quality, and thereby also exacerbate the growing global health challenge of serious drug-resistant infections [7, 8]. Reportedly, 29 low- and middle-income countries purchased TB medicines of unknown quality between 2016 and 2018 [8]. National procurement agencies, regulatory authorities and non-governmental organizations therefore need information how to further improve quality assurance in drug procurement. The present study attempts to report such information.

Quality-assured medicines are of particular importance in the case of anti-TB medicines since poor quality anti-TB medicines are among the drivers of the emergence of drug-resistant TB pathogens [9–12]. Tuberculosis is the ninth leading cause of death worldwide, and is the leading cause of death from a single infectious agent, ranking above HIV/AIDS [13]. In drug-susceptible TB, a six-months regimen involving four first-line drugs (rifampicin, isoniazid, ethambutol and pyrazinamide) achieves treatment success rates of at least 85% [13]. The required medicines could be purchased for only 27 US$ per treatment course from the Global Drug Facility in 2019 [14]. However, drug-resistant TB is a continuing threat, with 490,000 cases of multi-drug resistant TB (MDR-TB) reported in 2017 [13]. MDR-TB must be treated with second-line anti-TB drugs, and they currently cost approximately 485–1850 US$ per treatment course [14], i.e. 20–70 times more than first-line treatments.

The Global Drug Facility (GDF) of the Stop TB Partnership was founded in 2001, in order to ensure uninterrupted access to quality-assured anti-TB medicines. Today, GDF is the world's largest provider of TB products for national TB control programs. The Global Fund to

Fight AIDS, Tuberculosis and Malaria (GF), the United States Agency for International Development (USAID), as well as governments and other non-governmental organizations purchase anti-TB medicines and diagnostics from GDF for TB control programs especially in developing countries. Both donor funding and national government funding is used for these purchases. In 2017, GDF delivered TB medicines and diagnostics of a total value of 304 million US$ to 119 countries. GDF pursues active market shaping policies to optimize price, quality and sustainable supply of TB products, and also offers support and technical advice to national TB programs and policy makers. GDF's policies, market shares and its influence on price of TB products have been analysed in previous studies [15–17].

At least for essential medicines procured with donor funds, it has been suggested that results from quality assurance should be shared among different stakeholders [4]. Likewise, GDF's "Quality Assurance Policy and Procedures" state the aim to share information on quality aspects of medicines with other major international organisation and donors [18]. Yet, to the best of our knowledge there is no published study in the scientific literature which reports quantitative analytical results of medicine quality testing in drug procurement.

Therefore, the present study was carried out with two aims:

1. We report on the procedures, costs and time requirements of GDF's medicine quality assurance/quality control operation in the five-year period of 2013–2017. During this period, GDF procured 13,999 batches of medicines, and GDF's external quality control agent selected 1,388 of these batches for analysis in its WHO-prequalified medicine quality control laboratories.
2. We carried out an inter-laboratory comparison of the analytical results provided by GDF's commercial drug suppliers and GDF's external quality control agent (QCA). The results suggest that such comparisons are useful to guide further improvements of the QA/QC efforts in drug procurement and should be considered as a routine procedure in drug procurement organizations.

Methods

Data sources

In the procurement of anti-TB medicines by GDF, the IDA Foundation, Amsterdam, NL, has been contracted to provide procurement services for anti-TB medicines. Through this agency, SGS Netherlands B.V. (Spijkenisse, NL) has been subcontracted as external quality control agent (QCA), to provide quality control services. For the present study, the QCA provided Microsoft Excel files on all 13,999 batches of medicines procured and reviewed in the five-year study period 2013–2017, as well as pdf files with the results of external analysis carried out on 1,388 of these batches in the WHO-prequalified laboratories of the QCA in India and in Belgium. Since 2015, the QCA had furthermore carried out Critical CoA Reviews (see Results section), and GDF provided all customer complaints received in the period 2015–2017.

The QCA had routinely entered the data of the manufacturers' Certificates of Analysis (CoAs), including quantitative results on assay and dissolution, into Excel files. In contrast, the data of the medicine quality analyses in the QCA's laboratories had not been entered into a database prior to this study and were provided by the QCA in form of pdf files. For the present study, assay and dissolution results for selected samples (see below) were manually transferred from these pdf files into a single Excel data file. Additionally, the mean of the dissolution values of the six units investigated in S1 stage was calculated. Correct transfer was checked by two independent investigators.

Random selection of 196 medicine batches for inter-laboratory comparison of assay and dissolution results from manufacturer analysis and from external QCA laboratory analysis

Out of the 1,388 batches which had been analysed in the laboratories of the QCA in the study period 2013–2017, 196 were selected within the present study for a retrospective inter-laboratory comparison of assay and dissolution results. The 1,388 batches were sorted into strata according to manufacturers and Finished Pharmaceutical Products (FPPs). This resulted in 69 strata containing between 1 and 161 batches (median 10 batches). Random numbers were assigned to each batch using the RND function of Microsoft Excel, and batches were selected based on highest random numbers per stratum. According to the size of the respective stratum, different numbers of batches were selected: if a stratum contained 1–5; 6–25; 26–125; >125 batches, then 1; 2; 3; or 4 batches were selected, respectively. However, a minimum of five batches for each active pharmaceutical ingredient (API) from each manufacturer was selected if possible; if less than five batches for a given API from a given manufacturer had been analysed by the QCA in the study period, all analysed batches were included. This resulted in the selection of 196 batches for inter-laboratory comparison of assay and dissolution results.

Statistical analysis

Statistical analysis included the comparison of assay and dissolution results reported by the manufacturers and reported by the external QCA. The primary analysis was done graphically using ordinary scatterplots and Bland–Altman plots including limits of agreement [19]. Additionally, t-tests were done to examine systematic differences, and Spearman correlations were calculated. Analysis of variance was applied to compare results between APIs and manufacturers. In these analyses only groups with at least 15 samples were included. The level of significance was 0.05 (two-sided) in all statistical tests. Exact two-sided 95% confidence limits for proportions were reported. As the primary analysis was descriptive, no adjustment for multiple testing was applied. All analyses were done using SPSS for Windows release 24, exact confidence limits were obtained using the binom.test procedure in R release 3.2.2.

Results

Overview of products, their prequalification status and their manufacturers

During the study period 2013–2017, GDF's external Quality Control Agent (QCA) monitored quality data of 51 different medicines, representing 26 active pharmaceutical ingredients (APIs) in different formulations, dosages and fixed-dose-combinations. A list of these medicines, including the estimated annual quantities procured for each product [20, 21], is given in S1 Table. In total, quality data of 13,999 batches of medicines was monitored, including 6957 batches of first-line adult medicines, 852 batches of first-line paediatric medicines and 6190 batches of second-line medicines.

S1 Scheme summarizes the principles of GDF's supplier and product selection procedure. Any Finished Pharmaceutical Product (FPP) procured through GDF must either be prequalified within the WHO Prequalification of Medicines Programme (WHO PQP) [22], or approved by a Stringent Regulatory Authority (SRA) [18, 23]. When only one or no product with WHO prequalification or SRA approval is available on the global market, GDF may procure External Review Panel (ERP)-recommended products for a period of up to 12 months. In the beginning of GDF's operations, the progress of the prequalification of anti-TB medicines

was still limited [24]. Meanwhile, however, progress is remarkable: of all 13,999 medicine batches reviewed in the study period 2013–2017, 69.4% represented WHO-prequalified products, 24.4% SRA-approved products, and 6.2% ERP-approved products. An ongoing further shift from ERP-recommended to SRA-approved or WHO-prequalified products is noticeable: as of January 2018, only two medicines on the GDF medicines list were ERP-recommended, all the others were either WHO-prequalified, or SRA-approved (S1 Table). From the data in S1 Table, it can be estimated that at present 87% of all medicine batches procured for GDF represent WHO-prequalified products, 13% SRA-approved products, and only 0.2% ERP-recommended products. Among the first-line adult medicines, WHO-prequalified products constitute even 97%.

In order to ensure continuous supply and cost-effective procurement, GDF aims to contract more than one supplier for each product [18, 25]. As shown in S1 Table, within the study period 32 of the 51 provided medicines were procured from two or more manufacturers, and these products represented 91% of the reviewed batches. The most notable product which still had to be procured from only one single source was streptomycin injections.

Within the study period, GDF procured its medicines from a total of 33 manufacturers. Fig 1 shows the predominance of manufacturers from India for the supply of first-line anti-TB medicines, whereas second-line medicines come from a wider range of countries.

Procedures and methods for quality control

The principles of GDF's multi-step quality control procedure are shown in S2 Scheme. It comprises "Critical CoA Reviews" which are generated by GDF's Quality Control Agent (QCA) when a product is procured for the first time from a given manufacturer, and which reviews the appropriateness of the manufacturers' analytical methods and specifications. Thereafter, the QCA performs routine "CoA Reviews", i.e. reviews of the Certificates of Analysis provided by the manufacturers for every batch. This resulted in 13,999 CoA reviews prepared by the QCA in the study period 2013–2017. In 303 cases, this reviewing of the manufacturers' CoAs showed the need for clarifications or corrections by the manufacturer. The median time required for these clarifications was four days, although some cases required much longer time (range 1–113 days, mean 20 days).

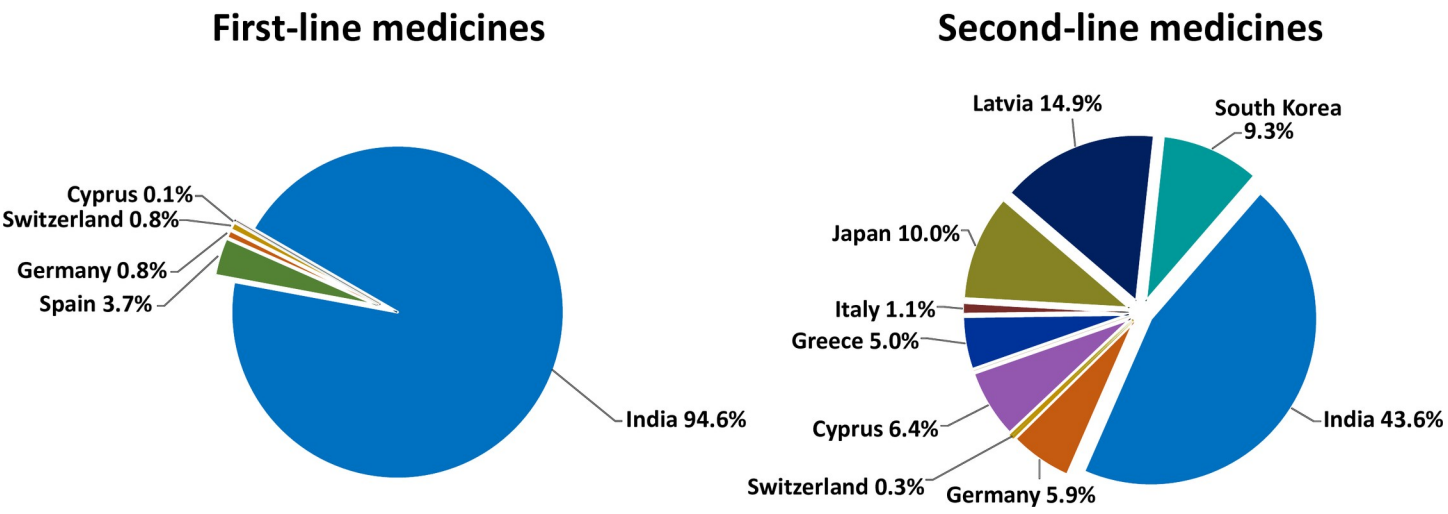


Fig 1. Origin of anti-tuberculosis medicines procured by the Global Drug Facility. Percentages are based on the number of batches procured in the years 2013–2017. Information on the number of units is given in S1 Table.

https://doi.org/10.1371/journal.pone.0243428.g001

Using a risk-based random selection process, GDF's QCA selected 1,388 batches in the study period for laboratory analysis in its own laboratories. These carry out analytical tests as listed in S2 Scheme. Whenever possible the methods of analysis of the International Pharmacopoeia (Ph. Int.), the British Pharmacopoeia (BP) and the United States Pharmacopeia (USP) are followed. However, Ph. Int. monographs exist for only 27 of the 51 products listed in S1 Table, and for six products no monographs exist at all in any of the three named pharmacopeias. Even when compendial methods exist, the manufacturer may follow his own in-house methods for analysis, e.g. since at the time of SRA/ERP approval or WHO prequalification of the product the manufacturer may have used and documented that in-house method. In such cases, it is sometimes necessary that the QCA establishes and validates the manufacturers' in-house method in his own laboratory ("method transfer"), a particularly time- and finance-consuming process. In the study period 2013–2017, such method transfers had to be carried out in 17 cases.

Medicines identified as out-of-specification

Within the study period, out of the 1,388 batches tested by GDF's external QCA following the above procedure, not a single batch was found to be out-of-specification at the time of shipment (upper 95% confidence limit 0.27%). However, 15 customer complaints were reported to GDF in the period 2015–2017, claiming quality problems observed after receipt of the shipment by the customers. In five of these cases, the products were indeed confirmed to be out-of-specifications, and these batches were replaced by the manufacturers upon request of GDF. Four of these five cases concerned pyridoxine tablets that showed discoloration; notably, three of these cases concerned the same batch. The fifth of these cases represented improperly sealed sachets of *para*-aminosalicylic acid, leading to swelling of the sachets. In one further case, the sample in question showed colour changes and the presence of degradation products which was most likely caused by inadequate storage temperature. In another case, the sample was expired. In four further cases, chemical analysis proved that the products were compliant with specifications. The four final cases were inconclusive as insufficient information or sample material was provided with the complaint.

Cost and time requirements of quality control measures

During most of the study period, GDF charged customers 1.2% of the purchase costs of the consignments for medicine quality analysis. Starting from June 2017, the charges were reduced to 0.8%. We estimated that laboratory analyses (of 1,388 batches) accounted for 64% of the quality control costs, while review of the manufacturer CoAs (of 13,999 batches) accounted for 29%, and other services for 7%.

The time from the random selection of batches for laboratory analysis to the conclusion of laboratory results (i.e. the time for sample collection, forwarding of samples to the laboratory, and analysis) was remarkably short. The QCA records showed that for 47% of the investigated batches, the lab result became available in the same calendar month in which it had been requested, and for 46% in the following calendar month. This process took longer only in 7% of the cases. The median time for analysis alone (i.e. from arrival of the samples in the QCA's laboratory until availability of the results in the QCA's Netherland office) was only 10 working days (mean: 11 working days; range: 0–64 working days).

Inter-laboratory comparison of assay and dissolution results from manufacturer analysis and from external QCA laboratory analysis

For inter-laboratory comparison of assay and dissolution results from manufacturer analysis and from external QC laboratory analysis, 196 of the 1,388 CoAs prepared by the QCA's

Table 1. Descriptive summary of assay and dissolution data included into the inter-laboratory comparison of assay and dissolution results from manufacturer analysis and from external QCA laboratory analysis.

		Assay		Dissolution		Difference	
		Manufacturer analysis	External QCA analysis	Manufacturer analysis	External QCA analysis	Assay	Dissolution
N		288	288	262	262	288	261[a]
Mean		99.8%	99.1%	98.5%	97.6%	0.67%	0.88%
Median		99.6%	99.3%	99.0%	98.3%	0.42%	0.62%
Standard deviation		1.86%	3.31%	3.55%	4.75%	3.74%	5.55%
Minimum		95.0%	90.0%	79.5%	82.0%	-15.20%	-16.65%
Maximum		108.2%	113.1%	107.5%	110.0%	15.30%	21.00%
Percentile	2.5	95.0%	92.8%	88.5%	86.7%	-6.85%	-11.52%
	25	98.7%	96.9%	97.0%	95.0%	-1.50%	-2.19%
	75	100.7%	100.7%	100.7%	100.5%	2.87%	3.50%
	97.5	103.7%	106.0%	103.6%	107.6%	8.70%	13.08%
Skewness		0.66	0.58	-1.29	-0.44	-0.31	0.22
Kurtosis		2.37	2.10	4.10	0.57	3.06	1.40

[a] Two dissolution results (one from manufacturer analysis, one from external QCA analysis) were unavailable for the comparison.

https://doi.org/10.1371/journal.pone.0243428.t001

quality control laboratory were selected using a stratified random selection procedure (see Methods). The focus of this analysis was not statistical testing of a hypothesis but an estimation of limits of agreement of assay and dissolution results between manufacturer analysis and external QC laboratory analysis.

Many of the selected medicines were fixed-dose combinations containing several APIs, and both solid oral formulations and injectable formulations were included. Therefore, the selected 196 samples represented 288 assay results and 261 dissolution results, each of them with a value reported by the manufacturer and another value reported by the QCA laboratory. A descriptive summary of these data is given in Table 1. In addition, S2 Table shows descriptive summaries for each of the 13 APIs included in this analysis.

Analysis of skewness showed that data were symmetrically distributed. Even though kurtosis exceeded the range of -1 to +1, parametrical procedures were chosen due the well-known robustness of t-tests and one-factorial ANOVAs (Table 1).

Fig 2A and 2C show scatterplots of the agreement of manufacturer analysis and external QCA analysis for assay and dissolution of the API. Over the narrow range of outcomes (95% of the assay results were between 93 and 106% of the declared content), correlation between the values reported by the compared laboratories was weak (see legend of Fig 2).

The results of Bland-Altman analysis are summarized in Table 2. A small bias was observed for both assay (0.67%) and dissolution (0.88%). As already obvious from the scatterplots, Bland-Altman analysis showed considerable random variation. Upper and lower 95% limits of agreement were calculated as -6.7 to 8.0% for assay, and -10.1 to 11.8% for dissolution. The pattern of relationship between difference and mean in Bland-Altman analysis for both assay and dissolution showed some heteroscedasticity, since values reported by the manufacturers showed less variation than values reported by the external QCA. However, over the investigated range of results this effect was small.

S1 and S2 Figs show separate scatterplots and Bland-Altman plots of assay and dissolution values for the four principal first-line anti-TB agents isoniazid, ethambutol, pyrazinamide and rifampicin. The results of the Bland-Altman analysis for these four APIs are included in Table 2. Consistent with the observation in the overall analysis shown in Fig 2, the assay values

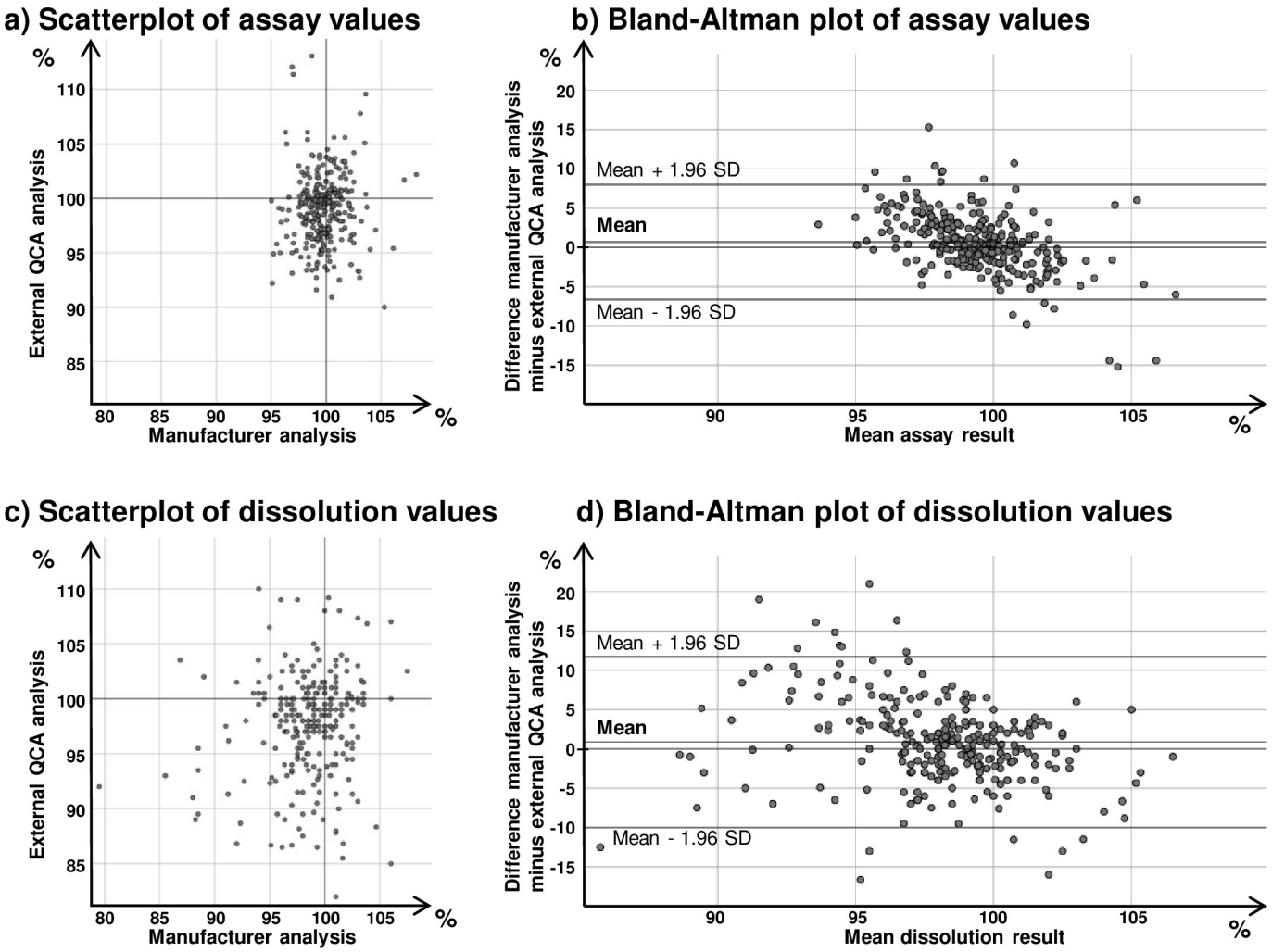


Fig 2. Inter-laboratory comparison of assay and dissolution results from manufacturer analysis and from external QCA laboratory analysis. Between the results of manufacturer analysis and external QCA analysis, correlation was calculated as r = 0.035 (p = 0.559) for assay results and as r = 0.132 (p = 0.034) for dissolution results. The bias depicted in the Bland-Altman plots was 0.67% for assay (two-sided t-test: p = 0.003) and 0.88% for dissolution (two-sided t-test: p = 0.011). Further results are shown in Table 2.

https://doi.org/10.1371/journal.pone.0243428.g002

show a small bias which reaches statistical significance in case of isoniazid, pyrazinamide and rifampicin. Dissolution values show no statistically significant bias for isoniazid, ethambutol and pyrazinamide. In contrast, data for rifampicin show a bias of 4.4% (two-sided t-test $p < 0.001$). An analysis of variance was carried out for the rifampicin dissolution differences using manufacturer and product as factors, but showed no significant influence of these factors on the observed differences.

In the Bland-Altman plot in Fig 2B, six of the investigated samples show assay differences of > 10% between manufacturer analysis and external QCA analysis. Notably, five of these represented kanamycin injection samples. This prompted us to investigate the data of all 81 kanamycin samples which had been analysed in the study period by the external QCA laboratory. The assay data were manually transferred from the different files provided by the external QCA into a single data file. S4 Table shows a descriptive summary of the assay data on kanamycin injection samples. Fig 3A and 3B show the scatterplot and Bland-Altman plot for these data, and the results of Bland-Altman analysis are shown in Table 2. Upper and lower 95%

Table 2. Inter-laboratory comparison of assay and dissolution results from manufacturer analysis and from external QCA laboratory analysis: Results of Bland-Altman analysis.

Data set compared (Manufacturer analysis minus external QCA analysis)	n	Difference Mean	Limits of agreement
Assay	288	0.67%**	- 6.69% to + 8.03%
Dissolution	261	0.88%*	- 10.05% to + 11.81%
Isoniazid assay	57	1.60%**	- 5.49% to + 8.69%
Ethambutol assay	37	0.71%	- 7.10% to + 8.52%
Pyrazinamide assay	37	0.77%*	- 3.21% to + 4.75%
Rifampicin assay	51	1.30%*	- 5.93% to + 8.53%
Isoniazid dissolution	57	0.67%	- 9.91% to + 11.25%
Ethambutol dissolution	36	0.04%	- 14.08% to + 14.16%
Pyrazinamide dissolution	36	1.00%	- 6.75% to + 8.75%
Rifampicin dissolution	51	**4.39%****	- 9.85% to + 18.63%
Kanamycin assay	81 [a]	-0.65%	- 14.52% to + 13.22%
Kanamycin assay, manufacturer 1	55 [a]	-0.19%	- 15.03% to + 14.65%
Kanamycin assay, manufacturer 2	16 [a]	1.39%	- 1.55% to 4.33%

The highest observed bias is highlighted in bold print. Detailed results, including standard deviation, 95% confidence intervals for mean and limits of agreement, and correlation coefficients, are given in S3 Table.

* Difference is significant with $p < 0.05$ (two-tailed).

** Difference is significant with $p < 0.01$ (two-tailed).

[a] Originally 15 kanamycin injection samples had been selected for the inter-laboratory comparison of results; a summary of these data is included in S2 Table. For the analysis shown in the last three lines of this table, the data of all 81 kanamycin injection samples which had been analysed in the study period by the external QCA were investigated; a summary of these data is given in S4 Table.

https://doi.org/10.1371/journal.pone.0243428.t002

limits of agreement are -14.5 to +13.2% for kanamycin assay, considerably higher as in the overall analysis of all APIs. In this case, ANOVA showed a clear influence of manufacturer. This is illustrated in the scatterplots and the Bland-Altman plots for the two most important manufacturers of kanamycin injections, which together supplied 71 of all 81 investigated kanamycin samples (Fig 3C, 3D, 3E and 3F). Manufacturer 1 (55 samples) had used a microbiological assay for kanamycin while the external QCA had used the HPLC assay of the United States Pharmacopeia; Bland-Altman analysis showed limits of agreement of -15.0 to +14.7%. In case of manufacturer 2 (16 samples), both manufacturer and the external QCA had used a microbiological assay; Bland-Altman analysis showed much narrower limits of agreement, i.e. -1.6 to +4.3%.

Discussion

In the study period, not a single batch was found to be out-of-specifications at the time of shipment. Also, the number of customer complaints was minimal, with only three batches confirmed to be out-of-specifications (two batches of pyridoxine tablets showing discolorations, one batch of *para*-aminosalicylic acid with improperly sealed sachets). Obviously, this success was achieved not only by quality control (QC) measures (i.e. pre-shipment inspections and laboratory analyses) but by a comprehensive system of quality assurance (QA). GDF's QA/QC procedures documented here present a successful example of quality assurance in drug procurement, evidenced both by virtual absence of out-of-specification batches and by very low requirements of time and costs. Drug procurement agencies both within and outside the field of anti-TB medicines may compare their procedures, including time and cost requirements, as well as their outcomes, including number of out-of-specification batches, to the results presented in this paper, to assess and further improve the efficiency of their operations.

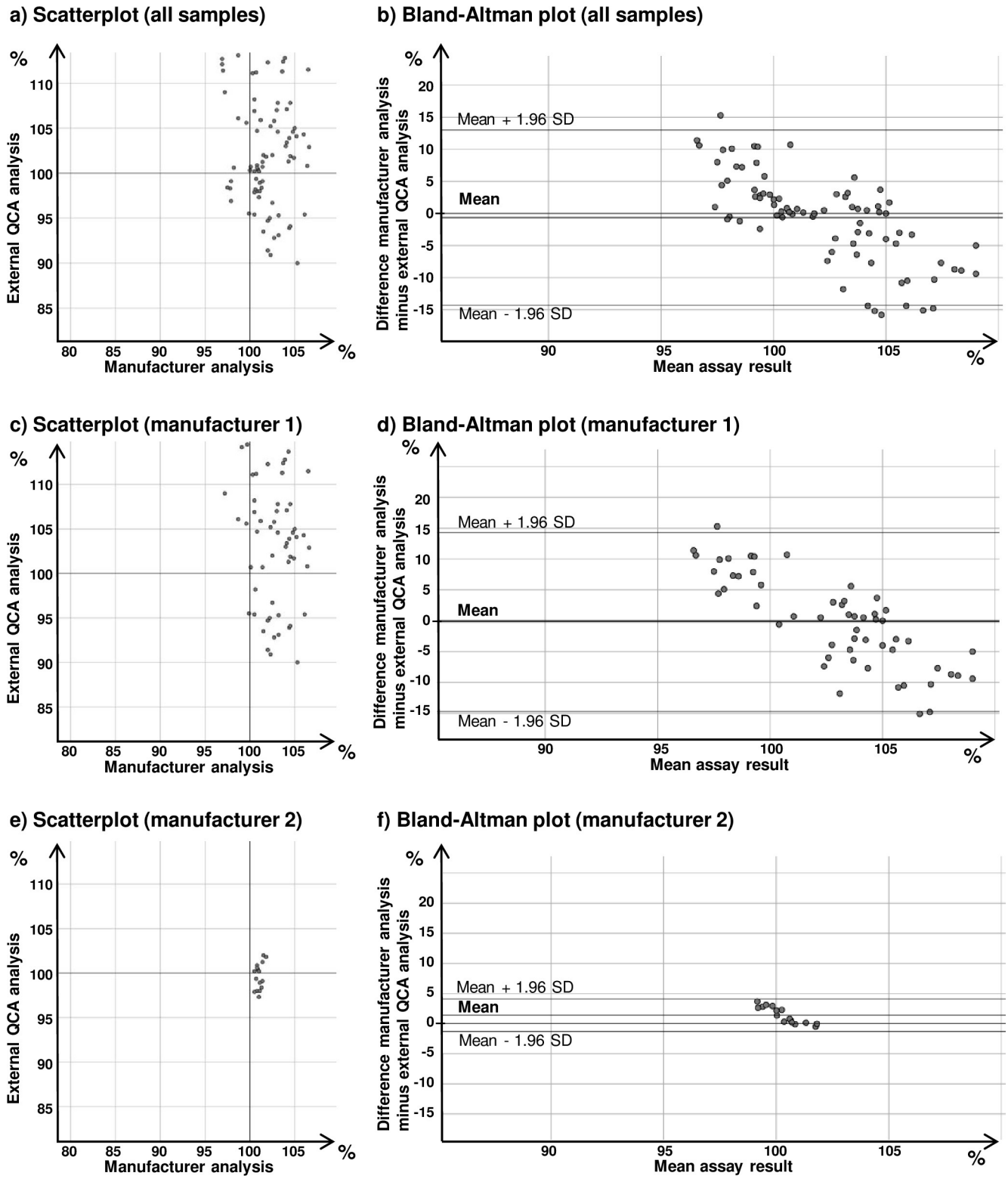


Fig 3. Inter-laboratory comparison of kanamycin injection assay results from manufacturer analysis and from external QCA laboratory analysis. See S4 Table for a descriptive summary of the data.

https://doi.org/10.1371/journal.pone.0243428.g003

Especially in the field of anti-TB medicines, impairments of their quality, as well as interruptions in their supply, may lead to an increase of cases of multi-drug resistant tuberculosis (MDR-TB) [11, 12] which thereafter can only be treated at significantly higher costs. Governments, national TB programs, technical and funding partners must ensure the continuous supply of quality assured TB medicines to avoid the amplification of multi-drug resistance of TB mycobacteria, to maintain the gains achieved so far globally and contain the cost of treatment. Therefore, while in future medicine financing is expected to shift increasingly from donor support to national funding schemes [7], it should be assured that procurement of anti-TB medicines, including QA/QC, is carried out effectively and on a sufficiently large scale.

Within the present study, an inter-laboratory comparison of the assay and dissolution values reported by the manufacturers and by GDF's external quality control agent (QCA) was conducted. The results need to be viewed in comparison to the pass/fail thresholds given in the relevant pharmacopeial monograph. For rifampicin capsules, as example, USP 2018 states the acceptable limits for assay (= content of API) as 90–110% and for dissolution as $>$ 75% of the declared content. Results of the inter-laboratory comparison can furthermore be viewed in comparison to the "acceptable difference" between manufacturer and external QCA analysis which is defined in a contract formulated by GDF and which specifies procedures for quality control testing by the external QCA. That contract specifies that results obtained for the tested batches by the external QCA must not differ more than 2% from the results provided by the manufacturer in case of analyses for which a manufacturer's method has been transferred to the external QCA laboratory. As explained above, methods transfers are only conducted for a small part of the conducted analyses, and larger differences than 2% may be expected when external QCA and manufacturer use different methods.

Overall evaluation of the results for all 196 samples included into this comparison (Fig 2 and Table 2) showed a small systematic bias, with the manufacturers reporting higher, i.e. more favourable results than the external QCA. However, these biases amounted only to 0.67% (assay) and 0.88% (dissolution) of the declared content and were therefore not relevant in comparison to the pass/fail thresholds of the pharmacopeial monographs. Furthermore, it must be pointed out that a large random variation of differences may obscure systematic differences, whereas a small random variation may show differences which are significant but not relevant.

A separate analysis of the dissolution results for the four principle first-line anti-TB agents showed that the manufacturer and external QCA results were similar for the highly water-soluble compounds isoniazid, ethambutol and pyrazinamide. However, for the poorly water-soluble compound rifampicin the dissolution values stated by the manufacturer (mean = 98.5%) were clearly higher than those given by the external QCA (mean = 94.1%; bias 4.4%; two-sided t-test: $p < 0.001$). Dissolution testing of rifampicin is known to be problematic [26, 27], and the dissolution testing methods currently given in USP 2018 and Ph. Int. 2017 are remarkably different (S5 Table). The reasons have been reviewed by Becker et al. [28]. Rifampicin exists in different polymorphic forms of different solubility. It is highly soluble in acidic aqueous solutions but decomposes rapidly under acid conditions. The influence of this decomposition is often not considered, and therefore the wisdom of the USP 2018 method for testing the dissolution of rifampicin capsules and of rifampicin/isoniazid capsules, in 0.1 N HCl (S5 Table) has been questioned [28]. At neutral pH, solubility of rifampicin is much lower and dissolution experiments often give erratic results. These have been attributed to poor wettability of rifampicin [28]. The dissolution testing procedure of Ph. Int. 2017, carried out at pH 6.8, therefore includes sodium dodecyl sulfate as detergent (S5 Table). In several monographs for fixed-dose combinations, Ph. Int. states that methods for rifampicin dissolution testing still have to be formulated (S5 Table), forcing pharmaceutical laboratories to use in-house methods for

rifampicin dissolution testing. The observed differences between manufacturer results and external QCA results for rifampicin dissolution are therefore most likely attributable to different methods employed. Notably, for all rifampicin samples investigated, the dissolution values determined by the external QCA (mean = 94.1%) were well above the pharmacopeial pass/fail thresholds (> 75% or > 80%, see S5 Table) and more conservative than the values reported by the manufacturers (mean = 98.5%). Therefore, the observed bias did not affect pass/fail decisions or patient safety. Nevertheless, the further development and harmonization of rifampicin dissolution testing methods may represent a priority for the national pharmacopeial conventions as well as for the WHO Expert Committee on Specifications for Pharmaceutical Preparations which is responsible for approving the monographs of the International Pharmacopoeia [3].

While bias (i.e. systematic difference) between manufacturer and external QCA analysis was low for most APIs, random variability was considerable. Overall 95% limits of agreement (LOAs) were calculated as -6.7 to +8.0% for assay, and -10.1 to +11.8% for dissolution (Table 2). This compared favourably with the LOAs reported in four earlier inter-laboratory comparisons in medicine quality analysis [29–32], reporting 95% LOAs of assay values of -19 to +24%; -15 to +18%; -20 to + 20%; and -13 to +20%, respectively (the latter values are calculated from the assay values of CENQAM and DCQL-Sana'a laboratories in ref. [32]). Nevertheless, the random differences observed in the present study are clearly higher than the ± 2% difference which is considered acceptable in cases when both laboratories use the same analytical method (see above). No true results for the individual analyses included in the present comparison are known, and therefore it cannot be decided to which extent manufacturer analysis and external QCA analysis contributed to the observed random variability between their results. Given that for most investigated medicines assay and dissolution results were close to 100% of the declared content (Table 1), the observed random variability will in most cases have no influence on the validity of the pass/fail classification according to the pharmacopeial limits. An exception may be presented by the investigated kanamycin assay values, where variability was especially high, and LOAs for assay were calculated as -14.5 to +13.2% (Table 2 and Fig 3). Given the USP 2018 threshold of 90–115% for kanamycin injection assay values, such wide LOAs may question the validity of the pass/fail classification of the analysis and call for careful validation of the analytical procedures both in the manufacturer's laboratory and in the external QCA laboratory. GDF's external QCA had already responded to this problem by arranging that all analyses for kanamycin were carried out in its especially well-experienced laboratory in Belgium. As mentioned in the results section, the high variability between manufacturer and external QCA results in kanamycin assay results could largely be attributed to samples from one manufacturer who used a microbiological assay for kanamycin while the external QCA had used the HPLC assay of the USP (Fig 3). This strikingly demonstrates the important influence of different analytical methods used. The variability of kanamycin assay results between manufacturer and external QCA analysis can apparently be resolved by method transfer, but the trueness of the results obtained with different methods should still be investigated.

Conclusions and recommendations

1. GDF's QA/QC procedures have proven to represent a very successful model to ensure uninterrupted access to quality-assured medicines at low prices. These procedures should be used as a benchmark when evaluating and improving QA/QC procedures of other medicine procurement operations, both within and beyond the area of anti-TB medicines.

2. GDF's QA/QC procedures have proven to achieve complete absence of out-of-specification batches at the time of procurement. Obviously, quality of anti-TB medicines may

deteriorate over time, especially (but not only) in case of inappropriate transport and storage conditions, and the stability of the medicines is dependent on the quality of formulation and packaging. Future investigations of the quality of anti-TB medicines obtained from GDF should therefore include the quality at the time of administration to the patient, in addition to quality at the time of procurement.

3. The inter-laboratory comparison carried out within this study showed that certain problems in quality analysis results, such as a bias in rifampicin dissolution values and high variability in kanamycin assay values, can be rapidly detected by systematic comparison of the results of manufacturer and external QCA analysis, e.g. during a semi-annual or annual review of the reported results. Therefore, based on the results of this study GDF has initiated steps to ensure that in future all results of manufacturer analysis and external QCA analysis are entered, by the manufacturers and/or by the external QCA, into a database of uniform format, and are evaluated routinely for criteria such as bias and limits of agreement, both for different APIs and for different manufacturers and products. This may also establish whether a given product demonstrates changing characteristics over time, e.g. undergoes significant dissolution changes compared to the original batch, which may indicate the need for the manufacturer to re-demonstrate the bioequivalence of the product.

4. Also other publicly funded procurement agencies may likewise collect and evaluate results of both manufacturer and external QCA analysis, and share results. This may facilitate the identification and dissemination of best practices in medicine QA/QC and allow to further improve procedures, e.g. with the aim to reduce the random variability observed in this study.

5. The WHO Expert Committee on Specifications for Pharmaceutical Preparations may take notice of the results of such inter-laboratory comparisons in pharmaceutical analysis and use them to identify priorities in the further development of norms, standards and guidelines, including monographs of the International Pharmacopoeia.

Supporting information

S1 Scheme. Supplier and product selection procedure of the Global Drug Facility (GDF). This scheme summarizes only the most basic principles; details are described in the references [18,25].
(PDF)

S2 Scheme. Principles of the quality control procedures of the Global Drug Facility (GDF).
(PDF)

S1 Fig. Inter-laboratory comparison of assay results from manufacturer analysis and from external QCA laboratory analysis for the four principal first-line anti-TB agents.
(PDF)

S2 Fig. Inter-laboratory comparison of dissolution results from manufacturer analysis and from external QCA laboratory analysis for the four principal first-line anti-TB agents.
(PDF)

S1 Table. Details of anti-tuberculosis medicines monitored in the quality control procedure of the Global Drug Facility in the study period 2013–2017.
(PDF)

S2 Table. Descriptive summary of assay and dissolution data for all 13 active pharmaceutical ingredients which had been analysed in the study period by the external QCA.
(PDF)

S3 Table. Detailed results of Bland-Altman analysis.
(PDF)

S4 Table. Descriptive summary of assay data for all 81 kanamycin injection samples which had been analysed in the study period by the external QCA. In addition, data from the two main manufacturers supplying kanamycin are presented.
(PDF)

S5 Table. Dissolution testing conditions for solid oral formulations containing rifampicin in the United States Pharmacopeia 2018 and the International Pharmacopoeia 2017.
(PDF)

Acknowledgments

We are grateful to SGS Netherlands B.V. (Spijkenisse, NL) and to the IDA Foundation, Amsterdam, NL, for their valuable help in assembling many of the data presented in this manuscript. We thank Harparkash Kaur (London School of Hygiene and Tropical Medicine, UK), Rainer Göb (University of Würzburg, Germany), Jennifer Dressman (University of Frankfurt, Germany), Deus Mubangizi (WHO Prequalification Team: medicines (PQTm), Geneva, Switzerland), as well as Lawrence Evans III and Hari Ramanathan (United States Pharmacopeial Convention), for helpful discussions, and Dorothy Amony (GDF) for help in the preparation of the manuscript.

Author Contributions

Conceptualization: Cathrin Hauk, Simon Schäfermann, Nigorsulton Muzafarova, Lutz Heide.

Data curation: Cathrin Hauk, Nigorsulton Muzafarova, Magali Babaley.

Formal analysis: Cathrin Hauk, Simon Schäfermann, Peter Martus.

Funding acquisition: Nigorsulton Muzafarova, Lutz Heide.

Investigation: Cathrin Hauk, Nigorsulton Muzafarova, Lutz Heide.

Methodology: Cathrin Hauk, Simon Schäfermann, Peter Martus, Nigorsulton Muzafarova, Brenda Waning, Lutz Heide.

Project administration: Nigorsulton Muzafarova, Magali Babaley, Brenda Waning, Lutz Heide.

Software: Peter Martus.

Supervision: Brenda Waning, Lutz Heide.

Visualization: Cathrin Hauk, Simon Schäfermann, Peter Martus.

Writing – original draft: Cathrin Hauk, Simon Schäfermann, Nigorsulton Muzafarova.

Writing – review & editing: Peter Martus, Magali Babaley, Brenda Waning, Lutz Heide.

References

1. Wirtz VJ, Hogerzeil HV, Gray AL, Bigdeli M, de Joncheere CP, Ewen MA, et al. Essential medicines for universal health coverage. Lancet. 2017; 389(10067):403–76. https://doi.org/10.1016/S0140-6736(16)31599-9 PMID: 27832874

2. World Health Organization. A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva, Switzerland, 2017. www.who.int/medicines/regulation/ssffc/publications/se-study-sf/en/.
3. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Model quality assurance system for procurement agencies. WHO Technical Report Series 986. Annex 3. World Health Organization. Geneva, Switzerland, 2014.
4. Moore T, Lee D, Konduri N, Kasonde L. Assuring the quality of essential medicines procured with donor funds. Health, Nutrition and Population (HNP) discussion paper. World Bank, Washington, DC, 2012. https://openknowledge.worldbank.org/handle/10986/13577.
5. van Valen M, Jamieson D, Parvin L, Ramirez CL. Dispelling myths about drug procurement policy. Lancet Glob Health. 2018; 6(6):e609–e10. https://doi.org/10.1016/S2214-109X(18)30190-6 PMID: 29773115
6. Management Sciences for Health. MDS-3: Managing Access to Medicines and Health Technologies. Arlington, VA. 2012.
7. 't Hoen EF, Tatay M, Torreele E. Ensuring access to life-saving medicines as countries shift from Gobal Fund support. Bull World Health Organ. 2019; 97:311-A.
8. Waning B. Risks of decentralized procurement in fragile TB markets: Observations, implications, and recommendations at national and global levels. The Hague: Union Conference Presentation, Global Drug Facility and Stop TB Partnership; 27 October 2018. Available from: https://www.dropbox.com/s/kze0ojd8r0yo4qs/WANING_Domestic_Procurement.
9. Nwokike J, Clark A, Nguyen PP. Medicines quality assurance to fight antimicrobial resistance. Bull World Health Organ. 2018; 96(2):135–7. https://doi.org/10.2471/BLT.17.199562 PMID: 29403117
10. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016; 387(10014):176–87. https://doi.org/10.1016/S0140-6736(15)00473-0 PMID: 26603922
11. Dye C. Doomsday postponed? Preventing and reversing epidemics of drug-resistant tuberculosis. Nat Rev Microbiol. 2009; 7(1):81–7. https://doi.org/10.1038/nrmicro2048 PMID: 19079354
12. Caminero JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. Int J Tuberc Lung Dis. 2010; 14(4):382–90. PMID: 20202293
13. World Health Organization. Global Tuberculosis Report 2017. Geneva, Switzerland, 2017. www.who.int/tb/publications/global_report/en/.
14. Stop TB Partnership News Stories 2018. USD 31 million saved by Stop TB Partnership's Global Drug Facility through newly-reduced prices for TB medicines. http://www.stoptb.org/news/stories/2018/ns18_043.asp.
15. Arinaminpathy N, Cordier-Lassalle T, Vijay A, Dye C. The Global Drug Facility and its role in the market for tuberculosis drugs. Lancet. 2013; 382(9901):1373–9. https://doi.org/10.1016/S0140-6736(13)60896-X PMID: 23726162
16. Arinaminpathy N, Cordier-Lassalle T, Lunte K, Dye C. The Global Drug Facility as an intervention in the market for tuberculosis drugs. Bull World Health Organ. 2015; 93(4):237–48A. https://doi.org/10.2471/BLT.14.147256 PMID: 26229188
17. Lunte K, Cordier-Lassalle T, Keravec J. Reducing the price of treatment for multidrug-resistant tuberculosis through the Global Drug Facility. Bull World Health Organ. 2015; 93(4):279–82. https://doi.org/10.2471/BLT.14.145920 PMID: 26229192
18. Global Drug Faclity. GDF Quality Assurance Policy 2010. www.stoptb.org/gdf/drugsupply/quality_sourcing_process.asp.
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986; 1(8476):307–10. PMID: 2868172
20. Global Drug Facility. Procurement Notices for ITB-IDA/GDF-FLD/2018/001, 12. December 2017. Annex H: Indicative non-binding estimated quantities FLD. www.stoptb.org/gdf/drugsupply/procurement_notice.asp.
21. Global Drug Facility. Procurement Notices for ITB-IDA/GDF-SLD/2018/002, 12. December 2017. Annex H: Indicative non-binding estimated quantities SLD. www.stoptb.org/gdf/drugsupply/procurement_notice.asp.
22. 't Hoen EF, Hogerzeil HV, Quick JD, Sillo HB. A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme. J Public Health Policy. 2014; 35(2):137–61. https://doi.org/10.1057/jphp.2013.53 PMID: 24430804
23. Global Fund Quality Assurance Policy for Pharmaceutical Products (as amended and restated on 14 December 2010). www.theglobalfund.org/media/5894/psm_qapharm_policy_en.pdf?u=636607536930000000.

