Supplementary Annex Book
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An evaluation of portable screening devices to assess medicines quality for national Medicines Regulatory Authorities

Supplementary Annex 1. List of devices created during the inception phase of the project (based on a non-systematic review of the literature and search on Google)

Device name	Technology	Developer Institution	Developer's website
TLC-Mobile-phone	TLC-UV	Micro and Nanotechnology Laboratory, University of Illinois	N/A
SOC-410DHR	Directional reflectance	Enformatics	http://www.enformatic.eu/en/for_business/reflectometers-and-Emissometers/SOC-410-DHR-Handheld-Directional-Hemispherical-Reflectometer.html
NanoRam	Raman	B & W Tek	http://bwtek.com/tag/miniram/
Guardion	Gaz chromatography - Mass spectrometry	Smiths detection	www.smithsdetection.com
NQR	Nitrogen-14 Nuclear Quadrupole Resonance Spectroscopy	ConPhirmer	http://www.conphirmer.com/
Minilab	TLC;disintegration test;visual inspection scheme	GPHF	https://www.gphf.org/en/index.htm
TruScan RM	Raman	Thermo Fisher Scientific Ahura Scientific	http://www.thermofisher.com/us/en/home.html
CD3/CD4	Light range-visual comparison	US FDA	http://www.fda.gov/
ScIO	Near Infrared	Consumer Physics	https://www.consumerphysics.com/myscio/
NIRscan	Near Infrared	Texas Instrument	http://www.ti.com/tool/dlpnirnanoevm
Renishaw System-1000 spectrometer	Raman	Waters	http://www.waters.com/waters/en_US/ACQUITY-QDa-Mass-Detector-for-Chromatographic-Analysis/nav.htm?cid=134761404&locale=en_US
M908	High Pressure Mass Spectrometry	908 Devices Inc. Is	http://908devices.com/products/
PharmaChk	Dissolution microfluidics with luminescence detection	Boston University	https://savinglivesatbirth.net/news/13/09/03/counterfeit-drug-screening-devices-nets-national-award
Paper Analytical Device	Paper-based color test	Faculty of Notre-Dame and Veripad	http://padproject.nd.edu/technology/

MIRA	Raman	Metrohm	http://www.metrohm.com/en/products/spectroscopy/raman-analyzers/
Miniram	Raman	B & W Tek	http://bwtek.com/tag/miniram/
LinkSquare	ShortWave Infrared	Stratio	http://www.stratiotechnology.com/
MicroNIR	Near Infrared	Viavi Solution Inc	vhttp://www.viavisolutions.com/en-us
MicroPHAZIR RX	Near Infrared	Thermo Fisher Scientific Ahura Scientific	http://www.thermofisher.com/us/en/home.html
Progeny	Raman	Rigaku Raman Technologies	www.rigakuprogeny.com
Waters Single-quadrupole Qda MS	Mass Spectrometry	Waters	http://www.waters.com/waters/en_US/ACQUITY-QDa-Mass-Detector-for-Chromatographic-Analysis/nav.htm?cid=134761404&locale=en_US
Unnamed-RDT test	Lateral flow immunoassay	Department of Entomology Penn State University	http://ento.psu.edu/research/labs/liwang-cui
Unnamed-XRF	X-ray fluorescence	Center for disease control, USA	https://www.cdc.gov/
CoDI	Laser photometric	Center for disease control, USA	https://www.cdc.gov/
C-Vue	HPLC-UV	C-Vue	http://www.c-vuelc.com/
Unnamed-Hyperspectral imaging	Hyperspectral imaging	Medical University of Silesia in Katowice	http://smk.sum.edu.pl/
4500a FTIR	Fourier Transformed Infrared	Agilent	http://www.agilent.com/home
NeoSpectra (sensor)	Fourier Transformed Infrared	SiWare	http://www.neospectra.com/
TruDefender	Near Infrared	Thermo Fisher Scientific Ahura Scientific	http://www.thermofisher.com/us/en/home.html
i-Spec 25	Near Infrared	B & W Tek	http://bwtek.com/tag/miniram/
i-Raman	Raman	B & W Tek	http://bwtek.com/tag/miniram/
i-Spec Series	Near Infrared	B & W Tek	http://bwtek.com/tag/miniram/