24. Matiru R, Ryan T. The Global Drug Facility: a unique, holistic and pioneering approach to drug procurement and management. Bull World Health Organ. 2007; 85(5):348–53. https://doi.org/10.2471/blt.06.035402 PMID: 17639218

25. Global Drug Facility. Invitation to bid 2018 ITB-IDA/GDF—FLD/2018/001 Issue date: 8 December 2017. www.stoptb.org/assets/documents/gdf/drugsupply/pn4/fld/ITB-GDF-IDA-FLD-2018%20document.pdf.

26. Ammar HO, Khalil RM. Discrepancy among dissolution rates of commercial tablets as a function of dissolution method. part 6: rifampicin. Pharmazie. 1996; 51(3):165–8. PMID: 8900866

27. Panchagnula R, Bhardwaj V. Effect of amorphous content on dissolution characteristics of rifampicin. Drug Dev Ind Pharm. 2008; 34(6):642–9. https://doi.org/10.1080/03639040701842451 PMID: 18568915

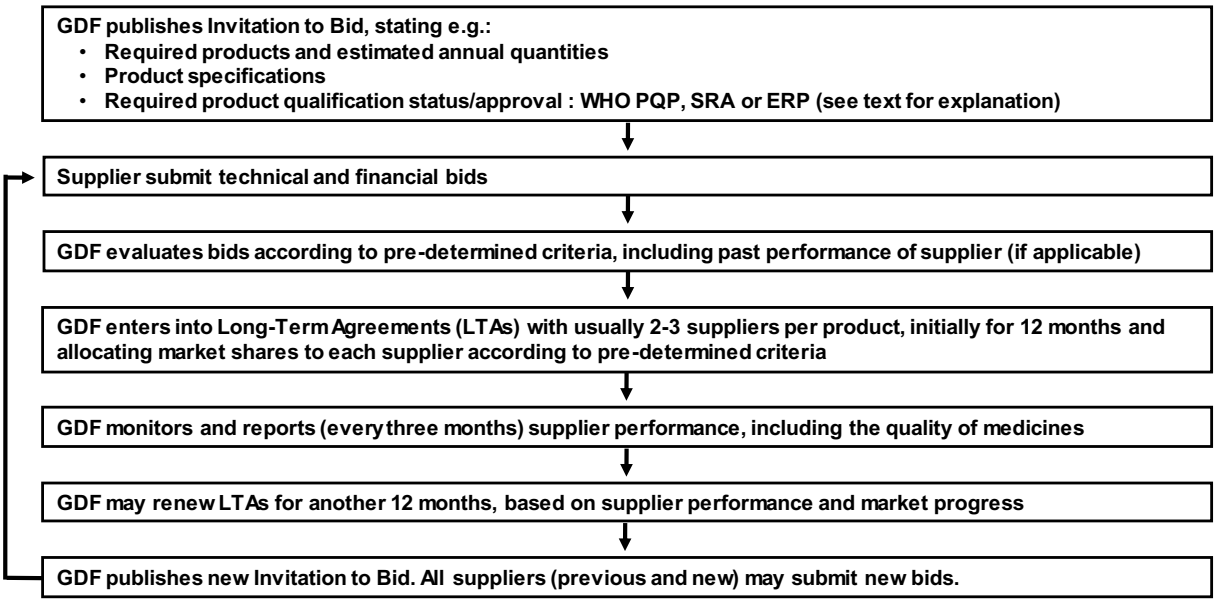
28. Becker C, Dressman JB, Junginger HE, Kopp S, Midha KK, Shah VP, et al. Biowaiver monographs for immediate release solid oral dosage forms: rifampicin. J Pharm Sci. 2009; 98(7):2252–67. https://doi.org/10.1002/jps.21624 PMID: 19160441

29. Kaur H, Allan EL, Mamadu I, Hall Z, Ibe O, El Sherbiny M, et al. Quality of artemisinin-based combination formulations for malaria treatment: prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. PLoS One. 2015; 10(5):e0125577. https://doi.org/10.1371/journal.pone.0125577 PMID: 26018221

30. Kaur H, Allan EL, Mamadu I, Hall Z, Green MD, Swamidos I, et al. Prevalence of substandard and falsified artemisinin-based combination antimalarial medicines on Bioko Island, Equatorial Guinea. BMJ Glob Health. 2017; 2(4):e000409. https://doi.org/10.1136/bmjgh-2017-000409 PMID: 29082025

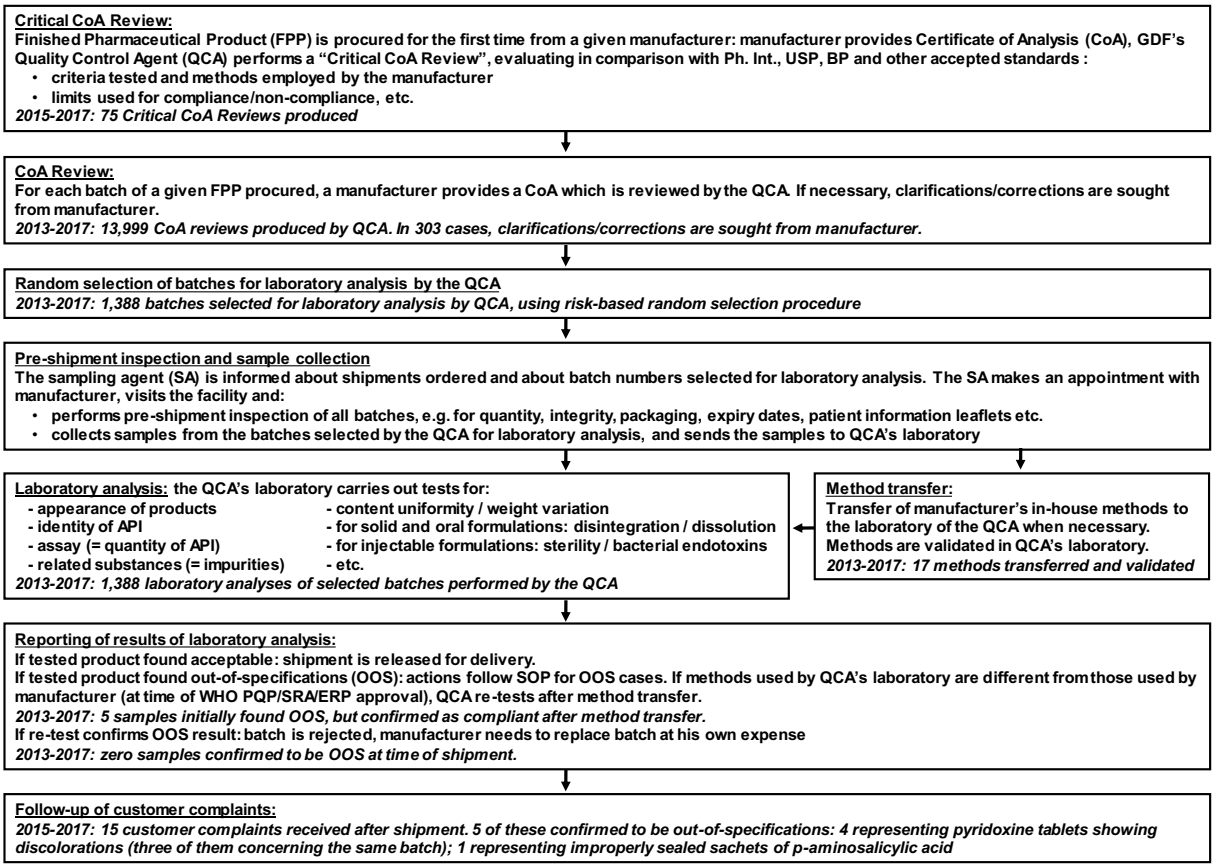
31. Team ACDQPTatIS. Quality of artemisinin-containing antimalarials in Tanzania's private sector—Results from a nationally representative outlet survey. Am J Trop Med Hyg. 2015; 92(6 Suppl):75–86. https://doi.org/10.4269/ajtmh.14-0544 PMID: 25897065

32. Abdo-Rabbo A, Bassili A, Atta H. The quality of antimalarials available in Yemen. Malar J. 2005; 4:28. https://doi.org/10.1186/1475-2875-4-28 PMID: 15987508

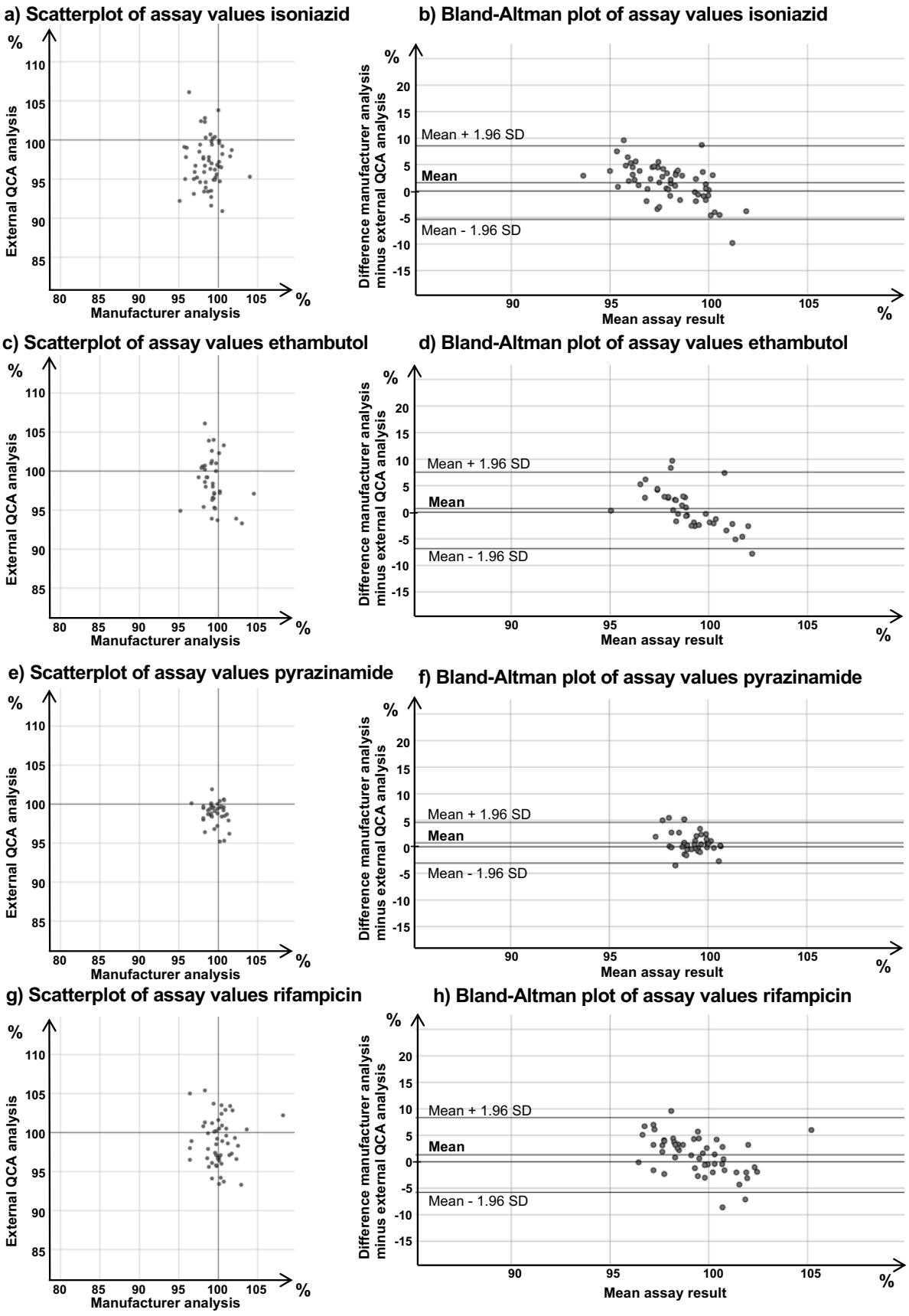


S1 Scheme. Supplier and product selection procedure of the Global Drug Facility (GDF).

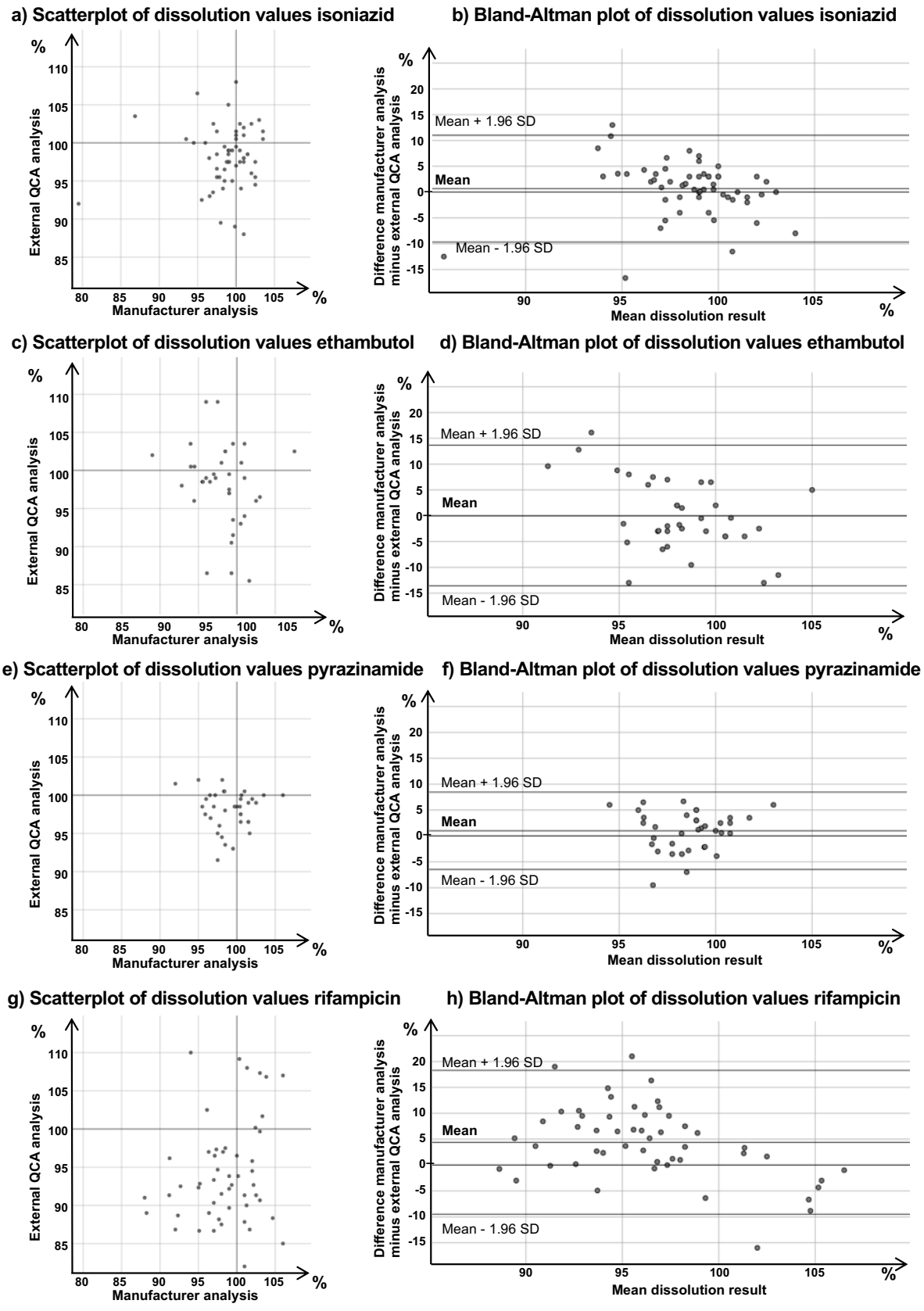
This scheme summarizes only the most basic principles; details are described in the references [18,25].



S2 Scheme. Principles of the quality control procedures of the Global Drug Facility (GDF).



S1 Fig. Inter-laboratory comparison of assay results from manufacturer analysis and from external QCA laboratory analysis for the four principal first-line anti-TB agents.



S2 Fig. Inter-laboratory comparison of dissolution results from manufacturer analysis and from external QCA laboratory analysis for the four principal first-line anti-TB agents.

Active Pharmaceutical Ingredient(s)	Strength	Formulation	Packaging	Number of batches 2013-2017	Estimated annual quantity (4/2018-3/2019)	Number of suppliers 2013-2017	Number of suppliers Jan. 2018	Number of WHO prequalified products (Jan. 2018)	Number of SRA-approved products (Jan. 2018)	Number of ERP-approved products (Jan. 2018)	Monograph in Ph. Int. 2017	Monograph in USP 2018	Monograph in BP 2016	Included in WHO EML 2017
First-line adult and injectable medicines														
Ethambutol	400 mg	Film coated tablet(s)	Blister(s)	307	30,000,000	4	2	2	0	0	y	y	y	y
Isoniazid	300 mg	Uncoated tablet(s)	Blister(s)	461	200,000,000	2	2	2	0	0	y	y	y	y
Pyrazinamide	400 mg	Uncoated tablet(s)	Blister(s)	217	20,000,000	2	1	1	0	0	y	y	y	y
Pyrazinamide	500 mg	Uncoated tablet(s)	Blister(s)	192	65,000,000	3	2	2	0	0	y	y	y	(n)
Rifabutin	150 mg	Capsule(s)	HDPE jar(s)	12	400,000	2	1	1	0	0	n	y	n (only API)	y
Rifampicin	150 mg	Film coated tablet(s), capsule(s)	Blister(s)	15	50,000	2	1	1	0	0	y	only cap	only cap	y
Rifampicin	300 mg	Film coated tablet(s)	Blister(s)	46	50,000	2	1	0	1	0	y	n (only cap)	y	y
Rifampicin/Isoniazid	150/75 mg	Film coated tablet(s)	Blister(s)	1630	400,000,000	5	3	3	0	0	y	n (only cap)	n (only APIs)	y
Rifampicin/Isoniazid /Ethambutol	150/75/275 mg	Film coated tablet(s)	Blister(s)	447	40,000,000	3	2	2	0	0	y	n (only APIs)	n (only APIs)	y
Rifampicin/Isoniazid /Pyrazinamide/Ethambutol	150/75/400/275 mg	Film coated tablet(s)	Blister(s)	3056	250,000,000	4	2	2	0	0	y	y	n (only APIs)	y
Rifapentine	150 mg	Film coated tablet(s)	Blister(s)	2		1	1	0	1	0	n	n (only cap)	n	y (LTBI)
Streptomycin	1 g	Powder for injection	Vial(s)	288	3,000,000	1	2	1	1	0	y	y	y	y (MDR-TB)
First-line paediatric medicines														
Ethambutol	100 mg	Film coated tablet(s)	Blister(s)	129	15,000,000	3	2	1	1	0	y	y	y	y
Isoniazid	100 mg	Uncoated tablet(s)	Blister(s)	161	50,000,000	2	3	2	1	0	y	y	y	y
Rifampicin/Isoniazid	75/50 mg	Dispersible tablet(s)	Strip(s)	163	65,000,000	1	1	1	0	0	y	n (only cap)	n (only APIs)	y
Rifampicin/Isoniazid /Pyrazinamide	75/50/150 mg	Dispersible tablet(s)	Blister(s)	87	35,000,000	1	1	1	0	0	y	y	n (only APIs)	y
Second-line medicines														
Amikacin	500 mg	Solution for injection	Ampoule(s)	140	500,000	3	2	0	2	0	(n)	y	y	(n) (MDR-TB)
Amoxicillin + Clavulanic acid	250/125 mg	Film coated tablet(s)	Blister(s)	5	*	2	2	0	2	0	n	y	y	n
Amoxicillin + Clavulanic acid	500/125 mg	Film coated tablet(s)	Blister(s)	22	300,000	2	2	0	2	0	n	y	y	n
Amoxicillin + Clavulanic acid	875/125 mg	Film coated tablet(s)	Blister(s)	54	500,000	4	2	0	2	0	n	y	y	n
Amoxicillin + Clavulanic acid	125/31,25 mg/5mL	Powder for oral suspension	HDPE container(s)	20	*	1	1	0	1	0	n	y	y	n
Capreomycin	0,5 g	Powder for injection	Vial(s)	4	*	1	1	0	0	1	y	y	n	n
Capreomycin	0,75 g	Powder for injection	Vial(s)	16		1	1	0	0	1	y	y	n	n
Capreomycin	1 g	Powder for injection	Vial(s)	312	2,000,000	3	2	1	1	0	y	y	n	y (MDR-TB)
Clarithromycin	250 mg	Film coated tablet(s)	Blister(s)	2		1	0	0	0	0	n	y	y	n
Clarithromycin	500 mg	Film coated tablet(s)	Blister(s)	35		3	0	0	0	0	n	y	y	n
Clofazimine	100 mg	Capsule(s)	HDPE jar(s)	33	12,000,000	1	1	0	1	0	n	y	y	y (MDR-TB)
Cycloserine	250 mg	Capsule(s)	Blister(s)	1098	30,000,000	2	2	2	0	0	y	y	n	y (MDR-TB)

Active Pharmaceutical Ingredient(s)	Strength	Formulation	Packaging	Number of batches 2013-2017	Estimated annual quantity (4/2018-3/2019)	Number of suppliers 2013-2017	Number of suppliers Jan. 2018	Number of WHO prequalified products (Jan. 2018)	Number of SRA-approved products (Jan. 2018)	Number of ERP-approved products (Jan. 2018)	Monograph in Ph. Int. 2017	Monograph in USP 2018	Monograph in BP 2016	Included in WHO EML 2017
Second-line medicines														
Delamanid	50 mg	Film coated tablet(s)	Blister(s)	19		1	1	0	1	0	n	n	n	y (MDR-TB)
Ethionamide	125 mg	Film coated tablet(s)	Blister(s)	10	210	1	1	1	0	0	n (only API)	y	n (only API)	y (MDR-TB)
Ethionamide	250 mg	Film coated tablet(s)	Blister(s)	408	28,000,000	4	2	2	0	0	n (only API)	y	n (only API)	y (MDR-TB)
Imipenem/Cilastatin	500/500 mg	Solution for injection	Vial(s)	54	250,000	4	3	0	3	0	n	y	n (only APIs)	n
Kanamycin	0,5 g	Powder for injection	Vial(s)								y	(n)	n (only API)	(n)
Kanamycin	0,5 g	Solution for injection	Ampoule(s)	107	*	2	1	1	0	0	(n)	y	n (only API)	(n)
Kanamycin	1 g	Powder for injection	Vial(s)								y	(n)	n (only API)	y (MDR-TB)
Kanamycin	1 g	Solution for injection	Ampoule(s)	774	4,500,000	2	2	1	1	0	(n)	y	n (only API)	(n)
Levofloxacin	250 mg	Film coated tablet(s)	Blister(s)	328	30,000,000	5	2	1	1	0	n	y	n	y (MDR-TB)
Levofloxacin	500 mg	Film coated tablet(s)	Blister(s)	209	1,800,000	4	2	1	1	0	n	y	n	y (MDR-TB)
Linezolid	600 mg	Film coated tablet(s)	Blister(s)	74	55,000,000	3	2	0	2	0	n	n (only API)	n	y (MDR-TB)
Meropenem	1 g	Powder for injection	Vial(s)	2	5,000	1	1	0	1	0	n	y	n (only API)	n
Moxifloxacin	400 mg	Film coated tablet(s)	Blister(s)	210	35,000,000	5	3	2	1	0	n	y	n (only API)	y (MDR-TB)
PAS Acid	4 g	Delayed-release granules	Sachet	136	10,000	1	1	0	1	0	n	n (only API)	n	y (MDR-TB)
PAS Sodium Salt	4 g	Powder for oral solution	Sachet								n	n (only API)	n	(n)
PAS Sodium Salt	4 g	Delayed-release granules	Sachet, jar	1874	3,500,000	2	2	2	0	0	n	n (only API)	n	(n)
Prothionamide	250 mg	Film coated tablet(s)	Blister(s)	217	20,000,000	3	2	2	0	0	n (only API)	n	n	y (MDR-TB, alternative to ethionamide)
Terizidone	250 mg	Capsule(s)	Blister(s)	14	*	1	1	0	1	0	n	n	n	y (MDR-TB, alternative to cycloserine)
Products not included in GDF Product List April 2018														
Clofazimine	50 mg	Capsule(s)		13	153,300	1	0	0	0	0	n	y	y	y (MDR-TB)
Ethambutol/Isoniazid	400/150 mg	Film coated tablet(s)		9		1	0	0	0	0	y	n	n	y
Ethambutol	800 mg	Tablet(s)		217		1	0	0	0	0	y	y	y	(n)
Pyrazinamide	750 mg	Tablet(s)		47		2	0	0	0	0	y	y	y	(n)
Rifampicin/Isoniazid	60/30 mg	Dispersible tablet(s)		98		2	0	0	0	0	y	n (only cap)	n (only APIs)	(n)
Rifampicin/Isoniazid	60/60 mg	Dispersible tablet(s)		111		1	0	0	0	0	y	n (only cap)	n (only APIs)	(n)
Rifampicin/Isoniazid /Pyrazinamide	60/30/150 mg	Dispersible tablet(s)		103		2	0	0	0	0	y	y	n (only APIs)	(n)
Rifampicin/Isoniazid	150/150 mg	Film coated tablet(s)		120		1	1	1	0	0	y	n (only cap)	n (only APIs)	y

S1 Table. Details of anti-tuberculosis medicines monitored in the quality control procedure of the Global Drug Facility in the study period 2013-2017.

Sources: GDF-Product List April 2018, GDF FLD and SLD list JAN 2018, Annex H: Indicative non-binding estimated quantities FLD and SLD; 1st April 2018 to 31 March 2019.[20 21] If the product is not mentioned in Annex H (Indicative non-binding estimated quantities FLD and SLD), no number of products is indicated in the column "Estimated annual quantity (4/2018-3/2019)". *) According to Annex H:[20 21] Insufficient demand information to generate volume estimates

Abbreviations: API, Active pharmaceutical ingredient; BP, British Pharmacopoeia; Cap, Capsules; EML, Essential Medicine List; FDC, Fixed Dose Combination; HDPE, High Density Polyethylene; Ph. Int., International Pharmacopoeia; LTBI, Latent TB infection; MDR, Multi drug resistant; n, No (not included in pharmacopeia or EML); (n), different formulation or strength is included in pharmacopeia or EML; PAS, *para*-aminosalicylic acid; USP, United States Pharmacopeia; y, Yes (included in pharmacopeia or EML)

	Assay		Dissolution		Difference	
	Manufacturer analysis	**External QCA analysis**	**Manufacturer analysis**	**External QCA analysis**	**Assay**	**Dissolution**
Capreomycin inj.						
N	10	10	-	-	10	-
Min/Max	95.5/107.1%	95.8/109.6%			-6.00/5.40%	
Mean	101.5%	103.0%	-	-	-1.49%	-
Median	101.2%	102.8%	-	-	-0.95%	-
Standard deviation	3.02%	3.77%	-	-	3.27%	-
Cycloserine						
N	10	10	10	10	10	10
Min/Max	97.75/103.1%	92.5/100.8%	95.7/100.5%	89.5/101.5%	-2.05/10.35%	-4.00/6.18%
Mean	100.3%	98.0%	97.9%	96.4%	2.28%	1.55%
Median	100.7%	99.1%	97.5%	97.3%	1.10%	1.92%
Standard deviation	1.87%	2.99%	1.53%	3.31%	4.17%	2.72%
Ethambutol						
N	37	37	37	36	37	36
Min/Max	95.2/104.5%	93.3/106.1%	89.0/107.5%	85.5/109.0%	-7.80/9.70%	-13.00/16.12%
Mean	99.3%	98.6%	98.0%	98.1%	0.71%	0.04%
Median	99.3%	98.4%	98.5%	98.8%	0.30%	-1.66%
Standard deviation	1.55%	3.20%	3.38%	5.45%	3.85%	6.96%
Ethionamide						
N	20	20	20	20	20	20
Min/Max	97.5/104.0%	96.5/104.5%	94.0/102.5%	94.0/104.5%	-5.50/2.80%	-7.50/3.50%
Mean	98.8%	97.2%	99.0%	99.9%	-1.00%	-0.91%
Median	99.0%	96.8%	99.5%	98.5%	-0.71%	-1.00%
Standard deviation	1.45%	2.26%	2.07%	2.65%	2.49%	2.91%
Isoniazid						
N	57	57	57	57	57	57
Min/Max	98.1/104.0%	90.9/106.1%	79.5/103.5%	88.0/108.0%	-9.80/9.60%	-16.65/13.00%
Mean	98.8%	97.2%	98.8%	98.1%	1.60%	0.67%
Median	99.0%	96.8%	99.5%	98.5%	2.10%	1.49%
Standard deviation	1.63%	3.11%	3.80%	4.01%	3.54%	5.28%
Kanamycin inj.						
N	15	15	-	-	15	-
Min/Max	96.9/106.1%	90.0/106.1%	-	-	-15.20/15.30%	-
Mean	100.9%	101.7%	-	-	-0.79%	-
Median	101.0%	100.3%	-	-	0.02%	-
Standard deviation	2.69%	6.59%	-	-	8.67%	-
Levofloxacin						
N	15	15	15	15	15	15
Min/Max	98.0/102.5%	96.7/104.2%	96.4/103.5%	98.5/104.0%	-4.10/2.90%	-7.60/3.00%
Mean	100.3%	100.8%	99.7%	101.2%	-0.54%	-1.77%
Median	100.0%	100.7%	99.0%	101.0%	0.00%	-1.35%
Standard deviation	1.50%	1.86%	2.05%	1.59%	2.19%	2.75%
Linezolid						
N	9	9	9	9	9	9
Min/Max	95.0/102.3%	99.0/102.3%	94.0/102.5%	95.0/101.0%	-4.80/3.30%	-6.50/6.00%
Mean	99.5%	100.5%	97.1%	98.5%	-1.9%	-1.44%
Median	100.3%	100.3%	96.0%	99.5%	-0.70%	-0.50%
Standard deviation	2.35%	1.06%	2.95%	2.22%	2.56%	4.14%
Moxifloxacin						
N	12	12	12	12	12	12
Min/Max	97.9/103.7%	96.2/103.3%	96.0/100.1%	97.0/102.5%	-2.60/6.00%	-4.05/3.05%
Mean	100.7%	100.0%	98.5%	99.2%	0.66%	-0.66%
Median	100.6%	100.2%	99.0%	98.8%	-0.10%	-1.00%
Standard deviation	1.81%	1.92%	1.42%	1.86%	2.97%	2.24%
Para-aminosalicylic acid						
N	5	5	5	5	5	5
Min/Max	98.7/102.5%	95.9/100.3%	85.5/91.0%	89.5/97.5%	0.20/6.60%	-7.50/-1.00%
Mean	100.2%	98.1%	88.4%	93.8%	2.10%	-5.40%
Median	99.5%	98.7%	88.5%	93.5%	0.90%	-6.50%
Standard deviation	1.60%	1.92%	1.95%	2.99%	2.66%	2.63%
Protionamide						
N	10	10	10	10	10	10
Min/Max	99.0/100.9%	97.2/101.9%	96.6/103.5%	96.0/101.15%	-2.60/2.80%	-2.90/4.00%
Mean	99.6%	99.3%	99.7%	99.1%	0.31%	0.62%
Median	99.5%	99.5%	98.8%	99.5%	0.10%	1.28%
Standard deviation	0.60%	1.50%	2.14%	1.55%	1.68%	2.45%
Pyrazinamide						
N	37	37	36	37	37	37
Min/Max	96.6/101.4%	95.2/101.9%	92.0/106.0%	91.5/102.0%	-3.50/5.45%	-9.50/6.67%
Mean	99.6%	98.8%	99.1%	98.0%	077%	1.00%
Median	99.5%	99.2%	99.0%	99.0%	0.44%	1.62%
Standard deviation	1.08%	1.46%	2.72%	2.51%	1.96%	3.82%
Rifampicin						
N	51	51	51	51	51	51
Min/Max	96.4/108.2%	93.3/105.4%	88.0/106.0%	82.0/110.0%	-8.60/9.60%	-16.00/21.00%
Mean	100.1%	98.8%	98.5%	94.1%	1.30%	4.39%
Median	100.1%	98.6%	99.0%	92.67%	1.60%	3.67%
Standard deviation	1.95%	3.05%	4.25%	6.67%	3.60%	7.09%

S2 Table. Descriptive summary of assay and dissolution data for all 13 active pharmaceutical ingredients which had been analysed in the study period by the external QCA.

Data set compared (Manufacturer analysis minus external QCA analysis)	Difference Mean (95 % CI)	Difference Standard deviation	Correlation coefficient (P value)	Limits of agreement (95 % CI)
Assay (n= 288)	0.67 % (0.24 to 1.10 %)	3.74 %	0.035 (p=0.559)	- 6.69 % (- 7.44 to - 5.94%) + 8.03 % (7.28 to 8.78 %)
Dissolution (n= 261)	0.88 % (0.20 to 1.56 %)	5.55 %	0.132 (p=0.034)	- 10.05 % (- 11.22 to - 8.88 %) + 11.81 % (10.64 to 12.98 %)
Isoniazid assay (n= 57)	1.60 % (0.66 to 2.54 %)	3.54 %	-0.018 (p=0.894)	- 5.49 % (- 7.12 to - 3.86 %) + 8.69 % (7.06 to 10.32 %)
Ethambutol assay (n= 37)	0.71 % (- 0.57 to 1.99 %)	3.85 %	- 0.221 (p=0.188)	- 7.10 % (- 9.32 to – 4.87 %) + 8.52 % (6.29 to 10.74 %)
Pyrazinamide assay (n= 37)	0.77 % (0.12 to 1.42 %)	1.96 %	- 0.173 (p=0.305)	- 3.21 % (- 4.34 to - 2.07 %) + 4.75 % (3.61 to 5.88 %)
Rifampicin assay (n= 51)	1.30 % (0.29 to 2.31 %)	3.60 %	0.010 (p=0.945)	- 5.93 % (- 7.68 to - 4.18 %) + 8.53 % (6.78 to 10.28 %)
Isoniazid dissolution (n= 57)	0.67 % (- 0.73 to 2.07 %)	5.28 %	0.088 (p=0.516)	- 9.91 % (- 12.33 to - 7.48 %) + 11.25 % (8.82 to 13.67 %)
Ethambutol dissolution (n= 36)	0.04 % (- 2.28 to 2.36 %)	6.96 %	- 0.201 (p=0.239)	- 14.08 % (- 18.09 to - 10.06 %) + 14.16 % (10.14 to 18.17 %)
Pyrazinamide dissolution (n= 36)	1.00 % (- 0.27 to 2.27 %)	3.82 %	- 0.056 (p=0.747)	- 6.75 % (- 8.95 to - 4.54 %) + 8.75 % (6.54 to 10.95 %)
Rifampicin dissolution (n= 51)	**4.39 %** (2.40 to 6.38 %)	7.09 %	0.217 (p=0.127)	- 9.85 % (- 13.30 to - 6.40 %) + 18.63 % (15.18 to 22.08 %)
Kanamycin assay (n=81) [a]	- 0.65 % (- 2.19 to 0.89 %)	6.97 %	- 0.063 (p=0.579)	- 14.52 % (- 17.19 to - 11.85 %) + 13.22 % (10.55 to 15.89 %)
Kanamycin assay, manufacturer 1 (n=55) [a]	- 0.19 % (- 2.19 to 1.81 %)	7.40 %	- 0.159 (p=0.246)	- 15.03 % (- 18.49 to - 11.56 %) + 14.65 % (11.18 to 18.11 %)
Kanamycin assay, manufacturer 2 (n=16) [a]	1.39 % (0.65 to 2.13 %)	1.38 %	0.355 (p=0.177)	- 1.55 % (- 2.83 to - 0.28 %) + 4.33 % (3.06 to 5.61 %)

S3 Table. Detailed results of Bland-Altman analysis

[a] Originally 15 kanamycin injection samples had been selected for the inter-laboratory comparison of results (see Methods section); a summary of these data is included in Table S2. Subsequently, the data of all 81 kanamycin injection samples which had been analysed in the study period by the external QCA were investigated; a summary of these data is given in Table S4.
The highest observed bias is highlighted in bold print.

	Assay		
	Manufacturer analysis	**External QCA analysis**	**Difference**
All kanamycin samples			
N	81	81	81
Mean	101.8 %	102.5 %	-0.65 %
Median	101.5 %	101.7 %	-0.20 %
Standard deviation	2.45 %	6.25 %	6.97 %
Kanamycin samples from manufacturer 1			
N	55	55	55
Mean	102.8 %	103.0 %	-0.19 %
Median	103.0 %	104.1 %	0.50 %
Standard deviation	2.2 %	6.78 %	7.40 %
Kanamycin samples from manufacturer 2			
N	16	16	16
Mean	101.0 %	99.6 %	1.39 %
Median	101.0 %	99.8 %	1.07 %
Standard deviation	0.37 %	1.48 %	1.38 %

S4 Table. Descriptive summary of assay data for all 81 kanamycin injection samples which had been analysed in the study period by the external QCA. In addition, data from the two main manufacturers supplying kanamycin are presented.

		USP 2018	Ph. Int. 2017
Rifampicin capsules and tablets	Medium, volume Apparatus: rpm, time: Limit:	0.1N HCl, 900mL 1 100 rpm, 45min >75% **(only for capsules)**	Buffer pH 6.8, 0.25% SDS TS, 500mL 2 75 rpm, 30min >80%
Rifampicin and isoniazid tablets	Medium, volume Apparatus: rpm, time: Limit:	0.1N HCl, 900mL 1 100 rpm, 45min >75% **(only for capsules)**	"Dissolution test. [To be added for rifampicin]" (**for dispersible tablets**; for tablets not mentioned)
Rifampicin/ isoniazid/ethambutol tablets	Medium, volume Apparatus: rpm, time: Limit:	No monograph	"Dissolution test. [To be added for rifampicin]"
Rifampicin/ isoniazid/pyrazin-amide tablets	Medium, volume Apparatus: rpm, time: Limit:	Simulated gastric fluid TS without pepsin, 900mL 1 100rpm, 30min >80%	"Dissolution test. [To be added for rifampicin]" (**for dispersible tablets**; for tablets not mentioned)
Rifampicin/isoniazid/ pyrazinamide/ ethambutol tablets	Medium, volume Apparatus: rpm, time: Limit:	10mM Sodium phosphate buffer pH 6.8, 900mL 2 100rpm, 45min >75%	Not mentioned

S5 Table. Dissolution testing conditions for solid oral formulations containing rifampicin in the United States Pharmacopeia 2018 and the International Pharmacopoeia 2017. (TS=Test Solution)

Am. J. Trop. Med. Hyg., 104(5), 2021, pp. 1936–1945
doi:10.4269/ajtmh.20-1612

Identification of Substandard and Falsified Medicines: Influence of Different Tolerance Limits and Use of Authenticity Inquiries

Cathrin Hauk, Nhomsai Hagen, and Lutz Heide*
Pharmaceutical Institute, Eberhard Karls University Tuebingen, Tuebingen, Germany

Abstract. Substandard and falsified medicines have severe public health and socioeconomic effects, especially in low- and middle-income countries. The WHO has emphasized the need for reliable estimates of the prevalence of such medicines to efficiently respond to this problem. In the present study, we used 601 medicine samples collected in Cameroon, the DR Congo, and Malawi to assess the rates of substandard and falsified medicines based on different criteria. Based on the specifications of the U.S. Pharmacopoeia for the amount of the active pharmaceutical ingredients, the rate of out-of-specification medicines was 9.3%. By contrast, this rate ranged from 3.3% up to 35.0% if the tolerance limits of other pharmacopoeias or recently published medicine quality studies were used. This shows an urgent need for harmonization. Principal methods to assess the rate of falsified medicines are packaging analysis, chemical analysis, and authenticity inquiries. In the present study, we carried out an authenticity inquiry for the aforementioned medicine samples, contacting 126 manufacturers and 42 distributors. Response rates were higher for samples stated to be manufactured in Asia (52.4%) or Europe (53.8%) than for samples manufactured in Africa (27.4%; $P < 0.001$). One sample had been identified as falsified by packaging analysis by the local researchers and two additional ones by chemical analysis. Notably, seven additional falsified samples were identified by the authenticity inquiries. The total rate of falsified medicines resulted as 1.7%. Considerations are discussed for assessing the rates of "substandard" and "falsified" medicines in future medicine quality studies.

INTRODUCTION

The spread of substandard and falsified medicines (SF medicines) has been described as a pandemic,[1] and its extremely severe public health and socioeconomic effects, especially in low- and middle-income countries (LMICs), are well documented.[2] To respond efficiently to this problem, reliable estimates of the prevalence of SF medicines, for different geographical regions, different parts of the supply chain, and different types of medicines, are of essential importance. However, the current estimates of the prevalence rate of SF medicines in LMICs differ considerably. From a systematic review of 100 medicine quality studies in the years 2007–2016 (total 48,218 samples), an authoritative review by the WHO[2] estimated the combined prevalence of SF medicines as 10.5% on average. Similarly, a systematic review of 96 studies up to the year 2017 (total 67,839 samples) by Ozawa et al.[3] reported a prevalence of 13.6%. By contrast, a systematic review of 15 studies up to January 2013 (total 3,931 samples) by Almuazini et al.[4] reported a prevalence of 28.5%, and a consecutive review by McManus and Naughton,[5] using the same methodology as Almuazini et al.[4] and including 33 studies published from January 2013 until December 2018 (total 19,921 samples), reported a prevalence of 25%. Notably, none of these four reviews was able to state the rate of falsified medicines separately from the rate of substandard medicines because the heterogeneity of the methodologies and definitions used in the reviewed studies did not allow to aggregate prevalence data for falsified medicines.

Even larger discrepancies can be observed between earlier reviews or between individual medicine quality studies. A review in Lancet Infectious Diseases by Nayyar et al.[6] reported that 20% out of 2,297 antimalarials collected in 21 countries of sub-Saharan Africa were falsified. In contrast, Kaur et al.[7] stated that only 1% of 10,079 samples of antimalarials, collected mostly in countries of sub-Saharan Africa, were falsified. Equally striking, Khuluza et al.[8] reported the prevalence of substandard antimalarials and antibiotics in Malawi to be 11%, while Chikowe et al.[9] reported for the same country and a similar time period a prevalence of 88% substandard antimalarials.

With such divergent estimates, an effective response to the problem of SF medicines becomes very difficult. The aforementioned review by the WHO[2] therefore emphasized the urgent need for additional, reliable prevalence estimates generated with appropriate and comparable methodologies.

After many years of controversy, the World Health Assembly of 2017 has adopted universally accepted definitions of "substandard," "falsified," and "unregistered/unlicensed" medical products,[2,10] and has thereby laid an indispensable foundation for the generation of reliable and comparable prevalence estimates:

1. "Substandard medical products: Also called 'out of specification'; these are authorized medical products that fail to meet either their quality standards or their specifications, or both."
2. "Falsified medical products: Medical products that deliberately/fraudulently misrepresent their identity, composition, or source."

According to the WHO, these definitions are mutually exclusive, so a sample can either be classified as "substandard" or as "falsified".[10]

The previously cited wording "Substandard medical products: Also called 'out of specification'. . ." appears to use the term "substandard" synonymous with the term "out of specification." This may sometimes cause confusion because, according to the U.S. Food and Drug Administration, out-of-specification (OOS) results include all test results that fall outside the relevant specifications or acceptance criteria,[11] irrespective of the absence or presence of deliberate intent as the reason for noncompliance of the investigated product.

* Address correspondence to Lutz Heide, Pharmaceutical Institute, Eberhard Karls University Tuebingen, Auf der Morgenstelle 8, Tuebingen 72076, Germany. E-mail: heide@uni-tuebingen.de

Notably, the cited WHO document adds a footnote to its definition of substandard medical products: "When the authorized manufacturer deliberately fails to meet these quality standards or specifications due to misrepresentation of identity, composition, or source, then the medical product should be considered 'falsified'."[10,12]

In this study, we use the term "out of specification" for all medicines for which test results fall outside the relevant specifications. We use the term "substandard" for those medicines for which test results fall outside the relevant specifications AND for which no evidence is available that they deliberately/fraudulently misrepresent their identity, composition, or source. Substandard quality may result from shortcomings in the production process, and/or from degradation after the product has been manufactured (see also Discussion section).

Guidelines for the conduct and the reporting of medicine quality studies have been published by Newton et al.[13] and by the WHO,[14] and as documented by McManus and Naughton,[5] this led to a noticeable improvement of the quality of such studies in the recent years.

The present article aims to contribute to a further improvement of the methodology and reporting of medicine quality studies. We focus on two aspects mentioned in the WHO review[2]: first, different authors and even different pharmacopoeias use different thresholds to distinguish between "in-specification" and "out-of-specification" medicines. Using the analytical data of 601 medicine samples which were recently collected in Cameroon, the DR Congo, and Malawi, and analyzed in our laboratory,[15,16] we here determined the effect of the use of different thresholds on the resulting prevalence rates of OOS medicines. This exercise resulted in strikingly different rates. Second, we conducted an authenticity inquiry, contacting the manufacturers and distributors of the aforementioned medicine samples. Unexpectedly, this increased the number of falsified medicines from three (which had previously been identified by packaging and chemical analyses) to a new total of 10 falsified samples. We report details of the procedures used and the response rates obtained in this authenticity inquiry. Finally, we present considerations for assessing the rates of "substandard" and "falsified" medicines in future medicine quality studies.

METHODS

Ethical approval. Ethical approvals and permissions to conduct the medicine quality studies were obtained from the responsible authorities in Cameroon, the DR Congo, and Malawi.[15,16]

Study design and included medicines. The studies were designed according to the MEDQUARG guidelines[13] and the WHO guidelines on the conduct of surveys of the quality of medicines.[14] In Cameroon and the DR Congo, seven antibiotics and six medicines against noncommunicable diseases were included (see Figure 1), with all of them representing solid oral formulations in dosages for adults. In Malawi, oxytocin injections and misoprostol tables were sampled. All included medicines were contained in the essential medicines lists of the respective countries.[15,16]

Sample collection. Sample collection took place between August 2017 and November 2018. Details of the collection process have been described previously.[15,16] For the purpose of these studies, a "sample" was defined as medical product of a specific brand and batch, sampled at the same time and same place.

Chemical analysis, and classification of medicines as OOS using different tolerance limits. Solid oral formulations were analyzed for identity, assay (= content of the active pharmaceutical ingredient [API]) and dissolution at the Pharmaceutical Institute of Tuebingen University according to the monographs of the U.S. Pharmacopoeia (USP) 41, except for misoprostol tablets which were analyzed according to the International Pharmacopoeia (Ph. Int.), Seventh Edition (2017) because no USP monograph was available for this product. Oxytocin injections were analyzed for identity, assay, and pH according to USP 40.[15,16]

To allow a comparison of the quality of samples from different manufacturers, WHO guidelines[14] recommend that in one medicine quality study, all samples which contain the same API in the same dosage form should be tested using the same methods and specifications, irrespective of possibly different methods and specifications used by the manufacturers for the registration of their products. The specifications of USP 42 (2019), Ph. Int. Ninth Edition (2019) and BP (2020) were used to calculate the effect of different thresholds on the rate of OOS medicines in this study. Tolerance limits of USP 40, 41, and 42 are identical for the investigated medicines, and also tolerance limits of the seventh and the ninth edition of Ph. Int. are identical for misoprostol.

Packaging analysis and authenticity inquiries. The brand name, batch number, manufacturing date, expiry date, name of manufacturer and distributor, international nonproprietary names of the APIs, strength, dosage form, and package size were recorded. The information stated on the labels and on the package insert was examined for the presence of irregularities or possible signs of falsification, such as spelling mistakes.

Requests for authentication were sent to all stated manufacturers and distributors, irrespective of the results of packaging analysis and chemical analysis. Websites of these companies were identified from the labeling or from the package inserts as well as from the Internet using the search engines Google (Mountain View, CA), Microsoft Bing (Redmond, WA), and Baidu (Beijing, China). Manufacturers and distributors were contacted using the e-mail addresses stated on the packaging or on their respective website if possible. If no website could be found, or if no e-mail addresses were stated there, e-mail addresses were searched using the aforementioned search engines. Inquiries were sent by post, if no e-mail address could be found or obviously none of our e-mail inquiries reached the recipient, for example, if an error message was received in response. For 225 of these samples, not only a manufacturer but also a distributor was stated on the packaging, and both were contacted. Two samples only stated a distributor, but not the manufacturer. Six distributors are also contained in the list of manufacturers (Supplemental Table S3), because they acted as distributors for certain products, and as manufacturers for others. As stated in the footnotes of Supplemental Tables S3 and S4, our Internet searches revealed that a few manufacturers/distributors stated slightly different versions/abbreviations of their company's name on the labels of different collected medicines, however, with these different versions/abbreviations leading us to the same website, e-mail, or postal address. Despite the slightly different versions/abbreviations of the name, the respective manufacturers/distributors were considered as a single company in such cases.

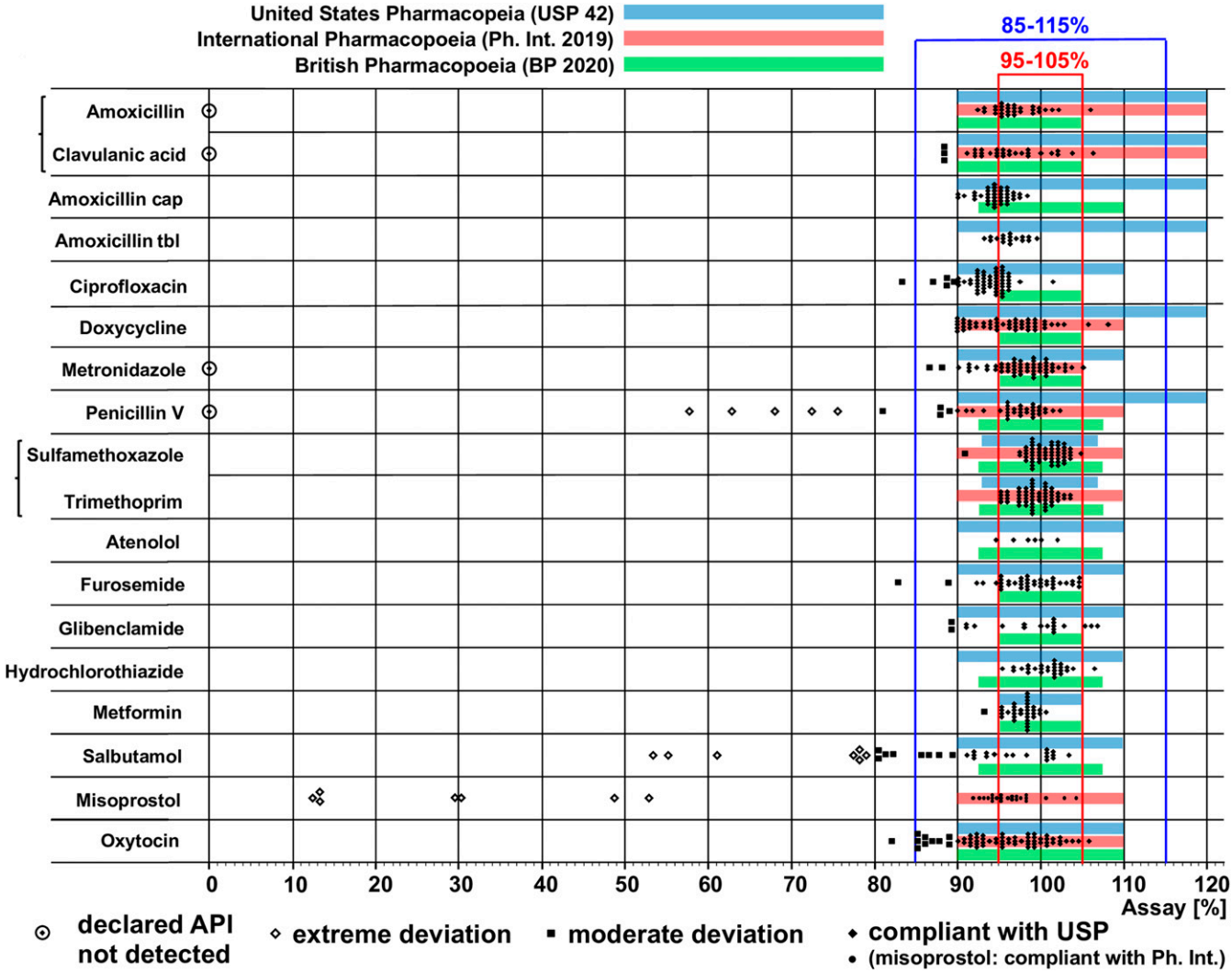


FIGURE 1. Assay results for 601 medicine samples collected in Cameroon, DR Congo, and Malawi in comparison to the tolerance limits of U.S. Pharmacopoeia (USP) 42, Ph. Int. Ninth Edition and BP 2020, and to arbitrary tolerance limits used in previous medicine quality studies (85–115%[7,28] and 95–105%[17]). Except for oxytocin injections, all medicines in this figure represent solid oral formulations (tablets or capsules; see Supplemental Table S1). All three pharmacopoeias contain separate monographs for doxycycline tablets and doxycycline capsules, but the stated tolerance limits are identical for both formulations. The USP contains separate monographs for amoxicillin tablets and amoxicillin capsules, but BP contains only a monograph for amoxicillin capsules. Therefore, amoxicillin capsules and tablets are listed separately here. This figure appears in color at www.ajtmh.org.

The first authenticity inquiries were sent to the manufacturers and distributors of oxytocin and misoprostol in December 2019, and to the manufacturers and distributors of the other medicines in March 2020. If there was no response within six weeks after the first inquiry, an e-mail reminder was sent to the same e-mail addresses which had been contacted previously, and in addition, other e-mail addresses were searched on the Internet and contacted. If the website of the manufacturer/distributor or another trading platform offered the option to write a message to that company, an inquiry was sent in this way. If, despite these reminders, no response was received within 3 months after the first inquiry, the respective company was classified as a nonresponder. Responses obtained within 3 months after the first inquiry were evaluated.

The inquiry letter is shown in Supplemental Figure S1. It provided the brand name, stated manufacturer and distributor, dosage form and strength, batch number, manufacturing and expiry dates, as well as photos of the packaging and of the dosage units (i.e., tablets, capsules, or ampoules). The letter stated the following questions: "1. Do the batch number and the manufacturing and expiry dates correspond to your records? If yes, do the product and packaging shown on the provided photographs appear to be genuine? 2. To your knowledge, has the batch been distributed in (*country of collection of the respective sample*)?" The letter also mentioned that a publication of the results of this study was intended, and that the cooperation of that company would be mentioned therein. If the manufacturers/distributors requested, further details were provided on the process and objectives of this study. However, the results of the chemical analysis of the respective samples were not stated before the manufacturer/distributor had responded regarding the authenticity of the samples.

Statistical evaluations. Statistical evaluations were performed using JMP 15 (SAS GmbH, Heidelberg, Germany).

Significance of differences in the response rate of manufacturer and distributors between different groups was calculated using Pearson's chi-square test.

RESULTS

Determination of the rate of OOS medicines using different tolerance limits. In our recent medicine quality studies in Cameroon, the DR Congo, and Malawi,[15,16] 601 samples of 15 different medicines had been collected. Thirteen of these medicines contained a single API each, and two were fixed-dose combinations of two APIs. Of these 15 medicines, 14 were covered by monographs in the current editions of USP and BP, and 7 by a monograph in Ph. Int.

As illustrated in Figure 1, the tolerance limits given in the three pharmacopoeias for assay testing (i.e., for the content of the API) are markedly different, ranging from 95–105% to 90–120% of the declared content. The numerical values for these tolerance limits are listed in Supplemental Table S1. Figure 1 also shows the arbitrary tolerance limits of 85–115% chosen by Kaur et al.[7] for a large study of antimalarials in various (mostly African) countries published in 2016, and of 95–105% chosen by Antignac et al.[17] for a large study of cardiac medicines in seven African countries published in 2017. Figure 1 also depicts the individual assay results obtained for each of the 601 samples collected in our studies. For a few of the investigated medicines, such as co-trimoxazole (sulfamethoxazole and trimethoprim) or metformin tablets, the percentage of OOS samples is similar, irrespective of which tolerance limits are applied. For most medicines, however, the choice of the tolerance limits has a huge influence on the resulting number of OOS medicines. For example, of the 57 collected samples of ciprofloxacin tablets, five (8.8%) were OOS using the tolerance limits of USP, whereas 43 (75.4%) were OOS using the tolerance limits of BP. Supplemental Table S2 shows the rate of OOS medicines for each type of medicine, using the different mentioned tolerance limits.

The overall rates of OOS samples for all types of medicines together, calculated using the different mentioned tolerance limits, are depicted in Figure 2 and in the Supplemental Figure S2. For exact mathematical comparison, Figure 2 includes only the results of those 300 samples for which monographs exist in all three mentioned pharmacopoeias. The rate of OOS samples resulting from the use of USP and Ph. Int. specifications is 9.3% and 12.3%, respectively, but it is markedly higher (22.7%) when the specifications of BP are used. Using the arbitrary limits of 85–115% chosen by Kaur et al.,[7] only 3.3% of the samples result as OOS. In sharp contrast, 35.0% (i.e., more than 10 times as many!) are OOS if the limits of 95–105% chosen by Antignac et al.[17] are used. Supplemental Figure S2 shows the same comparison including all samples collected in Cameroon, the DR Congo, and Malawi. The results are similar to those depicted in Figure 2.

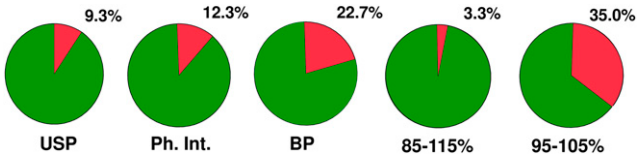


FIGURE 2. Influence of different tolerance limits on the rate of out-of-specification medicines (assay results) calculated for medicine samples collected in Cameroon, DR Congo, and Malawi (OOS: red; in-specification: green). The rates of out-of-specification medicines were calculated using the specifications of USP 42, Ph. Int. Ninth Edition and BP 2020, and the arbitrary tolerance limits 85–115%[7,28] and 95–105%,[17] respectively. For this figure, only the assay results of the six investigated medicines for which monographs exist in all three pharmacopoeias were compared ($n = 300$ samples). Supplemental Figure S2 shows a similar comparison including all medicines investigated in the three countries ($n = 601$ samples). This figure appears in color at www.ajtmh.org.

Different pharmacopoeias specify different methods to be used in quality analysis. For assay testing, results obtained with these different methods are expected to be similar at least in most cases.[18] By contrast, for the dissolution of an API (i.e., in vitro drug release from a solid oral formulation), different pharmacopoeial methods use different dissolution media and are well known to yield quite different results, for example, in the case of rifampicin.[19–22] Therefore, we did not attempt to evaluate the dissolution results which we obtained in our previous studies[15,16] with the tolerance limits of different pharmacopoeias.

Assessment of the rate of falsified medicines through packaging analysis. According to WHO guidelines,[14] the packaging of each collected sample, its labeling, and its package leaflet should be inspected visually for any signs of being a substandard or falsified product. Checklists for this purpose have been published[23,24] and may allow the identification of suspicious medicine samples by frontline health workers even before any chemical analysis is performed. Among the 601 samples collected in our studies, only one was readily identified as probably falsified by our local cooperation partners in Cameroon based on packaging analysis. It was stated to represent penicillin V tablets, but contained gross spelling errors in the labeling.[15,25] Further investigation showed that the stated manufacturer ("Oxford Pharma Co. Ltd. Belgium") was a non-existing company, and subsequent chemical analysis showed that the tablets contained no penicillin V but a small amount of paracetamol.[15] Based on these findings, the WHO classified this product as "falsified" in their Medical Product Alert N° 4/2017.[25]

Also, in the leaflet of an oxytocin brand produced in China, a high number of spelling errors were found. However, spelling errors in English language are not uncommon for products from some manufacturers in non–English-speaking countries, and were not considered to indicate a falsified medicine in this case. Indeed, in the authenticity inquiry (see in the following text), the distributor confirmed the authenticity of the samples of this brand. However, of the 38 samples of this brand, six samples were substandard because they contained only 85.2–86.8% of the declared amount of the API (USP tolerance limit: 90–110%).[16] Further testing also revealed shortcomings in the stability of this product.[26]

Assessment of the rate of falsified medicines through chemical analysis. In addition to the falsified penicillin V tablets mentioned earlier, chemical analysis of the 601 samples identified two further samples which did not contain detectable amounts of the stated API.[15] One sample was labeled as "Augmentin® GlaxoSmithKline - SmithKline Beecham Pharmaceuticals (Worthing, West Sussex, UK), (amoxicillin 500 mg/clavulanic acid 125 mg tablets)," but contained no detectable amounts of the active ingredients.[15,27] The stated manufacturer confirmed that this sample was falsified, and it was subsequently

reported as "falsified" by the WHO in their Medical Product Alert N° 2/2018.[27] Another sample, sold by an informal vendor from an opened plastic container, was labeled as "Metronyl® Metronidazole Tablets B.P., Mac's Pharmaceutical Ltd. (Nairobi, Kenya)," but contained a small amount of the prodrug metronidazole benzoate instead of metronidazole. The stated manufacturer was informed, but no answer was received.[15]

Assessment of the rate of falsified medicines through authenticity inquiries. Manufacturers and distributors were asked to confirm the authenticity of the medicine sample, and to state whether the sample had been distributed to the country where it had been collected in our studies (see Methods section). As shown in Figure 3, 582 samples were included into the authenticity inquiry. These represented 272 different brands (427 different batches). In 12 cases, the manufacturer or distributor could not be contacted online and was therefore only contacted by regular mail. Because of an interruption of the postal services to several African countries caused by the corona pandemic, three distributors could not be reached by regular mail, but for each of the concerned samples, the manufacturer could be contacted. Supplemental Tables S3 and S4 list all 126 manufacturers and 42 distributors that have been contacted, with the information whether or not they responded to our inquiry. An answer with a statement on authenticity was received for 288 (49.5%) of the samples. For 281 samples, the authenticity was confirmed by the manufacturer and/or the distributor, whereas seven samples were stated to be falsified. For 50 of the 288 samples (17.4%), answers were received both from the manufacturer and from the distributor; in all these cases, the information from both sources regarding the authenticity of the sample was in agreement (see Supplemental Table S5).

Table 1 summarizes the response rates received from different geographical regions. For samples stated to be manufactured in Asia, or in Europe and the Americas, response rates were slightly greater than 50% and therefore higher than those for samples stated to be manufactured in Africa (27.4%; $P < 0.001$). India and China were the most frequent countries of origin for the medicines collected in our studies, and overall response rates for samples manufactured in both countries were similar (53.7% and 50.3%, respectively). It should be noted, however, that for the samples manufactured in China, responses were in most cases only received from the distributors which were predominantly located in Africa and

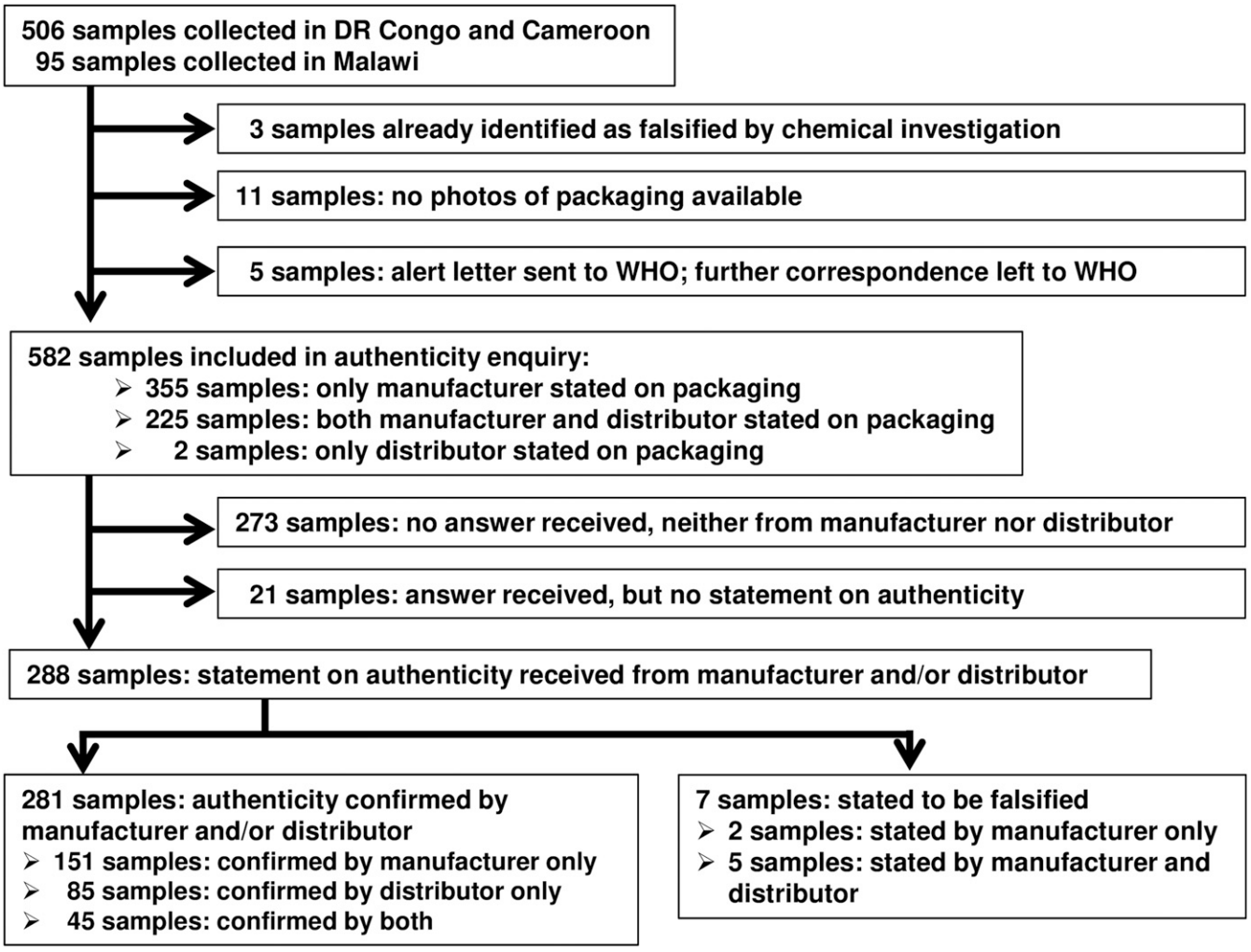


FIGURE 3. Flowchart of the identification of falsified medicines by authenticity inquiries to manufacturers and distributors. Five extremely substandard samples of misoprostol[16] were excluded, because upon our alert letter, the WHO had suggested that they contact the manufacturers and distributors.

TABLE 1
Response rates obtained in the authenticity inquiry, listed by geographic region

	Samples		Manufacturers		Distributors*	
	Number of samples manufactured in this region	Number (%) of samples with authenticity statement	Number contacted	Number (%) of responses with authenticity statement	Number contacted	Number (%) of responses with authenticity statement
Asia (total)	420	220 (52.4)	83	30 (36.1)	9	4 (44.4)
India	257	138 (53.7)	58	28 (48.3)	7	3 (42.9)
China and Hong Kong	161	81 (50.3)	24	1 (4.2)	1	0
Europe and Americas	96	51 (53.1)	24	13 (54.2)	16	7 (43.8)
Africa	62	17 (27.4)	19	6 (31.6)	17†	5 (29.4)
Total	582‡	288 (49.5)	126	49 (38.9)	42†	16 (38.1)

* Distributors were often located in another region than the manufacturers of the respective samples.
† There were 20 distributors from the African continent in this study, but for three of them, representing 14 samples, no e-mail address or contact website was found, and they could not be contacted by regular mail as postal services were interrupted because of the COVID-19 pandemic. Therefore, only 42 of the 45 distributors represented in this study could be contacted.
‡ Five hundred eighty-two samples were included into the authenticity inquiry, but for four samples, the country of origin was unknown; for three samples from Cinpharm, it was not stated whether they had been manufactured by Cinpharm in Cameroon or by their partner Cipla Ltd. in India; and for one sample, the available packaging only stated the distributor but not the manufacturer.

Europe, whereas of the 24 Chinese manufacturers, only a single one responded to our inquiry (Table 1).

We also investigated whether the response rates were related to the quality of the samples. For the 496 samples which had been found to comply to the assay and (if applicable) dissolution specifications of the USP, or of Ph. Int. in case of misoprostol samples, the response rate obtained was 51.2%. For the 86 samples which did not comply with pharmacopeial specifications, the response rate was 39.5%. This difference just reached statistical significance ($P = 0.0456$).

Including all the 49 manufacturers and 16 distributors who responded to our inquiry, the median time between the first inquiry and the receipt of a response with an authenticity statement was 16 days (range 0–84 days). Thirty eight (58.5%) of these manufacturers and distributors responded already to the first inquiry, whereas in 27 cases (41.5%), a reminder was required (see Methods sections). Notably, the median time between reminder and receipt of a response was only 2 days (range 0–54 days). Supplemental Tables S3 and S4 list all manufacturers and distributors who were contacted, with the respective number of days between first contact and response, and (if applicable) between reminder and response.

Of the 281 samples for which authenticity was confirmed, for 165 samples (58.7%), the manufacturer and/or distributor additionally confirmed that the sample had been distributed to the country from where it had been collected in our studies. For 45 samples (16.0%), it was denied that the sample had been distributed to the respective country, suggesting that these samples had been further traded to other countries by the first buyer. For 71 samples (25.3%), this question was not answered.

Falsified medicines identified by authenticity inquiries. Three falsified samples had been identified by packaging and chemical analyses (see aforementioned).[15] Seven further samples (representing four different brands) were only identified as falsifications through the authenticity inquiries. Notably, all seven samples passed chemical analysis for assay and dissolution testing according to the USP specifications. These falsified medicines are shown in Figure 4A–D. One of them (Figure 4A) had been collected in Cameroon from an informal vendor and was labeled as "Amoxicillin 500 mg + Clavulanic acid 125 mg BP" tablets, stated manufacturer: Medopharm Pvt. Ltd. (Guduvanchery, India), stated distributor: IDA Foundation (Amsterdam, The Netherlands). According to the information received from the stated manufacturer and distributor, the batch number did not match products of their companies, the stated shelf life (3 years) was different from that of the genuine product (2 years), and also the length of the blister pack (220 mm) did not match that of the genuine product (195 mm) (see Supplemental Figure S3). Also, some further details in the labeling (e.g., postal code in the address of the stated manufacturer) were stated to be incorrect.

Another sample (Figure 4B) had also been collected in Cameroon from an informal vendor, in another region of the country. It was labeled as "CO-TRIMOXAZOLE (sulfamethoxazole & trimethoprim)" tablets, batch number I3617, stated manufacturer: Sprukfield (Lomé, Togo). Notably, three further co-trimoxazole samples labeled as manufactured by Sprukfield had been collected in our study from church and government health facilities in Cameroon,[15] in these cases showing the batch numbers AT15001 (two samples) and AT15007 (one sample). On our inquiry, Sprukfield stated that the sample with the batch number I3617 had not been produced by them and was falsified, whereas the three other samples were confirmed to be genuine. The falsified product showed several differences in comparison to the genuine ones (Figure 4B): the falsified product was packaged in a slightly shorter blister pack, the batch number and expiry date were printed rather than being embossed on the blister, and the artwork of the Sprukfield logo and the green color used for blister labeling were different from those of the genuine products. Also, the embossing of the tablets was different (Figure 4B).

Four samples of "Furosemide 40 mg BP" tablets, stated manufacturer: Micro Labs Ltd. (Hosur, India), stated distributor: IDA Foundation, had been collected in church health facilities in four different regions of Cameroon. Packaging and labeling of all of them were identical, and all carried the same batch number FRIH0077. However, two of them showed as manufacturing and expiry dates "Dec. 2015/Nov. 2019" (i.e., a shelf life of 4 years), whereas two others showed "Dec. 2012/Nov. 2018" (i.e., an unusual long shelf life of 6 years). Figure 4C depicts one of the latter samples. The manufacturer and the distributor confirmed that a corresponding product with the same artwork had been supplied to Lagos, Nigeria, with the named batch number and a manufacturing date of December 2012, but that the expiry date of that product had been November 2015 (corresponding to a shelf life of 3 years). The stated manufacturer and distributor therefore stated that the four samples we had collected were falsified. As visible in Figure 4C, the part of the label where batch number, manufacturing, and expiry dates were printed appears slightly darker than the rest of the label, suggesting that this information may have been modified.

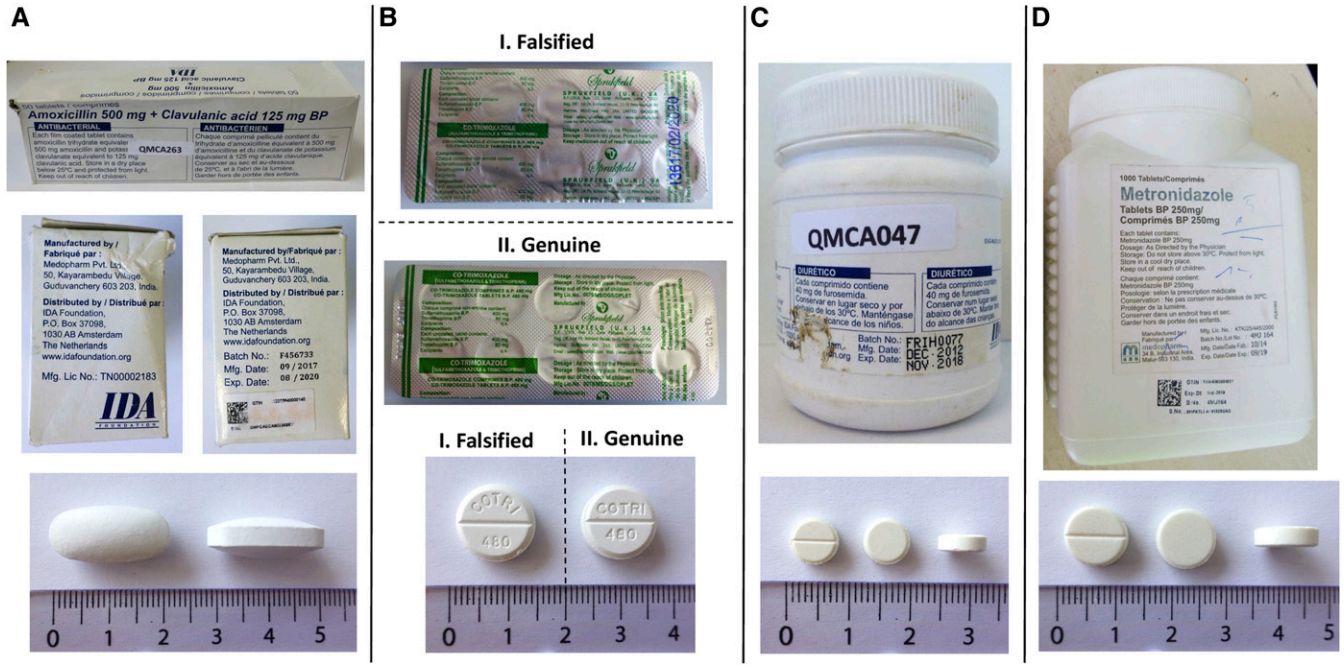


FIGURE 4. Photos of falsified medicines identified by authenticity inquiries. (**A**) Falsified "Amoxicillin 500 mg + Clavulanic acid 125 mg BP" tablets. Batch number, shelf life, blister length (shown in Supplemental Figure S2), and further labeling details do not match those of the genuine product, according to the stated manufacturer and distributor. (**B**) Falsified (I) and genuine (II) "CO-TRIMOXAZOLE (sulfamethoxazole & trimethoprim)" tablets. The falsified sample shows an incorrect batch number. Batch number and expiry date are printed rather than being embossed onto the blister; blister length, artwork, and color of the blister, as well as the embossing of the tablets, do not match those of the genuine product. The falsified product had been sold without secondary packaging. (**C**) One of the four falsified "Furosemide 40 mg BP" samples with a manipulated expiry date ("Nov. 2018", instead of the genuine expiry date "Nov. 2015"). (**D**) Falsified "Metronidazole Tablets BP 250 mg" also showing a manipulated expiry date ("09/19" instead of the genuine expiry date "09/17"). This figure appears in color at www.ajtmh.org.

Therefore, these four samples may have been genuine products in their genuine packages, but their expiry dates (and in two samples also their manufacturing dates) apparently had been manipulated with deliberate/fraudulent intent, turning them into falsified products.

Another sample (Figure 4D) had been collected in a government health facility in Nord Kivu, the DR Congo, and was labeled as "Metronidazole Tablets BP 250 mg," stated manufacturer: Medopharm (Malur, India). On inquiry, the stated manufacturer confirmed that a product with the same name, batch number, manufacturing date, and artwork had been manufactured by them, but that the expiry date of the sample ("09/19") did not match with that of the genuine product ("09/17"). The sample showed a second, small label with a two-dimensional bar code (Figure 4D), and the manufacturer reported that this encoded the correct expiry date (September 30, 2017), in contrast to the expiry date written in plain text on the same label ("Sep-2019"). This indicates that, on an otherwise genuine package, the labeling may have been modified to extend the expiry date by 2 years.

The WHO Rapid Alert System and the national drug regulatory authorities were informed about these falsifications.

DISCUSSION

A key aim of the present article is to contribute to an improved comparability of prevalence data of SF medicines reported in scientific studies. Figure 2 strikingly illustrates that the calculated prevalence rates of OOS medicines are extremely dependent on the choice of the tolerance limits used in the respective study. From the analytical data obtained for our "real-world" sample collection of medicines from three LMICs, the calculated rate of OOS medicine is as low as 3.3% or as high as 35.0%, simply by choosing different tolerance limits to distinguish "in-specification" and "out-of-specification" results for the content of the API. Notably, these different tolerance limits have been used in recent, large medicine quality studies,[7,17,28] and the results of these studies have been included into recent systematic reviews, which then calculated overall prevalence rates of SF medicines by aggregating numbers of "poor-quality" medicines reported in the included studies.[3,5]

As correctly stated by McManus and Naughton,[5] the results of systematic reviews are only as reliable as the original data to which they refer. If the arbitrary choice of tolerance limits allows the rate of OOS medicines in the same study to vary by a factor of more than 10 (as shown in Figure 2), the results of systematic reviews obviously become unreliable, and, for example, comparisons of the rates of OOS medicines between different time periods, as attempted in the systematic review by McManus and Naughton,[5] may become meaningless. Given the important public health and socioeconomic effects of SF medicines, and the importance of reliable and comparable prevalence data for such medicines, a harmonization of the tolerance limits used to distinguish compliant from OOS products in different medicine quality studies is urgently called for, as also concluded from a recent study by the Brazilian Health Regulatory Agency.[29] Figure 2 clearly demonstrates that arbitrary tolerance limits, such as 85–115% or 95–105%, should be avoided, and pharmacopoeial tolerance limits should be used instead. Indeed, the group of H. Kaur who had used the 85–115% limits in their cited studies[7,28] decided to use USP tolerance limits in their later studies.[30] The BP uses stricter tolerance limits than USP and Ph. Int. for many medicines. Both BP and USP state in their "General Notices" that these tolerance limits allow for analytical

errors, for unavoidable variations in manufacturing, and for deterioration to an acceptable extent.[31,32] To our knowledge, there is no published information why these tolerance limits differ between different pharmacopoeias.

In our real-world sample collection, the use of BP specifications for assay results led to an approximately 2-fold higher number of OOS medicines than the use of USP or Ph. Int. specifications. As mentioned in the Methods section, WHO guidelines[14] recommend that in one medicine quality study, all samples which contain the same API in the same dosage form should be tested using the same methods and specifications. In our studies, many products were labeled as manufactured according to USP specifications, and it would obviously be inappropriate to evaluate these samples according to the narrower tolerance limits of BP. Therefore, we suggest to use USP or the similar Ph. Int. specifications, rather than BP specifications, in medicine quality studies involving more than one country. Obviously, it is desirable that the specifications of different pharmacopoeias are harmonized as soon as possible, to create global and uniform public standards for medicines.[33–36]

For a number of medicines, no pharmacopoeial monograph exists,[34] and in these cases, the tolerance limits for medicines of the same therapeutic class which are included in the USP or Ph. Int. may be used. For assay, this would result in the use of tolerance limits of 90–110% in many cases.[29] Special considerations may be required for medicines with a narrow therapeutic index. The tolerance limits stated in the in-house specifications of the respective manufacturers may also be considered. However, as mentioned earlier, in one study, all samples which contain the same API in the same dosage form should be tested using the same specifications.[14]

The authoritative review by the WHO[2] stated the problem that most published medicine quality studies only report a pass or fail result for the medicines samples, rather than reporting the actual percentage of APIs detected (or dissolved). As illustrated in Figure 1, much more information can be gained if actual percentages for API content, and also dissolution,[15] are shown for each sample, and this also allows much more meaningful comparisons between different studies.

Several previous medicine quality studies published by the WHO[37,38] have differentiated "substandard" samples into samples showing "moderate deviations" and "extreme deviations" from pharmacopoeial specifications, with extreme deviations defined as the content of APIs deviating by more than 20% from the declared content, and/or the average dissolution value of tested units of solid oral formulations falling below the pharmacopoeial Q value minus 25%. Although this classification method is rapidly and universally applicable, it has the drawback that it does not consider the different health risks of dosage deviations from medicines with different therapeutic indices.

Based on the MEDQUARG guidelines by Newton et al.,[13] Almuazini et al.[4] have developed a 12-point checklist for the rating of the quality of published medicine quality studies, and this has been used in several subsequent systematic reviews.[2,3,5,39] We suggest that, in future, this checklist is expanded by the following two criteria:

1. "Actual percentages are shown for assay and (if applicable) for dissolution values of each sample."
2. "Preferentially, USP or Ph. Int. tolerance limits are used to distinguish in-specification from OOS medicine samples; the choice of other tolerance limits should be justified."

Within the present study, we carried out an authenticity inquiry by contacting the stated manufacturers and distributors of the same medicines. As noted by the WHO,[2] only few studies have reported the authentication of medicine samples using this method, and we therefore documented the procedures and results of this exercise in detail (see Methods and Results sections). Notably, although packaging and chemical analyses had identified three (0.5%) of 601 samples as falsified, authentication by manufactures and distributors increased this number to 10 (1.7%). This clearly shows that authentication is a powerful tool for medicine quality studies. However, the workload for such inquiries is high, both for the researchers and for the manufacturers and distributors. Furthermore, response rates are far from complete. Four recent studies by Kimura and coworkers reported that authenticity responses were received from the manufacturers for 0%, 8.7%, 9.5%, and 28.8% of the investigated samples, respectively.[40–43] In comparison, the response rate of 49.5% obtained in the present study is reasonably high, despite interference by the COVID-19 pandemic. Higher response rates were reported from two earlier studies of the Kimura group.[44,45]

Although the statement of the manufacturer and distributor is an important piece of evidence in the identification of falsified medicines, it cannot be taken for granted that this statement reflects the truth in all cases. If a manufacturer doubts whether his product passed quality testing in the respective study, he may be tempted to deny its authenticity rather than risking a published report that his genuine product was found to be substandard.

Notably, all seven falsified samples identified through the authenticity inquiry passed chemical analysis for assay and dissolution without any conspicuous deviations from USP specifications. Similar observations have been reported by Kimura and coworkers.[44,45] However, this does not mean that such falsifications are of no concern for patient safety. A medicine which misrepresents its source, or which carries an illegally modified expiry date, must be considered dangerous, as it may fail specifications which had not been tested in our studies, such as limits for chemical and microbial contaminations.

Some researchers have suggested that in medicine quality studies, it may be sufficient to report a single prevalence rate for "substandard and falsified medicines" combined together. In contrast to this suggestion, however, the WHO has defined "substandard" and "falsified" medicines as different categories.[2,10] We believe this was a prudent decision, because very different interventions are required to respond to the problem of falsified medicines, as compared with the problem of substandard medicines. Informed decision-making requires knowledge of both prevalence rates.

In a medicine quality study, the number of "out-of-specification" medicines can be determined by laboratory analysis. "Substandard" medicines are those OOS medicines for which no evidence is available that they deliberately/fraudulently misrepresent their identity, composition, or source. By contrast, "falsified" medicines are those for which evidence of such deceit is available, irrespective of whether their analytical results are "in specification" or "out of specification." The present study has shown examples for all these categories. Of 601 medicine samples which we collected in Cameroon, the DR Congo, and Malawi, 99 (16.5%) have thereby been identified as substandard based on USP specifications for assay

and dissolution (or Ph. Int. specifications in case of misoprostol tablets), and 10 (1.7%) have been identified as falsified.

These categorizations cannot be free of ambiguity in scientific practice.[12] For example, even when a product has passed visual inspection, chemical analysis, and authenticity inquiries, it may still be falsified if labeling and chemical composition of the authentic product have been imitated very closely. Furthermore, defining criteria by which deliberate/fraudulent intent should be proven will always be a controversial issue.[12] And in case of OOS medicines, definitive proof of absence of such intent is virtually impossible.

To harmonize the reporting of "falsified" medicine samples, also in the absence of authoritative legal proof of deliberate intent or fraud, it may be considered that medicine quality studies by academia or NGOs use the term "falsified" in the following cases:

1. A responsible national or international authority has declared that the medicine is falsified, based on the WHO definitions.[10,46]
2. The stated manufacturer has declared that the medicine is falsified, or that its expiry date or other details of the labeling have been illegally manipulated.[46]
3. Packaging analysis gives conclusive evidence for falsification, for example, the stated manufacturer does not exist.
4. The medicine contains no APIs, or an incorrect API instead of the stated one. (In the very rare event that this mistake resulted from non-intentional errors in both production and quality control, the medicine has to be classified as "substandard".)

In addition, it may be considered to use the term "probably falsified" for medicines which contain less than 50% of the stated amount of the API AND for which there is no evidence that the low content is due to degradation (evidenced usually by the presence of decomposition products). An example for such a medicine is given by chloroquine tablets which we recently found in Cameroon and which contained only 21.7% of the declared amount of the API.[47,48] On the other hand, we identified a brand of misoprostol tablets in Malawi which contained only 13.1% of the stated amount of the API,[16] but HPLC analysis clearly showed the presence of decomposition products of misoprostol, and therefore, this product was considered as "extremely substandard" rather than "probably falsified".[16]

We realize that different opinions exist in the scientific community and within the stakeholders regarding the best possible categorization of SF medicines in scientific studies. We hope that the facts and suggestions presented in this article may help to stimulate discussions in search of a consensus, and contribute to the urgently needed harmonization of the methodology and reporting of future medicine quality studies.

Limitations of this study. Comparability of the results of medicine quality studies also depends on other factors beyond the scope of the present article, such as sampling design (e.g., random or convenience sampling, overt or mystery shopping, inclusion or exclusion of informal vendors, and choice of included medicines), methods of chemical analysis, and choice of tests included into the investigation (e.g., assay, dissolution, content uniformity, related compounds, etc.). This article focuses on the classification of medicines as "substandard" and "falsified," but does not reflect on the classification as "unregistered/unlicensed" which was also defined by the World Health Assembly of 2017.[10,49] Also, this article focuses only on the APIs, and did not consider quality issues related to excipients.

Received December 21, 2020. Accepted for publication February 5, 2021.

Published online March 31, 2021.

Note: Supplemental tables and figures appear at www.ajtmh.org

Acknowledgments: We are grateful to Richard Neci (Ecumenical Pharmaceutical Network, Nairobi, Kenya), Georges Mutombo (Le Dépôt Central Médico-Pharmaceutique de la 8e CEPAC [DCMP], Bukavu, the Democratic Republic of the Congo), Edward Ngah Ndze and Tambo Cletus (Cameroon Baptist Convention [CBC], Central Pharmacy, Mutengene, Cameroon), Fidelis Nyaah and Manyi Pattinora (Presbyterian Church in Cameroon [PCC], Central Pharmacy, Limbe, Cameroon), Felix Khuluza (Pharmacy Department, College of Medicine, University of Malawi), Simon Schäfermann, Emmanuel Wemakor, Irina Helmle, Dorothee Wistuba and Harald Gross (Eberhard Karls University Tuebingen, Germany), and Christine Häfele-Abah (German Institute for Medical Mission [Difaem], Tuebingen, Germany) for their contributions to the cited medicine quality studies carried out in the DR Congo, in Cameroon, and in Malawi.

Financial support: This study was funded by the Eberhard Karls University, Tuebingen.

Authors' addresses: Cathrin Hauk, Nhomsai Hagen, and Lutz Heide, Pharmaceutical Institute, Eberhard Karls University, Tuebingen, Germany, E-mails: cathrin.hauk@uni-tuebingen.de, nhomsai.hagen@uni-tuebingen.de, and heide@uni-tuebingen.de.