Supplementary Annex 2. Systematic review of the literature- draft submitting for publication

Field detection devices for medicines quality screening: a systematic review

Short title: Medicine quality field detection devices – systematic review

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Abbreviations

AMR, antimicrobial resistance; API, Active Pharmaceutical Ingredient; FT-IR, Fourier Transform; IR, Infrared; HPLC, High-Performance Liquid Chromatography; L/MIC, low- and middle-income country; MIR, Mid-infrared; NIR, Near-infrared; NQR, Nuclear quadrupole resonance; PAD, Paper Analytical Device; PMS, Post-Marketing Surveillance; TLC, Thin Layer Chromatography; UV-Vis, Ultraviolet-Visible Light

Word count; 6,042

Key words: medicine quality, devices, falsified, substandard, counterfeit, medicines regulatory authorities, quality control, portable, screening

ABSTRACT

Background

Poor quality medicines have devastating consequences. A plethora of innovative portable devices to screen for poor quality medicines has become available, leading to hope that they could empower medicine inspectors and enhance surveillance. However, information comparing these new technologies is woefully scarce.

Methods

We undertook a systematic review of Embase, PubMed, Web of Science, and SciFinder databases up to 30 April 2018. Scientific studies evaluating the performances/abilities of portable devices to assess any aspect of the quality of pharmaceutical products were included.

Results

Forty-one devices, from small benchtop spectrometers to 'lab-on-a-chip' single-use devices, with prices ranging from <USD 10 to >USD 20,000 were included. Only six devices had been field-tested [GPHF-Minilab, CD3/CD3+, Truscan RM, lateral flow dipstick immunoassay, CBEx and Speedy Breedy]. The median (range) number of active pharmaceutical ingredients (APIs) assessed per device was only 2 (1-20). The majority of devices showed promise to distinguish genuine from falsified medicines. Devices with the potential to assay API (semi-)quantitatively required consumables and were destructive (GPHF-Minilab, PharmaChk, aPADs, lateral flow immunoassay dipsticks, paper-based microfluidic strip, capillary electrophoresis), except for spectroscopic devices. However, the ten spectroscopic devices tested for their abilities to quantitate APIs required processing complex API-specific calibration models. Scientific evidence on the ability of the devices to accurately test liquid, capsule or topical formulations, or to distinguish between chiral molecules, was limited. There was no comment on cost-effectiveness, and little information on where in the pharmaceutical supply chain these devices could be best deployed.

Conclusion

Although a diverse range of portable field detection devices for medicines quality screening is available, there is a vitally important lack of independent evaluation of the majority of devices, particularly in field settings. Intensive research is needed in order to inform national medicines regulatory authorities of the optimal choice of device to combat poor-quality medicines.

What is already known about this topic?

- ~10% of medical products circulating in L/MICs are either substandard or falsified, leading to increased morbidity and mortality, adverse drug reactions, economic losses and diminished public confidence in health systems.
- Despite this, the majority of drug inspectors and customs officers worldwide rely simply on visual inspection, and can identify only the most crudely falsified medicines.
- A large number of portable screening devices have recently been developed that could aid medicines regulatory authorities in detection of poor quality medicines, but there is scanty evidence to inform policy makers as to which device to use and where.

What are the new findings?

- Forty-one devices covering nineteen technologies were identified; more than half of these devices employed spectroscopic techniques.
- Field-evaluation has been published for only six of forty-one devices.
- Significant knowledge gaps exist, impairing evidence-based policy decisions (see **Box 3**).