REFERENCES

1. Nayyar GM, Attaran A, Clark JP, Culzoni MJ, Fernandez FM, Herrington JE, Kendall M, Newton PN, Breman JG, 2015. Responding to the pandemic of falsified medicines. *Am J Trop Med Hyg 92 (Suppl 6):* 113–118.
2. World Health Organization, 2017. *A Study on the Public Health and Socioeconomic Impact of Substandard and Falsified Medical Products*. Available at: http://www.who.int/medicines/regulation/ssffc/publications/se-study-sf/en/. Accessed February 4, 2021.
3. Ozawa S, Evans DR, Bessias S, Haynie DG, Yemeke TT, Laing SK, Herrington JE, 2018. Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries: a systematic review and meta-analysis. *JAMA Netw Open 1:* e181662.
4. Almuzaini T, Choonara I, Sammons H, 2013. Substandard and counterfeit medicines: a systematic review of the literature. *BMJ Open 3:* e002923.
5. McManus D, Naughton BD, 2020. A systematic review of substandard, falsified, unlicensed and unregistered medicine sampling studies: a focus on context, prevalence, and quality. *BMJ Glob Health 5:* e002393.
6. Nayyar GM, Breman JG, Newton PN, Herrington J, 2012. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis 12:* 488–496.
7. Kaur H et al., 2016. Fake anti-malarials: start with the facts. *Malar J 15:* 86.
8. Khuluza F, Kigera S, Heide L, 2017. Low prevalence of substandard and falsified antimalarial and antibiotic medicines in public and faith-based health facilities of southern Malawi. *Am J Trop Med Hyg 96:* 1124–1135.
9. Chikowe I, Osei-Safo D, Harrison JJ, Konadu DY, Addae-Mensah I, 2015. Post-marketing surveillance of anti-malarial medicines used in Malawi. *Malar J 14:* 127.
10. World Health Organization, 2017. *Who Member State Mechanism on Substandard/Spurious/Falsely-Labelled/Falsified/Counterfeit (SSFFC) Medical Products. Working Definitions*. Available at:

https://www.who.int/medicines/regulation/ssffc/definitions/en/. Accessed February 4, 2021.
11. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 2006. *Guidance for Industry. Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*. Available at: https://www.fda.gov/media/71001/download.
12. Olliaro E, Olliaro P, Ho CWL, Ravinetto R, 2020. Legal uncertainty—the gray area around substandard medicines: where public health meets law. *Am J Trop Med Hyg 102:* 262–267.
13. Newton PN et al., 2009. Guidelines for field surveys of the quality of medicines: a proposal. *PLoS Med 6:* e52.
14. WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2016. *Guidelines on the Conduct of Surveys of the Quality of Medicines. WHO Technical Report Series No. 996*. Available at: https://www.who.int/medicines/publications/pharmprep/trs_996/en/. Accessed February 4, 2021.
15. Schafermann S et al., 2020. Substandard and falsified antibiotics and medicines against noncommunicable diseases in western Cameroon and northeastern Democratic Republic of Congo. *Am J Trop Med Hyg 103:* 894–908.
16. Hagen N, Khuluza F, Heide L, 2020. Quality, availability and storage conditions of oxytocin and misoprostol in Malawi. *BMC Preg Childbirth 20:* 184.
17. Antignac M et al., 2017. Fighting fake medicines: first quality evaluation of cardiac drugs in Africa. *Int J Cardiol 243:* 523–528.
18. FDA, 2017. *Acceptability of Standards from Alternative Compendia (BP/EP/JP)*. Available at: https://www.fda.gov/media/72412/download.
19. Ammar HO, Khalil RM, 1996. Discrepancy among dissolution rates of commercial tablets as a function of dissolution method. Part 6: rifampicin. *Pharmazie 51:* 165–168.
20. Panchagnula R, Bhardwaj V, 2008. Effect of amorphous content on dissolution characteristics of rifampicin. *Drug Dev Ind Pharm 34:* 642–649.
21. Becker C, Dressman JB, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM, 2009. Biowaiver monographs for immediate release solid oral dosage forms: rifampicin. *J Pharm Sci 98:* 2252–2267.
22. Hauk C, Schäfermann S, Martus P, Muzafarova N, Babaley M, Waning B, Heide L, 2020. Quality assurance in anti-tuberculosis drug procurement by the Stop TB Partnership—Global Drug Facility: procedures, costs, time requirements, and comparison of assay and dissolution results by manufacturers and by external analysis. *PLoS One 15:* e0243428.
23. Schiavetti B, Wynendaele E, Melotte V, Van der Elst J, De Spiegeleer B, Ravinetto R, 2020. A simplified checklist for the visual inspection of finished pharmaceutical products: a way to empower frontline health workers in the fight against poor-quality medicines. *J Pharm Policy Pract 13:* 9.
24. World Health Professions Alliance, 2011. *Be Aware: Tool for Visual Inspection of Medicines*. Available: https://www.whpa.org/sites/default/files/2018-12/Toolkit_BeAware_Inspection.pdf, 4. Accessed February 4, 2021.
25. World Health Organization, 2017. *Medical Product Alert N° 4/2017. Falsified Penicillin V Circulating in Cameroon. Ref. RHT/SAV/Alert_n4.2017*. Available at: https://www.who.int/medicines/publications/drugalerts/drug_alert4-2017/en/. Accessed February 4, 2021.
26. Hagen N, Bizimana T, Kayumba PC, Khuluza F, Heide L, 2020. Stability of oxytocin preparations in Malawi and Rwanda: stabilizing effect of chlorobutanol. *Am J Trop Med Hyg 103:* 2129–2141.
27. World Health Organization, 2018. *Medical product alert N° 2/2018. Falsified "Augmentin" circulating in Cameroon. Ref. RHT/SAV/Alert_n2.2018*. Available at: https://www.who.int/medicines/publications/drugalerts/drug_alert2-2018/en/. Accessed December 14, 2020.
28. Kaur H et al., 2015. Quality of artemisinin-based combination formulations for malaria treatment: prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. *PLoS One 10:* e0125577.
29. Neves EO, de Sales PM, Silveira D, 2020. Pharmacopeial specifications and analytical data from post-marketing quality sampling and testing programs: a perspective beyond out-of-specification results. *J Pharm Biomed Anal 178:* 112935.
30. Redfern J, Kaur H, Adedoyin RA, Ofori S, Anchala R, Vamadevan AS, De Andrade L, Zelaya J, Balabanova D, Sani MU, 2019. Equivalence in active pharmaceutical ingredient of generic antihypertensive medicines available in Nigeria (EQUIMEDS): a case for further surveillance. *Glob Heart 14:* 327–333.
31. USP 42 - NF 37, 2019. *The United States Pharmacopeia and National Formulary 2019*. Rockville, MD: United States Pharmacopeial Convention.
32. British Pharmacopoiea (BP), 2020. London, United Kingdom: British Pharmacopoiea Commission.
33. World Health Organization, 2020. *White Paper for the WHO International Meeting of World Pharmacopoeias - Value of Pharmacopoeial Standards for Access to Quality Medicines*. Available at: https://www.who.int/docs/default-source/medicines/norms-and-standards/value-of-pharm-stds-updated-final-oct-2020.pdf?sfvrsn=2d4e5052_4. Accessed February 4, 2021.
34. Roth L, Adler M, Jain T, Bempong D, 2018. Monographs for medicines on WHO's model list of essential medicines. *Bull World Health Organ 96:* 378–385.
35. EDQM Council of Europe. *The Need for International Harmonisation*. Available at: https://www.edqm.eu/en/international-harmonisation. Accessed February 4, 2021.
36. World Health Organization. *Norms and Standards for Pharmaceuticals*. Available at: https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/. Accessed February 4, 2021.
37. World Health Organization, 2015. *Survey of the Quality of Medicines Identified by the United Nations Commission on Life-Saving Commodities for Women and Children*. Availabel at: https://apps.who.int/iris/handle/10665/255550. Accessed February 4, 2021.
38. World Health Organization, 2011. *Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa*. Available at: http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. Accessed February 4, 2021.
39. Torloni MR, Bonet M, Betran AP, Ribeiro-do-Valle CC, Widmer M, 2020. Quality of medicines for life-threatening pregnancy complications in low- and middle-income countries: a systematic review. *PLoS One 15:* e0236060.
40. Rahman MS, Yoshida N, Sugiura S, Tsuboi H, Keila T, Kiet HB, Zin T, Tanimoto T, Kimura K, 2018. Quality of omeprazole purchased via the Internet and personally imported into Japan: comparison with products sampled in other Asian countries. *Trop Med Int Health 23:* 263–269.
41. Islam MR et al., 2018. An investigation into the quality of medicines in Yangon, Myanmar. *Pharmacy (Basel) 6:* 96.
42. Rahman MS et al., 2019. A cross-sectional investigation of the quality of selected medicines for noncommunicable diseases in private community drug outlets in Cambodia during 2011–2013. *Am J Trop Med Hyg 101:* 1018–1026.
43. Sakuda M, Yoshida N, Takaoka T, Sanada T, Rahman MS, Tanimoto T, Zin T, Kimura K, Tsuboi H, 2020. Substandard and falsified medicines in Myanmar. *Pharmacy (Basel) 8:* 45.
44. Aka E, Legris C, Tanimoto T, Matsushita R, Kimura K, 2005. Counterfeit medicine detection by authenticity investigation. A pilot study in the street market of Côte d'Ivoire. *Jpn J Soc Pharm 24:* 7–16.
45. Khan MH, Okumura J, Sovannarith T, Nivanna N, Akazawa M, Kimura K, 2010. Prevalence of counterfeit anthelminthic medicines: a cross-sectional survey in Cambodia. *Trop Med Int Health 15:* 639–644.
46. World Health Organization, 2017. *WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products*. Available at: http://www.who.int/medicines/regulation/ssffc/publications/gsms-report-sf/en/. Accessed February 4, 2021.
47. Gnegel G, Hauk C, Neci R, Mutombo G, Nyaah F, Wistuba D, Hafele-Abah C, Heide L, 2020. Identification of falsified chloroquine tablets in Africa at the time of the COVID-19 pandemic. *Am J Trop Med Hyg 103:* 73–76.
48. World Health Organization, 2020. *Medical Product Alert N°4/2020. Falsified Chloroquine Products Circulating in the WHO Region of Africa*. Available at: https://www.who.int/news-room/detail/09-04-2020-medical-product-alert-n4-2020. Accessed February 4, 2021.
49. World Health Organization, 2017. *Seventieth World Health Assembly Update*. Available at: http://www.who.int/en/news-room/detail/29-05-2017-seventieth-world-health-assembly-update-29-may-2017. Accessed February 4, 2021.

Supplemental information

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

Mathematisch-Naturwissenschaftliche Fakultät

Pharmazeutisches Institut
Pharmazeutische Biologie

Prof. Dr. L. Heide

Telefon [redacted]
Telefax [redacted]
E-Mail: [redacted]

Pharmazeutische Biologie · Auf der Morgenstelle 8 · 72076 Tübingen

To
[redacted]
[redacted]
[redacted]
Email: [redacted]

Tübingen, 14.04.2020

Request for authentication of Sulfatrim® Tablets collected in the Democratic Republic of Congo

Dear Madams and Sirs,

During a study on essential medicines, we have collected approximately 500 medicine samples in Cameroon and the Democratic Republic of Congo in the years 2017 and 2018. These included a product which shows the name of your company on the packaging.

The product details are as follows (photos attached):

Name	**Sulfatrim® Co-trimoxazole Tablets BP** Sulfamethoxazole and trimethoprim tablets
Stated strength	400/80mg
Manufacturer	[redacted]
Collected batches (Mfg./Exp. Date)	J7007 (01.2017/12.2019)

For all the approximately 500 medicine samples which we collected in that study, we would like to verify whether they are genuine (or falsified) products by contacting the manufacturers and distributors. We intend to publish the result in a forthcoming paper. It would be most helpful if you could assist us by answering the following two questions to confirm the authenticity of the product:

1. Do the batch number and the manufacturing and expiry dates correspond to your records? If yes, do the product and packaging shown on the provided photographs appear to be genuine?
2. To your knowledge, has the batch been distributed in the Democratic Republic of Congo?

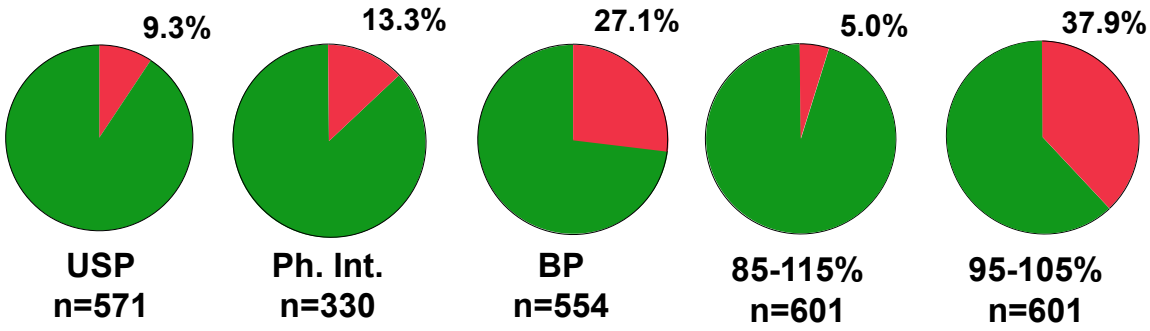
We look forward to your response at your earliest convenience, and we will be happy to mention your kind cooperation in the forthcoming publication.

With thanks for your help,

and best wishes

(Prof. Dr. Lutz Heide)

Supplemental Figure S1: Example of an inquiry letter sent to a manufacturer. The original letters included photos of the packaging and dosage units, but these are not shown here.



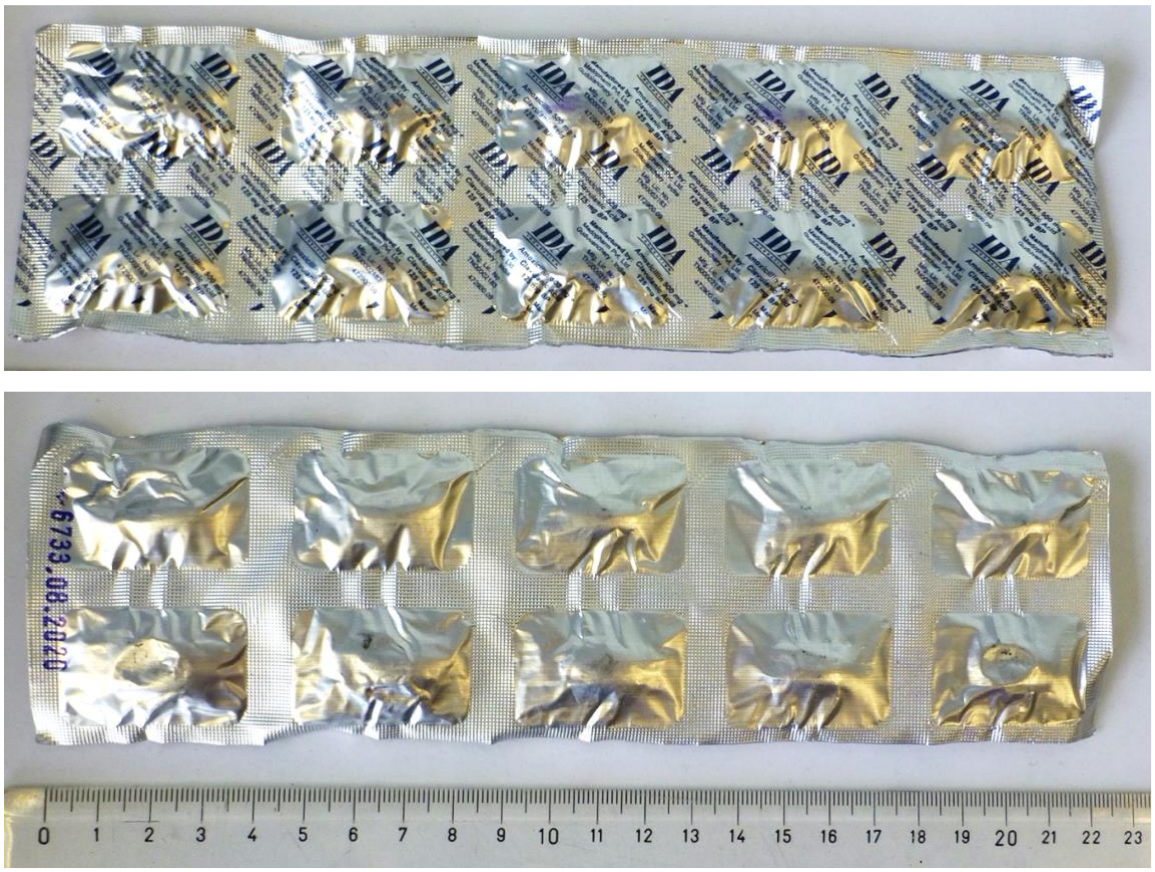
Supplemental Figure S2: Influence of different tolerance limits on the rate of out-of-specification medicines (assay results) calculated for medicine samples collected in Cameroon, DR Congo and Malawi.

The rates of out-of-specification medicines (OOS: red; in-specification: green) were calculated using the specifications of USP, Ph. Int., BP, and the arbitrary tolerance limits 85-115%[a, b] and 95-105%,[c] respectively. For this figure, the assay results of all medicines investigated in the three countries were included.

[a] Kaur H et al., 2016. Fake anti-malarials: start with the facts. *Malar J 15*:86.

[b] Kaur H et al., 2015. Quality of artemisinin-based combination formulations for malaria treatment: prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. *PLoS One 10(5)*:e0125577.

[c] Antignac M et al., 2017. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa. *Int J Cardiol 243*:523-528



Supplemental Figure S3: Additional photo of "Amoxicillin 500 mg + Clavulanic acid 125 mg BP" tablets identified as falsified by authenticity inquiries.

Blister pack with a length of 220 mm, not matching the length of the blister pack of the genuine product which was 195 mm according to the stated distributor.

Supplemental Table S1: Comparison of tolerance limits for assay in USP 42 (2019), BP 2020 and Ph. Int. Ninth Edition (2019)

Product	USP 42 [%]	BP 2020 [%]	Ph. Int. 2019 [%]
Amoxicillin and clavulanic acid tablets	90-120 **both**	90-105 **both**	90-120 **both**
Amoxicillin capsules	90-120	92.5-110.0	no monograph
Amoxicillin tablets	90-120	no monograph	no monograph
Ciprofloxacin tablets	90-120	95-105	no monograph
Doxycycline capsules	90-120	95-105	90-110
Doxycycline tablets	90-120	95-105	90-110
Metronidazole tablets	90-110	95-105	95-105
Penicillin V tablets	90-120	92.5-107.5	90-110
Co-Trimoxazole tablets (sulfamethoxazole and trimethoprim)	93-107 **both**	92.5-107.5 **both**	90-110 **both**
Atenolol tablets	90-110	92.5-107.5	no monograph
Furosemide tablets	90-110	95-105	no monograph
Glibenclamide tablets	90-110	95-105	no monograph
Hydrochlorothiazide tablets	90-110	92.5-107.5	no monograph
Metformin tablets	95-105	95-105	no monograph
Salbutamol tablets	90-110	92.5-107.5	no monograph
Misoprostol tablets	no monograph	no monograph	90-110
Oxytocin injections	90-110	90-110	90-110

Supplemental Table S2: Rate of out-of-specification medicines (assay result) for each type of medicine collected in Cameroon, DR Congo and Malawi, using different tolerance limits.

The rate of out-of-specification medicines was calculated using the specifications of USP 42 (2019), Ph. Int. Ninth Edition (2019) and BP 2020, and the arbitrary tolerance limits 85-115%[a,b] and 95-105%[c] used in previous medicine quality studies. The assay results of all medicines investigated in the three countries were included (n= 601).

Product	n	USP	Ph. Int.	BP	85-115%	95-105%
Amoxicillin and clavulanic acid tablets	31	4 (12.9%)	4 (12.9%)	6 (19.4%)	1 (3.2%)	20 (64.5%)
Amoxicillin capsules	39	0	-	6 (15.4%)	0	22 (56.4%)
Amoxicillin tablets	17	0	-	-	0	4 (23.5%)
Ciprofloxacin tablets	57	5 (8.8%)	-	43 (75.4%)	1 (1.8%)	43 (75.4%)
Doxycycline capsules	28	0	0	12 (42.9%)	0	12 (42.9%)
Doxycycline tablets	22	0	0	13 (59.1%)	0	13 (59.1%)
Metronidazole tablets	57	3 (5.3%)	13 (22.8%)	13 (22.8%)	1 (1.8%)	13 (22.8%)
Penicillin V tablets	41	10 (24.4%)	10 (24.4%)	13 (31.7%)	7 (17.1%)	14 (34.1%)
Co-Trimoxazole tablets (sulfamethoxazole and trimethoprim)	56	1 (1.8%)	0	1 (1.8%)	0	1 (1.8%)
Atenolol tablets	6	0	-	0	0	1 (16.7%)
Furosemide tablets	40	2 (5.0%)	-	5 (12.5%)	1 (2.5%)	5 (12.5%)
Glibenclamide tablets	19	2 (10.5%)	-	8 (42.1%)	0	8 (42.1%)
Hydrochlorothiazide tablets	27	0	-	0	0	1 (3.7%)
Metformin tablets	33	1 (3.0%)	0	1 (3.0%)	0	1 (3.0%)
Salbutamol tablets	33	15 (45.5%)	-	19 (57.6%)	11 (33.3%)	22 (66.7%)
Misoprostol tablets	30	-	7 (23.3%)	-	7 (23.3%)	16 (53.3%)
Oxytocin injections	65	10 (15.4%)	10 (15.4%)	10 (15.4%)	1 (1.5%)	32 (49.2%)

[a] Kaur H et al., 2016. Fake anti-malarials: start with the facts. *Malar J 15*:86.

[b] Kaur H et al., 2015. Quality of artemisinin-based combination formulations for malaria treatment: prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. *PLoS One 10(5)*:e0125577.

[c] Antignac M et al., 2017. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa. *Int J Cardiol 243*:523-528

Supplemental Table S3: Manufacturers contacted in the authenticity inquiry

The authors express their gratitude to those manufacturers who responded to our inquiry and thereby supported this study. These manufacturers are listed in bold letters below.

Stated continent of origin	Stated country of origin	Stated manufacturer	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
Africa	Benin	Pharmaquick	7	1/1/-	no answer		
	Burundi	Société industrielle Pharmaceutique (SIPHAR)	1	1/-*/-	no answer		
	Cameroon	**Africure Pharmaceuticals Cameroon S.A.**	**2**	**2/-/-**	**72/29**	**confirmed**	**confirmed**
		Cinpharm[1]	3	1/-*/-	no answer		
	DR Congo	Phatkin B.P.	5	2*/-/-*	no answer		
		Zenufa Laboratoire[2]	4	2/-/-	no answer**		
	Ghana	Entrance Pharmaceuticals & Research Centre	5	2*/-/-	no answer		
	Kenya	**Cosmos Limited**	**1**	**1/1/-**	**84/41**	**confirmed**	**denied**
		DAWA Limited	7	5/1/-	no answer		
		Elys Chemical Industries Ltd.	**3**	**1/-/-**	**44/1**	**confirmed**	**denied**
		Laboratory & Allied Ltd.	**2**	**2/-/-**	**58/14**	**confirmed**	**denied**
		MAC'S Pharmaceuticals Ltd.	1	-/-/1	no answer		
		Pharmaceutical Manufacturing Co. Ltd.	1	1/1/-	no answer		
		Regal Pharmaceuticals Ltd.	**5**	**1/-/-**	**3**	**confirmed**	**denied**
	Nigeria	New Divine Favour Pharmaceutical Industries Ltd.	1	1*/1/-	no answer		
	Senegal	Wintrop Pharma Sénégal Group SANOFI	1	3/1/-	no answer**		

Stated continent of origin	Stated country of origin	Stated manufacturer	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
	Togo	**Sprukfield**	**3**	**-*/1/1**	**21**	**confirmed**	**confirmed**
			1			**denied**	**denied**
	Uganda	Kampala Pharmaceutical Industries	7	1/1/-	no answer		
		Rene Industries Ltd.	2	2/-*/-	no answer		
Americas	British West Indies	Prost Pharma (France)	2	1/1/-	no answer		
	USA	**Sandoz US**	**1**	**1/-/-**	**1**	**confirmed**	**not stated**
Asia	China	Anhui Chengshi Pharmaceutical Co. Ltd	1	1/1/-	no answer		
		Anhui Medipharm Co. Ltd.	1	1/-/-	no answer		
		Chifeng Wanze Pharmaceutical Co. Ltd.	1	-*/1/-	no answer		
		CSPC Ouyi Pharmaceutical Co. Ltd.	21	1*/-/-	no answer		
		CSPC Zhongnuo Pharmaceuticals Co. Ltd.	10	1/-/-	no answer		
		Farmasino Pharmaceutical (Jiangsu) Co. Ltd.	6	2/-/-	no answer		
		Greenfield Pharmaceuticals (Jiang Su) Co. Ltd.	1	3/1/-	no answer		
		Guilin Pharmaceutical Co. Ltd.	4	1*/2/-	no answer		
		Jiangsu Pengyao Pharmaceutical Co. Ltd./ JSPY Pharmaceutical Co. Ltd.[3]	5	-*/-/1	no answer		
		Jiangsu Ruinian Qianjin Pharmaceutical Co. Ltd.	4	-/-/1	no answer		

Stated continent of origin	Stated country of origin	Stated manufacturer	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
		Jiangxi Xier Kangtai Pharmaceutical Co. Ltd./ Shanxi Lianbang Pharmaceutical Co. Ltd. [4]	7	3/1/-	no answer		
		Jinzhou Jiuyang Pharmaceutical Co. Ltd	3	1/1/-	no answer		
		Nanjing Baijingyu Pharmaceutical Co. Ltd.	3	2*/-*/-	no answer		
		Nanjing Sino Pharmaceutical Ltd.	1	1/1/-	no answer		
		NCPC North Best/ NCPC, PRC/ North China Pharmaceutical Co. Ltd.[5]	8	2/1/-	no answer		
		Ningbo Pharma Biotech Co. Ltd. China	38	1/-/1	no answer		
		Ningbo Shuangwei Pharmaceutical Co. Ltd	6	-/-/1	no answer		
		Reyoung Pharmaceutical Co. Ltd.	**9**	**3/-/-**	**34/1**	**confirmed**	**confirmed**
		Shandong Shenglu Pharmaceutical Co. Ltd/ Sishui xier Kang Pharmaceutical Co.Ltd.[6]	5	1/1*/-	no answer		
		Shandong Xier Kangtai Pharm Co. Ltd/ Yanzhou Xierkangtai pharmaceutical Co. Ltd.[7]	4	1/-/-	no answer		
		Shandong Yikang Pharmaceutical Co. Ltd.	2	-*/1/-	no answer		
		Shanghai Juchen Import and Exports Co. Ltd.	4	1/-/-	no answer		

Stated continent of origin	Stated country of origin	Stated manufacturer	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
		Sinochem Jiangsu Co. Ltd	14	2/-*/-	no answer		
	Hong Kong	Hongkong Prost Medicines and Health Products Co. Ltd.	3	-/-/1	no answer		
	India	**Acme Formulation Pvt. Ltd.**	**1**	**1/-/1**	**36/0**	**confirmed**	**confirmed**
		Aculife Healthcare Pvt. Ltd.	2	-*/-/1	no answer		
		Agog Pharma Ltd.	**4**	**2*/-/-**	**1**	**confirmed**	**denied**
		Alkem Laboratories Ltd.	**1**	**1/1/-**	**4**	**confirmed**	**not stated**
		Arco Pharma Pvt. Ltd.	**7**	**2/-/-**	**45/2**	**confirmed**	**confirmed**
		Asence Pharma Pvt. Ltd.	6	2/-*/-	no answer		
		Astra Lifecare Pvt. Ltd.	11	2/-*/-	no answer		
		Aura pharmaceuticals Pvt. Ltd.	9	3/1/-	no answer		
		Aurobindo Pharma Ltd.	**1**	**3*/-/-**	**66/23**	**confirmed**	**denied**
		Axon Drugs Pvt. Ltd.	**1**	**2/-/-**	**59/15**	**confirmed**	**denied**
		Bliss GVS Pharma Ltd.	1	3/-*/-	no answer		
		Cadila Healthcare Ltd.	1	3/1/-	no answer		
		Centurion Healthcare Private Limited	**2**	**1/-/1**	**36**	**confirmed**	**not stated**
		Cipla Ltd.	**1**	**1/-/-**	**21**	**confirmed**	**confirmed**
		Ciron Drugs and Pharmaceuticals Pvt. Ltd.* **	**4**	**1/-/-**	**5**	**confirmed**	**confirmed**
			2	3/1/-	no answer		
		Combitic Global Caplet Pvt. Ltd.	**1**	**2/-/-**	**4**	**confirmed**	**confirmed**
		Fourrts (India) Laboratories Pvt. Limited***	3	2/1/-	no answer		
			21	1/-/1	no answer		
		Gland Pharma Ltd.	**2**	**1/-/-**	**1**	**confirmed**	**not stated**

Stated continent of origin	Stated country of origin	Stated manufacturer	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
		Global Pharma Healthcare Pvt. Ltd.	**4**	**3/-/-**	**45/1**	**confirmed**	**confirmed**
		Holden Medical Laboratories Pvt. Ltd.	**3**	**2/-/-**	**44/0**	**confirmed**	**confirmed**
		Intermed	**1**	**3/-/-**	**44/0**	**confirmed**	**not stated**
		Ipca Laboratories Ltd.	1	3*/1/-	no answer**		
		J. B. Chemicals and Pharmaceuticals Ltd.	1	3/-/-	no answer		
		Kopran Limited	2	3*/1/-	no answer		
		Leben Laboratories Pvt. Ltd.	**1**	**1/-/-**	**6**	**confirmed**	**denied**
		Lincoln Pharmaceuticals Ltd.	8	3/1/-	no answer		
		Lord Lifescience Pvt. Ltd.	1	1/1/-	no answer		
		Macin Remedies India Ltd.	1	1/-/1	no answer		
		Macleods Pharmaceuticals Ltd.	4	3/-/-	no answer**		
		Mancare pharmaceutical Ltd.	3	1*/-/-	no answer		
		Maneesh Pharmaceuticals Ltd.	1	1*/1/-	no answer		
		Maxheal Laboratories Pvt. Ltd.	2	2/1/-	no answer		
		Maxtar Bio-Genics	**14**	**3*/-/-**	**44/1**	**confirmed**	**confirmed**
		Medicamen Biotech Ltd.	**8**	**2/-/-**	**2**	**confirmed**	**confirmed**
		Medicef Pharma	**4**	**3/-/-**	**6**	**confirmed**	**not stated**
		Medico Remedies Pvt. Ltd.	**2**	**2/-/-**	**2**	**confirmed**	**denied**
		Medley Pharmaceuticals Ltd.	**5**	**3*/-/-**	**6**	**confirmed**	**denied**

Stated continent of origin	Stated country of origin	Stated manufacturer	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
		Medopharm Pvt. Ltd.	**37**	**2/-/-**	**51/6**	**confirmed**	**not stated**
			2			**denied**	**not stated**
		Mepro Pharmaceuticals Pvt. Ltd.	1	2*/-/-	no answer		
		Micro Labs Ltd.	**4**	**2/-/-**	**44/1**	**denied**	**denied**
		Milan Laboratories (India) Pvt. Ltd.	**3**	**2/-/-**	**0**	**confirmed**	**confirmed**
			1			**confirmed**	**denied**
		Nem Laboratories Pvt. Ltd.	**1**	**1/1/-**	**44/2**	**confirmed**	**denied**
		Osaka Pharmaceuticals Pvt. Ltd.	3	1/-*/-	no answer		
		PIL Pharmaceuticals Pvt. Ltd.	**1**	**3/-/-**	**1**	**confirmed**	**not stated**
		Prashi Pharma Pvt. Ltd.	6	1/-*/-	no answer		
		Sakar Healthcare Ltd.	1	1/-/1	no answer		
		Shalina Laboratories Pvt. Ltd.	**1**	**1/-/-**	**3**	**confirmed**	**confirmed**
		Sparsh Bio-Tech Pvt. Ltd.	**7**	**1/-/-**	**50/1**	**confirmed**	**denied**
		Strides Arcolab Limited/ Strides Shasun Limited[8]	34	3/1/-	no answer		
		Triveni Formulations Limited	1	1/-/-	no answer		
		Ultra Care International	2	-/-*/1	no answer		
		Umedica Laboratories Pvt. Ltd.* **	**1**	**1/-/1**	**71/35**	**confirmed**	**confirmed**
			1	3/1/-	no answer		
		Zee Laboratories	1	3/1/-	no answer		
		ZIM Laboratories Ltd.	1	1/1/-	no answer		
		One sample stating “Made in India”, but stating only	1	not contacted			

Stated continent of origin	Stated country of origin	Stated manufacturer	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
		the distributor but not manufacturer on the available packaging					
	Sultanat of Oman	National Pharmaceutical Industries Co. (SAOG)	1	1*/-/1	no answer		
	Turkey	**Bilim Pharmaceuticals**	**1**	**1/-/-**	**16**	**confirmed**	**confirmed**
Europe	Austria	Sandoz GmbH	10	1*/1/-	no answer		
	Belgium	**Merck n.v./s.a**	**3**	**2/-/-**	**8**	**confirmed**	**denied**
	Cyprus	**Medochemie Ltd.**	**2**	**1/1/-**	**9**	**confirmed**	**denied**
		Remedica Ltd.	**2**	**1/-/-**	**1**	**confirmed**	**denied**
	France	Delpharm Reims	1	3/1/-	no answer		
		Famar Lyon	1	1/-*/-	no answer		
		Glaxo Welcome Production	**3**	**1/-/-**	**46/3**	**confirmed**	**confirmed**
		Laboratoire Bailly-Creat	6	1/1/-	no answer		
		Rotexmedica GmbH Arzneimittelwerk	**2**	**1/-/-**	**1**	**confirmed**	**not stated**
		Sanofi-Winthrop Industrie	**6**	**2/1/-**	**3**	**confirmed**	**confirmed**
	Germany	Aspen Bad Oldesloe GmbH	1	3/1/-	no answer**		
		Berlin Chemie	**1**	**1/-/-**	**1**	**confirmed**	**confirmed**
		Denk Pharma GmbH & Co. KG	12	1/-/-	no answer		
		Salutas Pharma GmbH	2	2/1/-	no answer		
	Italy	**Biologici Italia Laboratories S.r.l.**	**14**	**1/-/1**	**41/5**	**confirmed**	**not stated**
		Errekappa Euroterapici S.p.A	**1**	**1*/-/-**	**53/9**	**confirmed**	**denied**
		Laboratori Guidotti S.p.A	1	-*/1/-	no answer		
	Spain	Ferrer Internacional S.A.	3	2/1/-	no answer		

Stated continent of origin	Stated country of origin	Stated manufacturer	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
		Novartis Farmacéutica S.A.	**14**	**1/-/-**	**5**	**confirmed**	**confirmed**
	Sweden	**Bluefish Pharmaceuticals AD**	**1**	**1/-/-**	**4**	**confirmed**	**denied**
	UK	**Piramal Healthcare UK Ltd.**	**1**	**1/-/-**	**14**	**confirmed**	**not stated**
		Sonmart Pharma (UK)	6	-/-/1	no answer		
Not stated	Not stated	Cinpharm[1]	3	1/-*/-	no answer		
		One sample stating only the distributor but not the manufacturer on the available packaging	1	not contacted			
	Number of contacted manufacturers and total number of samples		**126 manufacturers; 582 samples**				
	Response rate (based on number of contacted manufacturers who provided an authenticity statement)		**49 (38.9%)**				
	Response rate (based on number of samples from contacted manufacturers with authenticity statement)		**203 (34.9%)**				

[1] For three of the six samples from Cinpharm, it was not stated whether they had been manufactured in Cameroon or by their partner Cipla Ltd. in India, therefore these three samples were listed in the category "Continent of origin not stated". Inquires for all six samples were sent to Cinpharm in Cameroon.

[2] Zenufa Laboratoire stated that they were not able to check the authenticity of the requested medicines, as their records were lost during a fire.

[3] The name of this manufacturer was given on different samples as "Jiangsu Pengyao Pharmaceutical Co. Ltd." or as " JSPY Pharmaceutical Co. Ltd.". Since they appear to have the same contact address, they were considered as a single manufacturer in this study.

[4] According to our research "Jiangxi Xier Kangtai Pharmaceutical Co. Ltd." and "Shanxi Lianbang Pharmaceutical Co. Ltd." belong both to the company "Jiangxi Medicine Imp. & Exp. Co. Ltd." and were therefore considered as a single manufacturer in this study.

[5] The name of this manufacturer was given on different samples as "North China Pharmaceutical Co. Ltd.", or as "NCPC, PRC", or as "NCPC North Best". Since all of them appear to have the same contact address, they were considered as a single manufacturer in this study.

[6] The name of this manufacturer was given on different samples as "Shandong Shenglu Pharmaceutical Co. Ltd" or "Sishui xier Kang Pharmaceutical Co. Ltd.". Since all of them appear to have the same contact address, they were considered as a single manufacturer in this study.

[7] The name of this manufacturer was given on different samples as "Shandong Xier Kangtai Pharm Co. Ltd." or as "Yanzhou Xierkangtai pharmaceutical Co. Ltd.". Since all of them appear to have the same contact address, they were considered as a single manufacturer in this study.

[8] Strides Arcolab Ltd. changed its name to Strides Shasun Ltd. in 2015 after the amalgamation of Shasun Pharmaceuticals with Strides Arcolab in 2014. “Strides Arcolab Limited” and “Strides Shasun Limited” were therefore considered as a single manufacturer in this study.

* Authenticity inquiries were sent to additional e-mail addresses, websites or postal addresses, which turned out to be invalid or could not be contacted due to other reasons (e.g. full mailbox, interruption of postal services due to the Corona pandemic).

** An answer was received from the respective manufacturer, but without statement of authenticity.

*** The three manufacturers Ciron Drugs and Pharmaceuticals Pvt. Ltd., Fourrts (India) Laboratories Pvt. Limited and Umedica Laboratories Pvt. Ltd. were contacted twice, in December 2019 for authentication of oxytocin or misoprostol samples and again in March 2020 for authentication of other types of medicines. The results of both inquiries were evaluated separately.

Supplemental Table S4: Distributors contacted in the authenticity inquiry

The authors express their gratitude to those distributors who responded to our inquiry and thereby supported this study. These distributors are listed in bold letters below.

Stated continent of origin of distributor	Stated country of origin of distributor	Stated distributor	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
Africa	Cameroon	**3N PHARMA DISTRI Sarl**	**1**	**3/-/-**	**41/0**	**confirmed**	**confirmed**
	DRC	Arauphar Production	1	-*/-/-* not contacted			
		Asrams	2	1*/-/-	no answer		
		New Cesamex S.P.R.L.	21	1/1/-	no answer		
		New Span Kinshasa R.D. Congo	2	1/1/-	no answer**		
		Pharma Plus S.A.R.L. (Paloma)	7	-/-/-* not contacted			
		Prince Pharma	6	1/-*/-	no answer		
	Kenya	Medisel (K) Ltd.	1	1/1/-	no answer		
	Malawi	**Banja La Mtsogolo**	**1**	**1/-/1**	**39/4**	**confirmed**	**confirmed**
		WORLDWIDE PHARMACEUTICAL DISTRIBUTORS	**38**	**1/-/-**	**11**	**confirmed**	**not stated**
	Nigeria	Aphantee Pharmaceuticals Nig. Ltd	1	1/-/-	no answer		
		Embassy Pharmaceuticals & Chemicals Ltd. Lago Nigeria	1	-*/1*/-	no answer		
		Jamelia Pharm. Nig. Ltd.	1	1/-/-	no answer		
		Klusyl International Co. Ltd.	2	1/-/-	no answer		
		Manfes Pharmaceuticals Ltd.	6	-/-/-* not contacted			

Stated continent of origin of distributor	Stated country of origin of distributor	Stated distributor	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
		Nkoyo Chemists Nigeria	**1**	**1/-/-**	**50/1**	**confirmed**	**not stated**
		Surelife Pharmaceutical Industry Ltd.	2	-*/1/-*	no answer		
		Transglobe Pharmaceuticals Co. Ltd.	4	1*/-*/*	no answer		
	Togo	**Sprukfield**	**2**	**-/1/1**	**21**	**confirmed**	**confirmed**
	Uganda	Abacus Pharma (A) Ltd. East Africa	2	-*/1/-	no answer		
Americas	British West Indies	Prost Pharma (France) Co. Ltd.	3	1/1/-	no answer		
Asia	Dubai	**Shalina Healthcare DMCC/ Shalina Laboratoire Pvt. Ltd.**[1]	**10**	**1/-/-**	**3**	**confirmed**	**confirmed**
	Hong Kong	CMEC Hongkong Co. Ltd.	6	1/-*/-	no answer		
	India	Bliss GVS Pharma Ltd.	1	3/-*/-	no answer		
		Cachet Pharmaceuticals Pvt. Ltd.	1	2/1/-	no answer		
		Cadila Healthcare Ltd.	2	3/1/-	no answer		
		Fourrts (India) Laboratories Pvt. Limited	1	2/1/-	no answer		
		Indus Lifescience Pvt. Ltd.	**1**	**1/-/-**	**2**	**confirmed**	**denied**
		Naman Pharma Drugs	**1**	**1/-/-**	**50/2**	**confirmed**	**confirmed**
		Ubithera Pharma Pvt. Ltd.	**5**	**1/-/-**	**1**	**confirmed**	**confirmed**
Europe	Austria	Sandoz GmbH	2	1*/1/-	no answer		
	Belgium	**TABRAD SPRL**	**6**	**-/-/1**	**12**	**confirmed**	**confirmed**
	Denmark	**Missionpharma**	**16**	**1/-/-**	**12**	**confirmed**	**confirmed**
			1			**confirmed**	**denied**
	France	Merck Santé s.a.s	1	1/-/-	no answer		

Stated continent of origin of distributor	Stated country of origin of distributor	Stated distributor	Number of medicine samples collected in Cameroon, DRC and Malawi	Number of contacted e-mail addresses/websites/ postal addresses	Number of days between first contact and answer/between reminder and answer	Authenticity confirmed/ denied	Distribution in respective country confirmed/ denied/ not stated
	Germany	GSK	4	4/1/-	no answer**		
	Germany	ZMC Hamburg GmbH[2]	8	4/-/1*	no answer**		
	Luxembourg	Laboratoires Bailleul	1	-*/1/-	no answer		
	The Netherlands	**Amstelpharma**	**2**	**1/-/-**	**21**	**confirmed**	**confirmed**
		IDA Foundation* **	**2**	**1/-/-**	**1**	**confirmed**	**confirmed**
			27	**8/1/-**	**109/82[3]**	**confirmed**	**confirmed**
			1			**denied**	**denied**
			4		**81/54[3]**	**denied**	**denied**
		Imres B.V.	**15**	**2/-/-**	**50/2**	**confirmed**	**confirmed**
		Svizera Europe B.V.	1	1/1/-	no answer		
	UK	GB Pharma Limited	1	1/-/-	no answer		
		Pfizer Limited	**1**	**1/-/-**	**1**	**confirmed**	**not stated**
		Unimed International Ltd.[4]	1	1/-/-	no answer**		
	Number of stated distributors and respective number of samples. (Three distributors, representing 14 samples, could not be contacted)		**45 distributors, 227 samples** (42 contacted distributors, representing 213 samples)[5]				
	Response rate (based on number of contacted distributors who provided an authenticity statement)		**16 (38.1%)**				
	Response rate (based on number of samples from contacted distributors with authenticity statement)		**135 (63.4%)**				

[1] The name of this distributor was given on different samples as “Shalina Healthcare DMCC” or as “Shalina Laboratoire Pvt. Ltd.”. Since they state the same website and company logo on the packaging, they were considered as a single distributor in this study.

[2] The letter to "ZMC Hamburg GmbH" could not be delivered to the specified address (Rantzaustr. 102, 22041 Hamburg, Germany). According to our investigations, the name of the manufacturer's company is "Zhejiang Medicines and Health Products Import & Export Co., Ltd.". E-mails and a letter were therefore sent to the company's Chinese address.
[3] A reminder was sent to IDA Foundation immediately after the two falsifications were identified by the respective manufacturer (Micro Labs Ltd. and Medopharm Pvt. Ltd.). Therefore, the time between first contact and reminder was four instead of six weeks. The confirmation of the second falsified medicine and the authenticity confirmation of the other 27 other samples was only received after 109 days and therefore not within the time frame of three month. However, this response was still included in our evaluation, as we already received a response from IDA earlier.
[4] A message was received that the company Unimed International Ltd. had ceased its trading activities and the directors have retired. It was stated that the records were in storage and could not be checked due to the Corona pandemic restrictions. It has been reported that Unimed International Ltd. distributed substandard propofol to Zambia (Mumphansha *et al.*, 2017. An analysis of substandard propofol detected in use in Zambian anesthesia. Anesthesia & Analgesia 125:616-619) and went into voluntary liquidation in January 2019 (Bannenberg W, 2020. [e-drug] Substandard propofol supplied by UNIMED in Zambia (17). Available at: http://lists.healthnet.org/archive/html/e-drug/2020-04/msg00002.html)
[5] Arauphar Production, Pharma Plus S.A.R.L. (Paloma) and Manfes Pharmaceuticals Ltd. could not be contacted.
* Authenticity inquiries were sent to additional e-mail addresses, websites or postal addresses, which turned out to be invalid or could not be contacted due to other reasons (e.g. full mailbox, interruption of postal services due to the Corona pandemic).
** An answer was received from the respective distributor, but without statement of authenticity.
*** IDA Foundation was contacted twice, in December 2019 for authentication of oxytocin or misoprostol samples and again in March 2020 for authentication of other types of medicines. The results of both inquiries were evaluated separately.

Table S5 List of all products, investigated through authenticity inquiries and the responses of the contacted manufacturer and distributors.

* An answer was received from the respective manufacturer/distributor, but without statement of authenticity.

** The name of this manufacturer/distributor was stated differently on different medicine samples (see Suppl. Table S3 and S4). Since all of them appear to have the same website, e-mail or postal address, they were considered as a single company in this study.

[1] Cinpharm is a Cameroonian company. However, for three of the six samples the country of manufacture was not stated, therefore these three samples were listed in the category "not stated". Inquires for all six samples were sent to Cinpharm in Cameroon.

[2] Zenufa Laboratoire stated that they were not able to check the authenticity of the requested medicines, as their records were lost during a fire.

[3] The manufacturers Ciron Drugs and Pharmaceuticals Pvt. Ltd., Fourrts (India) Laboratories Pvt. Limited, Umedica Laboratories Pvt. Ltd. and the distributor IDA Foundations were contacted two times. One inquiry for the study in Malawi and one for the study in Cameroon and DRC. These inquiries were prepared and evaluated separately and they were treated as two different manufactures/distributor, respectively.

[4] The letter to "ZMC Hamburg GmbH" could not be delivered to the specified address (Rantzaustr. 102, 22041 Hamburg, Germany). According to our research, the name of the manufacturer's company is "Zhejiang Medicines and Health Products Import & Export Co., Ltd.". E-mails and a letter were therefore sent to the company's Chinese address.

[5] Arauphar Production, Pharma Plus S.A.R.L. (Paloma) and Manfes Pharmaceuticals Ltd. could not be contacted.

[6] A message was received that the company Unimed International Ltd. had ceased its trading activities and the directors have retired. It was stated that the records were in storage and could not be checked due to the Corona pandemic restrictions.

Stated continent of origin	Stated country of origin	Stated product name	N	Active pharmaceutical ingredient(s)	Stated manufacturer	Authenticity statement received	Manufacturer confirmed/ denied authenticity	Manufacturer confirmed/ denied/ did not state distribution in respective country	Stated continent of distributor	Stated country of distributor	Stated distributor (if different from manufacturer)	Distributor confirmed/ denied authenticity	Distributor confirmed/ denied/ did not state distribution in respective country
Africa	Benin	Furosemide Pharmaquick	1	Furosemide	Pharmaquick	**no**							
Africa	Benin	Glibenclamid Pharmaquick	2	Glibenclamide	Pharmaquick	**no**							
Africa	Benin	Hydrochlorothiazide Pharmaquick	4	Hydrochlorothiazide	Pharmaquick	**no**							
Africa	Burundi	Siphadox 100	1	Doxycycline	Société industrielle Pharmaceutique (SIPHAR)	**no**							
Africa	Cameroon	Doxycycline Capsules BP	2	Doxycycline	Africure Pharmaceuticals Cameroon S.A.	**yes**	**confirmed**	**confirmed**					
Africa	Cameroon	Cinamox	1	Amoxicillin	Cinpharm[1]	**no**							
Africa	Cameroon	Cincotrim	1	Sulfa/Trimet	Cinpharm[1]	**no**							
Africa	Cameroon	Proloxcin	1	Ciprofloxacin	Cinpharm[1]	**no**							
Africa	DRC	Amoxin 250	1	Amoxicillin	Phatkin B.P.	**no**							
Africa	DRC	Amoxin 500	1	Amoxicillin	Phatkin B.P.	**no**							
Africa	DRC	Ciprokin-500	2	Ciprofloxacin	Phatkin B.P.	**no**							
Africa	DRC	Peni-V	1	Penicillin V	Phatkin B.P.	**no**							
Africa	DRC	Ciproz 500	1	Ciprofloxacin	Zenufa Laboratoire[2]	**no**		**not stated**					
Africa	DRC	Zenamide	2	Furosemide	Zenufa Laboratoire[2]	**no**		**not stated**					
Africa	DRC	Zenogyl 250	1	Metronidazole	Zenufa Laboratoire[2]	**no**		**not stated**					
Africa	Ghana	Co-Trimoxazole	2	Sulfa/Trimet	Entrance Pharmaceuticals & Research Centre	**no**							
Africa	Ghana	Glibenclamide	1	Glibenclamide	Entrance Pharmaceuticals & Research Centre	**no**							
Africa	Ghana	Metronidazole	2	Metronidazole	Entrance Pharmaceuticals & Research Centre	**no**							
Africa	Kenya	Cosatrim	1	Sulfa/Trimet	Cosmos Limited	**yes**	**confirmed**	**denied**					
Africa	Kenya	Eflaron 250	2	Metronidazole	DAWA Limited	**no**							
Africa	Kenya	Frusemide	1	Furosemide	DAWA Limited	**no**							
Africa	Kenya	Moxacil-250	1	Amoxicillin	DAWA Limited	**no**							
Africa	Kenya	Moxacil-500	1	Amoxicillin	DAWA Limited	**no**							
Africa	Kenya	Sabulin	2	Salbutamol	DAWA Limited	**no**							
Africa	Kenya	CO-TRI	1	Sulfa/Trimet	Elys Chemical Industries Ltd.	**yes**	**confirmed**	**denied**					
Africa	Kenya	Frusemide	2	Furosemide	Elys Chemical Industries Ltd.	**yes**	**confirmed**	**denied**					
Africa	Kenya	Kemoxyl 250	1	Amoxicillin	Laboratory & Allied Ltd.	**yes**	**confirmed**	**denied**					
Africa	Kenya	Lecotrim	1	Sulfa/Trimet	Laboratory & Allied Ltd.	**yes**	**confirmed**	**denied**					
Africa	Kenya	Metronyl	1	Metronidazole	MAC'S Pharmaceuticals Ltd.	**no**							
Africa	Kenya	Astalin	1	Salbutamol	Pharmaceutical Manufacturing Co. Ltd.	**no**							
Africa	Kenya	Unipen	1	Penicillin V	Regal Pharmaceuticals Ltd.	**yes**	**confirmed**	**denied**					
Africa	Kenya	Unipen 250	3	Penicillin V	Regal Pharmaceuticals Ltd.	**yes**	**confirmed**	**denied**					
Africa	Kenya	Unitrim	1	Sulfa/Trimet	Regal Pharmaceuticals Ltd.	**yes**	**confirmed**	**denied**					
Africa	Nigeria	New Divine Doxycycline Capsules	1	Doxycycline	New Divine Favour Pharmaceutical Industries Ltd.	**no**							

Stated continent of origin	Stated country of origin	Stated product name	N	Active pharmaceutical ingredient(s)	Stated manufacturer	Authenticity statement received	Manufacturer confirmed/ denied authenticity	Manufacturer confirmed/ denied/ did not state distribution in respective country	Stated continent of distributor	Stated country of distributor	Stated distributor (if different from manufacturer)	Distributor confirmed/ denied authenticity	Distributor confirmed/ denied/ did not state distribution in respective country
Africa	Senegal	Flagyl 500	1	Metronidazole	Wintrop Pharma Sénégal Group SANOFI*	no							
Africa	Togo	Co-Trimoxazole	3	Sulfa/Trimet	Sprukfield	yes	confirmed	confirmed					
Africa	Togo	Co-Trimoxazole	1	Sulfa/Trimet	Sprukfield	yes	denied	denied					
Africa	Uganda	Azudox	1	Doxycycline	Kampala Pharmaceutical Industries	no							
Africa	Uganda	Kam Amoxy Capsules	1	Amoxicillin	Kampala Pharmaceutical Industries	no							
Africa	Uganda	Kam Cotri	1	Sulfa/Trimet	Kampala Pharmaceutical Industries	no							
Africa	Uganda	Kam Vent	4	Salbutamol	Kampala Pharmaceutical Industries	no							
Africa	Uganda	Doxyren	1	Doxycycline	Rene Industries Ltd.	no							
Africa	Uganda	Renetrim	1	Sulfa/Trimet	Rene Industries Ltd.	no							
Americas	British West Indies	Amoxdels-500	1	Amoxicillin	Prost Pharma (France)	no							
Americas	British West Indies	Cotrimo-480mg	1	Sulfa/Trimet	Prost Pharma (France)	no							
Americas	USA	Furosemide	1	Furosemide	Sandoz US	yes	confirmed	not stated					
Asia	China	Metronidazole Tablets	1	Metronidazole	Anhui Chengshi Pharmaceutical Co. Ltd	no							
Asia	China	Cipro 500	1	Ciprofloxacin	Anhui Medipharm Co. Ltd.	no							
Asia	China	Metazol	1	Metronidazole	Chifeng Wanze Pharmaceutical Co. Ltd.	yes			Asia	Dubai	Shalina Healthcare DMCC/Laboratoire Pvt. Ltd.**	confirmed	confirmed
Asia	China	Ciprofloxacine Tablets USP 500 mg	3	Ciprofloxacin	CSPC Ouyi Pharmaceutical Co. Ltd.	yes			Europe	The Netherlands	Imres B.V.	confirmed	confirmed
Asia	China	Ciprofloxacine Tablets USP 500 mg	3	Ciprofloxacin	CSPC Ouyi Pharmaceutical Co. Ltd.	yes			Europe	Denmark	Missionpharma	confirmed	confirmed
Asia	China	Ciprofloxacine Tablets USP 500 mg	3	Ciprofloxacin	CSPC Ouyi Pharmaceutical Co. Ltd.	no							
Asia	China	Cotrimoxazole Tablets BP	2	Sulfa/Trimet	CSPC Ouyi Pharmaceutical Co. Ltd.	no			Africa	DRC	Asrams		
Asia	China	Cotrimoxazole Tablets BP	2	Sulfa/Trimet	CSPC Ouyi Pharmaceutical Co. Ltd.	no							
Asia	China	Doxycycline Hyclate tablets USP	1	Doxycycline	CSPC Ouyi Pharmaceutical Co. Ltd.	yes			Europe	Denmark	Missionpharma	confirmed	confirmed
Asia	China	Doxycycline Hyclate tablets USP	1	Doxycycline	CSPC Ouyi Pharmaceutical Co. Ltd.	no							
Asia	China	Metronidazole 250 mg tables BP	2	Metronidazole	CSPC Ouyi Pharmaceutical Co. Ltd.	yes			Europe	The Netherlands	Imres B.V.	confirmed	confirmed
Asia	China	Metronidazole 250 mg tables BP	3	Metronidazole	CSPC Ouyi Pharmaceutical Co. Ltd.	no							
Asia	China	Unidoxy	1	Doxycycline	CSPC Ouyi Pharmaceutical Co. Ltd.	no			Africa	Kenya	Medisel (K) Ltd.		
Asia	China	Amoxicillin Capsules BP	1	Amoxicillin	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	no							
Asia	China	Amoxicillin Tablets USP	2	Amoxicillin	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	yes			Europe	The Netherlands	IDA Foundation[3]	confirmed	confirmed
Asia	China	Amoxicillin Tablets for Oral Suspension	3	Amoxicillin	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	yes			Europe	Denmark	Missionpharma	confirmed	confirmed
Asia	China	Amoxy-500	2	Amoxicillin	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	yes			Asia	Dubai	Shalina Healthcare DMCC/Laboratoire Pvt. Ltd.**	confirmed	confirmed
Asia	China	Phenoxymethylpenicillin Tablets BP	2	Penicillin V	CSPC Zhongnuo Pharmaceuticals Co. Ltd.	no							
Asia	China	Amoxyn-500	1	Amoxicillin	Farmasino Pharmaceutical (Jiangsu) Co. Ltd.	no			Africa	Uganda	Abacus Pharma (A) Ltd. East Africa		
Asia	China	Doxiciclina	3	Doxycycline	Farmasino Pharmaceutical (Jiangsu) Co. Ltd.	no			Africa	DRC	New Cesamex S.P.R.L.		
Asia	China	Mefagyl	1	Metronidazole	Farmasino Pharmaceutical (Jiangsu) Co. Ltd.	no							
Asia	China	Peni-V	1	Penicillin V	Farmasino Pharmaceutical (Jiangsu) Co. Ltd.	no			Africa	DRC	New Cesamex S.P.R.L.		
Asia	China	Cipromax Fort 500	1	Ciprofloxacin	Greenfield Pharmaceuticals (Jiang Su) Co. Ltd.	no							
Asia	China	Co-trimoxazole USP	3	Sulfa/Trimet	Guilin Pharmaceutical Co. Ltd.	yes			Europe	The Netherlands	IDA Foundation[3]	confirmed	confirmed
Asia	China	Sulfamethoxazole and trimethoprim	1	Sulfa/Trimet	Guilin Pharmaceutical Co. Ltd.	yes			Europe	The Netherlands	Imres B.V.	confirmed	confirmed

Stated continent of origin	Stated country of origin	Stated product name	N	Active pharmaceutical ingredient(s)	Stated manufacturer	Authenticity statement received	Manufacturer confirmed/ denied authenticity	Manufacturer confirmed/ denied/ did not state distribution in respective country	Stated continent of distributor	Stated country of distributor	Stated distributor (if different from manufacturer)	Distributor confirmed/ denied authenticity	Distributor confirmed/ denied/ did not state distribution in respective country
Asia	China	Ciprofloxacine Tablets USP	1	Ciprofloxacin	Jiangsu Pengyao Pharmaceutical Co. Ltd./ JSPY Pharmaceutical Co. Ltd.**	**yes**			Europe	Denmark	Missionpharma	**confirmed**	**confirmed**
Asia	China	Ciproin - 750	1	Ciprofloxacin	Jiangsu Pengyao Pharmaceutical Co. Ltd./ JSPY Pharmaceutical Co. Ltd.**	**no**			Americas	British West Indies	Prost Pharma (France) Co. Ltd.		
Asia	China	Ciproinh - 500	1	Ciprofloxacin	Jiangsu Pengyao Pharmaceutical Co. Ltd./ JSPY Pharmaceutical Co. Ltd.**	**no**			Americas	British West Indies	Prost Pharma (France) Co. Ltd.		
Asia	China	Metrole-500	1	Metronidazole	Jiangsu Pengyao Pharmaceutical Co. Ltd./ JSPY Pharmaceutical Co. Ltd.**	**no**			Americas	British West Indies	Prost Pharma (France) Co. Ltd.		
Asia	China	Metronidazole Tablets BP	1	Metronidazole	Jiangsu Pengyao Pharmaceutical Co. Ltd./ JSPY Pharmaceutical Co. Ltd.**	**yes**			Europe	Denmark	Missionpharma	**confirmed**	**confirmed**
Asia	China	Doxycycline Sprukfield	2	Doxycycline	Jiangsu Ruinian Qianjin Pharmaceutical Co. Ltd.	**yes**			Africa	Togo	Sprukfield	**confirmed**	**confirmed**
Asia	China	Zeprox-500	2	Ciprofloxacin	Jiangsu Ruinian Qianjin Pharmaceutical Co. Ltd.	**no**			Europe	Germany	ZMC Hamburg GmbH*[4]		
Asia	China	Amoxycillin Capsules	1	Amoxicillin	Jiangxi Xier Kangtai Pharmaceutical Co. Ltd./ Shanxi Lianbang Pharmaceutical Co. Ltd.**	**no**							
Asia	China	Deominal	2	Glibenclamide	Jiangxi Xier Kangtai Pharmaceutical Co. Ltd./ Shanxi Lianbang Pharmaceutical Co. Ltd.**	**no**			Africa	Nigeria	Klusyl International Co. Ltd.		
Asia	China	Doxycycline Capsules	2	Doxycycline	Jiangxi Xier Kangtai Pharmaceutical Co. Ltd./ Shanxi Lianbang Pharmaceutical Co. Ltd.**	**no**							
Asia	China	Surelife Doxycyline	2	Doxycycline	Jiangxi Xier Kangtai Pharmaceutical Co. Ltd./ Shanxi Lianbang Pharmaceutical Co. Ltd.**	**no**			Africa	Nigeria	Surelife Pharmaceutical Industry Ltd.		
Asia	China	Metronidazole Tablets	2	Metronidazole	Jinzhou Jiuyang Pharmaceutical Co. Ltd	**no**			Asia	Hong Kong	CMEC Hongkong Co. Ltd.		
Asia	China	Metronidazole Tablets B.P. 250mg	1	Metronidazole	Jinzhou Jiuyang Pharmaceutical Co. Ltd	**no**			Asia	Hong Kong	CMEC Hongkong Co. Ltd.		
Asia	China	Doxycycline Hyclate Tablets USP	1	Doxycycline	Nanjing Baijingyu Pharmaceutical Co. Ltd.	**yes**			Europe	Denmark	Missionpharma	**confirmed**	**confirmed**
Asia	China	Doxycycline Hyclate Tablets USP	1	Doxycycline	Nanjing Baijingyu Pharmaceutical Co. Ltd.	**yes**			Europe	Denmark	Missionpharma	**confirmed**	**denied**
Asia	China	Sulfamethoxazole and Trimethoprim Tablets USP	1	Sulfa/Trimet	Nanjing Baijingyu Pharmaceutical Co. Ltd.	**yes**			Europe	Denmark	Missionpharma	**confirmed**	**confirmed**
Asia	China	Amoxicillin	1	Amoxicillin	Nanjing Sino Pharmaceutical Ltd.	**no**							
Asia	China	WW-OXY 10 Oxytocin injection 10 IU/1ml	38	Oxytocin	Ningbo Pharma Biotech Co.,Ltd, China	**yes**			Africa	Malawi	WORLDWIDE PHARMACEUTICAL DISTRIBUTORS	**confirmed**	**not stated**
Asia	China	Amoxzem	2	Amoxicillin	Ningbo Shuangwei Pharmaceutical Co. Ltd	**no**			Europe	Germany	ZMC Hamburg GmbH*[4]		
Asia	China	Amoxzem Tab.	3	Amoxicillin	Ningbo Shuangwei Pharmaceutical Co. Ltd	**no**			Europe	Germany	ZMC Hamburg GmbH*[4]		
Asia	China	Metrozem-500	1	Metronidazole	Ningbo Shuangwei Pharmaceutical Co. Ltd	**no**			Europe	Germany	ZMC Hamburg GmbH*[4]		
Asia	China	Phenoxymethylpencillin 250mg BP	1	Penicillin V	North China Pharmaceutical Co. Ltd./ NCPC North Best/ NCPC, PRC**	**yes**			Europe	The Netherlands	IDA Foundation[3]	**confirmed**	**confirmed**
Asia	China	Phenoxymethylpenicillin Tablets 250mg	2	Penicillin V	North China Pharmaceutical Co. Ltd./ NCPC North Best/ NCPC, PRC**	**no**							
Asia	China	Phenoxymethylpenicillin Tablets BP	4	Penicillin V	North China Pharmaceutical Co. Ltd./ NCPC North Best/ NCPC, PRC**	**yes**			Europe	Denmark	Missionpharma	**confirmed**	**confirmed**
Asia	China	Phenoxymethylpenicilline	1	Penicillin V	North China Pharmaceutical Co. Ltd./ NCPC North Best/ NCPC, PRC**	**yes**			Asia	Dubai	Shalina Healthcare DMCC/Laboratoire Pvt. Ltd.**	**confirmed**	**confirmed**
Asia	China	Amoxiciline Ubigen	1	Amoxicillin	Reyoung Pharmaceutical Co. Ltd.	**yes**	**confirmed**	**confirmed**	Asia	India	Ubithera Pharma Pvt. Ltd.	**confirmed**	**confirmed**
Asia	China	Amoxicillin Capsules	1	Amoxicillin	Reyoung Pharmaceutical Co. Ltd.	**yes**	**confirmed**	**confirmed**	Africa	Cameroon	3N PHARMA DISTRI Sarl	**confirmed**	**confirmed**

Stated continent of origin	Stated country of origin	Stated product name	N	Active pharmaceutical ingredient(s)	Stated manufacturer	Authenticity statement received	Manufacturer confirmed/ denied authenticity	Manufacturer confirmed/ denied/ did not state distribution in respective country	Stated continent of distributor	Stated country of distributor	Stated distributor (if different from manufacturer)	Distributor confirmed/ denied authenticity	Distributor confirmed/ denied/ did not state distribution in respective country
Asia	China	Amoxicillin Capsules BP	1	Amoxicillin	Reyoung Pharmaceutical Co. Ltd.	**yes**	**confirmed**	**confirmed**	Europe	The Netherlands	Imres B.V.	**confirmed**	**confirmed**
Asia	China	Amoxicillin Capsules BP	1	Amoxicillin	Reyoung Pharmaceutical Co. Ltd.	**yes**	**confirmed**	**confirmed**	Europe	Denmark	Missionpharma	**confirmed**	**confirmed**
Asia	China	Amoxyn-500	1	Amoxicillin	Reyoung Pharmaceutical Co. Ltd.	**yes**	**confirmed**	**confirmed**	Africa	Uganda	Abacus Pharma (A) Ltd. East Africa		
Asia	China	Amoxyn-500	1	Amoxicillin	Reyoung Pharmaceutical Co. Ltd.	**yes**	**confirmed**	**confirmed**	Asia	Dubai	Shalina Healthcare DMCC/Laboratoire Pvt. Ltd.**	**confirmed**	**confirmed**
Asia	China	Ciprofloxacin Tablets	3	Ciprofloxacin	Reyoung Pharmaceutical Co. Ltd.	**yes**	**confirmed**	**confirmed**					
Asia	China	Penicillin V	3	Penicillin V	Shandong Shenglu Pharmaceutical Co. Ltd./ Sishui xier Kang Pharmaceutical Co.Ltd.**	**no**			Africa	Nigeria	Manfes Pharamceuticals Ltd.[5]		
Asia	China	Penicillin V Potassium - 5000,000	1	Penicillin V	Shandong Shenglu Pharmaceutical Co. Ltd./ Sishui xier Kang Pharmaceutical Co.Ltd.**	**no**			Africa	Nigeria	Embassy Pharmacueticals & Chemicals Ltd. Lago Nigeria		
Asia	China	Transglobe Pen Tabs	1	Penicillin V	Shandong Shenglu Pharmaceutical Co. Ltd./ Sishui xier Kang Pharmaceutical Co.Ltd.**	**no**			Africa	Nigeria	Transglobe Pharamceuticals Co. Ltd.		
Asia	China	Amoxicillin	1	Amoxicillin	Shandong Xier Kangtai Pharm Co. Ltd./ Yanzhou Xierkangtai pharmaceutical Co. Ltd.**	**no**			Asia	Hong Kong	CMEC Hongkong Co. Ltd.		
Asia	China	Doxycycline	1	Doxycycline	Shandong Xier Kangtai Pharm Co. Ltd./ Yanzhou Xierkangtai pharmaceutical Co. Ltd.**	**no**			Asia	Hong Kong	CMEC Hongkong Co. Ltd.		
Asia	China	Jeo-Phage Tablets	1	Metformin	Shandong Xier Kangtai Pharm Co. Ltd./ Yanzhou Xierkangtai pharmaceutical Co. Ltd.**	**no**			Africa	Nigeria	Jamelia Pharm. Nig. Ltd.		
Asia	China	Penicillin VK Tablets	1	Penicillin V	Shandong Xier Kangtai Pharm Co. Ltd./ Yanzhou Xierkangtai pharmaceutical Co. Ltd.**	**no**			Asia	Hong Kong	CMEC Hongkong Co. Ltd.		
Asia	China	Penicillin V Potassium 250mg	2	Penicillin V	Shandong Yikang Pharmaceutical Co. Ltd.	**no**							
Asia	China	Konmoxy Capsules	3	Amoxicillin	Shanghai Juchen Import and Exports Co. Ltd.	**no**							
Asia	China	Metronidazole Tablets	1	Metronidazole	Shanghai Juchen Import and Exports Co. Ltd.	**no**							
Asia	China	Amoxicillin 500mg	1	Amoxicillin	Sinochem Jiangsu Co. Ltd.	**no**							
Asia	China	Amoxicillin Capsules B.P	2	Amoxicillin	Sinochem Jiangsu Co. Ltd.	**no**			Africa	DRC	New Cesamex S.P.R.L.		
Asia	China	Ciprofloxacine Tablets USP	5	Ciprofloxacin	Sinochem Jiangsu Co. Ltd.	**no**			Africa	DRC	New Cesamex S.P.R.L.		
Asia	China	Ciprolif-500	2	Ciprofloxacin	Sinochem Jiangsu Co. Ltd.	**no**							
Asia	China	Metronidazole GP	3	Metronidazole	Sinochem Jiangsu Co. Ltd.	**no**							
Asia	China	Peni-V	1	Penicillin V	Sinochem Jiangsu Co. Ltd.	**no**			Africa	DRC	New Cesamex S.P.R.L.		
Asia	Hong Kong	Hydrochlorothiazide	3	Hydrochlorothiazide	Hongkong Prost Medicines and Health Products Co. Ltd.	**no**							
Asia	India	Misoprostol Tablets 200mcg Misoclear	1	Misoprostol	Acme Formulation Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Africa	Malawi	Banja La Mtsogolo	**confirmed**	**confirmed**
Asia	India	OXYNIR OXYTOCIN INJECTION BP 10.0 IU/ml	2	Oxytocin	Aculife Healthcare Pvt. Ltd.	**no**							
Asia	India	Agodox	2	Doxycycline	Agog Pharma Ltd.	**yes**	**confirmed**	**denied**					
Asia	India	Co-Trimoxazole Tablets BP Trimago	2	Sulfa/Trimet	Agog Pharma Ltd.	**yes**	**confirmed**	**denied**					
Asia	India	Acinet	1	Amoxi/Clav	Alkem Laboratories Ltd.	**yes**	**confirmed**	**not stated**	Asia	India	Cachet Pharmaceuticals Pvt. Ltd		
Asia	India	Frusema	7	Furosemide	Arco Pharma Pvt. Ltd.	**yes**	**confirmed**	**confirmed**	Africa	DRC	Pharma Plus S.A.R.L. (Paloma)[5]		
Asia	India	Furosemide Tabrad	2	Furosemide	Asence Pharma Pvt. Ltd.	**yes**			Europe	Belgium	TABRAD SPRL	**confirmed**	**confirmed**
Asia	India	Metronidazole 500	1	Metronidazole	Asence Pharma Pvt. Ltd.	**yes**			Europe	Belgium	TABRAD SPRL	**confirmed**	**confirmed**
Asia	India	Tafuros 40	2	Furosemide	Asence Pharma Pvt. Ltd.	**yes**			Europe	Belgium	TABRAD SPRL	**confirmed**	**confirmed**

Stated continent of origin	Stated country of origin	Stated product name	N	Active pharmaceutical ingredient(s)	Stated manufacturer	Authenticity statement received	Manufacturer confirmed/ denied authenticity	Manufacturer confirmed/ denied/ did not state distribution in respective country	Stated continent of distributor	Stated country of distributor	Stated distributor (if different from manufacturer)	Distributor confirmed/ denied authenticity	Distributor confirmed/ denied/ did not state distribution in respective country
Asia	India	Tamclav 1G	1	Amoxi/Clav	Asence Pharma Pvt. Ltd.	**yes**			Europe	Belgium	TABRAD SPRL	**confirmed**	**confirmed**
Asia	India	As-V	2	Penicillin V	Astra Lifecare Pvt. Ltd.	**no**							
Asia	India	Asbutol-P4	1	Salbutamol	Astra Lifecare Pvt. Ltd.	**no**							
Asia	India	Asdoxin	1	Doxycycline	Astra Lifecare Pvt. Ltd.	**no**							
Asia	India	Asflox-500	3	Ciprofloxacin	Astra Lifecare Pvt. Ltd.	**no**							
Asia	India	Asix	2	Furosemide	Astra Lifecare Pvt. Ltd.	**no**							
Asia	India	Astrogyl	1	Metronidazole	Astra Lifecare Pvt. Ltd.	**no**							
Asia	India	Hyperlok-100	1	Atenolol	Astra Lifecare Pvt. Ltd.	**no**							
Asia	India	Cotrimex-480	1	Sulfa/Trimet	Aura pharmaceuticals Pvt. Ltd.	**no**			Africa	DRC	New Cesamex S.P.R.L.		
Asia	India	Megyl	3	Metronidazole	Aura pharmaceuticals Pvt. Ltd.	**no**			Africa	DRC	New Cesamex S.P.R.L.		
Asia	India	Salbutamol Tablets BP	5	Salbutamol	Aura pharmaceuticals Pvt. Ltd.	**no**			Africa	DRC	New Cesamex S.P.R.L.		
Asia	India	Koact 625	1	Amoxi/Clav	Aurobindo Pharma Ltd.	**yes**	**confirmed**	**denied**					
Asia	India	Asur-850	1	Metformin	Axon Drugs Pvt. Ltd.	**yes**	**confirmed**	**denied**	Asia	India	Indus Lifescience Pvt. Ltd.	**confirmed**	**denied**
Asia	India	BGMET 850	1	Metformin	Bliss GVS Pharma Ltd.	**no**							
Asia	India	Catenol 100	1	Atenolol	Cadila Healthcare Ltd.	**no**							
Asia	India	Misoprostol Tablets 200 mcg	2	Misoprostol	Centurion Healthcare Private Limited	**yes**	**confirmed**	**not stated**					
Asia	India	Ciplox-500	1	Ciprofloxacin	Cipla Ltd.	**yes**	**confirmed**	**confirmed**					
Asia	India	OXYTOCIN INJECTION BP	4	Oxytocin	Ciron Drugs and Pharmaceuticals Pvt. Ltd.[3]	**yes**	**confirmed**	**confirmed**					
Asia	India	Shalformin	2	Metformin	Ciron Drugs and Pharmaceuticals Pvt. Ltd.[3]	**yes**			Asia	Dubai	Shalina Healthcare DMCC/Laboratoire Pvt. Ltd.**	**confirmed**	**confirmed**
Asia	India	Doxynol 200	1	Doxycycline	Combitic Global Caplet Pvt. Ltd.	**yes**	**confirmed**	**confirmed**	Asia	India	Naman Pharma Drugs	**confirmed**	**confirmed**
Asia	India	Co-Trimoxazole Tablets BP Megatrim	1	Sulfa/Trimet	Fourrts (India) Laboratories Pvt. Limited[3]	**no**							
Asia	India	Doxycycline Hyclate Tablets USP	1	Doxycycline	Fourrts (India) Laboratories Pvt. Limited[3]	**no**							
Asia	India	KONTRAC 200	21	Misoprostol	Fourrts (India) Laboratories Pvt. Limited[3]	**no**							
Asia	India	METFIL	1	Metformin	Fourrts (India) Laboratories Pvt. Limited[3]	**no**							
Asia	India	OXYTOCIN 10 IU INJECTION BP	2	Oxytocin	Gland Pharma Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	IDA Foundation[3]	**confirmed**	**confirmed**
Asia	India	Hydrochlorothiazide comprimes BP	4	Hydrochlorothiazide	Global Pharma Healthcare Pvt. Ltd.	**yes**	**confirmed**	**confirmed**					
Asia	India	Atenolol Tablets BP	1	Atenolol	Holden Medical Laboratories Pvt. Ltd.	**yes**	**confirmed**	**confirmed**	Europe	The Netherlands	Imres B.V.	**confirmed**	**confirmed**
Asia	India	Ciprofloxacin Tablets USP	1	Ciprofloxacin	Holden Medical Laboratories Pvt. Ltd.	**yes**	**confirmed**	**confirmed**	Europe	The Netherlands	Imres B.V.	**confirmed**	**confirmed**
Asia	India	Glibenclamide Tablets BP	1	Glibenclamide	Holden Medical Laboratories Pvt. Ltd.	**yes**	**confirmed**	**confirmed**	Europe	The Netherlands	Imres B.V.	**confirmed**	**confirmed**
Asia	India	Amoxicillin and Clavulanate Potassium Tablets	1	Amoxi/Clav	Intermed	**yes**	**confirmed**	**not stated**	Europe	United Kingdom	Unimed International Ltd.[6]		**denied**
Asia	India	Rapiclav-1g	1	Amoxi/Clav	Ipca Laboratories Ltd.*	**no**							
Asia	India	Unique's Metrogyl 200	1	Metronidazole	J. B. Chemicals and Pharmaceuticals Ltd.	**no**							
Asia	India	AMYN-250	1	Amoxicillin	Kopran Limited	**no**							
Asia	India	Trim - 480	1	Sulfa/Trimet	Kopran Limited	**no**							
Asia	India	Doxyleb	1	Doxycycline	Leben Laboratories Pvt. Ltd.	**yes**	**confirmed**	**denied**					
Asia	India	Alldox	2	Doxycycline	Lincoln Pharmaceuticals Ltd.	**no**							
Asia	India	CEEPRO-500	1	Ciprofloxacin	Lincoln Pharmaceuticals Ltd.	**no**							
Asia	India	Ciprofloxacine Ubigen	2	Ciprofloxacin	Lincoln Pharmaceuticals Ltd.	**yes**			Asia	India	Ubithera Pharma Pvt. Ltd.	**confirmed**	**confirmed**
Asia	India	Cotrimoxazole Ubigen	2	Sulfa/Trimet	Lincoln Pharmaceuticals Ltd.	**yes**			Asia	India	Ubithera Pharma Pvt. Ltd.	**confirmed**	**confirmed**
Asia	India	Sulphatrim	1	Sulfa/Trimet	Lincoln Pharmaceuticals Ltd.	**no**							
Asia	India	Salbesone	1	Salbutamol	Lord Lifescience Pvt. Ltd.	**no**							
Asia	India	Oxytocin Injection IP Oxykop	1	Oxytocin	Macin Remedies India Ltd.	**no**							

Stated continent of origin	Stated country of origin	Stated product name	N	Active pharmaceutical ingredient(s)	Stated manufacturer	Authenticity statement received	Manufacturer confirmed/ denied authenticity	Manufacturer confirmed/ denied/ did not state distribution in respective country	Stated continent of distributor	Stated country of distributor	Stated distributor (if different from manufacturer)	Distributor confirmed/ denied authenticity	Distributor confirmed/ denied/ did not state distribution in respective country
Asia	India	Co-trimoxazole Tablets BP 480mg	2	Sulfa/Trimet	Macleods Pharmaceuticals Ltd.*	**no**							
Asia	India	Coflox-500	2	Ciprofloxacin	Macleods Pharmaceuticals Ltd.*	**no**							
Asia	India	Frunnmide	1	Furosemide	Mancare pharmaceutical Ltd.	**no**			Africa	Nigeria	Manfes Pharamceuticals Ltd.[5]		
Asia	India	Lancize	2	Furosemide	Mancare pharmaceutical Ltd.	**no**							
Asia	India	Doxycycline Tablets	1	Doxycycline	Maneesh Pharmaceuticals Ltd.	**no**			Europe	The Netherlands	Svizera Europe B.V.		
Asia	India	Salbutamol	1	Salbutamol	Maxheal Laboratories Pvt. Ltd.	**yes**			Africa	Nigeria	Nkoyo Chemists Nigeria	**confirmed**	**not stated**
Asia	India	Wincip-500	1	Ciprofloxacin	Maxheal Laboratories Pvt. Ltd.	**no**			Africa	Nigeria	Aphantee Pharmaceuticals Nig. Ltd.		
Asia	India	Cotrimoxazole Pextran SS	2	Sulfa/Trimet	Maxtar Bio-Genics	**yes**	**confirmed**	**confirmed**					
Asia	India	Maxformin-500	3	Metformin	Maxtar Bio-Genics	**yes**	**confirmed**	**confirmed**					
Asia	India	Metzole-500	2	Metronidazole	Maxtar Bio-Genics	**yes**	**confirmed**	**confirmed**					
Asia	India	Salbutamol Comprimes BP	7	Salbutamol	Maxtar Bio-Genics	**yes**	**confirmed**	**confirmed**					
Asia	India	Ciprofloxacine USP 500 mg	1	Ciprofloxacin	Medicamen Biotech Ltd.	**yes**	**confirmed**	**confirmed**					
Asia	India	Doxycycline Hyclate	1	Doxycycline	Medicamen Biotech Ltd.	**yes**	**confirmed**	**confirmed**					
Asia	India	Glibenclamide	3	Glibenclamide	Medicamen Biotech Ltd.	**yes**	**confirmed**	**confirmed**					
Asia	India	Metformin	2	Metformin	Medicamen Biotech Ltd.	**yes**	**confirmed**	**confirmed**					
Asia	India	Metronidazole	1	Metronidazole	Medicamen Biotech Ltd.	**yes**	**confirmed**	**confirmed**					
Asia	India	Arauclav	1	Amoxi/Clav	Medicef Pharma	**yes**	**confirmed**	**not stated**	Africa	DRC	Arauphar Production[5]		
Asia	India	Moxyclav	3	Amoxi/Clav	Medicef Pharma	**yes**	**confirmed**	**not stated**	Asia	Dubai	Shalina Healthcare DMCC/Laboratoire Pvt. Ltd.**	**confirmed**	**confirmed**
Asia	India	Salbutamol Tablets BP	2	Salbutamol	Medico Remedies Pvt. Ltd.	**yes**	**confirmed**	**denied**	Africa	Nigeria	Manfes Pharamceuticals Ltd.[5]		
Asia	India	Ecoflox-500	5	Ciprofloxacin	Medley Pharmaceuticals Ltd.	**yes**	**confirmed**	**denied**					
Asia	India	Amoxicillin 500mg + Clavulanic acid 125mg BP	1	Amoxi/Clav	Medopharm Pvt. Ltd.	**yes**	**denied**	**not stated**	Europe	The Netherlands	IDA Foundation[3]	**denied**	**denied**
Asia	India	Amoxicillin Gelules	1	Amoxicillin	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**					
Asia	India	Amoxicillin Tablets USP 250	1	Amoxicillin	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	IDA Foundation[3]	**confirmed**	**confirmed**
Asia	India	Amoxicillin Tablets USP 500	2	Amoxicillin	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**					
Asia	India	Ciprofloxacine 500 mg USP	1	Ciprofloxacin	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	IDA Foundation[3]	**confirmed**	**confirmed**
Asia	India	Ciprofloxacine Comprimes USP	4	Ciprofloxacin	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**					
Asia	India	Clavumoccid	1	Amoxi/Clav	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Asia	India	Bliss GVS Pharma Ltd. (IMEX)		
Asia	India	Cledomox 562.5	1	Amoxi/Clav	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**					
Asia	India	Co-amoxiclav	1	Amoxi/Clav	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**					
Asia	India	Co-trimoxazole BP	9	Sulfa/Trimet	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	IDA Foundation[3]	**confirmed**	**confirmed**
Asia	India	Doxycycline Hyclate USP	4	Doxycycline	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	IDA Foundation[3]	**confirmed**	**confirmed**
Asia	India	Furosemid BP	1	Furosemide	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	IDA Foundation[3]	**confirmed**	**confirmed**
Asia	India	Generic Plus Doxycycline Hyclate 100mg USP	2	Doxycycline	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	Amstelpharma	**confirmed**	**confirmed**
Asia	India	Metronidazole	1	Metronidazole	Medopharm Pvt. Ltd.	**yes**	**denied**	**not stated**					
Asia	India	Metronidazole 250 mg BP	5	Metronidazole	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	IDA Foundation[3]	**confirmed**	**confirmed**
Asia	India	Salbutamol Tablets BP	4	Salbutamol	Medopharm Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	Imres B.V.	**confirmed**	**confirmed**
Asia	India	Ciprofloxacin	1	Ciprofloxacin	Mepro Pharmaceuticals Pvt. Ltd.	**no**							
Asia	India	Furosemide 40mg BP	4	Furosemide	Micro Labs Ltd.	**yes**	**denied**	**denied**	Europe	The Netherlands	IDA Foundation[3]	**denied**	**denied**
Asia	India	Miloxy 250	3	Amoxicillin	Milan Laboratories (India) Pvt. Ltd.	**yes**	**confirmed**	**confirmed**					
Asia	India	Miloxy 250	1	Amoxicillin	Milan Laboratories (India) Pvt. Ltd.	**yes**	**confirmed**	**denied**					
Asia	India	Frusemide	1	Furosemide	Nem Laboratories Pvt. Ltd.	**yes**	**confirmed**	**denied**					
Asia	India	Oxynic	1	Amoxi/Clav	*not stated*	**no**			Europe	United Kingdom	GB Pharma Limited		
Asia	India	Transglobe glibenclamide	3	Glibenclamide	Osaka Pharmaceuticals Pvt. Ltd.	**no**			Africa	Nigeria	Transglobe Pharamceuticals Co. Ltd.		
Asia	India	Co-amoxiclav Tablets BP 625mg	1	Amoxi/Clav	PIL Pharmaceuticals Pvt. Ltd.	**yes**	**confirmed**	**not stated**	Europe	The Netherlands	Imres B.V.	**confirmed**	**confirmed**
Asia	India	Frusemide	5	Furosemide	Prashi Pharma Pvt. Ltd.	**no**			Africa	DRC	Prince Pharma		
Asia	India	Metro 250	1	Metronidazole	Prashi Pharma Pvt. Ltd.	**no**			Africa	DRC	Prince Pharma		
Asia	India	Oxytocin Injection BP OXYCIN -10	1	Oxytocin	Sakar Healthcare Ltd.	**no**							
Asia	India	Sulfatrim	1	Sulfa/Trimet	Shalina Laboratories Pvt. Ltd.	**yes**	**confirmed**	**confirmed**					

Stated continent of origin	Stated country of origin	Stated product name	N	Active pharmaceutical ingredient(s)	Stated manufacturer	Authenticity statement received	Manufacturer confirmed/ denied authenticity	Manufacturer confirmed/ denied/ did not state distribution in respective country	Stated continent of distributor	Stated country of distributor	Stated distributor (if different from manufacturer)	Distributor confirmed/ denied authenticity	Distributor confirmed/ denied/ did not state distribution in respective country
Asia	India	HIPEN	2	Amoxicillin	Sparsh Bio-Tech Pvt. Ltd.	**yes**	**confirmed**	**denied**	Asia	India	Cadila Healthcare Ltd. (Zydus Cadila)		
Asia	India	Speniv Tablets 250	5	Penicillin V	Sparsh Bio-Tech Pvt. Ltd.	**yes**	**confirmed**	**denied**					
Asia	India	Amoxicillin Tablets	2	Amoxicillin	Strides Arcolab Limited/ Strides Shasun Limited**	**no**							
Asia	India	Ciprofloxacine Tablets USP	3	Ciprofloxacin	Strides Arcolab Limited/ Strides Shasun Limited**	**no**							
Asia	India	Co-trimoxazole Tablets BP	6	Sulfa/Trimet	Strides Arcolab Limited/ Strides Shasun Limited**	**no**							
Asia	India	Doxycycline Gelules BP	4	Doxycycline	Strides Arcolab Limited/ Strides Shasun Limited**	**no**							
Asia	India	Frusemide BP	2	Furosemide	Strides Arcolab Limited/ Strides Shasun Limited**	**no**							
Asia	India	Metformin Tablets BP	5	Metformin	Strides Arcolab Limited/ Strides Shasun Limited**	**no**							
Asia	India	Metronidazole Comprimes BP	8	Metronidazole	Strides Arcolab Limited/ Strides Shasun Limited**	**no**							
Asia	India	Metrosim-200	4	Metronidazole	Strides Arcolab Limited/ Strides Shasun Limited**	**no**							
Asia	India	Doxycycline Capsules B.P	1	Doxycycline	Triveni Formulations Limited	**no**							
Asia	India	Cotrimoxazole Tablets B.P	2	Sulfa/Trimet	Ultra Care International	**no**			Africa	DRC	New Span Kinshasa R.D. Congo*		
Asia	India	Glibenclamide	1	Glibenclamide	Umedica Laboratories Pvt. Ltd.[3]	**no**							
Asia	India	OXYTOCIN INJECTION BP 10.0 IU/ml	1	Oxytocin	Umedica Laboratories Pvt. Ltd.[3]	**yes**	**confirmed**	**confirmed**					
Asia	India	Monamox-250 DT	1	Amoxicillin	Zee Laboratories	**no**							
Asia	India	Atenolol Tablets BP	1	Atenolol	ZIM Laboratories Ltd.	**no**							
Asia	Sultanat of Oman	Omacip 500	1	Ciprofloxacin	National Pharmaceutical Industries Co. (SAOG)	**no**							
Asia	Turkey	Klacin BID	1	Amoxi/Clav	Bilim Pharmaceuticals	**yes**	**confirmed**	**confirmed**					
Europe	Austria	Amoxycillin Sandoz	3	Amoxicillin	Sandoz GmbH	**no**							
Europe	Austria	Curam 625	1	Amoxi/Clav	Sandoz GmbH	**no**							
Europe	Austria	Ospen	5	Penicillin V	Sandoz GmbH	**no**							
Europe	Austria	Starpen	1	Penicillin V	Sandoz GmbH	**no**							
Europe	Belgium	Glucophage	3	Metformin	Merck n.v./s.a	**yes**	**confirmed**	**denied**					
Europe	Cyprus	Moxiclav 1g	1	Amoxi/Clav	Medochemie Ltd.	**yes**	**confirmed**	**denied**					
Europe	Cyprus	Moxiclav 625mg	1	Amoxi/Clav	Medochemie Ltd.	**yes**	**confirmed**	**denied**					
Europe	Cyprus	Glyformin 500	2	Metformin	Remedica Ltd	**yes**	**confirmed**	**denied**					
Europe	France	Tolexine Ge	1	Doxycycline	Delpharm Reims	**no**			Europe	Luxembourg	Laboratoires Bailleul		
Europe	France	Glucophage 500 mg	1	Metformin	Famar Lyon	**no**			Europe	France	Merck Serono /Merck Sante s.a.s		
Europe	France	Augmentin Adultes	3	Amoxi/Clav	Glaxo Welcome Production	**yes**	**confirmed**	**confirmed**	Europe	Germany	GSK*		
Europe	France	Cotrim Fort	1	Sulfa/Trimet	Laboratoire Bailly-Creat	**no**							
Europe	France	Creazol	1	Metronidazole	Laboratoire Bailly-Creat	**no**							
Europe	France	Doxycreat	4	Doxycycline	Laboratoire Bailly-Creat	**no**							
Europe	France	OXYTOCIN 10, OXYTOCIN INJECTION BP 10 UNITS-1ml	2	Oxytocin	Rotexmedica GmbH Arzneimittelwerk	**yes**	**confirmed**	**not stated**					
Europe	France	Daonil	3	Glibenclamide	Sanofi-Winthrop Industrie	**yes**	**confirmed**	**confirmed**					
Europe	France	Lasilix 40 mg	3	Furosemide	Sanofi-Winthrop Industrie	**yes**	**confirmed**	**confirmed**					
Europe	Germany	Ventoline	1	Salbutamol	Aspen Bad Oldesloe GmbH*	**no**			Europe	Germany	GSK*		
Europe	Germany	Berlocid	1	Sulfa/Trimet	Berlin Chemie	**yes**	**confirmed**	**confirmed**					
Europe	Germany	AmoxiClav-Denk	5	Amoxi/Clav	Denk Pharma GmbH & Co. KG	**no**							
Europe	Germany	Atenolol Denk	1	Atenolol	Denk Pharma GmbH & Co. KG	**no**							
Europe	Germany	Metformin Denk	6	Metformin	Denk Pharma GmbH & Co. KG	**no**							
Europe	Germany	Novartis Access Hydrochlorothiazide	2	Hydrochlorothiazide	Salutas Pharma GmbH	**no**			Europe	Austria	Sandoz GmbH		

Stated continent of origin	Stated country of origin	Stated product name	N	Active pharmaceutical ingredient(s)	Stated manufacturer	Authenticity statement received	Manufacturer confirmed/ denied authenticity	Manufacturer confirmed/ denied/ did not state distribution in respective country	Stated continent of distributor	Stated country of distributor	Stated distributor (if different from manufacturer)	Distributor confirmed/ denied authenticity	Distributor confirmed/ denied/ did not state distribution in respective country
Europe	Italy	OXYTOCIN OXYTOCINE 10 IU/ml	14	Oxytocin	Biologici Italia Laboratories S.r.l.	**yes**	**confirmed**	**not stated**					
Europe	Italy	Atenol	1	Atenolol	Errekappa Euroterapici S.p.A	**yes**	**confirmed**	**denied**					
Europe	Italy	Metforal	1	Metformin	Laboratori Guidotti S.p.A	**no**							
Europe	Spain	Glidiabet	3	Glibenclamide	Ferrer Internacional S.A.	**no**							
Europe	Spain	Esidrex	14	Hydrochlorothiazide	Novartis Farmacéutica S.A.	**yes**	**confirmed**	**confirmed**					
Europe	Sweden	Metformina Bluefish	1	Metformin	Bluefish Pharmaceuticals AD	**yes**	**confirmed**	**denied**					
Europe	United Kingdom	Cytotec© 200 microgram Tablets	1	Misoprostol	Piramal Healthcare UK Ltd.	**yes**	**confirmed**	**not stated**	Europe	United Kingdom	Pfizer Limited	**confirmed**	**not stated**
Europe	United Kingdom	Doxycycline Capsules	2	Doxycycline	Sonmart Pharma (UK)	**no**							
Europe	United Kingdom	Metformin Tablets	2	Metformin	Sonmart Pharma (UK)	**no**							
Europe	United Kingdom	Metronidazole Tablets 250mg	1	Metronidazole	Sonmart Pharma (UK)	**no**							
Europe	United Kingdom	Sonmamox Amoxicilline 500mg	1	Amoxicillin	Sonmart Pharma (UK)	**no**							
not stated	*not stated*	Cinclamox	3	Amoxi/Clav	Cinpharm[1]	**no**							
not stated	*not stated*	Filmox 500	1	Amoxicillin	*not stated*	**no**			Asia	India	Fourrts (India) Laboratories Pvt. Limited		

Medicine quality screening: TLCyzer, an open-source smartphone-based imaging algorithm for the quantitative evaluation of thin layer chromatographic analyses using the GPHF Minilab

Running title: Evaluation of a smartphone-based TLC imaging algorithm

Hauk, Cathrin*[1]; Boss, Mark*[2]; Schäfermann, Simon[1]; Lensch, Hendrik[§2]; Heide, Lutz[§1]

* These authors contributed equally

[1] Pharmaceutical Institute, Eberhard Karls University Tübingen, Tübingen, Germany

[2] Computer Graphics, Faculty of Science, Eberhard Karls University Tübingen, Tübingen, Germany

§ Authors for correspondence

Keywords: medicine quality, screening device, mobile phone, app, substandard

Introduction

One of the urgent health challenges of our time is the spread of substandard and falsified medicines. The WHO estimated that 10.5% of the medicines in low- and middle-income countries (LMICs) were substandard or falsified in 2017.[1] Substandard and falsified (SF) medicines may not only fail to cure diseases but can induce toxic effects from incorrect active ingredients (APIs) and lead to a loss of confidence in health care professionals and health systems. Besides, they also have economic and socioeconomic impacts, as SF medicines represent a waste of human and financial efforts and increase the financial burden for health systems but also for patients and their families, especially in LMICs where the out-of-pocket percentage for health expenditures is still high.[1] At the same time, the trade with SF medicines is highly profitable for criminals and criminal organisations with little risk of detection and prosecution.[2] Pharmacopeial methods for medicine analysis use sophisticated and expensive techniques such as high performance liquid chromatography (HPLC), require highly trained personal and are difficult to maintain in resource limited settings.[3] Simple and inexpensive field-testing tools to detect and combat substandard and falsified medicines play therefore a vital role in countries with weak regulatory control and enforcement and limited technical capacities.[4, 5] The high sample throughput of screening tools allows LMICs to increase their testing capacities without large investments in laboratory facilities and equipment.[6] The use of screening tools can reduce the time between the collection of suspect samples and the analysis result and therefore the damage of SF medicine that can spread unchecked in the meantime.[7, 8] Furthermore, screening tools with a high selectivity can reduce costs by reducing the number of samples requiring full pharmacopeial analysis for confirmatory testing.[9]

The number of different screening devices used in the field is constantly growing.[4, 7, 10] However, it should be noted that screening tools which are based on different technologies also differ significantly in their characteristics and thus in the suitability of their use at different points within the medicine supply chain.[7, 11] To give recommendations on the optimal choice of devices e.g. to medicine regulatory authorities, more research on the evaluation of screening methods including a comprehensive validation process is essential.[7, 9, 12] Kovacs et al. evaluated the suitability of several screening technologies for usage in LMICs according to field-relevant characteristics such as need for electricity and sample preparation, portability, level of training required and speed of analysis.[11] Recently, the U.S. Pharmacopeial Convention introduced a guideline for the characterization and validation of screening tools in the Unites States Pharmacopeia (USP) 42.[10]

Medicines screening starts in general with a visual inspection of the outer packaging, the blisters and the solid or liquid dosage units such as tablets, capsules or vials.[13] This can even be done at the point of care by frontline health workers by using simple checklists for visual inspection, and is an efficient

method to detect suspicious products that can be selected for further analysis.[14-16] There are also screening devices, e.g. the Counterfeit Detection Device version 3 (CD3+) and X-Rite Eye-One which focus on examining the sample, the packaging material and printing using ultraviolet, visible and infrared wavelength and compare it with images of a genuine product in a library.[7, 17]

Safety features on the packaging, such as barcodes, radio-frequency identification (RFID) tags, tracking codes and unique serial numbers are particularly in high income countries used for the authentication of medicines,[13, 18] e.g. in the EU the packaging of pharmaceuticals require a 2-dimensional barcode as unique identifier and packages have to be visibly sealed according to the Falsified Medicines Directive 2011/62/EU since February 2019.[19] Mobile medicines authentication tools even down to the patient level, such as mPedigree were introduced in several countries in Africa, Asia and the Middle East, however limited reliability and acceptance were reported.[13, 18, 20]

The huge number of different packaging and labelling for the same product, the high degree of packaging variability and also inconsistencies in the packaging information of an authentic product present a challenge for the reliable detection of falsifications through packaging screening in LMICs.[17] Falsified medicines often represent well-made replicates of the genuine product concerning the packaging and the dosage forms.[16] Besides, re-packaging, re-use of packaging material and usage of containers without tamper-evident closures limit the effectiveness of this approach. [2, 5, 13]

For the screening of finished pharmaceutical products (FPPs) a variety of different destructive and non-destructive methods are available.[9] Portable and handheld spectrometers using infrared, near-infrared or Raman spectroscopy are non-destructive, relatively expensive compared to other screening tools and require a reference library that contains the spectra of an authentic product.[12] Up to now these spectroscopic devices are only used for qualitative evaluation and do not provide an automated option for the quantification of the API from finished products, making it difficult to distinguish substandard products from genuine products.[7] Thin-layer chromatography (TLC) and colorimetric screening tools, such as paper cards (PADs) are more economic but require sample pre-treatment and are therefore destructive methods. In addition to identifying the API, they can however also provide (semi-) quantitative results, e.g. by using iodometric back-titration of amoxicillin and ampicillin on paper cards (aPADs).[21] The Minilab of the Global Pharma Health Fund (GPHF) is a widely-used field-tested tool with almost 900 units supplied across 98 countries worldwide and also supported by the WHO and the USAID's Promoting the Quality of Medicines Plus (PQM+) program.[22] The main manuals were issued in 1998 and 2008 and are since then constantly extended and updated. It consists of a self-contained kit for medicine testing on the spot and can be used as a first-line screening tool, that includes visual inspection, TLC and a disintegration test.[22, 23] Initially the Minilab methods mainly focused on the quality of anti-infective medicines,[3] which are

comparatively often reported to be substandard and falsified in LMICs and may not only lead to treatment failures but potentially contribute to the spread of drug-resistant infections if they contain an insufficient amount of API.[1, 24] Meanwhile, the Minilab manual covers methods for more than 100 essential APIs in multiple dosage forms, including also a growing number of medicines against non-communicable diseases.[22, 25]

The Minilab can reliably indicate the presence or absence of an API making it well suited for proof of identity but shows shortcomings in the detection of products that do not contain the correct amount of the stated API. [3, 6, 26-29] According to an evaluation of portable screening devices of the Infectious Disease Data Observatory (IDDO), the Minilab shows high accuracy to identify samples with no or the wrong API and a good sensitivity to identify APIs that contain only 50% of the stated amount. However, most of the samples that contained 80% of the declared API were incorrectly identified as genuine.[12] A WHO survey revealed that in studies using the GPHF Minilab the number of non-compliant samples is underestimated, i.e. an average of 5.0% of the samples failed analysis whereas in studies using more advanced techniques such as HPLC, 15.6% of the samples were identified as "out-of-specification".[1] In a survey on the quality of antimalarials in six countries in sub-Saharan Africa of the WHO, the Minilab was able to classify 75% of the samples with an API content below 80% of the stated content as non-compliant (due to lower intensity spots, no spots, but sometimes also for contaminant spots) and falsely identified only 3.1% of the samples as non-compliant, that complied to pharmacopeial analysis.[28] The evaluation of the TLC analysis with the Minilab is based on visual comparison of the sample spots to a 100% and 80% reference solution spot on the same TLC plate under UV light or by using staining reagents. This semi-quantitative evaluation of the spots requires visual acuity and a certain training of the eye.[30] The reliability and accuracy of the spot assessment is largely subjective, depends on the competency and experience of the operator and can therefore be improved through appropriate training.[28, 30-32]

Over the last decades improvements in thin-layer chromatography towards automated high performance thin-layer chromatography (HPTLC) in combination with densitometers and other detection techniques such as Raman and mass spectroscopy have made planar chromatography a powerful tool for the quantification of pharmaceutical products.[33-35] Kaale et al. demonstrated that personal trained with the Minilab was able to perform reliable HPTLC analysis coupled to densitometric scanners after some additional training.[30] However, quantification from TLC plates is not necessarily limited to applications coupled to non-portable benchtop plate readers. In 2008 Tie-xin et al. described an image analysis system for the quantification of cichoric acid, using images taken from TLC plates with a digital camera.[36] Yu et al. were able to take this approach one step further towards a field screening application by developing a smartphone-based imaging system that is able to analyse images of TLC plates taken with the smartphone camera in a 3D printed cradle.[37] By

analysing the retention factor and the intensity of the spots on the image, they were able to differentiate between 75%, 95% and 100% spots of paracetamol, amodiaquine and nevirapine. Boulgakov et al. showed that a black box made of LEGO™ bricks for photographing the TLC plates is a simple and cost-effective alternative to a 3D cradle.[38] Recently a commercially available smartphone app was used for the quantitative determination of antibiotics separated by TLC and stained with iodine vapour.[39] The combination of TLC with a digital image analysis on a smartphone was also suggested for cost-effective and rapid quantification of cocaine in sized street drugs.[40]

The GPHF Minilab was originally developed for low-cost and rapid field testing but may in the future be combined with a specific software application on a smartphone for more accurate spot quantification and improved reporting of suspicious samples through TLC images.[25] With our research we want to combine the capabilities of the Minilab that is a widely used screening tool with the technological improvements in quantification possibilities for TLC analysis. Pictures of the TLC plates were recorded in a simple and easy to build wooden box. We here developed and tested an algorithm that can directly quantify different APIs from images taken of TLC plates prepared according to the Minilab methods. This algorithm has been developed as an Android-based smartphone app that is provided as GPL open-source software (free of charge) in the Google Play Store (Mountain View, CA, U.S.) and F-Droid. Both the app, and its source code as compiled .apk file, are also available in the Supplementary Information of this publication, and from the homepages of the authors.