How might this influence practice

- There is inadequate independent evaluation of these devices to inform policy-makers about optimal choice of device to combat poor-quality medicines.
- Intensive research is needed to understand the comparative advantages and limitations of the different devices and technologies.

INTRODUCTION

According to a recent WHO report, ~10% of medical products circulating in low- and middle-income countries (L/MICs) are either substandard or falsified [1] Though this problem is as old as the medicinal trade,[2,3] its impact on global health has been largely under-recognised. L/MICs are significantly affected,[4–6] but wealthier countries with good regulatory systems are not immune.[7–9] Substandard and falsified medicines (SF, **Box 1**) have devastating consequences, including increased morbidity and mortality, economic losses and diminished public confidence in health systems. Poor quality antimicrobials, particularly those containing reduced quantities of active pharmaceutical ingredients (API), may be a key but neglected driver of antimicrobial resistance (AMR).[10] Despite this, the oversight and penalties for perpetrators are weak, and falsifying medicines remains an attractive criminal activity.[11]

Box 1: Definitions of substandard and falsified medicines [93]

- **Substandard** also called "out of specification", these are authorized medical products that fail to meet either their quality standards or specifications, or both.
- **Falsified** medical products that deliberately/fraudulently misrepresent their identity, composition or source.

Medicines regulatory authorities (MRAs) are responsible for preventing, detecting and removing SF medicines. Others actors involved in medicine procurement (e.g. non-governmental organisations, procurement agencies and hospital pharmacies) are, together with MRAs, the keystones for the majority of potential interventions to prevent, detect and remove poor quality medicines. Currently, in L/MICs these key actors often have only their own senses and knowledge to rely on as they seek circulating SF medicines. Samples may then be sent for formal chemical analysis laboratory testing, using API- (and dosage formulation) specific validated pharmacopeial protocols, or non-validated in-house procedures when pharmacopeial methods do not exist. However, these tests [such as high-performance liquid chromatography

(HPLC)] are expensive, time consuming, and scarce in many countries (**Box 2**). There are often significant delays between collection of suspicious medicines and confirmation of their poor quality, with harm spreading unchecked in the interim.

Box 2. Main technologies used in pharmaceutical quality analysis

Colorimetry

Colorimetric techniques use analysis of the color developed by a sample in the presence of specific reagents. The presence or absence of the color gives information on the presence or absence of the chemical compound (or specific chemical groups) being investigated. The intensity of the color, interpreted either by the naked eye or by specific devices (called colorimeters or photometers), can provide quantitative information on the amount of the chemical within the medicine.

Chromatography

This technology separates different ingredients in a mixture to obtain pure compounds to show their presence (or absence) and quantity. As many compounds are colourless, specific detectors are used to reveal them, such as those based on refraction index changes, fluorescence, or absorbance at various wavelengths.
Individual compounds are separated from each other through their interaction with a solid 'stationary phase,' which remains fixed in a column or support. A liquid or a gas 'mobile phase' flows through the stationary phase and the captured compounds gradually move along the stationary phase in the same direction as the mobile phase. Each compound of a mixture will travel through the stationary phase, ejecting at varying times due to their different affinities with the stationary vs. mobile phases. For examining medicines quality, the result from the test sample is compared to the result yielded by the authentic product, tested under the same conditions.

Thin-layer chromatography uses a thin-layer of silica or paper as the stationary phase. The mobile phase travels through the stationary phase via capillary action when the base of the device is placed with one end dipped in a solution. Once the device is pulled from the solution, the separation process stops and the separated compounds are retained spatially on the stationary phase, and revealed with the use of a lamp or chemical reagent.
High performance liquid chromatography forces the mobile phase through a column of stationary phase silica particles by high pressure pumps. A detector monitors the compounds as they are released, allowing the identification of the compounds based on their specific retention times and quantitation based on their peak area. Typical detectors vary in terms of cost and specificity, and include UV-Vis light absorbance detectors and (quadrupole, ion trap, time-of-flight, orbitrap) mass spectrometers.

Spectroscopy: Near-infrared (NIR), Mid-infrared (MIR), Raman and Ultraviolet-Visible Light (UV-Vis)

Different chemicals have their own unique interaction with electromagnetic radiation. The type of interaction depends on the nature of the compound's molecular structure and the radiation used. When a sample is irradiated with a specific wavelength (energy) of light, structures within the sample absorb that energy and vibrate along different chemical bonds which can be measured by ***NIR***, ***MIR*** and ***Raman spectroscopy,*** types of '***vibrational spectroscopy***'. These 'vibrations' cause the absorbance or emittance of light by the sample in a characteristic spectrum, unique to the sample - often called a 'spectral fingerprint'. Usually, this unique spectrum has to undergo mathematical transformation (spectral processing) to be readable by the user. In order to identify whether a sample is authentic or substandard/falsified, the sample spectrum generated is compared to the spectrum of the authentic product to assess its similarity. This requires the construction of a 'reference library' or database consisting of the spectra of authentic products.

UV-Vis spectroscopy utilizes light within the ultraviolet and visible regions of the electromagnetic spectrum. UV-Vis absorbance measurements, which monitor the amount of light within this part of the spectrum that is transmitted through a material, does not reveal as much structural information as ***NIR***, ***MIR***, and ***Raman***. However, fluorescence and luminescence signals can be measured within the ***UV-Vis*** region. Signals from samples that can emit ***UV-Vis*** light through fluorescence (i.e. the sample can be excited by a wavelength of light and then emit a different wavelength of light) and luminescence (a chemical reaction emits light from the sample) can thus be used to characterize and quantify the amount of API within a sample.

Structurally-based separation techniques

Molecules of different mass and charge move differently when under the influence of an external electric field (heavier molecules travel slower or require stronger electric fields to be transported). These travel times or electric field conditions are recorded by a detector and are correlated to the mass and charge of the molecule, allowing its identification. ***Mass spectrometry, ion mobility spectroscopy*** and ***capillary electrophoresis*** all exploit this phenomenon. Mass spectrometry measures movement through a vacuum; ion mobility in the gas-phase; and capillary electrophoresis in the liquid-phase. For examining medicines quality, the result from the test sample is compared to the result yielded by the authentic product, tested under the same conditions.

Over the last two decades a plethora of portable medicine analysis screening tools have been developed, offering the potential for objective analysis of medicines in the 'field'. A previous review compared the suitability of different existing chemical analysis technologies for L/MICs [12] (e.g. Raman spectroscopy, colorimetry). With more devices and more data now available, we undertook a systematic review to understand the performance and characteristics of portable devices for the field evaluation of medicines. This review identifies multiple gaps in the evidence for optimal device selection to inform policy decisions on which devices to use to screen medicine quality before sending samples for confirmatory analyses, where and when.

METHODS

Search strategy and selection criteria

A systematic review was conducted, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (**additional material 1,** PRISMA checklist) with registration in the international prospective register of systematic reviews (PROSPERO, ID 42016043216). We searched for English language scientific articles on portable technologies used to assess the quality of pharmaceutical products, using Embase (from 1947), PubMed (from 1946), Web of Science (from 1900) and SciFinder (from 1840) to April 30, 2018. Search terms included those related to the equipment (e.g. 'device', 'instrument'), terms referring to the portability of the equipment (e.g. 'portable', 'handheld') and terms related to the quality of pharmaceutical products (e.g. 'substandard', 'falsified'). The full search strategies are provided in **additional material 2**.