The application follows a split architecture, where the user interface (UI) is developed in Kotlin (Kotlin Foundation, https://kotlinlang.org) for the Android operating system and the image analysis is performed in a high-performance Rust (Rust Foundation, https://www.rust-lang.org) implementation. Due to the high-performance Rust implementation the entire processing and analysis of the image can be run on any modern smartphone with short analysis times, aiding the practical on-site capture and analysis setup. The advantage of this split architecture is that the image analysis can be compiled for various operating systems and future ports of the application to Apple's iOS or Windows systems are easily possible without any modification to the analysis. Therefore, the analysis will remain consistent between various operating system and devices.

The intention of the developed app is obviously not to replace HPLC analysis or to achieve similar results as high-end benchtop TLC plate densitometer, but to improve the evaluation of TLC plates by combining the screening tool with an imaging box and a smartphone app to reliably identify substandard samples. Furthermore, our developed app will offer a simple way to store good quality photos of a TLC plate analysis for documentation purposes and to quickly share photos of suspicious samples in a network.

Following the structure of the USP technology reviews and the suggestions of the general chapter <1850> "Evaluation of Screening Technologies for Assessing Medicine Quality"[10] in the United States Pharmacopeia (USP), we provide information on the technology, its handling and capabilities, we present the results of a laboratory-based technical performance evaluation and several pre-tests to assess the field utility of this screening tool combination. Additionally, the parameters of the ICH guideline on validation of analytical procedures Q2 (R1)[41] were used to investigate and validate the capabilities of this method to quantify 14 selected anti-infectives and medicines against non-communicable diseases.

Methods and general information

Thin-layer chromatography

For the validation process antibiotics and medicines against non-communicable diseases were selected to cover different therapeutic indications. Twelve of the 14 selected active pharmaceutical ingredients (APIs) are included in the 22nd WHO essential medicines list.[42] Instead of the prodrug cefuroxime axetil, only cefuroxime powder for injection (as sodium salt) is included in the list. Atenolol is listed as a therapeutic alternative and glibenclamide is no longer included (since 2013; EML 18).

TLC plates were prepared according to the Minilab Manual 2020 of the Global Pharma Health Fund (GPHF) for medicines containing atenolol, ceftriaxone, cefuroxime axetil, chloroquine, ciprofloxacin, dexamethasone, fluconazole, furosemide, glibenclamide, hydrochlorothiazide, metformin, metronidazole, sulfamethoxazole and trimethoprim.[25] The latter two APIs are mostly used in combination preparations and were therefore evaluated together on one TLC plate using the Minilab method: "Sulfamethoxazole in trimethoprim co-formulations (co-trimoxazole)". The analysis followed the specifications of the Minilab manual. Table 1 lists these conditions for each of the investigated 14 APIs. We used certified secondary reference standards from Sigma Aldrich (St. Louis, MO, U.S.) and from EDQM (European Directorate for the Quality of Medicines & HealthCare, Strasbourg, France) for the preparation of the solutions to ensure in the first step that the result is not influenced by excipients contained in the finished pharmaceutical product (FPP), such as tablets or capsules. TLC plates of 5 x 10 cm, coated with a fluorescence indicator (TLC Silica gel 60 F_{254} plates from Merck KGaA, Darmstadt, Germany and Precoated TLC sheets ALUGRAM ® Xtra SIL G/UV_{254} from Macherey-Nagel GmbH & Co. KG, Düren, Germany) were used. Samples were applied to these plates with 2µl micro capillaries (minicaps®, Hirschmann Laborgeräte GmbH & Co. KG, Eberstadt, Germany).

194 **Table 1: Preparation of the TLC plates according to the Minilab Manual 2020.**[25] Concentration of the

195 100% reference standard, solvent for the API and composition of the mobile phase are indicated

API	100% Concentration	Solvent for API	Composition of the mobile phase in the development chamber (based on 20 ml)							
			Metha-nol	Acetone	Water	Ammonia solution (25%)	Acetic acid solution (96%)	Ethyl-acetate	Toluene	Magnesium chloride hexahydrate
Atenolol	5mg/ml	Methanol	20ml			0.2ml				
Ceftriaxone sodium in powder for injections (=ceftriaxone disodium salt hemiheptahydrate) calculated as ceftriaxone free base	0.5mg/ml	Water: methanol (1:10)	6ml	4ml	2ml			8ml		1g
Cefuroxime axetil (cefuroxime free base: 1.25mg/m)	1.5mg/ml	Methanol		10ml			1ml		10ml	
Chloroquine phosphate (calculated as free base)	1.5mg/ml	Water	20ml			0.5ml		5ml		
Ciprofloxacin HCl (calculated as free base)	0.625mg/ml	Acetic acid solution (9.6%): methanol (1:8)	10ml	5ml		5ml			2.5ml	
Dexamethasone	1mg/mL	Methanol		2mL	0.2mL			20mL		
Fluconazole	10mg/ml	Methanol	6ml			0.5ml			14ml	
Furosemide	1.25mg/ml	Acetone	15ml				1 ml		5ml	
Glibenclamide	2mg/ml	Acetic acid: methanol (1:20)	7ml			1ml		11ml	1ml	
Hydrochlorothiazide	2mg/ml	Acetone	2ml				1ml	17 ml		
Metformin HCl	4mg/ml	Methanol	15ml		5ml		1ml			
Metronidazole	5mg/ml	Methanol	5ml			10 drops		15ml		
Cotrimoxazole (sulfamethoxazole and trimethoprim)	5mg/ml and 1mg/ml	Methanol	5ml					15ml		

196

According to the Minilab methods, a 100% and 80% and reference standard together with two sample points is applied to the plate for semi-quantitative estimations. In the Minilab instructions, however, it is pointed out that up to five spots can be placed on a 5 x 10 cm plate (section 6.6 Sample application).[25] Since our algorithm for sample spot quantification uses the intensities of the reference spots to perform linear regression, we decided to add a 60% reference spot and placed a total of five spots on the plate: three different reference solutions and two sample spots. Figure 1 shows the typical Minilab spotting pattern and the pattern used for the validation with the three reference spote 60%, 80% and 100%. We prepared sample solutions containing 50%, 60%, 70%, 85%, 90%, 100% and 120% of the concentration specified in the Minilab manual.

The TLC plates used emit green light, when illuminated with UV light with a wavelength of around 254nm. The selected APIs can weaken the fluorescence by quenching and are therefore easily recognized by the resulting dark spots on the bright green background of the plate. To obtain consistent results, all plates were air dried for at least 30 minutes after development. Subsequent staining of the spots with iodine or other colouring agents, as suggested by the Minilab for additional verification of identity and content was not carried out.

TLC imaging application

The general processing steps are visualized in **Figure 2**. After a JPEG photo of approximately 12 megapixel is taken, the first step is to detect the TLC plate in the image. This plate detection is performed in an image downscaled by a factor of four, using thresholding and line detection in Hough space (D.H. Ballard, "Generalizing the Hough Transform to Detect Arbitrary Shapes", Pattern Recognition, Vol.13, No.2, p.111-122, 1981). In case of inaccurate or misdetection of the plate, the user can update the suggested plate corners in the application. The selected corner points are then used to remove the perspective warp and crop the image to contain the plate.

For an accurate spot integration, only the intensity of the spot needs to be considered. Compared to Yu et al.[37] our method does not require multiple input images of a blank TLC plate for the background illumination subtraction. For the fitting and spot integration the image is converted to grayscale: $Y = 0.2126 * R + 0.7152 * G + 0.0722 * B$, where R, G, B respond to linear red, green and blue channel, respectively. We remove the lighting by fitting the 15 a coefficients of the two-dimensional quartic polynomial function:

$$f(x,y) = a_1y^4 + a_2xy^3 + a_3x^2y^2 + a_4x^3y + a_5x^4 + a_6y^3 + a_7xy^2 + a_8x^2y + a_9x^3 + a_{10}y^2 + a_{11}xy + a_{12}x^2 + a_{13}x + a_{14}y + a_{15}$$

, where x and y define the image pixel coordinate. Here, we leverage the linregress library of Kacprowski et al. (Kacprowski, Tim – linregress 0.4 https://github.com/n1m3/linregress - 2020). The result is a smooth approximation of the illumination. As the background fitting on the full resolution images is time-consuming on a smartphone processor and the illumination is smooth, we downsample the image by a factor of 4 for this process. The fitted polynomial illumination model is then subtracted from the image, leaving just the spots and pencil markings.

The resulting image is then thresholded based on the remaining image mean value μ_I: $t(v) = \begin{cases} 1 & if\ v \geq \mu_I \\ 0 & otherwise \end{cases}$, and a connected component algorithm labels all remaining areas. Based on the shape and size, all components are filtered, and only the spots remain. Here, shapes with a wide or tall aspect ratio, small shapes, and shapes larger than a quarter of the image are filtered. The center of the spots is calculated by calculating the mean of the pixel coordinates weighted by the intensity values: $\frac{\sum_1^N cv}{\sum_1^N v}$, where c describes the two-dimensional coordinate and v the pixel intensity. The radius is then selected to cover the whole spot. The integral of the intensity values is then calculated by summing the pixel values in this circular region. We found that the robustness is improved by only selecting the top 15% of the pixels in the spot region, therefore this procedure was followed.

With the user-provided reference values and the corresponding integrant values, a linear regression is performed, which is evaluated for the sample spots.

Practical procedure of the image analysis process

Photos of the developed plates were taken with the developed smartphone application in a black wooden box modified from the 3D plastic cradle of Yu et al.[37] to fix the position of the UV lamp (Prinz Verlag GmbH Passau, Germany 256 nm) and the smartphone (Motorola Moto G7, Motorola Inc., Schaumburg, Illinois, US). Figure 3 provides an overview of the TLC imaging box that was built by the workshop of Tübingen University. A detailed scheme of the box that allows a construction of this box can be found in the Supplemental Information (Supplemental Figure S1). The box provides a dark environment for optimal spot detection and was designed to be compatible with the rear-facing camera of smartphones. To avoid reflections when photographing the TLC plates, the wooden box was painted with a matt, black paint.

The developed smartphone application, called TLCyzer app, can be installed on any smartphone with an Android operating system. For the validation procedure, the lettering on top of the plate was cut off. The single steps of this process line are shown in Figure 2. A detailed step-by-step instruction of the app can be found in the Supplemental Information Figure S2 The evaluation of a photo does not require an internet connection and can be repeated as often as required however the previous evaluation is overwritten if a photo is re-evaluated. Every file of an evaluated photo consists of the

raw photo (caputure.jpg), the cropped photo (warped.png), the background (background_fit.png), the detected spots (blobs.png) and a text file (capture.json) that indicates the “agentName”, the “x” and “y” values, “radius”, “integrationValue” and “percentage” values of every spot. The percentages are indicated with decimal places in this file, whereas the app only displays whole numbers and cuts off the decimal places. These folders are saved as a ZIP file on the smartphone and can easily be shared using an app, send by e-mail or uploaded to a cloud if an internet connection is available. This allows a very quick and easy sharing of analysis results and photos and the (re-)evaluation of TLC plates on other smartphones. Pictures of the three image files are shown in Figure 2: A, C, D and E.

Validation and performance evaluation

The ICH guideline on validation of analytical procedures[41] and the USP chapter <1850> Evaluation of screening technologies for assessing medicine quality[10] were used to characterize and validate the quantification process and the results obtained with the developed app. In the mentioned chapter the USP indicates, that the quantification of APIs in FPP (“Application IV: Quantification of major components if bulk drug substances or active pharmaceutical products”) should be evaluated for the following qualitative analytical performance characteristics: accuracy, precision (repeatability and intermediate precision), specificity, linearity, robustness, detection limit. However, according to the ICH guidelines the range of the method should be validated instead of the detection limit.[41]

Accuracy and precision (repeatability and intermediate precision)

The accuracy of an analytical procedure is the closeness of a test result to the true value, while the precision refers to the degree of agreement within the individual test results. According to the ICH guidelines a minimum of nine determinations (e.g. three replicates with three different concentrations) is required for the validation of these parameters.[41] Certified reference material was used to prepare solutions representing 70%, 85% and 90% of the concentrations indicated in the Minilab manual. On each plate, three standard concentrations, representing 60%, 80% and 100% of the target concentration were placed on position 1, 3 and 5 to plot a linear regression curve for calibration purposes. To validate accuracy and repeatability, two sample spots of the same concentration were applied on position 2 and 4 on the plate and for each concentration, the plate was prepared twice in the same way to obtain 12 results for every API.

To determine the influence of different parameters under which the analysis is conducted, i.e. analysis on different days, by different operators and with different smartphones, the intermediate precision was evaluated. Therefore, TLC plates were photographed on two different days and evaluated by three different operators on two different days with the aforementioned smartphone (Motorola Moto G7) and two additional smartphones models (OnePlus 6T, OnePlus, Shenzhen,

Guangdong, China and Samsung Galaxy S7, Samsung Electronics Co., Ltd., Suwon, South Korea). As recommended by the ICH guidelines, these effects were not evaluated individually, but within an experimental matrix design.[41] For analysis day one and two, six of the nine possible combinations per API were randomly selected. This resulted in a total of 168 different combinations (12 results per API) and 336 analysis results (two results per TLC plate), which were evaluated to assess the intermediate precision. Supplemental Figure S3 shows a table of the matrix approach and the possible combinations.

Specificity

According to the ICH guidelines the specificity of a method is its ability to identify the analyte in the presence of impurities, degradation products and other components that are expected to be present.[41] API specific TLC methods were developed by the GPHF for the identification and semi-quantitative evaluation of the respective API.[25] We followed the Minilab methods for the preparation of the TLC plates and did not change any chromatographic parameters. As the app was developed for quantification purposes, the identification procedure was not further investigated. Concerning the content of FPP, specificity refers to the ability to provide an exact result that allows an accurate statement on the content of an API in a sample.[41] The aim of the app is to improve the quantitative evaluation of the Minilab concerning the reliability and objectivity of the evaluation. According to the Minilab a content below 80% is considered as “non-compliant” and a content above 80% as “compliant”.[25] For the validation of accuracy and precision we prepared solutions containing 70%, 80% and 95% of the Minilab standard solution. The results were used as a test to evaluate the ability of the app to correctly identify spots containing 70% as “non-compliant”, i.e., obtaining a result below 80% and to identify spot containing 90% as “compliant”, i.e., to obtain a result between 80% and 100%. In addition, we wanted to find out which result the app calculates when spots with 85% of the standard solution are evaluated. The ability of the app to quantify spots with a content above 100%, i.e. 120% was evaluated within the linearity studies.

Linearity

We prepared chromatographic plates with five concentrations representing 50%, 70%, 90%, 100% and 120% of the respective Minilab standard solution to demonstrate linearity. For each of the 14 APIs three TLC plates were prepared and the mean result was calculated. The response, recorded in percentage, was set in relation to the standard solution. Linear regression analysis was used for the evaluation of linearity.

Range

The detection limit of the algorithm depends on the respective UV quenching capabilities of a specific API and additionally on the concentration specified in the specific Minilab method. Therefore, no general statement can be made about the detection limit of the app. Visual

identification of spots on TLC plates is often still possible with very lower concentrations, as was shown in the case of falsified chloroquine samples that contained only 21.7% of the declared amount.[43] In order to demonstrate that the developed app is able to quantify spots with a low API content, we prepared sample solutions of sulfamethoxazole and trimethoprim that contained 12%, 14% and 15% of the concentration specified in the manual (100% corresponds to 5mg/mL sulfamethoxazole and 1mg/ml trimethoprim according to the Minilab manual, see Table 1). Sulfamethoxazole was selected because it shows very dark and large spots, while trimethoprim shows very weak and small spots, compared to the other APIs examined and also according to the spot description in the Minilab manual.[25] The reference solutions used for this test, contained 10%, 13% and 17% of the specified Minilab concentration. For each sample concentration two plates were prepared and evaluated. As aforementioned the results of this test cannot be transferred to other APIs. The working range of a method is the area between the smallest and highest concentration in which an acceptable accurate and repeatable result can be achieved, and can therefore be derived from linearity, accuracy and precision studies. Depending on the intended application a range between 80% and 120% of the test concentration should be considered, according to the ICH guideline.[41] We examined the linearity in the range between 50% and 120% of the indicated Minilab concentration for all 14 APIs. An API content below 50% of the stated one was not examined, as these products should be investigated in a fully equipped laboratory and the quantification of these very substandard or falsified products is not the intended purpose of this tool.

Robustness

Robustness is the ability to remain unaffected by small variations in the procedural parameters and it serves as an indicator of suitability during normal use.[10, 41] Although robustness is not considered as a typical validation characteristic, it should be evaluated during the development of an analytical procedure to find out if the measurement is susceptible to certain variations in analytical conditions.[41] Robustness plays a crucial role in field technologies, as the methods are not carried out under controlled laboratory conditions. Four different APIs (chloroquine, dexamethasone, hydrochlorothiazide and metformin) were selected to investigate different critical performance parameters. To assess the robustness, the measurements were performed as described in the section practical procedure of the image analysis process (= standard condition) and compared to the results obtained under seven different modified conditions. The modifications concerned both, the evaluation with the app, and external factors such as the box or smartphone model for the evaluation of the photo. The TLC plates were cropped in different ways with the app to examine the effect of pencil writing on the background of the plate on the result: including the upper and lower lettering, without any lettering or only with lower lettering – representing the standard procedure. We investigate the influence of a non-central position of the UV lamp and low battery charge of the

lamp, since the fluorescence of the TLC plates takes on a more intensely coloured green background when the battery charge is low. The influence of the box used and the smartphone camera was also examined and assessed. Photos of the same TLC plates were taken and evaluated in another box (built by the Pidinger Werkstätten, Piding, Germany; photos of the box see Supplemental Figure S5). Another smartphone (Fairphone 3, Fairphone B.V., Amsterdam, The Netherlands) was used to photograph and evaluate the same plates. Each measurement was repeated three times, using a reference standard that contained 90% of the concentration specified in the Minilab manual.

Field utility

To ensure field suitability of a screening tool, the USP suggests several parameters that should be considered during the development of a new tool and evaluated as a follow-up to the performance evaluation.[10] The aim is to assess if the technology can operate effectively and efficiently not only in the laboratory but also in field settings. The USP recommends to consider handling, maintenance and repair as well as durability and use of the developed technology.[10] We therefore considered several aspects concerning the construction of the box, the evaluation with the smartphone and the handling of the app to evaluate the field utility. Smartphones, nowadays widely used in all parts of the world, are normally equipped with a rear-facing camera. Ideally, the result of the evaluation with the app should not depend on the smartphone model, and reproduction of results should be possible if photos are (re-) evaluated on different devices. As part of the validation of the intermediate precision, the influence of three different smartphones on the result was evaluated. The influence of the smartphone camera for the evaluation was examined within the scope of the robustness evaluation. In addition, two TLC plates were evaluated on nine different smartphones as part of an online training workshop (see below).

Training requirements play a major role in the field evaluation of the technology. The evaluation with the app should be easy to learn, fast and as far as possible self-explanatory. The average time to take a photo of the TLC plate and evaluate it with the app takes about one to two minutes. With a group of pharmacists and pharmacy students we carried out a 45-minute online training workshop on using the TLCyzer app. To assess if the provided online training was sufficient to learn how to use the app, the participants were afterwards asked to independently evaluate two TLC plates with an unknown sample concentration using their private smartphones.

To verify whether the results we obtained with the certified reference standards can in general be transferred to FPP, we purchased ciprofloxacin, dexamethasone, hydrochlorothiazide and metronidazole tablets from the dispensary in Tübingen university. In order to facilitate the procedure, we wanted to find out if the app produces comparable robust and reliable results if only an 100% and 80% reference spot is present on the TLC plate as indicated in the Minilab manual. We prepared TLC plates according to the spotting pattern we used for the validation process (60%, 80%

and 100% reference) and additionally plates, showing only an 100% and 80% - and no 60% reference spot as indicated in the Minilab manual. Both spotting patterns are shown on Figure 1. These TLC plates were evaluated with the developed wooden box and the TLCyzer app.

To carry out a first proof of concept with real samples in addition to the validation of the screening tool, we tested two substandard ciprofloxacin and metronidazole samples, that were collected in the course of a medicine quality study in the Democratic Republic of Congo (DRC).[15] The two substandard samples were analysed with HPLC in our laboratory according to the methods of USP 42, showing only 83.4% and 86.7% of the stated content, respectively.[15] This serves as a preliminary test to find out if the TLCyzer app is able to differentiate between substandard samples with a content between 80% and 90% of the stated amount and good quality samples. For each sample and spotting pattern three plate were prepared and two photos of every plate were taken and evaluated with the app.

Results of the validation and performance evaluation

Accuracy and precision (repeatability and intermediate precision)

Of every API six TLC plates, with sample solutions representing 70%, 85% and 90% of the concentration indicated in the Minilab manual were prepared and evaluated to validate accuracy as well as repeatability of the procedure. Since two spots from two plates were developed and measured, our results also include the variation derived from the application of the solutions with the microcapillary pipette and the variations through thin layer chromatographic development. The accuracy, indicated as percentage recovery ranged for individual results between 93.4% and 107.9% (mean 100.3%). All APIs were quantified with a precision, indicated as relative standard deviation (RSD) between 5.68% and 0.77% (mean RSD 2.79%). The median RSD of all four individual determinations for each applied concentration of each API was 2.59%. In Table 2 the mean of the four measurements, the RSD and the mean recovery are indicated for all APIs. The individual results and the mean results for every concentration and API are depicted in Figure 4 and Supplemental Table S1 shows the individual results of all measurements, SD, RSD and recovery.

The average RSD for intermediate precision using a matrix approach was 4.46% and therefore below the ≤5% threshold that is widely accepted as RSD for intermediate precision of chromatographic methods.[35] In Table 2 the mean results, the SD and the RSD of the 24 determinations per API are shown. The single results of the matrix approach are shown in the Supplemental Table S2. Glibenclamide showed the lowest RSD (3.17%). Sulfamethoxazole was the only API that showed a RSD higher than 5% (8.02%). It should be noted that automatic spot detection was not possible due

438 to the large size of the spots that were positioned very close to one another on the TLC plate (see
439 Supplemental Figure S4) and therefore had to be selected manually.
440
441 **Table 2 Repeatability, recovery and intermediate precision results of the investigated 14 APIs**
442

API	Repeatability (n=4)				Recovery mean (n=4) [%]	Intermediate precision (conc. 90%) (n=24)		
	Conc. [%]	Mean [%]	SD [%]	Relative SD [%]		Mean [%]	SD [%]	RSD [%]
Atenolol	70	72.5	0.59	0.81	103.5	88.5	4.38	4.94
	85	85.9	1.59	1.85	101.1			
	90	91.7	3.97	4.33	101.8			
Ceftriaxone	70	70.1	3.99	5.68	100.2	88.1	2.82	3.20
	85	84.1	1.00	1.18	99.8			
	90	90.4	3.31	3.63	101.3			
Cefuroxime axetil	70	72.0	3.09	4.29	102.9	91.2	4.57	5.01
	85	82.3	2.13	2.59	96.8			
	90	90.5	3.82	4.23	100.5			
Chloroquine	70	68.7	0.93	1.36	98.1	91.8	3.67	4.00
	85	85.5	0.95	1.11	100.5			
	90	91.9	2.11	2.30	102.1			
Ciprofloxacin	70	69.8	1.93	2.77	99.7	90.5	4.55	5.03
	85	84.7	3.53	4.17	99.6			
	90	92.5	2.86	3.09	102.8			
Dexamethasone	70	67.5	2.75	4.08	96.4	90.8	4.04	4.45
	85	85.2	2.07	2.43	100.3			
	90	92.1	2.08	2.26	102.3			
Fluconazole	70	70.4	1.68	2.39	100.6	89.6	3.22	3.60
	85	84.3	1.54	1.82	99.1			
	90	89.1	2.68	3.01	99.0			
Furosemide	70	70.3	1.82	2.59	100.5	91.1	3.58	3.93
	85	85.1	2.20	2.58	100.1			
	90	92.6	1.54	1.66	102.8			
Glibenclamide	70	68.5	2.04	2.98	97.9	90.5	2.87	3.17
	85	83.0	4.34	5.23	97.6			
	90	90.6	1.17	1.29	100.6			
Hydrochloro-thiazide	70	70.8	1.27	1.80	101.2	90.4	4.07	4.50
	85	85.5	1.24	1.45	100.6			
	90	90.9	2.46	2.70	101.0			
Metformin	70	72.0	3.45	4.80	102.8	89.1	3.70	4.15
	85	83.7	1.94	2.32	98.5			

API	Repeatability (n=4)				Recovery mean (n=4) [%]	Intermediate precision (conc. 90%) (n=24)		
	Conc. [%]	Mean [%]	SD [%]	Relative SD [%]		Mean [%]	SD [%]	RSD [%]
	90	89.1	2.25	2.53	99.0			
Metronidazole	70	69.2	2.38	3.44	98.8	91.6	4.32	4.71
	85	85.0	0.66	0.77	100.0			
	90	90.0	2.50	2.77	100.0			
Sulfamethoxazole	70	70.1	3.38	4.82	100.2	88.3	7.08	8.02
	85	87.4	2.91	3.33	102.8			
	90	93.5	3.17	3.39	103.9			
Trimethoprim	70	68.6	1.53	2.22	98.0	91.9	3.38	3.68
	85	84.0	2.86	3.41	98.8			
	90	88.2	1.61	1.82	97.9			
Mean				**2.79**	**100.3**	**90.2**	**4.02**	**4.46**

Specificity

The results of the precision and accuracy validation were evaluated to determine the specificity of the method. In total 168 spots were evaluated, and in all cases, it was possible to correctly identify the 70% spots as “non-compliant”, i.e. a result below 80% was calculated by the app and correctly identify the 90% spots as “compliant”, i.e. showing results above 80%. Furthermore, the app always displayed a result between 80% and 90% for the 56 examined spots containing 85%. Table 2 shows the mean result, individual results are shown in Supplemental Table S1 and are depicted in Figure 4.

Linearity

Linearity was investigated by linear regression of five different concentrations versus the result for the corresponding spots on a TLC plate evaluated with our smartphone algorithm. Over a range of 50% to 120% the test result was directly proportional to the prepared concentration of reference standard for all investigated APIs. Linearity was confirmed with a determination coefficient R^2 between 0.989 and 1.00. Table 3 shows the target concentration, the mean result calculated from three different TLC plates, y-intercept and slope of the regression equation, residual sum of squares (RSS), the correlation and determination coefficients R and R^2. The smaller the RSS, the better the linear regression model created by the algorithm fits to the results. Furosemide showed the smallest RSS (0.57), ciprofloxacin the highest (29.26). The median RSS was 7.13 (mean 10.39). The individual results for the three analysed plates, the mean values for each concentration and API, as well as the recovery can be found in the Supplemental Table S2.

Table 3: Evaluation of linearity in the range between 50% and 120% based on the concentration of the Minilab standard solution for the 14 APIs

466

API	Conc. [%]	Result mean (n=3) [%]	y-Intercept	Slope	Residuals^2	RSS (residual sum of squares)	Correlation coefficient R	Determination coefficient R2
Atenolol	50	50.2	-2.701	1.026	2.591	15.52	0.997	0.995
	70	66.0			9.653			
	90	89.9			0.077			
	100	101.6			2.953			
	120	119.9			0.248			
Ceftriaxone	50	50.5	-0.795	0.999	1.777	6.77	0.999	0.998
	70	67.8			1.828			
	90	89.1			0.001			
	100	97.9			1.512			
	120	120.4			1.653			
Cefuroxime axetil	50	49.2	1.376	0.984	1.862	9.62	0.998	0.997
	70	71.3			1.124			
	90	92.1			4.774			
	100	98.6			1.329			
	120	118.7			0.530			
Chloroquine	50	48.7	1.568	0.984	4.200	24.05	0.996	0.992
	70	71.1			0.460			
	90	93.9			14.482			
	100	99.7			0.053			
	120	117.4			4.855			
Ciprofloxacin	50	49.5	3.310	0.958	3.008	29.26	0.995	0.989
	70	73.3			8.386			
	90	91.3			2.979			
	100	95.4			14.129			
	120	119.2			0.759			
Dexametha-sone	50	49.8	0.228	0.991	0.000	3.81	0.999	0.999
	70	69.6			0.000			
	90	90.5			1.113			
	100	97.8			2.428			
	120	119.7			0.266			
Fluconazole	50	49.7	-1.060	1.012	0.021	3.18	0.999	0.999
	70	68.8			1.005			
	90	90.7			0.423			
	100	101.2			1.056			
	120	119.6			0.671			
Furosemide	50	50.1	0.853	0.992	0.114	0.57	1.000	1.000

API	Conc. [%]	Result mean (n=3) [%]	y-Intercept	Slope	Residuals^2	RSS (residual sum of squares)	Correlation coefficient R	Determination coefficient R2
	70	70.9			0.394			
	90	90.0			0.011			
	100	99.8			0.050			
	120	119.9			0.002			
	50	49.2			1.047			
	70	70.4			0.119			
Glibenclamide	90	92.1	0.645	0.992	4.900	7.30	0.999	0.997
	100	99.2			0.362			
	120	118.7			0.872			
	50	49.3			2.644			
	70	71.9			0.694			
Hydrochloro-thiazide	90	91.8	0.573	1.007	0.350	17.44	0.997	0.994
	100	104			7.405			
	120	118.9			6.350			
	50	50.1			4.166			
	70	75.1			13.069			
Metformin	90	90.1	3.782	0.967	0.531	18.41	0.997	0.993
	100	99.7			0.641			
	120	119.8			0.002			
	50	50.4			0.003			
	70	70.7			0.162			
Metronidazole	90	89.2	0.460	0.998	1.104	1.46	1.000	0.999
	100	100.6			0.139			
	120	120.4			0.048			
	50	49.3			1.999			
	70	71.6			1.296			
Sulfamethoxa-zole	90	91.8	1.344	0.987	2.529	6.97	0.999	0.998
	100	99.8			0.080			
	120	118.8			1.064			
	50	50.1			0.323			
	70	71.3			0.627			
Trimethoprim	90	90.2	1.069	0.992	0.022	1.12	1.000	1.000
	100	100.5			0.054			
	120	119.8			0.095			
Mean						**10.39**	**0.998**	**0.996**

Range

As an example, we examined whether the sulfamethoxazole and trimethoprim spot can still be reliably evaluated with the app if we apply solutions containing only 12%, 14% or 15% of the concentration specified in the Minilab manual. Sulfamethoxazole showed still clearly visible dark spots whereas the trimethoprim spots, that are already small and weak if spotted in the concentration indicated in the Minilab manual showed now very pale spots. In our opinion, a semiquantitative visual detection of the very weak spots was no longer possible, see Supplemental Figure S4. However, the app was able to detect and quantify the low concentrated sulfamethoxazole and trimethoprim spots with a mean recovery of 100.3% (RSD 4.1%, n=12) and 100.9% (RSD 5.2%, n=12) respectively, comparable to the mean results obtained with the standard concentration specified in the Minilab target concentrations (see section accuracy and precision; mean recovery: sulfamethoxazole 102.3%, RSD 3.84%, n=12 and trimethoprim 98.2%, RSD 2.48%, n=12) (see Table 2). As aforementioned, these results cannot be transferred to other APIs, but the working range of a method can be derived from the linearity studies which were performed for all 14 APIs. Within the range of 50% and 120% based on the Minilab standard solution an acceptable degree of linearity (determination coefficient between 0.989 and 1.00), accuracy (recovery between 94.3% and 107.2%) and precision (RSD ≤ 5%) was shown for all APIs in all concentrations, except for ceftriaxone 70% (RSD 5.41%), chloroquine 70% (RSD 5.27%) and sulfamethoxazole 100% (RSD 7.52%), that showed the highest standard deviations (see Supplemental Table S4). As mentioned in the section accuracy and precision, the sulfamethoxazole spots were very large and had to be selected manually, resulting in a higher RSD. A similar degree of precision with an overall standard deviation below 5.7% for all 14 APIs was achieved by evaluating plates that contained a range between 60% and 100% of the Minilab standard concentration (see Table 2).

Robustness

The quantitative evaluation of four selected APIs (chloroquine, dexamethasone, hydrochlorothiazide and metformin) was performed under several modified conditions to find out more about the robustness of the method. Table 4 indicates the mean result, the difference in relation to the result obtained under standard conditions and the RSD of different cropping of the TLC plate – with and without pencil labelling on the TLC plate, manual instead of automatic spot detection, non-central position of the UV lamp, low battery charge of the UV lamp resulting in more intensely coloured green background of the plates, usage of another box (build by Pidinger Werkstätten) and another smartphone (Fairphone 3). The RSD of the results obtained under modified conditions was below 4.0% and the differences between the mean results obtained under standard conditions compared to the modified conditions was below 4.7%. This shows that the evaluation with the app and the imaging box remained unaffected by all tested modifications during the measurements. The highest mean RSD (3.99%) was observed when the UV lamp was not in a central position. Using the box from

Pidinger Werkstätten showed the lowest RSD (1.37%) and very similar results (difference <2%) compared to the results obtained with the imaging box used for the validation process. Different cropping of the TLC plate also led to comparable results and showed a similar or the identical RSD (2.17% and 2.52%). Remarkably, manual instead of automatic spot selection did not lead to inaccurate or less precise results (difference < 3%, RSD 2.65%), as was observed with the large sulfamethoxazole spots, if five spots are place one plate. Individual results are shown in Supplemental Table S4.

Table 4: Modifications in the evaluation process to assess the robustness of the method.
The mean results and RSDs obtained under standard condition (described in the section practical procedure of the image analysis process) and under the indicated modified conditions are shown for the specified APIs, as well as the difference between the mean result obtained under standard conditions and modified conditions. The average RSD for each modification calculated from the RSD of the four APIs is also indicated.

Modification	API	Mean (target conc. 90%) (n=6) [%]	Difference modification and standard condition [%]	RSD of respective API (n=6) [%]	Mean RSD of the four APIs [%]
Standard condition	Chloroquine	92.1		2.67	2.17
	Dexamethasone	89.1		2.12	
	Hydrochlorothiazide	93.1		1.12	
	Metformin	89.3		2.75	
Cropping: full plate with labelling	Chloroquine	93.7	1.6	1.81	2.17
	Dexamethasone	91.9	2.9	3.31	
	Hydrochlorothiazide	93.3	0.2	2.12	
	Metformin	90.7	1.4	1.44	
Cropping: without labelling	Chloroquine	91.5	-0.6	3.63	2.52
	Dexamethasone	88.9	-0.1	2.42	
	Hydrochlorothiazide	91.8	-1.3	1.82	
	Metformin	89.0	-0.3	2.22	
Manual spot detection	Chloroquine	93.7	1.6	1.84	2.65
	Dexamethasone	91.9	2.9	3.51	
	Hydrochlorothiazide	92.6	-0.4	3.57	
	Metformin	89.8	0.5	1.66	
UV lamp not central	Chloroquine	92.4	0.3	4.51	3.99
	Dexamethasone	93.2	4.2	4.39	
	Hydrochlorothiazide	92.9	-0.2	5.07	

	Metformin	89.4	0.1	2.00	
Low battery charge of UV lamp	Chloroquine	89.3	-2.8	1.08	3.04
	Dexamethasone	87.7	-1.4	2.36	
	Hydrochlorothiazide	88.5	-4.6	5.11	
	Metformin	90.9	1.7	3.63	
Different box (from Pidinger Werkstätten)	Chloroquine	90.4	-1.7	1.97	1.37
	Dexamethasone	89.7	0.6	1.29	
	Hydrochlorothiazide	91.2	-1.9	1.06	
	Metformin	89.8	0.5	1.16	
Different smartphone for photo and analysis (Fairphone 3)	Chloroquine	88.2	-4.0	2.90	2.88
	Dexamethasone	89.5	0.4	2.86	
	Hydrochlorothiazide	89.4	-3.7	2.82	
	Metformin	90.4	1.1	2.95	

Field utility

The enhanced screening tool consists of the ready-to-use Minilab kit, a portable imaging box and a smartphone with the installed TLCyzer app. The GPHF Minilab itself is successfully used in the field since many years and was already evaluated in a technology review by the U.S. Pharmacopeial Convention.[23] Apart from the box and a smartphone with a rear facing camera, no additional consumables or standards are necessary, if the Minilab is already available on site. Different parameters concerning the handling and usability of the imaging box and the smartphone (app), also in field settings were evaluated. Once the app is installed on the smartphone, no internet connection is necessary for the evaluation of the TLC plates. Power supply is not required if the smartphone is charged and if batteries for the UV lamp are available. The design of the developed wooden box is stable, user-friendly and simple to enable a construction of the box also in resource constrained settings. The wooden box was replicated by a carpenter in Zimbabwe according to our plans at a cost of 36 US$ which showed that production on site is possible also to an affordable price. Photos of this box can be found in the Supplemental Figure S6. The box we used within the scope of the robustness evaluation can be purchased from Pidinger Werkstätten for 69 € (photos see Supplemental Figure S5). This box was also built according to our construction plan (see Supplemental Figure S1) and is made of birch, painted with a matt black paint and the lid is glued together using a waterproof adhesive. It is stable to changes in temperature and humidity, tolerant to dust, light and rough handling and therefore well suited for field settings. A similar preliminary construction of this box was already successfully used in a medicine quality study conducted in the DRC and Cameroon in 2017 and 2018.[15] In this study the box was used to provide a dark environment for the spot detection

and to take photos for evaluation and photographic documentation. These photos were also sent to Tübingen University for verification of the results.

The training requirements of the app were evaluated through a short online workshop. After the online teaching the participants were able to independently evaluate two photos with the app on their own smartphones. Each photo was evaluated twice by the nine participants to obtain four results for every TLC plate. The RSD of the 36 results obtained by nine different operators and smartphones for one photo was 2.17% and 7.48%, respectively. Individual results are shown in Supplemental Tables S5. The variance between different smartphone cameras and a different replicate of the box was already evaluated in the robustness section.

We analysed ciprofloxacin, dexamethasone, hydrochlorothiazide and metronidazole tablets purchased from the dispensary in Tübingen as well as substandard metronidazole and ciprofloxacin tablets collected in DRC.[15] TLC plates with three reference spots, as prepared for the validation procedure and plates with only two reference spots (100% and 80%), as indicated in the Minilab manual were prepared. The individual analysis results shown in Supplemental Table S6 indicate that the quantitative evaluation with the TLCyzer app, which was validated with certified reference standards is also applicable to FPP. For each sample and spotting pattern 12 results were obtained. The SD of the 12 determinations was between 2.50% and 4.10% (mean 3.25%). Irrespective of the spotting pattern, the app was able to "differentiate" between substandard metronidazole and ciprofloxacin tablets from DRC with a content between 80% and 90% and the tablets showing good quality: the mean result of the evaluation with the app for the good quality tablets was 97.2% (mean SD 3.39%) whereas the mean result for the substandard ciprofloxacin tablets was 84.1%; SD 3.70% (HPLC analysis 83.4%) and for the substandard metronidazole tablets 85.1%; SD 3.27% (HPLC analysis 86.7%), including the results of both spotting patterns.

Discussion

Our results show that an enhanced sample quantification of TLC analysis performed with GPHF Minilab methods and evaluated with an inexpensive smartphone-based imaging algorithm is possible. We were able to develop a smartphone application that uses an imaging software to evaluate the intensity of the sample spots. Based on the cradle published by Yu et al.,[37] a simple constructed wooden box was developed that provides a fixed setup for a UV lamp, the TLC plate and a smartphone with a rear facing camera.

There is still a lack of studies that evaluate the field readiness, utility and training requirements of different screening tools. More research is needed to provide information for organizations and

national medicines regulatory authorities on the suitability, training costs and the range of medicines that can be evaluated.[7, 9] As suggested by Roth et al. we therefore addressed critical questions regarding the utilization of this screening tool using the recommendation on screening technologies developed by an USP expert panel consisting of professionals from regulatory agencies, the pharmaceutical industry, academia and non-governmental organizations.[9] We followed the structure of the USP technology review to evaluate the capability of this app and imaging box and provided general information on the technology, a laboratory-based technical performance evaluation and several pre-tests to assess the field utility of the method, including the evaluation by different operators, smartphones and imaging boxes. The necessary level of training was examined as well as the capability to identify good quality samples and substandard samples, collected in DRC.