After removal of duplicates, titles and abstracts were independently screened for eligibility by two authors (SV, MB). Any reservations on eligibility for inclusion were resolved by discussion between the three reviewers (SV, MB, CC), with final adjudication from FMF. References in English and French provided by colleagues working in the field, in addition to

references within reviews of specific techniques, and those in all included articles, were examined to identify additional relevant articles. We included all studies evaluating the performances/abilities of portable devices to assess any aspect of the quality of pharmaceutical products in a laboratory environment, in field surveys, and proof-of-concept articles in which the authors stress the potential portability of a method. Only studies with the aim to estimate medicine quality prevalence that contained information of the performances/abilities of the device as a portable technology for field use were included. Devices currently under-development, (although not yet marketed) and devices no longer marketed but superseded by other devices, were included. Non-portable devices, devices used for testing the quality of non-pharmaceutical products or for identification of traditional medicines, devices for measuring APIs in biological fluids, and product security technologies were excluded. Patent application publications, articles on the development of a method (e.g. a new thin layer chromatography (TLC) method) not intended for deployment in a field-detection kit, reviews/general discussions and articles describing or comparing methods for spectral analysis (chemometrics) rather than the performance of the device itself, were also excluded.

CC, MB, and SV independently reviewed and extracted data from the eligible articles. For included devices, additional information on objective characteristics (e.g. physical appearance, approximate cost and market status) was obtained from manufacturers' websites and enquiries to them.

Key variables and definitions

In this review, 'portable' refers to transportable equipment (i.e. intended to be moved from one place to another whether or not connected to a mains electrical supply [13]) able to be carried by a maximum of two persons, that requires minimal set-up on arrival at the field detection site (set-up can be managed by technician-level staff after short training on the device). Devices that require an initial laboratory phase set-up from highly trained staff (e.g.

Raman spectrometers which require creation of reference libraries and complex processing of spectral data) but that are subsequently portable and easy-to-use in the field by technician-level staff were included. 'Field-tested' device refers to a device assessed on-site, i.e. near where the medicines were collected, as opposed to formal laboratory-based studies. A reference standard refers to a specimen of the medicine API intended for use in compendial methods, which is of the highest possible purity and highly characterised by analytical chemistry techniques, utilised as a direct chemical comparator or to generate a signature.[14] A reference library refers to a library of measurements of authentic medicines collected by the device and with which the device compares the measurement obtained from a test sample, most commonly spectral libraries of authentic measurements stored within the spectrometer software ('Spectral Reference Library'). Semi-quantitative is defined as an approximate measurement of the amount of a substance, between a qualitative and a quantitative result (e.g. between 80 and 100% of the stated amount). 'Non-destructive' refers to devices used to test intact dosage units of medicines (predominantly tablets) either through packaging or without perturbing the dosage unit.

Sensitivity is defined as the proportion of medicines that are detected as poor quality by the device out of all the medicines determined as poor quality by a reference technique. Specificity is defined as the proportion of medicines that are identified as authentic by the device out of all the medicines determined as good quality by a reference technique.

Data analysis

Data was extracted and entered into a Microsoft Excel spreadsheet. For each device, the developer's names, type of technology used, main technical specifications (e.g. resolution, spectral range), reported sensitivity, specificity and other laboratory or field-test results, practical aspects of the use of the device (e.g. the measurement time per sample, consumables required), and the pluses and minuses quoted by the authors were extracted when available.

For clarity, we have presented only the key results from devices tested on finished pharmaceutical products and only when poor quality medicines (either field-collected or simulated products) were used for evaluation. The quality of the included studies could not be objectively assessed because of the wide heterogeneity of study designs and a lack of consensus guidelines for reporting.

RESULTS

Of the 5,718 reports screened, 282 full text papers were assessed for eligibility (**additional material 3,** PRISMA flow diagram). Of these, 62 matched the inclusion criteria and were included in the review.

Forty-one devices (including 21 handheld devices and 4 lab-on-a-chip single use devices, and 12 under development) were identified in the 62 articles (**Table 1, Figure 1**).

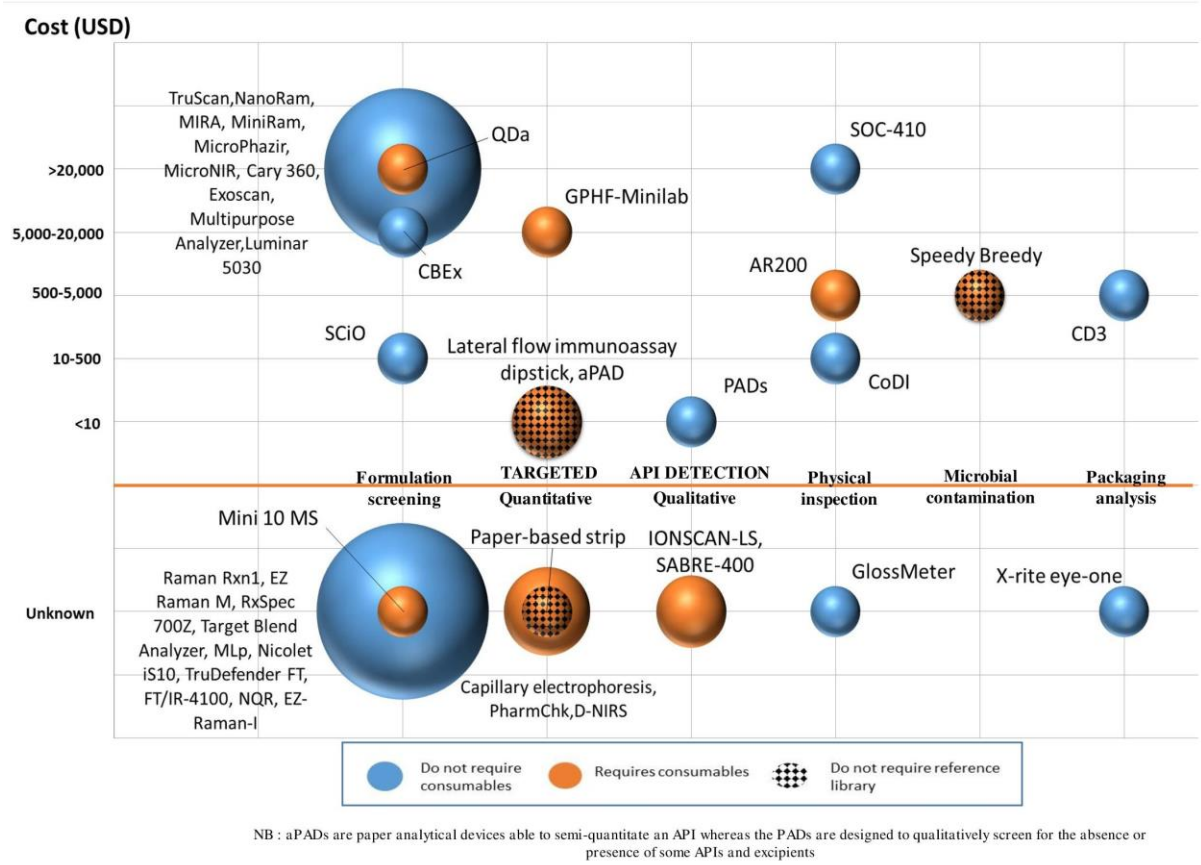

Figure 1. Main characteristics of the included devices by type of analysis, cost at purchase, requirement for consumables and/or reference library. The size of the circles is proportional to the number of devices

Table 1. Main characteristics of portable devices included in the literature review. Devices in italics have been superseded