We were able to show that the quantification of 14 different APIs with the TLCyzer app showed accurate and repeatable results (recovery of individual results between 93.4% and 107.9%; precision between 0.77% and 5.68%). According to the Minilab manual trimethoprim and atenolol, both APIs that show weak spots on the TLC plate, should additionally be exposed to iodine vapour for spot identification and quantification.[25] However, by using the smartphone app, we were able to obtain accurate and repeatable results for the quantitative evaluation under UV light (mean recovery 98.3% and 102.2%; precision 2.48% and 2.33%, respectively). The results of the intermediate precision using a matrix design showed for all APIs, except sulfamethoxazole, an acceptable level of precision (RSD ≤5%) when comparing photos from different days, evaluated by different operators with different smartphones. As aforementioned, the sulfamethoxazole spots were too close to each other and therefore manual selection of the very large spots was necessary, which was less accurate and requires additional training. However, this problem did not occur when we placed four instead of five spots are placed on the TLC plate (mean recovery 95,7%, RSD <5%). These results indicate that the app enables a more objective assessment of the spots and thus more reliable results in contrast to the visual evaluation of Minilab TLC plates that depends very much on the experience, the observation skills, and the visual acuity of the user. Spots containing 90% were reliably identified as "compliant" by the app, i.e. the app displayed a result above 80%, and spots containing 70% were correctly identified as "non-compliant", i.e. a result below 80% was calculated by the app. This improved quantification could vastly increase the reliability of the Minilab identifying substandard medicines that contain 20% or less of the declared amount. Through the increase in selectivity, the number of samples forwarded to a fully equipped laboratory for confirmatory analysis will be reduced, thereby saving costs.[9] Several medicine quality studies have shown that the substandard samples contained in many cases between 80% and 90% of the declared API. [15, 28, 44] According to the Minilab, spots representing 85% of the stanrad solution are considered as "compliant". With the

611 TLCyzer app it was possible to obtain results between 80% and 90% for these spots (see Table 2).
612 Further investigations with substandard samples may show if it is worthwhile to subject samples that
613 show a result between 80% and 90% to an additional analysis. As aforementioned, the Minilab is a
614 screening tool and cannot replace pharmacopeial analysis. Furthermore, it should be noted that
615 according to commonly used pharmacopoeias, such as the International Pharmacopoeia (Ph. Int.),
616 the USP or the British Pharmacopoeia (BP) the tolerance limits differ considerably for different APIs
617 in FPP,[16] e.g. in the USP 42 they range between 95-105% and 90-120% for the APIs investigated.
618 Therefore, the introduction of a stricter and API-independent tolerance limit of screening tools, i.e.
619 narrower than 80% may be problematic as this is not compatible with pharmacopeial specification.
620 All 14 APIs showed a linear relationship between the concentration of the API and the results
621 determined with the app within the range of 50% to 120% of the Minilab standard solution
622 (coefficient of determination R^2 between 0.989 and 1.00). This area is considered as an acceptable
623 working range of the app for the investigated 14 APIs (recovery between 94.3% and 107.2%; RSD
624 ≤5%, not including the sulfamethoxazole 100% spots). Trimethoprim and sulfamethoxazole could still
625 be successfully quantified if applied in a concentration containing 12% of the Minilab standard
626 solution. This indicates that the app may even be used for the quantification of lower API amounts.
627 Within the scope of the robustness evaluation the analysis was performed under several modified
628 conditions. Different cropping of the TLC plate including and not including the labelling, a different
629 position and low charge of the UV lamp, usage of another box and smartphone did not affect the
630 result of the analysis, showing a mean difference from the results obtained with the standard
631 procedure below 4.7%. It was observed that the position of the UV lamp had the biggest influence on
632 the result, showing a RSD of 3.99%, if the lamp is not in a central position. The position of the UV
633 lamp should therefore always be checked before the photo is taken. Besides, it was shown that very
634 similar results were obtained with the photos taken in the box from Pidinger Werkstätten (difference
635 ≤2%; RSD 1.37%).
636 As already indicated in the current Minilab manual, the Minilab may in future be equipped with a
637 smartphone and a software application that improves the semi-quantitative evaluation and also the
638 reporting and transfer of data.[25] The developed TLCyzer app and the constructed box are well suited
639 for resource limited field settings and there are no major costs associated with this enhancement to
640 the Minilab analysis. The box can either be built by a local carpenter even in resource limited settings
641 or purchased from the indicated workshop (Pidinger Werkstätten). A construction plan for the
642 imaging box, photos of a wooden box built by a carpenter in Zimbabwe according to our plans as well
643 as photos of the boxes used for the validation can be found in the Supplemental information
644 (Supplemental Figure S1, S5 and S6). From our experience it is important that as little light as
645 possible enters the box from outside to achieve the most reliable analysis results. In particular, the

opening for the UV lamp should not be much larger than necessary to push the UV lamp easily in and out.

We have chosen a smartphone in the low-price range (Motorola Moto G7) for the validation of the app with a 12 MP camera. Besides the chemicals, additional consumables and reference standards that come with the Minilab, no database or further calibration procedures are required. The TLCyzer app will be offered free of charge in Google Play store F-Droid. The file of the evaluated phots can be stored at the smartphone, on a computer or other devices and may also be transferred between different devices as ZIP file by using an app to share them, sending them by e-mail or uploading them to a cloud. This enables a very easy exchange of photos and analysis results as well as a re-evaluation of photos and serves additionally as a photographic documentation of TLC plates and results. According to our experience, the brand and model of the smartphone has no significant influence on the result of the analysis, and it is therefore also possible to use another or even different smartphones to perform the analysis. We were able to show, that the use of different smartphones for the analysis as well as different operators conducting the analysis with the app, led to comparable results (see intermediate precision: mean RSD 4.46%). Besides it was shown that the photos taken and evaluated with another smartphone camera (Fairphone 3, camera 12 MP) showed similar results (see robustness: RSD 2.88%, difference ≤4%). The analysis is insusceptible to plate-to-plate variations because the corresponding reference spots is always included on the TLC plate and is developed and exposed to UV light in the same way as the sample spot. Different smartphone cameras, boxes and operators are therefore not a crucial factor in the evaluation of samples. This is an important advantage of the app also in comparison to other screening tools that use libraries that store the characteristic information of a reference and must be routinely updated when new generics of medicines or different APIs want to be analysed.[11]

For healthcare professionals in the management of medicine quality control, who are familiar with the Minilab methods the additional training required to use the app is minimal. However, training is crucial for the usage of the Minilab and the TLCyzer app and it was also shown more practical experience and additional training leads to more reliable results with the Minilab.[23, 28] We were able to show that training with the app can also be provided online. A short online training of 45 minutes was sufficient to teach pharmacy students and pharmacist the handling of the app as they were afterwards able to practise on their own and carry out the analysis of two plates (furosemide and chloroquine) without further assistance using their private smartphone.
The results of this test show however that the accuracy of the individual results was in parts relatively low (recovery between 74% and 105%; mean 96.9%) showing a RSD of 2.17% and 7.48% for

the two plates, respectively (n=33), see Supplemental Table S5. This low recovery rate possibly resulted from an inaccurate selection of the TLC platte (see instruction in Supplemental Figure??) Even though not only one, but three different photos of the same TLC plate were included in the evaluation of intermediate precision, the degree of recovery for individual results ranged between 84.9% und 113.7% (mean 100.3%) showing a RSD ≤5% (n=24); not including the manual detection of sulfamethoxazole spots (see Supplemental Table S2). Two additional operators were involved in the evaluation - both pharmacy students that took part in the workshop followed by some additional practice with 15 test TLC plates. That indicates that even a small amount of additional practice has a positive effect and is very effective to obtain more reliable and precise results.

Careful preparation of the reference and sample solutions as well as careful spotting on the TLC plate with the microcapillary pipette is essential when preparing TLC plates for quantitative evaluation. As emphasised by the USP Technology Review of the GPHF Minilab, the manual should be closely followed to avoid dilution errors that could result in samples being incorrectly declared non-compliant.[23] For the detection of the spots, it is important, that they are not too close to the edge of the TLC plate and not too close to each other. This can more easily be achieved if four spots, as indicated in the Minilab methods, are spotted on one plate instead of five spots. Therefore, we recommended to use only an 100% and 80% reference spot for the preparation of the plates. The USP Technology Review also recommends the application of four instead of five spots to reduce interpretation issues and to make sure that spots near the sides, which can differ in shape and distance are correctly interpreted.[23] The UV fluorescence of the TLC plates is masked if they are not completely dry and they should always be dried in the same way.[23] We recommend air drying for a minimum of 30 minutes to ensure that the plates are completely dry and to obtain uniform results, also in the case that electricity is not available on site. The developed TLC plates can change their colour, especially when exposed to light and humidity. Therefore, we recommend storing the TLC plates in a cool, dry place protected from light and performing the evaluation with the smartphone app within three days after the analysis with the Minilab.
Before concluding non-compliance of a sample, it is advisable to repeat the TLC plate evaluation with the app and to take care that the plate recognition is done properly, e.g. without including black parts from the background. As aforementioned, it should also be ensured, that the UV lamp is positioned central when taking the photos of the plate in the box. The Minilab manual even suggested that non-compliance has to be observed in three independent experiments.[25]

Ciprofloxacin, dexamethasone, hydrochlorothiazide and metronidazole tablets from the dispensary in Tübingen were identified as “compliant” according to the Minilab classification by the app, i.e.

showing results between 88.3% and 106.7% (mean 97.2%). We analysed also substandard ciprofloxacin and metronidazole tablets from DRC, containing 83.4% and 86.7% of the stated content. The same ciprofloxacin and metronidazole samples were also examined in DRC after collection and were not found to be suspicious as they passed the visual Minilab TLC test (as well as the disintegration test).[15] This is not surprising, as the Minilab was not developed to detect a deviation of less than 20% from the stated content.[25] However, 23 of the 24 result obtained with the smartphone app for theses samples showed values below 90% and above 80% for these sample – irrespective of the applied spotting pattern, see Supplemental Table S6. These results indicate that it may be worthwhile to subject samples that show a result between 80% and 90% to further analysis, first a repetition of the Minilab and TLCyzer evaluation and, if the result remains the same, a subsequent analysis in a fully equipped laboratory for pharmacopeial analysis. We recently initiated a collaborative medicine quality study in Nigeria that includes the Minilab in combination with the TLCyzer app and the imaging box for field testing of medicines. Within this study we want compare the results obtained by our partners in Nigeria using the TLCyzer app with the results obtained through pharmacopeial analysis at Tübingen University using the USP. We hope to get a deeper insight and more information on the practicability and field-suitability of the technology. The training effectiveness of the workshops we provided for our partners in Nigeria online - due to Covid-19 travel restrictions - will also be further investigated.

Through this cooperation, we will also obtain more information concerning the reliability of the app to identify substandard samples that contain less than 20% of the declared content and between 80% and 90% of the stated content.

With the Minilab a very broad range of different APIs in different formulations (solid FPP as well as injections) can be analysed. The evaluation with the developed app is probably also applicable for more APIs than the 14 investigated, as most of the 102 APIs in the Minilab quench the fluorescence of the TLC plates when exposed to 254nm. Our findings show that even samples with fixed dose combinations can be analysed with the developed app.

The combination of the Minilab with the developed app will help to empower medicine inspectors to identify not only falsified medicine with no API or the wrong API, but also more reliably medicines that contain less than 20% of the declared amount. Screening tools are essential for the detection of substandard and falsified medicines in LMICs and are fundamentally important to help achieving universal health coverage and access to safe, effective, quality and affordable essential medicines, as indicated in target 3.8 of the Sustainable Development Goals.[45] We hope to contribute with our developed app and imaging box to an enhanced quantitative evaluation of TLC plates and to a more reliable, fast, simple and also low-cost detection of SF medicines.

However, our findings obtained from solutions of certified reference materials and a small set of FPP can only serve as a proof of concept. By making the smartphone algorithm and the schemes of the imaging box publicly available and free of charge, we want to encourage current Minilab users to test our setup in the field on real medicine samples. In addition, the developed TLCyzer app can be updated to allow adaption to further APIs and to add further functions to the app.

Limitations of this study

The app is only suitable for quantification purposes therefore the identity of the sample must be confirmed first. To assess the identity, the Minilab indicates to check if the spots of the sample correspond in colour, size and intensity, shape and travel distance to the spots of the reference standard.[25]

The procedure is a proof of concept that was so far only demonstrated and validated for 14 APIs included in the Minilab. However, the majority of the 102 essential APIs included in the Minilab show visible spots under UV light of 254nm and it might be worthwhile to expand the number of APIs to assess the versatility of the developed app. So far only two substandard medicine samples were tested with the app and the applicability of the app in the field will need to be demonstrated with more real samples in a field set-up. Therefore, we hope to get more practical experience during the planned medicine quality study in Nigeria, that will test the field suitability of the app.

Acknowledgements

We are grateful to the workshop of Tübingen University for the construction of a wooden imaging box, Pidinger Werkstätte for the preparation of a second imaging box that is now commercially available, Christa Zeller for ordering and delivering a box from Zimbabwe and Yvonne Wiedemann, Jonas Geywitz, Gesa Gnegel, Julia Gabel and the participants of the Pharmacy in Global Health Course in Tübingen for their contribution to the evaluation of TLC plates.

Financial Support

This study was founded by the Eberhard Karls University Tübingen.

Disclosures:

The authors declare no conflict of interest.

Authors' addresses

Cathrin Hauk, Simon Schäfermann, Lutz Heide: Pharmaceutical Institute, Eberhard Karls University, Tübingen, Germany. cathrin.hauk@uni-tuebingen.de; simon.schaefermann@t-online.de, heide@uni-tuebingen.de

Mark Boss, Hendrik Lensch: Computer Graphics, Faculty of Science, Eberhard Karls University, Tübingen, Germany. mark.boss@uni-tuebingen.de, hendrik.lensch@uni-tuebingen.de

Figure legends

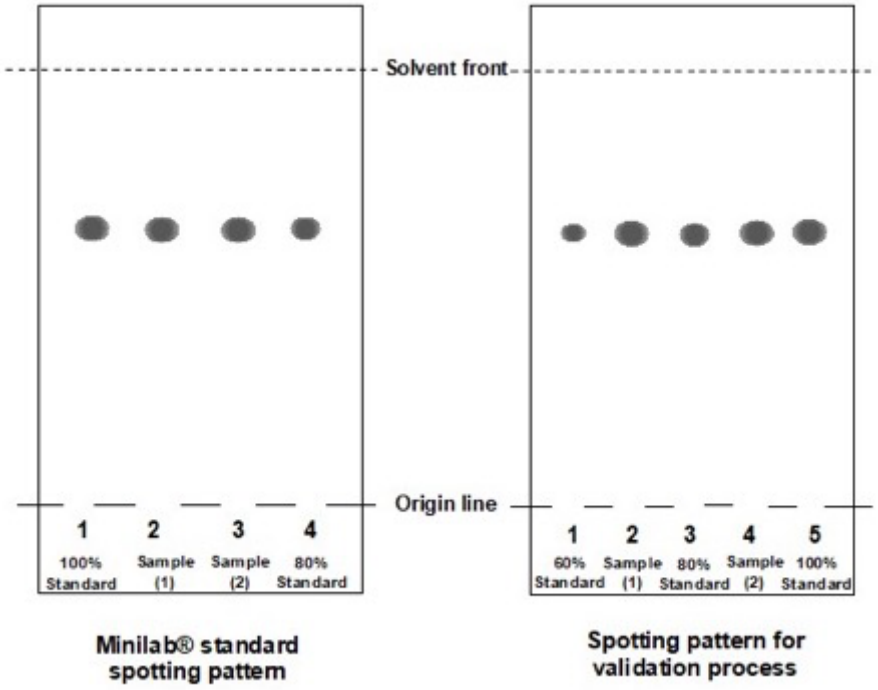


Figure 1: Comparison of the spotting pattern indicated in the Minilab manual (left) and the spotting pattern used for the validation processes with an additional 60% reference standard (right)

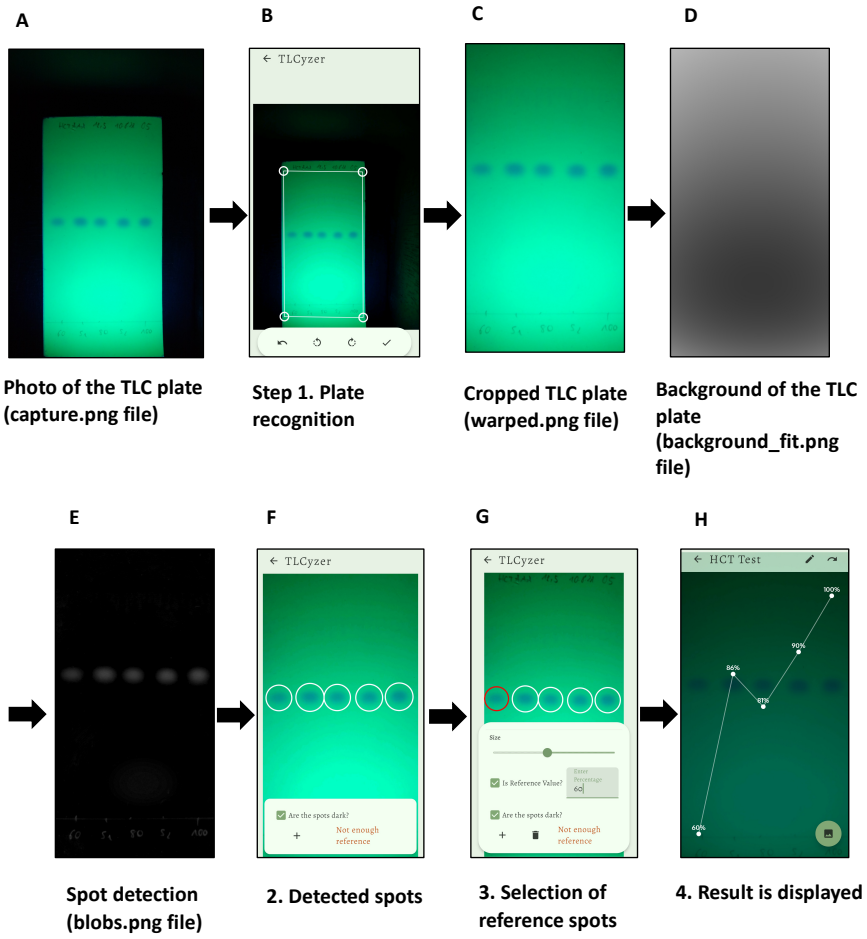


Figure 2: Multi-stage capture and processing pipeline of the TLC plate in the TLC imaging application. The TLC plate is photographed (**A**) and the outlines of the plate are recognized, perspectively warped, and cropped (**B, C**). The background is then fitted on the result and removed from the grayscale input (**D**). The result leaves only the blobs, which are detected by thresholding and connected component analysis (**E**). The now detected spots (**F**) are then integrated, and a reference value is applied to each spot (**G**). By fitting a linear function, the remaining unknown percentages are evaluated (**H**).

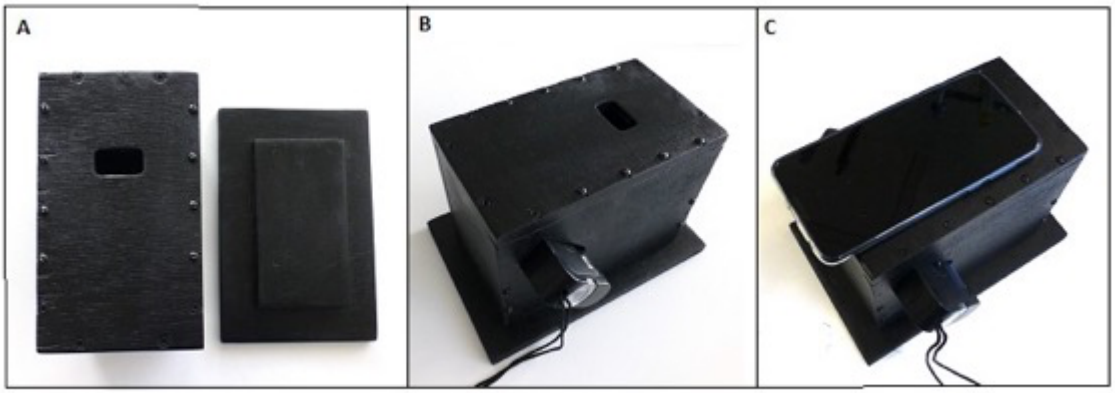


Figure 3: Overview of the TLC-imaging box. (A) The wooden box consists of a lid that provides a dark environment and a bottom plate where the position for the TLC plate is marked. **(B)** Assembled box with the UV lamp. **(C)** TLC imaging box in use with a smartphone, which is placed on top of the box with the smartphone camera above the camera slit.

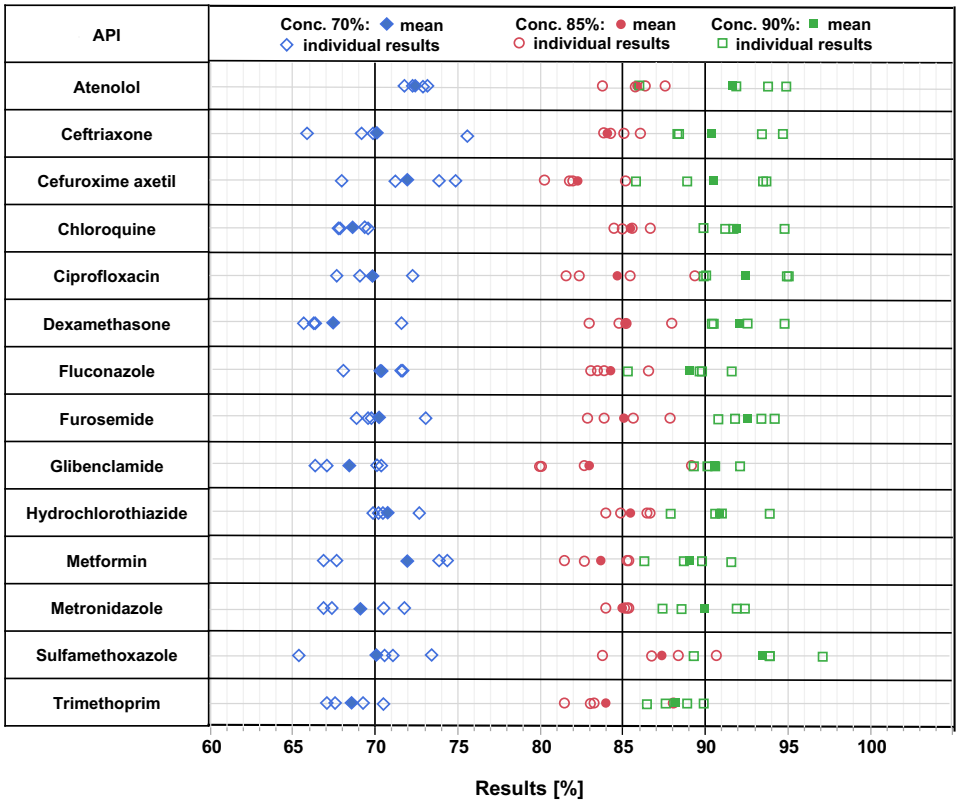


Figure 4: Individual results determined with the imaging algorithm for the evaluation of accuracy and repeatability. For each API and concentration (70%, 85% and 90%) two TLC plates with two sample spots were prepared and evaluated. The individual results and the mean results are depicted.

References

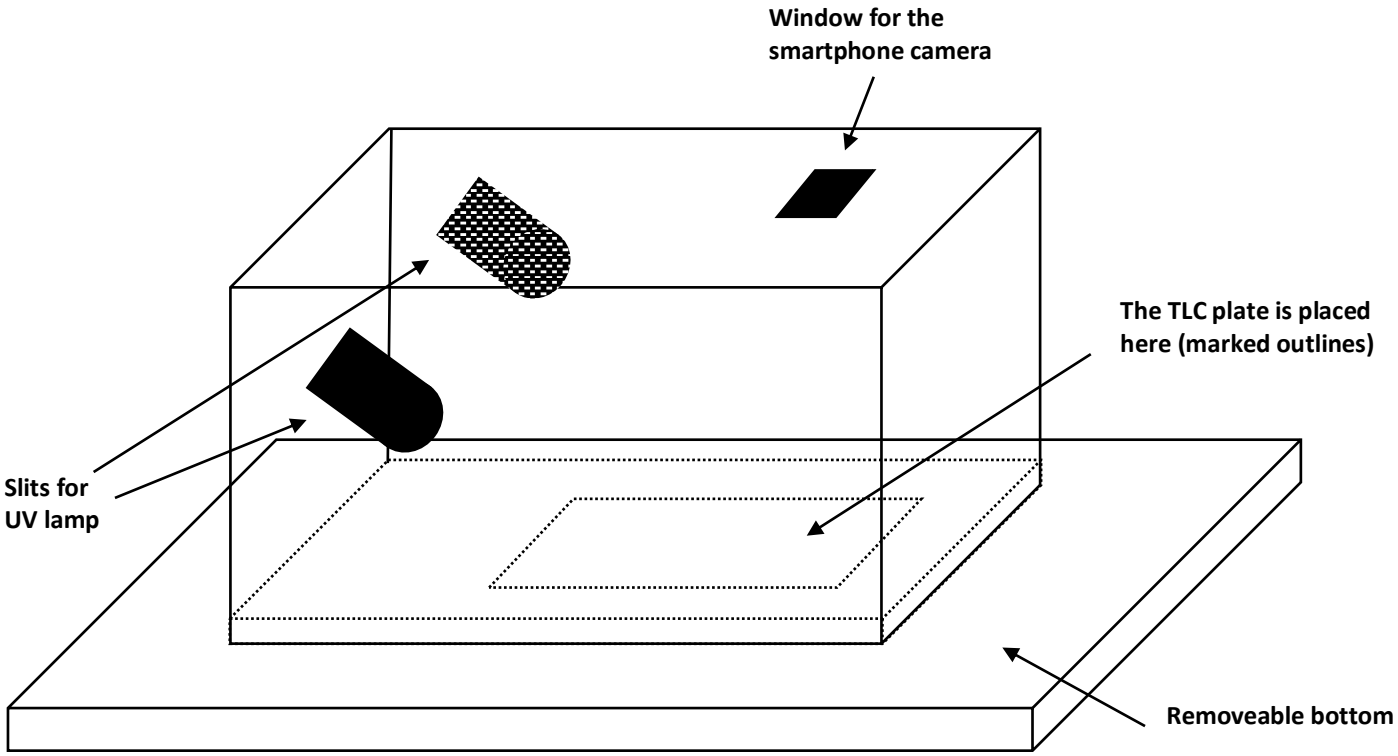
1. WHO, 2017. A study on the public health and socioeconomic impact of substandard and falsified medical products. Available at: https://apps.who.int/iris/bitstream/handle/10665/331690/9789241513432-eng.pdf?sequence=1&isAllowed=y. Accessed September 22, 2021.
2. UNODC. Combating falsified medical product-related crime: a guide to good legislative practices. Vienna: United Nations Office on Drugs and Crime; 2019. Available from: https://www.unodc.org/documents/treaties/publications/19-00741_Guide_Falsified_Medical_Products_ebook.pdf.
3. Petersen A, Held N, Heide L, Difäm - EPN Minilab Survey Group, 2017. Surveillance for falsified and substandard medicines in Africa and Asia by local organizations using the low-cost GPHF Minilab. *PLoS One 12(9)*:e0184165.
4. Lalani M, Kitutu FE, Clarke SE, Kaur H, 2017. Anti-malarial medicine quality field studies and surveys: a systematic review of screening technologies used and reporting of findings. *Malar J 16(1)*:197.
5. WHO. WHO Global Surveillance and Monitoring System for substandard and falsified medical products. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/handle/10665/326708.
6. Risha PG, Msuya Z, Clark M, Johnson K, Ndomondo-Sigonda M, Layloff T, 2008. The use of Minilabs to improve the testing capacity of regulatory authorities in resource limited settings: Tanzanian experience. *Health Policy 87(2)*:217-222.
7. Vickers S, Bernier M, Zambrzycki S, Fernandez FM, Newton PN, Caillet C, 2018. Field detection devices for screening the quality of medicines: a systematic review. *BMJ Glob Health 3(4)*:e000725.
8. Chen HH, Higgins C, Laing SK, Bliese SL, Lieberman M, Ozawa S, 2021. Cost savings of paper analytical devices (PADs) to detect substandard and falsified antibiotics: Kenya case study. *Med Access Point Care 5*.
9. Roth L, Biggs KB, Bempong DK, 2019. Substandard and falsified medicine screening technologies. *AAPS Open 5(1)*:2.
10. USP. <1850> Evaluation of Screening Technologies for Assessing Medicines Quality. USP 42-NRF 38. Rockville, MD: United States Pharamcopeial Convention; 2020.
11. Kovacs S, Hawes SE, Maley SN, Mosites E, Wong L, Stergachis A, 2014. Technologies for Detecting Falsified and Substandard Drugs in Low and Middle-Income Countries. *PLoS One 9(3)*:e90601.
12. IDDO, 2018. An evaluation of portable screening devices to assess medicines quality for national Medicines Regulatory Authorities. Available at: https://www.iddo.org/external-publication/evaluation-portable-screening-devices-assess-medicines-quality-national. Accessed September 22, 2021.
13. Bakker-'t Hart IME, Ohana D, Venhuis BJ, 2021. Current challenges in the detection and analysis of falsified medicines. *J Pharm Biomed Anal 197*:113948.
14. Schiavetti B, Wynendaele E, Melotte V, Van der Elst J, De Spiegeleer B, Ravinetto R, 2020. A simplified checklist for the visual inspection of finished pharmaceutical products: a way to empower frontline health workers in the fight against poor-quality medicines. *J Pharm Policy Pract 13*:9.
15. Schäfermann S et al., 2020. Substandard and falsified antibiotics and medicines against noncommunicable diseases in western Cameroon and northeastern Democratic Republic of Congo. *Am J Trop Med Hyg 103(2)*:894-908.

16. Hauk C, Hagen N, Heide L, 2021. Identification of substandard and falsified medicines: influence of different tolerance limits and use of authenticity inquiries. *Am J Trop Med Hyg 104(5)*:1936-1945.
17. Batson JS, Bempong DK, Lukulay PH, Ranieri N, Satzger RD, Verbois L, 2016. Assessment of the effectiveness of the CD3+ tool to detect counterfeit and substandard anti-malarials. *Malaria Journal 15(1)*:119.
18. Rasheed H, Höllein L, Holzgrabe U, 2018. Future information technology tools for fighting substandard and falsified medicines in low- and middle-income countries. *Front Pharmacol 9*:995.
19. EMA, 2017. EMA/785582/2014 rev.2: Implementation plan for the introduction of the safety features on the packaging of centrally authorised medicinal products for human use. Available at: https://www.ema.europa.eu/en/documents/other/implementation-plan-introduction-safety-features-packaging-centrally-authorised-medicinal-products_en.pdf. Accessed August 16, 2021.
20. Oyetunde OO, Ogidan O, Akinyemi MI, Ogunbameru AA, Asaolu OF, 2019. Mobile authentication service in Nigeria: An assessment of community pharmacists' acceptance and providers' views of successes and challenges of deployment. *Pharm Pract (Granada) 17(2)*:1449.
21. Myers NM, Kernisan EN, Lieberman M, 2015. Lab on paper: iodometric titration on a printed card. *Anal Chem 87(7)*:3764-3770.
22. Global Pharma Health Fund e.V. The GPHF-Minilab™ [Available from: https://www.gphf.org/en/index.htm.
23. U.S. Pharmacopeial Convention. USP Technology Review: Global Pharma Health Fund (GPHF) - Minilab™. Technology Review Program Rockville, MD; 2020.
24. Newton PN, Caillet C, Guerin PJ, 2016. A link between poor quality antimalarials and malaria drug resistance? *Expert Review of Anti-infective Therapy 14(6)*:531-533.
25. Jähnke R, Dwornik K. A Concise Quality Control Guide on Essential Drugs and other Medicines. Physikal Testing & Thin-Layer Chromatography. Review and Extensions 2020. 3 ed: Global Pharma Health Fund e. V. (GPHF); 2020.
26. Visser BJ et al., 2015. Assessing the quality of anti-malarial drugs from Gabonese pharmacies using the MiniLab(R): a field study. *Malar J 14*:273.
27. Khuluza F, Kigera S, Jahnke RW, Heide L, 2016. Use of thin-layer chromatography to detect counterfeit sulfadoxine/pyrimethamine tablets with the wrong active ingredient in Malawi. *Malar J 15*:215.
28. WHO, 2011. Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. Available at: http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf. Accessed September 22, 2021.
29. Pan H, Ba-Thein W, 2018. Diagnostic accuracy of Global Pharma Health Fund Minilab in assessing pharmacopoeial quality of antimicrobials. *Am J Trop Med Hyg 98(1)*:344-348.
30. Kaale E, Risha P, Layloff T, 2011. TLC for pharmaceutical analysis in resource limited countries. *J Chromatogr A 1218(19)*:2732-2736.
31. Pribluda VS et al., 2012. Implementation of basic quality control tests for malaria medicines in Amazon Basin countries: results for the 2005-2010 period. *Malar J 11*:202.
32. Risha P, Msuya Z, Ndomondo-Sigonda M, Layloff T, 2006. Proficiency testing as a tool to assess the performance of visual TLC quantitation estimates. *J AOAC Int 89(5)*:1300-1304.

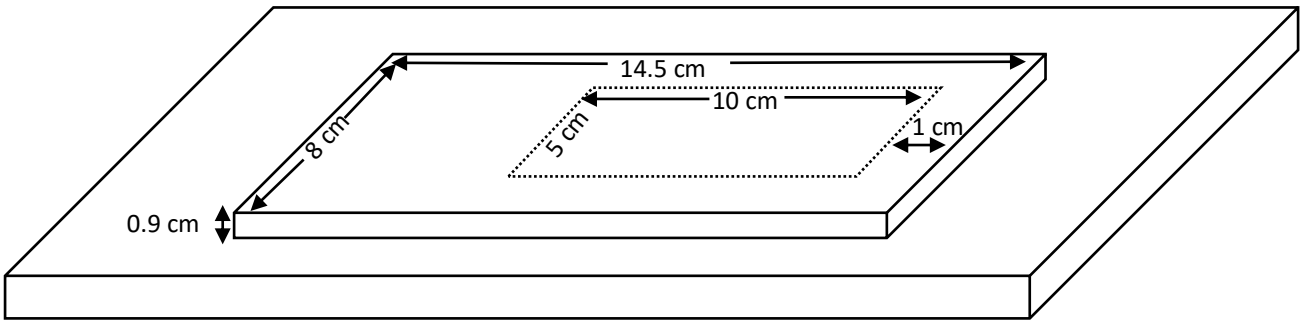
33. Sherma J, Rabel F, 2019. Advances in the thin layer chromatographic analysis of counterfeit pharmaceutical products: 2008–2019. *J Liq Chromatogr Relat Technol 42(11-12)*:367-379.
34. Sherma J, 2000. Planar Chromatography. *Anal Chem 72(12)*:9-26.
35. Shewiyo DH, Kaale E, Risha PG, Dejaegher B, Smeyers-Verbeke J, Vander Heyden Y, 2012. HPTLC methods to assay active ingredients in pharmaceutical formulations: a review of the method development and validation steps. *J Pharm Biomed Anal 66*:11-23.
36. Tie-xin T, Hong W, 2008. An image analysis system for thin-layer chromatography quantification and its validation. *J Chromatogr Sci 46(6)*:560-564.
37. Yu H, Le HM, Kaale E, Long KD, Layloff T, Lumetta SS, Cunningham BT, 2016. Characterization of drug authenticity using thin-layer chromatography imaging with a mobile phone. *J Pharm Biomed Anal 125*:85-93.
38. Boulgakov AA, Moor SR, Jo HH, Metola P, Joyce LA, Marcotte EM, Welch CJ, Anslyn EV, 2020. Next-generation TLC: a quantitative platform for parallel spotting and imaging. *J Org Chem 85(15)*:9447-9453.
39. Gad A, Fayez Y, Kelani K, Mahmoud A, 2021. TLC-smartphone in antibiotics determination and low-quality pharmaceuticals detection. *RSC Advances 11*:19196-19202.
40. Tosato F, Rosa TR, Morais CLM, Maldaner AO, Ortiz RS, Filgueiras PR, Gomes Lima KM, Romão W, 2016. Direct quantitative analysis of cocaine by thin layer chromatography plus a mobile phone and multivariate calibration: a cost-effective and rapid method. *Anal Methods 8(42)*:7632-7637.
41. ICH, 2005. Validation of analytical procedures: text and methodology Q2(R1). ICH harmonised tripartite guidline. *August 3, 2021*. Available at: http://academy.gmp-compliance.org/guidemgr/files/Q2(R1).PDF. Accessed September 22, 2021.
42. WHO. World Health Organization Model List of Essential Medicines – 22nd List. Geneva: World Health Organization; 2021. Available from: https://apps.who.int/iris/bitstream/handle/10665/345533/WHO-MHP-HPS-EML-2021.02-eng.pdf.
43. Gnegel G, Hauk C, Neci R, Mutombo G, Nyaah F, Wistuba D, Häfele-Abah C, Heide L, 2020. Identification of falsified chloroquine tablets in Africa at the time of the COVID-19 pandemic. *Am J Trop Med Hyg 103*:73 - 76.
44. Schäfermann S, Wemakor E, Hauk C, Heide L, 2018. Quality of medicines in southern Togo: Investigation of antibiotics and of medicines for non-communicable diseases from pharmacies and informal vendors. *PLoS One 13(11)*:e0207911.
45. UN. Sustainable Development Goal 3: Ensure healthy lives and promote well-being for all at all ages: United Nations; 2021 [Available from: https://sdgs.un.org/goals/goal3.

Supplemental Information

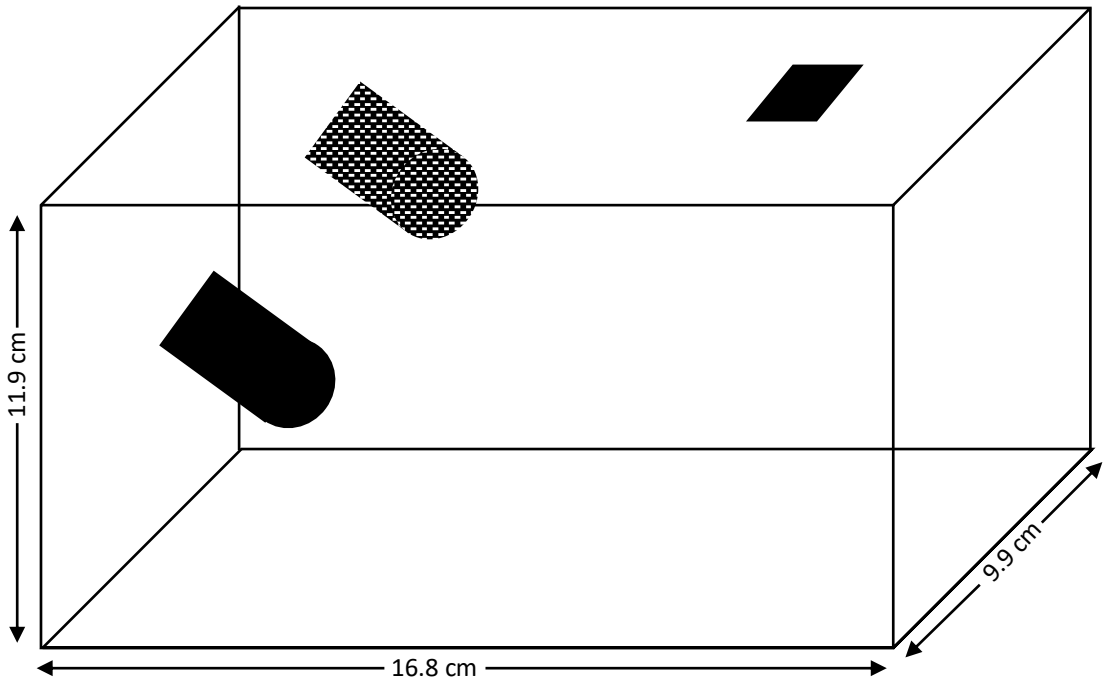
A: Assembled box



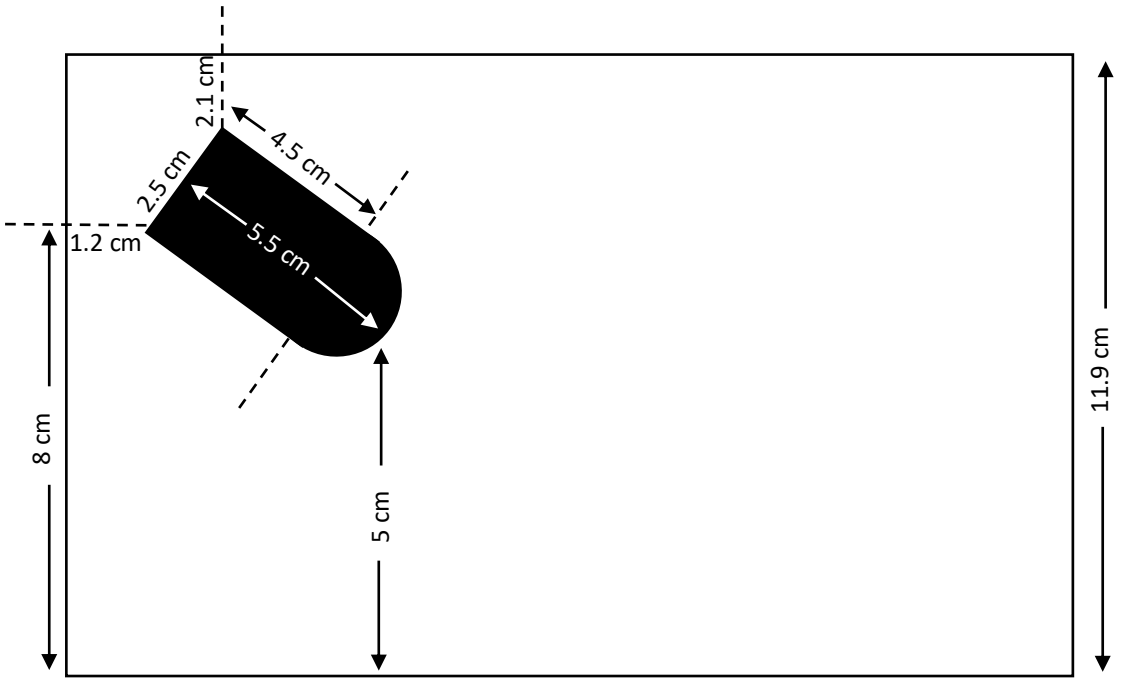
B: Bottom of the box



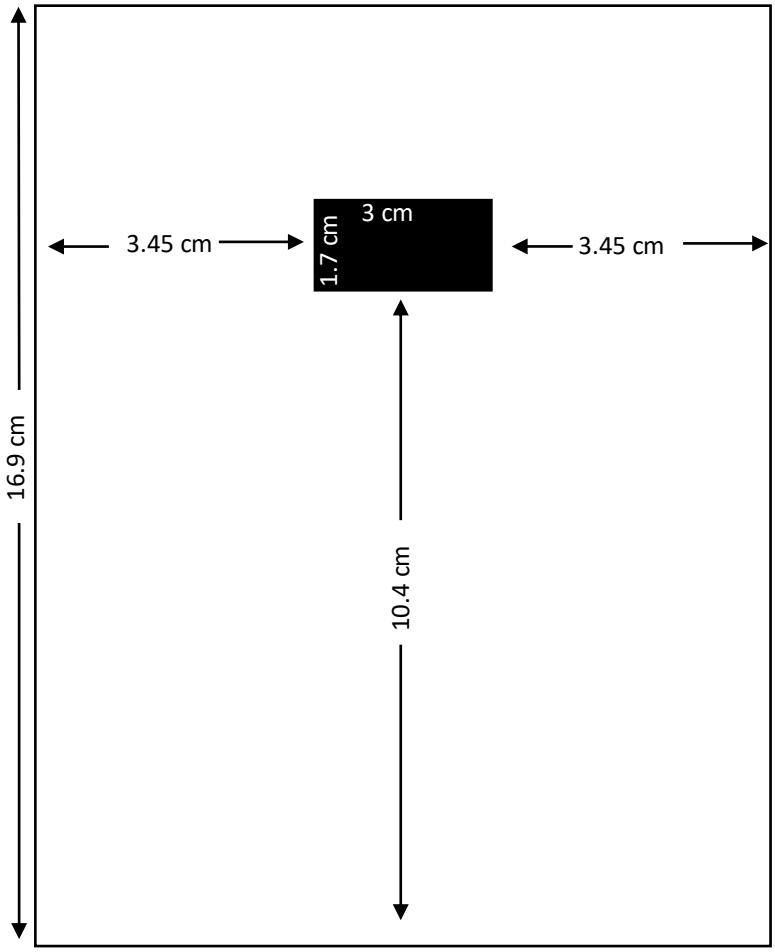
C: Lid of the box



D: Side view of the lid



E: Top view on the box

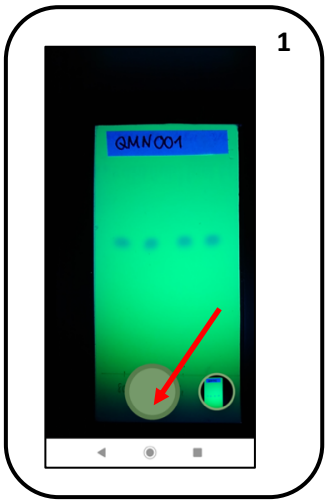


Supplemental Figure S1: Construction plan of the TLC imaging box.
The box is coloured with a black, matt colour to avoid reflections. **(A)** The box consists of a removeable lid and a bottom plate. When the box is assembled, no light penetrates from the sides into the box. The TLC plate is placed on a marked rectangle on the bottom of the box. The smartphone is placed on the lid of the box with the camera above the window. All specified dimensions of the box apply to a box with a wall thickness of approx. 0.9 cm. If boards with a different thickness are used, the dimensions of the box must be adjusted. **(B)** The bottom of the box consists of one piece and has the shape of two cuboids. **(C)** Lid of the box. **(D)** Side view of the lid, showing the position of the slits for the UV lamp. (E) Top view of the box showing the position of the window for the smartphone camera.

What you need:

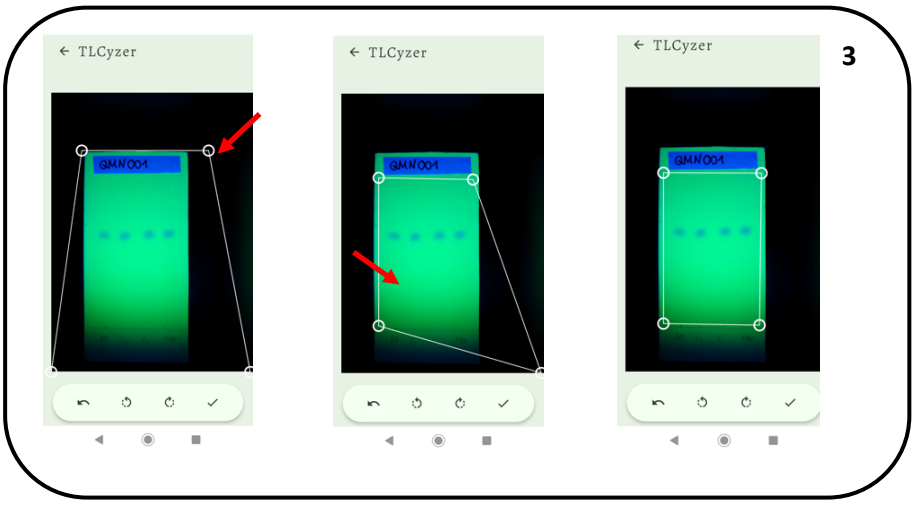
- developed TLC plate
- UV lamp 254nm
- imaging box, as described in Suppl Figure 1
- smartphone with a rear facing camera and the TLCyzer app installed

Before you start:
Put the TLC plate in the box and assemble the box, switch on the UV lamp and start the TLCyzer app on your smartphone.

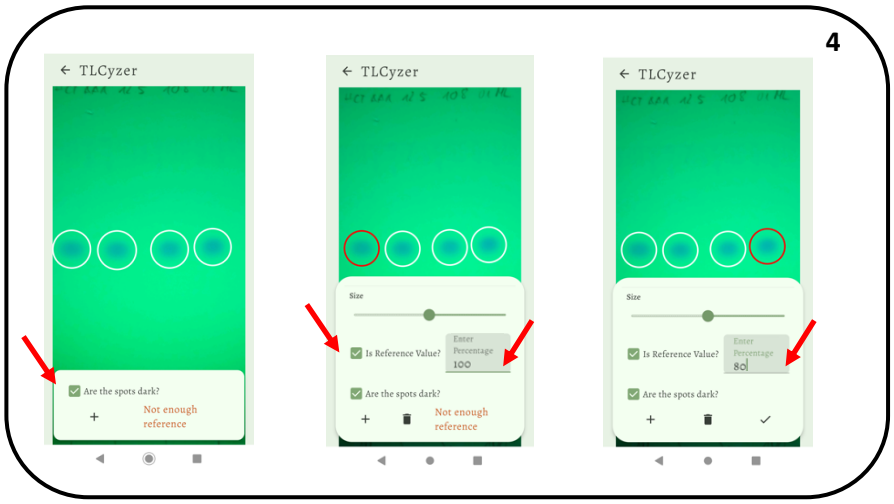


1. After starting the app, the smartphone camera turns on. Take a photo by tapping on the large circle

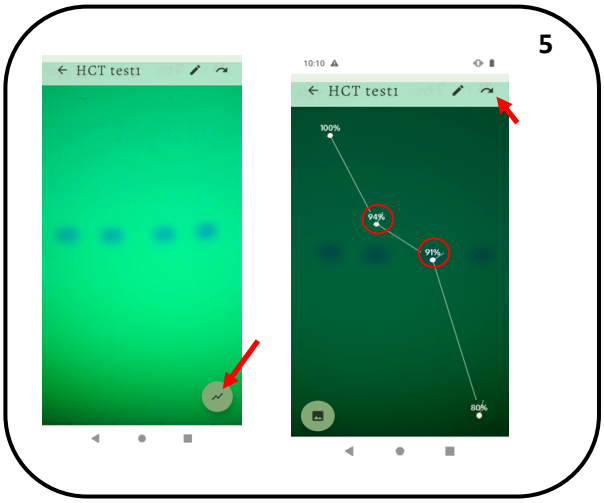
2. Tap on “Set Name”, enter the sample name and tap on “Save”..



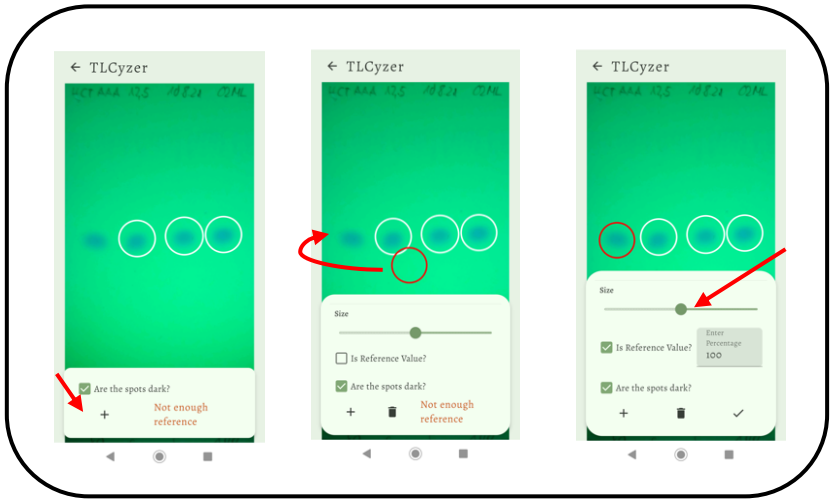
3. If the outlines of the plate are not correctly recognized by the app, you have to set them manually.
The four adjustable corner points can be used to set the correct outlines of the plate. Make sure that the selected rectangle only contains the plate and no parts of the black background.



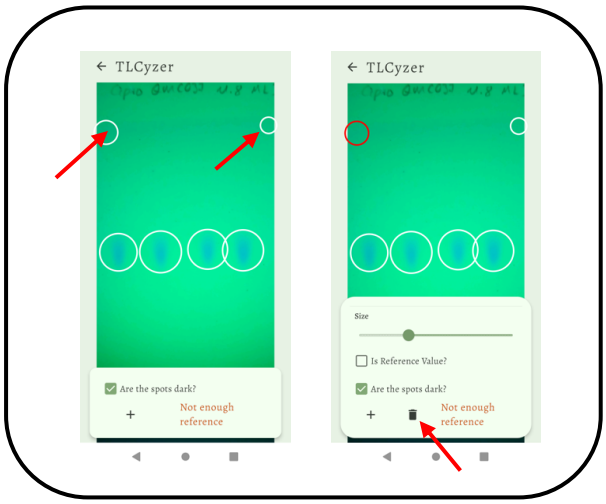
4. The spots are automatically detected, recognizable by the white circles around the spots. Please leave the tick at “Are the spots dark?”.
To select a reference spot, tap on it and place a tick at “Is Reference value”. Then you can enter the respective concentration in the field “Enter percentage” (normally 100% and 80%).
Tap on the tick at the bottom right to start the evaluation.



5. The result of the analysis is now displayed on the smartphone screen.
You can repeat the analysis by tapping at the arrow at the top right corner.
By tapping at the pencil at the upper right corner you can (re)name the sample plate.



<u>How to add circles:</u>
If no or not all spots have been detected automatically, circles can be added manually. Tap at the + symbol and a circle appears. Place the circle centrally over the spot. The size can be adjusted using the slide.



How to delete circles:
Excess circles must be deleted. To do this, tap on the circle (it turns reed) and tap on the bin.

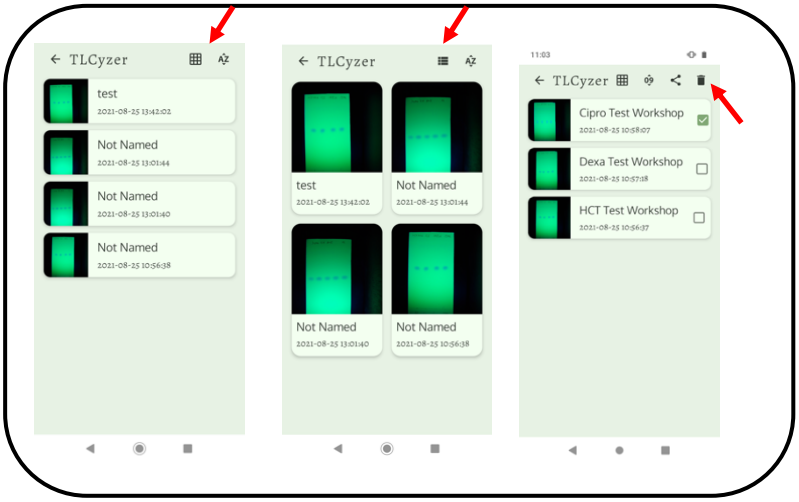
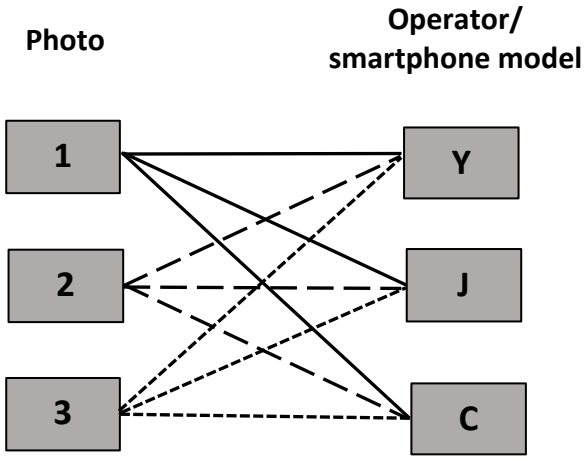


Photo gallery:
All photos are stored within the app and can be sorted by date and alphabetically by name. In the photo gallery, it is possible to switch between grid and list view.
Photos can be selected by tapping on them for two seconds (a tick appears). These photos can then be shared as zip file e.g. by e-mail.
Photos can be deleted by tapping at the bin.

Supplemental Figure S2: Step-by-step-instruction of the TLCyzer app



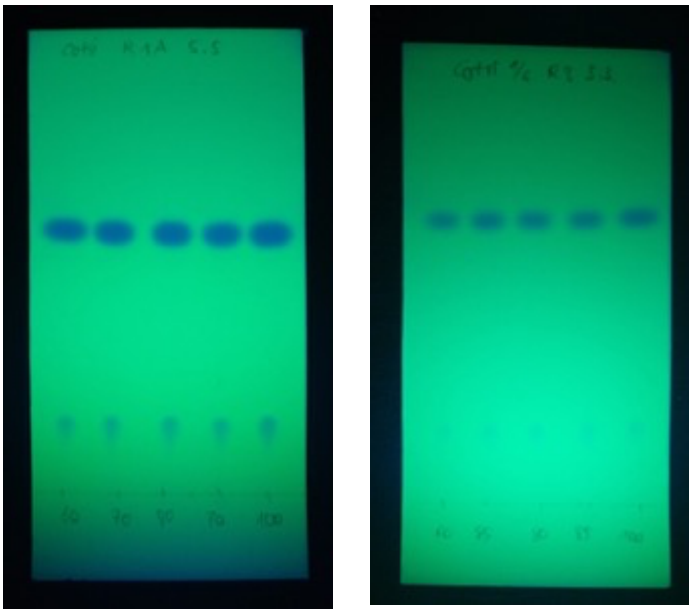
Possible combinations

Combination (I-IX)	Photo (1-3)	Operator/smartphone model (Y, J, C)
I	1	Y
II	1	J
III	1	C
IV	2	Y
V	2	J
VI	2	C
VII	3	Y
VIII	3	J
IX	3	C

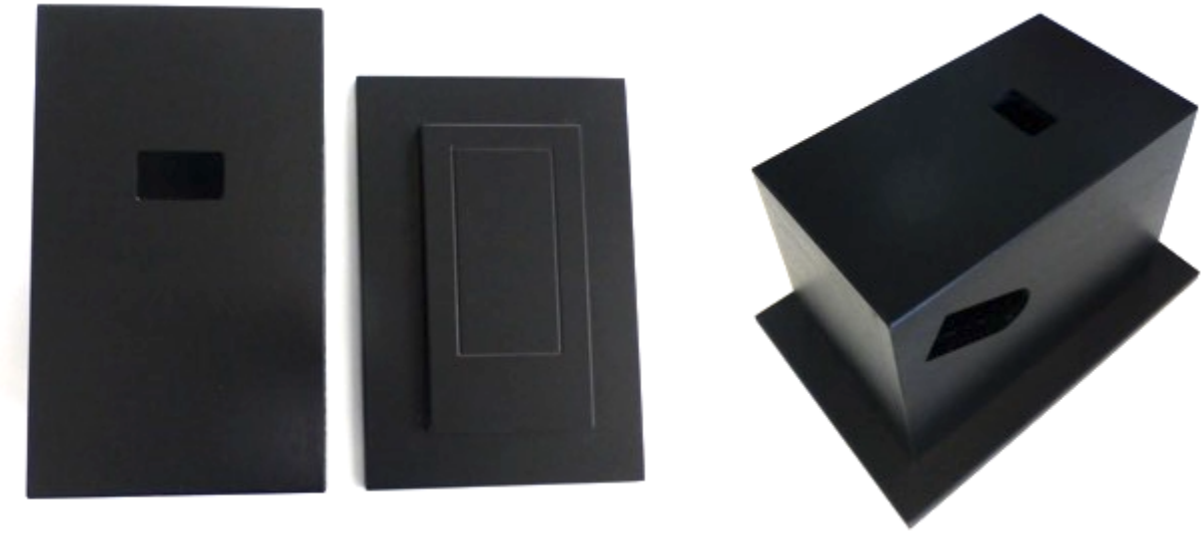
Example:

Analysis day	Combination					
1	I	III	IV	V	VI	VIII
2	II	III	V	VI	VII	IX

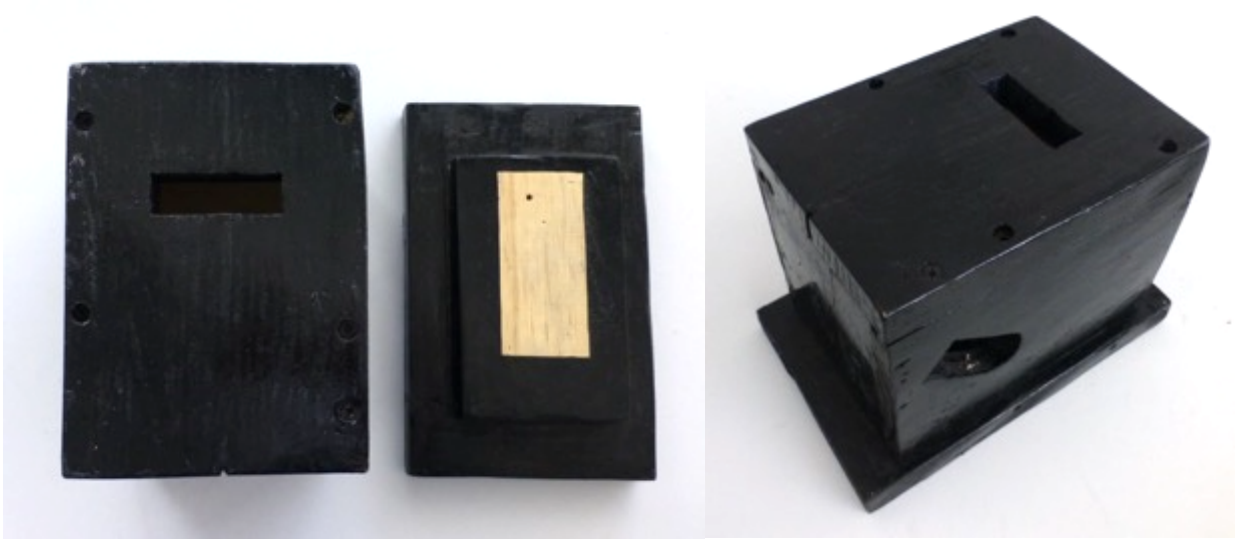
Supplemental Figure S3: Matrix approach for the evaluation of intermediate precision. Three different photos of each TLC plate, photographed on different days and named as 1, 2, 3 were evaluated by three different operators (Y, J, C) using different smartphone models. Hence for each API nine (I-IX) combination are possible. The photos were also evaluated on two different days (analysis day 1 and 2). For each day and API, six combinations were randomly selected, resulting in 168 different combinations.



Supplemental Figure S4: TLC plates of sulfamethoxazole and trimethoprim showing sample spots with 70% (left) and 17% (right) of the concentration indicated in the Minilab manual. The TLC plate at the left shows the reference concentrations 60%, 80% and 100% of the concentration indicated in the Minilab manual (100% corresponds to 5mg/mL sulfamethoxazole and 1mg/ml trimethoprim) The reference standards at the right TLC plate represent 10%, 14% and 17% of the concentration indicated in the Minilab manual. Sulfamethoxazole shows still highly visible spots whereas trimethoprim shows very pale and barely visible spots.



Supplemental Figure S5: TLC imaging box from Pidinger Werkstätten.
Lid and bottom plate of the box (left) and the assembled box (right). The box was built by Pidinger Werkstätten (Piding, Germany) according to our construction plans. It is stable to changes in temperature and humidity, tolerant to dust, light and rough handling. The box is made of birch, painted with a matt black paint. The lid is glued together using a waterproof adhesive.



Supplemental Figure S6: TLC imaging box build by a carpenter in Zimbabwe.
Lid and bottom plate of the boy (left) and the assembled box (right). The wooden box was built by a carpenter in Zimbabwe according to our construction plans.

Supplemental Table S1: Accuracy and precision (recovery) data

API	Target [%]	Result (accuracy) [%]						Recovery [%]				
		1 left	1 right	2 left	2 right	Mean	RSD	1 left	1 right	2 left	2 right	Mean
Atenolol	70	72.6	72.3	73.2	71.8	72.5	**0.81**	103.7	103.3	104.6	102.6	**103.5**
	85	85.9	87.6	86.4	83.8	85.9	**1.85**	101.1	103.1	101.6	98.6	**101.1**
	90	91.9	94.9	86.0	93.8	91.7	**4.33**	102.1	105.4	95.6	104.2	**101.8**
Ceftriaxone	70	75.5	69.9	69.2	65.9	70.1	**5.68**	107.9	99.9	98.9	94.1	**100.2**
	85	83.8	84.3	85.1	86.1	84.8	**1.18**	98.6	99.2	100.1	101.3	**99.8**
	90	93.3	88.3	94.7	88.4	91.2	**3.63**	103.7	98.1	105.2	98.2	**101.3**
Cefuroxime axetil	70	71.2	73.9	74.9	68.0	72.0	**4.29**	101.7	105.6	107.0	97.1	**102.9**
	85	80.1	82	85.2	81.8	82.3	**2.59**	94.2	96.5	100.2	96.2	**96.8**
	90	93.7	85.8	93.5	88.9	90.5	**4.23**	104.1	95.3	103.9	98.8	**100.5**
Chloroquine	70	69.3	67.9	67.8	69.6	68.7	**1.36**	99.0	97.0	96.9	99.4	**98.1**
	85	85.0	84.5	85.6	86.7	85.5	**1.11**	100.0	99.4	100.7	102.0	**100.5**
	90	89.8	91.2	94.8	91.7	91.9	**2.30**	99.8	101.3	105.3	101.9	**102.1**
Ciprofloxacin	70	70.0	67.7	69.1	72.3	69.8	**2.77**	100.0	96.7	98.7	103.3	**99.7**
	85	85.4	81.6	89.4	82.4	84.7	**4.17**	100.5	96.0	105.2	96.9	**99.6**
	90	95.0	90.1	89.9	94.9	92.5	**3.09**	105.6	100.1	99.9	105.4	**102.8**
Dexametha-sone	70	71.6	66.4	65.7	66.3	67.5	**4.08**	102.3	94.9	93.9	94.7	**96.4**
	85	85.1	83.0	88.0	84.8	85.2	**2.43**	100.1	97.6	103.5	99.8	**100.3**
	90	92.6	90.5	90.4	94.8	92.1	**2.26**	102.9	100.6	100.4	105.3	**102.3**
Fluconazole	70	70.2	71.7	71.6	68.1	70.4	**2.39**	100.3	102.4	102.3	97.3	**100.6**
	85	86.5	83.9	83.5	83.1	84.3	**1.82**	101.8	98.7	98.2	97.8	**99.1**
	90	89.7	91.6	85.3	89.8	89.1	**3.01**	99.7	101.8	94.8	99.8	**99.0**
Furosemide	70	73.0	68.9	69.8	69.6	70.3	**2.59**	104.3	98.4	99.7	99.4	**100.5**
	85	85.7	87.9	83.9	82.9	85.1	**2.58**	100.8	103.4	98.7	97.5	**100.1**
	90	90.8	91.8	93.4	94.2	92.6	**1.66**	100.9	102.0	103.8	104.7	**102.8**
Glibenclamide	70	70.1	70.4	67.1	66.4	68.5	**2.98**	100.1	100.6	95.9	94.9	**97.9**
	85	80.0	80	89.2	82.7	83.0	**5.23**	94.1	94.1	104.9	97.3	**97.6**
	90	90.2	92.1	89.3	90.6	90.6	**1.29**	100.2	102.3	99.2	100.7	**100.6**
Hydrochloro-thiazide	70	70.2	72.7	70.5	69.9	70.8	**1.80**	100.3	103.9	100.7	99.9	**101.2**
	85	86.5	84.9	86.5	84	85.5	**1.45**	101.8	99.9	101.8	98.8	**100.6**
	90	91.1	90.6	93.9	87.9	90.9	**2.70**	101.2	100.7	104.3	97.7	**101.0**
Metformin	70	72.6	66.9	73.9	74.4	72.0	**4.80**	103.7	95.6	105.6	106.3	**102.8**
	85	82.7	81.5	85.4	85.3	83.7	**2.32**	97.3	95.9	100.5	100.4	**98.5**
	90	91.7	88.7	89.8	86.3	89.1	**2.53**	101.9	98.6	99.8	95.9	**99.0**
Metronidazole	70	70.5	67.4	66.9	71.8	69.2	**3.44**	100.7	96.3	95.6	102.6	**98.8**
	85	85.2	84	85.4	85.3	85.0	**0.77**	100.2	98.8	100.5	100.4	**100.0**
	90	88.4	87.4	92.4	91.9	90.0	**2.77**	98.2	97.1	102.7	102.1	**100.0**
	70	73.4	65.4	70.6	71.1	70.1	**4.82**	104.9	93.4	100.9	101.6	**100.2**

API	Target [%]	Result (accuracy) [%]						Recovery [%]				
		1 left	1 right	2 left	2 right	Mean	RSD	1 left	1 right	2 left	2 right	Mean
Sulfamethoxazole	85	86.7	83.8	88.4	90.7*	87.4	**3.33**	102.0	98.6	104.0	106.7	**102.8**
	90	97.0	93.9	89.3	93.9	93.5	**3.39**	107.8	104.3	99.2	104.3	**103.9**
Trimethoprim	70	70.4	67.1	69.3	67.6	68.6	**2.22**	100.6	95.9	99.0	96.6	**98.0**
	85	83.0	81.5	83.3	88.1	84.0	**3.41**	97.6	95.9	98.0	103.6	**98.8**
	90	86.2	87.6	89.9	88.9	88.2	**1.82**	95.8	97.3	99.9	98.8	**97.9**
Mean							**2.79**					**100.3**

*) 90.7% is displayed as 90% on the smartphone app.

Supplemental Table S2: Intermediate precision data using a matrix approach.
Supplemental Figure S1 shows the different combinations.

API	Analysis day	Combi-nation	Result [%]					Recovery [%]	
			Left	Right	Mean	SD	RSD	Left	Right
Atenolol	1	I	88.2	88.8	88.5	4.38	4.94	98.0	98.7
	1	III	83.2	91.4				92.4	101.6
	1	IV	80.7	90.0				89.7	100.0
	1	V	88.7	88.3				98.6	98.1
	1	VI	85.1	88.0				94.6	97.8
	1	VIII	89.8	94.4				99.8	104.9
	2	II	88.9	91.3				98.8	101.4
	2	III	88.4	92.8				98.2	103.1
	2	V	86.6	83.6				96.2	92.9
	2	VI	82.1	84.6				91.2	94.0
	2	VII	89.5	100.9				99.4	112.1
	2	IX	86.2	93.2				95.8	103.6
Ceftriaxone	1	I	89.3	89.0	88.1	2.82	3.20	99.2	98.9
	1	II	87.4	84.1				97.1	93.4
	1	III	89.8	88.0				99.8	97.8
	1	V	91.1	86.8				101.2	96.4
	1	VI	95.3	88.8				105.9	98.7
	1	VII	92.4	87.7				102.7	97.4
	2	I	89.5	90.3				99.4	100.3
	2	III	87.0	84.1				96.7	93.4
	2	V	87.9	85.7				97.7	95.2
	2	VII	90.8	86.7				100.9	96.3
	2	VIII	84.9	83.5				94.3	92.8
	2	IX	88.9	85.2				98.8	94.7
Cefuroxime axetil	1	II	94.7	89.7	91.2	4.57	5.01	105.2	99.7
	1	III	83.5	82.7				92.8	91.9
	1	V	97.4	88.5				108.2	98.3
	1	VI	87.8	87.5				97.6	97.2
	1	VII	96.5	89.6				107.2	99.6
	1	IX	87.8	87.5				97.6	97.2
	2	II	94.7	89.7				105.2	99.7
	2	III	95.1	89.8				105.7	99.8
	2	IV	93.7	90.0				104.1	100.0
	2	V	98.7	88.6				109.7	98.4
	2	VII	93.8	87.6				104.2	97.3
	2	VIII	100.3	92.9				111.4	103.2
Chloroquine	**1**	I	93.1	99.2	91.8	3.67	4.00	103.4	110.2
	1	III	85.8	89.8				95.3	99.8

API	Analysis day	Combi-nation	Result [%]					Recovery [%]	
			Left	Right	Mean	SD	RSD	Left	Right
	1	V	88.2	91.5				98.0	101.7
	1	VII	94.3	93.5				104.8	103.9
	1	VIII	85.2	90.6				94.7	100.7
	1	IX	92.0	94.4				102.2	104.9
	2	II	100.3	92.9				111.4	103.2
	2	III	86.7	90.7				96.3	100.8
	2	IV	89.0	97.0				98.9	107.8
	2	V	91.3	92.2				101.4	102.4
	2	VI	90.1	91.3				100.1	101.4
	2	IX	92.3	91.1				102.6	101.2
Ciprofloxacin	1	I	94.0	86.6	90.5	4.55	5.03	104.4	96.2
	1	II	90.6	85.3				100.7	94.8
	1	III	93.7	87.1				104.1	96.8
	1	VI	95.7	86.3				106.3	95.9
	1	VII	93.5	90.0				103.9	100.0
	1	VIII	92.2	85.7				102.4	95.2
	2	I	93.1	87.6				103.4	97.3
	2	III	90.5	87.9				100.6	97.7
	2	IV	94.8	86.3				105.3	95.9
	2	VI	96.0	91.8				106.7	102.0
	2	VIII	101.5	80.7				112.8	89.7
	2	IX	92.9	87.8				103.2	97.6
Dexametha-sone	1	I	94.3	87.5	90.8	4.04	4.45	104.8	97.2
	1	II	91.0	87.7				101.1	97.4
	1	III	93.5	88.7				103.9	98.6
	1	IV	96.4	88.9				107.1	98.8
	1	V	99.1	88.0				110.1	97.8
	1	VII	91.7	90.3				101.9	100.3
	2	II	99.8	88.9				110.9	98.8
	2	III	94.5	87.0				105.0	96.7
	2	IV	92.5	89.8				102.8	99.8
	2	VI	90.2	86.8				100.2	96.4
	2	VIII	83.8	86.3				93.1	95.9
	2	IX	93.6	88.0				104.0	97.8
Fluconazole	**1**	I	90.7	92.5	89.6	3.22	3.60	100.8	102.8
	1	III	90.9	93.6				101.0	104.0
	1	V	86.6	85.6				96.2	95.1
	1	VII	87.8	90.1				97.6	100.1
	1	VIII	99.9	89.3				111.0	99.2
	1	IX	82.5	86.5				91.7	96.1
	2	II	87.7	90.1				97.4	100.1

API	Analysis day	Combi-nation	Result [%]					Recovery [%]	
			Left	Right	Mean	SD	RSD	Left	Right
	2	III	88.3	88.9				98.1	98.8
	2	IV	89.1	91.4				99.0	101.6
	2	V	90.0	90.7				100.0	100.8
	2	VI	90.8	88.9				100.9	98.8
	2	VII	87.7	90.0				97.4	100.0
Furosemide	1	II	85.0	90.0	91.1	3.58	3.93	94.4	100.0
	1	III	90.3	87.3				100.3	97.0
	1	V	88.4	94.4				98.2	104.9
	1	VII	95.8	97.1				106.4	107.9
	1	VIII	87.8	89.8				97.6	99.8
	1	IX	95.0	89.4				105.6	99.3
	2	I	97.1	93.2				107.9	103.6
	2	III	88.6	87.8				98.4	97.6
	2	IV	85.5	92.8				95.0	103.1
	2	V	88.4	91.0				98.2	101.1
	2	VI	90.9	89.4				101.0	99.3
	2	VII	94.7	95.5				105.2	106.1
Glibencla-mide	**1**	I	89.2	92.9	90.5	2.87	3.17	99.1	103.2
	1	III	89.7	93.7				99.7	104.1
	1	IV	88.4	93.1				98.2	103.4
	1	V	88.4	92.0				98.2	102.2
	1	VI	88.7	92.7				98.6	103.0
	1	VIII	89.6	93.4				99.6	103.8
	2	II	91.0	92.4				101.1	102.7
	2	III	88.7	92.5				98.6	102.8
	2	IV	88.7	93.6				98.6	104.0
	2	VI	86.4	85.4				96.0	94.9
	2	VII	86.3	95.7				95.9	106.3
	2	VIII	86.5	93.4				96.1	103.8
Hydrochloro-thiazide	**1**	I	91.3	84.5	90.4	4.07	4.50	101.4	93.9
	1	III	94.7	90.3				105.2	100.3
	1	V	91.6	88.4				101.8	98.2
	1	VII	97.7	88.8				108.6	98.7
	1	VIII	84.7	92.5				94.1	102.8
	1	IX	92.8	85.4				103.1	94.9
	2	II	88.5	88.8				98.3	98.7
	2	III	88.8	89.9				98.7	99.9
	2	IV	95.1	92.3				105.7	102.6
	2	V	81.3	87.5				90.3	97.2
	2	VI	95.6	89.3				106.2	99.2
	2	VII	93.8	96.0				104.2	106.7

API	Analysis day	Combi-nation	Result [%]					Recovery [%]	
			Left	Right	Mean	SD	RSD	Left	Right
Metformin	1	I	88.5	89.1	89.1	3.70	4.15	98.3	99.0
	1	III	92.4	89.1				102.7	99.0
	1	V	92.9	83.9				103.2	93.2
	1	VII	88.2	87.5				98.0	97.2
	1	VIII	96.7	97.1				107.4	107.9
	1	IX	91.6	87.2				101.8	96.9
	2	I	88.0	87.7				97.8	97.4
	2	III	89.4	86.5				99.3	96.1
	2	IV	86.3	87.3				95.9	97.0
	2	V	90.1	83.8				100.1	93.1
	2	VI	86.7	87.4				96.3	97.1
	2	VIII	96.4	85.2				107.1	94.7
Metronida-zole	1	II	95.1	93.4	91.6	4.32	4.71	105.7	103.8
	1	III	90.3	86.2				100.3	95.8
	1	IV	100.8	88.4				112.0	98.2
	1	V	95.6	91.4				106.2	101.6
	1	VI	91.9	87.2				102.1	96.9
	1	IX	83.5	90.3				92.8	100.3
	2	I	88.3	85.7				98.1	95.2
	2	III	91.8	92.5				102.0	102.8
	2	IV	102.3	92.3				113.7	102.6
	2	V	89.9	92.5				99.9	102.8
	2	VIII	95.6	92.3				106.2	102.6
	2	IX	89.9	92.3				99.9	102.6
Sulfamethox-azole	**1**	I	87.9	93.5	88.3	7.08	8.02	97.7	103.9
	1	II	76.4	76.8				84.9	85.3
	1	IV	93.0	91.4				103.3	101.6
	1	V	79.1	99.3				87.9	110.3
	1	VI	91.0	93.3				101.1	103.7
	1	VIII	79.6	88.8				88.4	98.7
	2	II	94.9	95.8				105.4	106.4
	2	III	80.8	83.5				89.8	92.8
	2	IV	92.4	97.4				102.7	108.2
	2	VI	86.7	100.1				96.3	111.2
	2	VII	86.3	87.4				95.9	97.1
	2	IX	82.9	81.1				92.1	90.1
Trimethoprim	**1**	I	89.7	95.6	91.9	3.38	3.68	99.7	106.2
	1	II	88.5	89.4				98.3	99.3
	1	IV	95.1	93.6				105.7	104.0
	1	V	92.6	87.5				102.9	97.2
	1	VI	91.8	91.2				102.0	101.3

API	Analysis day	Combi-nation	Result [%]					Recovery [%]	
			Left	Right	Mean	SD	RSD	Left	Right
	1	VIII	95.5	88.5				106.1	98.3
	2	II	94.7	89.5				105.2	99.4
	2	III	86.4	91.9				96.0	102.1
	2	IV	92.4	97.4				102.7	108.2
	2	VI	88.4	89.6				98.2	99.6
	2	VII	96.9	98.8				107.7	109.8
	2	IX	91.2	89.9				101.3	99.9
Mean					**90.2**	**4.02**	**4.46**	**100.3**	

Supplemental Table S3: Linearity data

API	Target [%]	Result [%]						Mean recovery (n=3) [%]
		Plate 1	Plate 2	Plate 3	Mean (n=3)	SD (n=3)	RSD (n=3)	
Atenolol	50	49.9	48.9	51.7	50.2	1.42	2.83	100.3
	70	68.4	65.1	64.5	66.0	2.10	3.18	94.3
	90	90.2	92.9	86.6	89.9	3.16	3.52	99.9
	100	101.7	102.6	100.5	101.6	1.05	1.04	101.6
	120	119.9	118.2	121.7	119.9	1.75	1.46	99.9
Ceftriaxone	50	50.3	49.6	51.5	50.5	0.96	1.90	100.9
	70	72.0	65.6	65.7	67.8	3.67	5.41	96.8
	90	89.3	91.1	87.0	89.1	2.06	2.31	99.0
	100	95.4	98.8	99.5	97.9	2.19	2.24	97.9
	120	120.4	119.3	121.5	120.4	1.10	0.91	100.3
Cefuroxime axetil	50	49.3	49.0	49.3	49.2	0.17	0.35	98.4
	70	73.0	72.7	68.3	71.3	2.63	3.69	101.9
	90	91.8	92.6	91.9	92.1	0.44	0.47	102.3
	100	98.7	100.7	96.5	98.6	2.10	2.13	98.6
	120	118.9	118.4	118.9	118.7	0.29	0.24	98.9
Chloroquine	50	48.7	48.6	48.7	48.7	0.06	0.12	97.3
	70	71.1	67.4	74.9	71.1	3.75	5.27	101.6
	90	93.7	94.1	93.9	93.9	0.20	0.21	104.3
	100	100.5	99.4	99.2	99.7	0.70	0.70	99.7
	120	117.6	117.3	117.4	117.4	0.15	0.13	97.9
Ciprofloxacin	50	49.5	49.4	49.6	49.5	0.10	0.20	99.0
	70	74.2	73.5	72.1	73.3	1.07	1.46	104.7
	90	91.3	91.6	91.1	91.3	0.25	0.28	101.5
	100	95.7	95.2	95.2	95.4	0.29	0.30	95.4
	120	119.2	119.0	119.4	119.2	0.20	0.17	99.3
Dexamethasone	50	49.0	49.9	50.6	49.8	0.80	1.61	99.7
	70	69.7	66.7	72.5	69.6	2.90	4.17	99.5
	90	92.7	90.2	88.6	90.5	2.07	2.28	100.6
	100	99.3	98.2	95.9	97.8	1.73	1.77	97.8
	120	118.3	119.9	120.8	119.7	1.27	1.06	99.7
Fluconazole	50	49.1	50.3	49.8	49.7	0.60	1.21	99.5
	70	71.4	65.3	69.6	68.8	3.13	4.56	98.2
	90	92.2	89.3	90.6	90.7	1.45	1.60	100.8
	100	100.4	98.0	105.1	101.2	3.61	3.57	101.2
	120	118.6	120.4	119.7	119.6	0.91	0.76	99.6
Furosemide	50	50.3	51.3	48.8	50.1	1.26	2.51	100.3
	70	74.7	70.0	67.9	70.9	3.48	4.91	101.2
	90	89.3	87.4	93.4	90.0	3.07	3.41	100.0

API	Target [%]	Result [%]						Mean recovery (n=3) [%]
		Plate 1	Plate 2	Plate 3	Mean (n=3)	SD (n=3)	RSD (n=3)	
	100	98.3	98.4	102.6	99.8	2.45	2.46	99.8
	120	120.4	121.4	117.8	119.9	1.86	1.55	99.9
Glibenclamide	50	49.9	49.1	48.7	49.2	0.61	1.24	98.5
	70	70.1	72.6	68.5	70.4	2.07	2.94	100.6
	90	90.2	92.4	93.7	92.1	1.77	1.92	102.3
	100	99.0	98.9	99.6	99.2	0.38	0.38	99.2
	120	119.9	118.5	117.6	118.7	1.16	0.98	98.9
Hydrochlorothiazide	50	49.1	49.8	49.0	49.3	0.44	0.88	98.6
	70	68.9	74.1	72.8	71.9	2.71	3.76	102.8
	90	92.3	90.5	92.6	91.8	1.14	1.24	102.0
	100	103.0	106.5	102.4	104.0	2.21	2.13	104.0
	120	118.6	119.7	118.4	118.9	0.70	0.59	99.1
Metformin	50	49.0	51.6	49.7	50.1	1.35	2.69	100.2
	70	75.6	73.3	76.3	75.1	1.57	2.09	107.2
	90	92.6	86.8	90.8	90.1	2.97	3.30	100.1
	100	101.5	97.3	100.4	99.7	2.18	2.18	99.7
	120	118.4	121.6	119.5	119.8	1.63	1.36	99.9
Metronidazole	50	51.1	49.9	50.2	50.4	0.62	1.24	100.8
	70	72.0	69.2	70.9	70.7	1.41	2.00	101.0
	90	87.8	90.2	89.6	89.2	1.25	1.40	99.1
	100	101.3	99.4	101.0	100.6	1.02	1.02	100.6
	120	121.2	119.9	120.2	120.4	0.68	0.57	100.4
Sulfamethoxazole	50	49.4	49.9	48.7	49.3	0.60	1.22	98.7
	70	71.4	70.5	73.0	71.6	1.27	1.77	102.3
	90	91.6	90.2	93.6	91.8	1.71	1.86	102.0
	100	107.3	92.3	99.7	99.8	7.50	7.52	99.8
	120	119.0	119.9	117.6	118.8	1.16	0.98	99.0
Trimethoprim	50	49.3	51.8	49.1	50.1	1.50	3.00	100.1
	70	72.4	71.5	69.9	71.3	1.27	1.78	101.8
	90	91.7	86.4	92.4	90.2	3.28	3.64	100.2
	100	105.0	96.1	100.5	100.5	4.45	4.43	100.5
	120	119.0	121.8	118.5	119.8	1.78	1.49	99.8
Mean							**1.99**	**100.1**

Supplemental Table S4: Robustness data

API	Modifications	Result [%]								Difference to standard condition [%]
		1 left	1 right	2 left	2 right	3 left	3 right	Mean	RSD	
Chloroquine	Standard condition	94.3	91.3	95.5	89.5	92.6	89.6	92.1	2.67	x
	Cropping: full plate (with labelling)	91.0	93.7	93.9	95.5	92.7	95.4	93.7	1.81	1.6
	Cropping: without labelling	91.6	90.4	90.6	87.7	97.7	91.1	91.5	3.63	-0.6
	Manual spot detection	96.1	92.4	94.4	91.7	95	92.6	93.7	1.84	1.6
	UV-lamp not central	92.4	92	94.1	89.7	99.2	86.9	92.4	4.51	0.2
	Low battery charge of UV-lamp	88.3	89.6	89.5	90.1	88	90.4	89.3	1.08	-2.8
	Different box (from Pidinger Werkstätten)	91.2	89.1	89.7	87.9	91.8	92.6	90.4	1.97	-1.8
	Different smartphone for photo and analysis (Fairphone 3)	86.6	88.4	90.4	84.8	91.7	87	88.2	2.90	-4.0
Dexametha-sone	Standard condition	92.2	88.4	90.0	87.1	89.2	87.4	89.1	2.12	x
	Cropping: full plate (with labelling)	96.2	88.8	93.4	88.3	93.5	91.3	91.9	3.31	2.9
	Cropping: without labelling	91.9	87.5	90.9	86.5	89.3	87.4	88.9	2.42	-0.1
	Manual spot detection	92.4	88.2	94.2	88.9	96.7	91	91.9	3.51	2.9
	UV-lamp not central	93.3	90.7	98.9	90.8	97.2	88.4	93.2	4.39	4.2
	Low battery charge of UV-lamp	84.3	88.8	88.6	90.3	87.1	86.9	87.7	2.36	-1.4
	Different box (from Pidinger Werkstätten)	88.3	90.8	90.5	90.6	89.4	88.3	89.7	1.29	0.6
	Different smartphone for photo and analysis (Fairphone 3)	92.8	91	87.7	90.5	89.1	85.6	89.5	2.86	0.4
Hydrochlo-rothiazide	Standard condition	91.4	93.4	94.5	93.5	93	92.5	93.1	1.12	x
	Cropping: full plate (with labelling)	90.7	93.2	96.4	93.1	94.4	91.9	93.3	2.12	0.2
	Cropping: without labelling	88.8	91.8	92.3	93.7	92.8	91.4	91.8	1.82	-1.3
	Manual spot detection	94.8	89.6	95.3	89.3	96.6	90.0	92.6	3.57	-0.4
	UV-lamp not central	90.9	86.9	99	91.9	98.1	90.5	92.9	5.07	-0.2
	Low battery charge of UV-lamp	94.0	84.1	90.7	82	89.2	90.7	88.5	5.11	-4.6
	Different box (from Pidinger Werkstätten)	91.6	90.5	91.3	90.5	92.8	90.2	91.2	1.06	-1.9
	Different smartphone for photo and analysis (Fairphone 3)	92.2	90.4	85.3	89.2	87.8	91.3	89.4	2.82	-3.7
Metformin	Standard condition	91.7	86.6	88.6	87.9	92.9	88.0	89.3	2.75	x

API	Modifications	Result [%]								Difference to standard condition [%]
		1 left	1 right	2 left	2 right	3 left	3 right	Mean	RSD	
	Cropping: full plate (with labelling)	91.6	88.2	91.5	90.4	91.4	91.2	90.7	1.44	1.4
	Cropping: without labelling	88.2	85.9	90.7	88.9	91.5	88.8	89.0	2.22	-0.3
	Manual spot detection	90.8	88.4	90.8	88.1	91.7	89	89.8	1.66	0.5
	UV-lamp not central	89.4	89.1	89.5	87.6	92.7	88.1	89.4	2.00	0.1
	Low battery charge of UV-lamp	96.5	88.9	92.7	88.1	91.3	88.1	90.9	3.63	1.7
	Different box (from Pidinger Werkstätten)	91.1	89.3	90	90.5	88.1	89.6	89.8	1.16	0.5
	Different smartphone for photo and analysis (Fairphone 3)	91.1	87.9	95.4	89.1	89.1	89.8	90.4	2.95	1.1
Mean								**90.8**	**2.60**	

Supplemental Table S5: Results of the evaluation of two TLC plate photos after an online teaching workshop with the TLCyzer app.

The results of nine participant using different smartphone are shown. Results are indicated without decimals, as the TLCyzer app only displays whole numbers (see: general information and practical approach to the image analysis procedure).

Partici-pant	Smartphone model	API (target conc.)	Result [%]							Recovery [%]
			1 left	1 right	2 left	2 right	Mean	SD	RSD	
1	Honor 8X	Furo-semide (90%)	89	85	85	85	84.1	6.28	7.48	Range 74% - 101% Mean: 93.4%
2	OnePlus 6T		89	87	87	86				
3	SonyXperia Z5		86	87	85	86				
4	Huawei P30 lite		82	89	88	85				
5	Huawei P smart 2019		89	83	79	77				
6	Fairphone 3		90	85	83	90				
7	Google Pixel 5		91	86	88	85				
8	Sony Xperia XZ1 compact		84	86	86	89				
9	Samsung Galaxy A51		70	67	68	69				
1	Honor 8X	Chloro-quine (85%)	83	85	84	88	85.3	1.85	2.17	Range 93% - 105% Mean: 100.4%
2	OnePlus 6T		84	85	85	85				
3	SonyXperia Z5		85	85	86	86				
4	Huawei P30 lite		84	86	84	86				
5	Huawei P smart 2019		84	87	85	87				
6	Fairphone 3		79	84	85	87				
7	Google Pixel 5		83	84	86	89				
8	Sony Xperia XZ1 compact		87	89	86	87				
9	Samsung Galaxy A51		84	85	87	86				

Supplemental Table S6: Results of the evaluation of good quality and substandard finished pharmaceutical products. Tablets with good quality from the dispensary in Tübingen and substandard tables from the DR Congo (DRC) were analysed. The content of the tablet from DRC was measured with HPLC.[1]

API	Origin of tablets and content	Spotting pattern (no. of spots)	No. of photo	Results [%]							
				1 left	1 right	2 left	2 right	3 left	3 right	Mean (n=12)	SD (n=12)
Dexametha-sone	Dispensary Tübingen (approx. 100%)	5	1	99.3	100.0	97.7	101.2	98.5	93.3	98.8	2.98
			2	101.9	95.4	103	97.1	102.2	96.5		
		4	1	92.2	94.8	100.9	98.4	99.8	91.4	95.8	4.10
			2	90.7	93.3	97.6	98.4	101.3	90.3		
Hydrochloro-thiazide		5	1	92.1	92.8	95.4	89.6	99.2	95.1	93.3	2.89
			2	92.8	94.3	91.1	88.3	94.9	93.8		
		4	1	99.4	97.8	94.3	95.9	94.7	95.0	95.9	2.56
			2	100.5	96.4	97.0	92.1	95.7	92.1		
Metronida-zole		5	1	101.0	95.1	101.4	103.8	104.1	99.6	100.6	3.54
			2	103.1	96.9	105.1	102.8	94.5	99.6		
		4	1	91.5	93.6	96.6	95.0	95.2	96.1	94.2	3.29
			2	94.7	90.3	91.6	91.2	92.3	102.3		
	DRC (86.7%)	5	1	82.6	87.7	83.3	88.8	80.8	83.4	86.0	3.95
			2	86.8	85.2	81.3	88.9	94.0	89.5		
		4	1	85.5	83.6	90.3	83.3	83.7	84.8	84.2	2.59
			2	83.6	81.9	85.3	80.5	81.5	86.5		
Ciprofloxacin	Dispensary Tübingen (approx. 100%)	5	1	99.6	94.7	103.2	99.4	92.5	96.0	97.4	3.77
			2	104.5	96.7	97.5	95.0	97.0	92.5		
		4	1	105.3	102.0	100.8	92.8	102.5	103.1	101.3	3.99
			2	101.7	97.9	103.3	95.9	104.1	106.7		
	DRC (83.4%)	5	1	87.6	87.9	80.2	83	86.9	79.4	84.2	2.89
			2	87.2	83.5	84.9	81.2	84.3	84.3		
		4	1	87.1	88.3	83.8	79.1	84.5	83.5	84.1	2.50
			2	85.9	82.7	85.2	82.6	84.6	81.3		
Mean											**3.25**

[1] Schäfermann S et al., 2020. Substandard and falsified antibiotics and medicines against noncommunicable diseases in western Cameroon and northeastern Democratic Republic of Congo. *Am J Trop Med Hyg 103(2)*:894-908.