Technology	Name of the device (developer)	Market status*§	Approximate Purchase cost (USD)§	Handheld **	References
Raman	TruScan RM (Thermo Scientific, previously Ahura)	M	>20,000	Y	[15],[16],[17]***,[18],[19],[20]***,[21],[22],[23],[24],[25],[26],[27],[28],[29],[30]
	FirstDefender TruScan (Thermo Scientific)	*N-Superseded by TruScan RM*	-	Y	[31]
	NanoRam (B&W Tek)	M	>20,000	Y	[32]
	MiniRam II (B&W Tek)	N-Superseded by i-Raman (B&W Tek)	N/A (i-Raman: >20,000)	N	[15]
	MIRA (Metrohm)	M	>20,000	Y	[33]
	Raman Rxn1 Microprobe (Kaiser Optical)	M	Unknown	N	[34]
	EZRaman-I (TSI, Inc)	M	Unknown	N	[35]
	EZ Raman M Analyzer (Enwave Optronics)	Unknown	-	Y	[36]
	CBEx (Metrohm Raman)	M	5,000-20,000	Y	[37]
NIR - Fourier Transform	MicroPhazir (Thermo Scientific)	M	>20,000	Y	[38],[23],[27],[28]
	Phazir RX (Polychromix)	*N-Superseded by MicroPhazir (Thermo Scientific)*	*N/A*	Y	[15],[17]***,[39]***,[40]
	Phazir RX (Thermo Scientific)	*N-Superseded by MicroPhazir (Thermo Scientific)*	*N/A*	Y	[31]
	Luminar 5030 (Brimrose)	M	Unknown	Y	[15]
	Target Blend Analyzer (Thermo Scientific)	M	Unknown	N	[15]
	Multipurpose Analyzer (Bruker Optics)	M	Unknown	N	[41]
NIR - Dispersive	MicroNIR (JDSU) ¥	M - Taken over by Viavi Solution	>20,000	Y	[42],[43]
	D-NIRS (School of Science and Technology, Kwansei Gakuin University) ¥	D	Unknown	N	[44],[45]
	SCiO (Consumer Physics)	M	10-500	Y	[46]
	RxSpec 700Z (ASD)	N-Superseded by other technologies from ASD	Unknown	N	[15]
MIR - Fourier Transform	MLp (A2 technologies)	N-Superseded by 4500 Series Portable FTIR (Agilent Technologies)	Unknown	N	[15]
	Nicolet iS 10 (Thermo Scientific)	M	Unknown	N	[15]
	Exoscan (A2 Technologies)	N –Now commercialized by Agilent (Exoscan 4100)	>20,000	Y	[15]
Combined NIR/MIR - Fourier Transform	TruDefender FT (Thermo Scientific)	M	Unknown	Y	[31]
	FT/IR-4100 (JASCO, Tokyo, Japan)	Superseded by FT/IR-4600 (JASCO)	Unknown	N	[24]
	Cary 630 (Agilent)	M	>20,000	N	[27],[28]
TLC, colorimetry, disintegration test	GPHF Minilab (Global Pharma Health Fund E.V.)	M	5,000-20,000	N	[47],[48],[16],[17]***,[49]***,[50],[51],[21],[52]***,[53]
Camera system with various LED sources	CD3/CD3+ (Counterfeit Detection Device version 3/3+) (US FDA) ¥	D	500-5,000	Y	[21],[54],[55],[56]
Lateral flow immunoassay dipsticks	Unnamed (China Agricultural University, Beijing and University of Pennsylvania) ¥	D	<10	L	[57],[58],[59]
Paper-based devices	PAD (Paper Analytical Devices) (University of Notre Dame) ¥	D	<10	L	[60],[61]
	aPAD (Iodometric titration on paper card) ¥ (University of Notre Dame)	D	<10	L	[62],[63]
	Paper-based microfluidic strip (Unnamed) ¥ (Oregon State University)	D	Unknown	L	[64]
Ion mobility spectrometry	IONSCAN-LS (Smiths Detection, Danbury)	M	Unknown	N	[65],[66]***
	SABRE 4000 (Smiths Detection, Danbury)	M	Unknown	Y	[65]
Capillary electrophoresis	Unnamed (Hanoi University of Science) ¥	D	Unknown	N	[67]
Reflectance	SOC-410 Directional Hemispherical reflectometer	M	>20,000	Y	[68]
	Glossmeter-Unnamed (University of Eastern Finland) ¥	D	Unknown	Y	[69]
Dissolution microfluidics with luminescence detection	PharmaChk beta 1.1 (Boston University) ¥	D	Unknown	N	[70]
Mass spectrometry	Mini 10 mass spectrometer (Purdue University)	D	Unknown	Y	[71]***
	QDa single quadrupole (Waters)	M	50,000	N	[72]
Nuclear quadrupole resonance (NQR)	Unnamed (King's College, London) ¥	D	Unknown	N	[73]
Reflectance colour measurement	X-rite eye-one (Regensdorf)	M	Unknown	Y	[74]
Low-cost laser absorption/fluorescence	CoDI (Counterfeit Drug Indicator) (Centres for Disease Control and Prevention)	D	10-500	Y	[55]
Refractometry	AR200 digital refractometer (Leica Microsystems)	M	500-5,000	Y	[75]***
Pressure changes measurement (respirometer)	Speedy Breedy (Bactest)	M	500-5,000	N	[76]

**D: Under development; M: marketed; N: no longer marketed*
***Y: Yes; N: No; L: Lab-on-a-chip or disposable device*
****indicates paper published before 2010*
¥ Indicates devices for which all articles found in our review were written by author(s) not indepenpdent from the manufacturre/develeopr
§: Information from manufacturer website or direct contact with manufacturer
LED: Light-emitting diode

All evaluations were performed in a laboratory setting unless stated otherwise. We classify devices into those (1) that examine the pharmaceutical formulation i.e. both API(s) and excipients present in the finished pharmaceutical product, ('formulation screening'); (2) those which focus on API(s) detection only; (3) those 'Physical Analysis Devices' which primarily assess the physical, rather than chemical, properties of samples and (4) those that have the ability to detect microbial contamination.

A summary of the reference requirements per device is available in the **additional material 4** and all the extracted information are presented in **additional material 5** and **6**.

Formulation Screening Devices

The devices in this section examine the chemical 'fingerprint' of a formulation (both API(s) and excipients) and are classified by whether they have been tested for their ability to perform quantitative API analysis or not. The ability of these devices to discriminate between poor quality *vs.* good quality medicines, and to quantitate APIs, depends on both the performance of the device and on the post-acquisition processing of spectral data by the associated software. All require a spectral reference library, but are typically non-destructive and do not require consumables.

Devices tested for their ability to do quantitative analysis of APIs

The Raman **TruScan RM** (Thermo Scientific) is one of the six devices tested in the field (**Table 2**). It discriminated between 14 poor quality (falsified and degraded medicines) and 70 authentic antimalarials with 100% sensitivity and 99% specificity.[21] Forty-four falsified samples (of 8 different products) and 62 formulations of genuine products (unstated APIs, 33 'product families' in total) were identified with 100% accuracy.[22] The TruScan showed similar match/fail performance for medicines identification (despite lower signal resolution) when compared to Raman benchtop instruments.[18,22,25].

Table 2. Main characteristics and performances results of the field-tested devices

Name of the device (Developer)	Field-test Location(s)	Therapeutic indication tested	Reported sensitivity	Reported specificity	Other information - User skill required
GPHF-Minilab (Global Pharma Health Fund E.V.)	Gabon, Angola, Brazil, Cameroon, China, Democratic Republic of Congo, Egypt, Ethiopia, Ghana, India, Kenya, Nigeria, Russia, Rwanda, Thailand, Turkey, Uganda, Tanzania, Zambia, Bolivia, Brazil, Colombia, Ecuador, Guyana, Suriname, Venezuela	Anti-malarials[21],[50],[51],[49]; Antibiotics[49]	29% of extremely non-compliant samples§[b] for both content and dissolution correctly identified by the Minilab[51] ; Se[a] for both ID test and content test=79% , Se[a] for ID test only=100% [21]	Sp[a] for both ID test and content test=100% , Sp[a] for ID test only=100% [21]	Visual appearance did not provide consistent results when performed by MRA staff or lab staff [51]- Some lab skills required – At least one week training and proficiency testing recommended
CD3/CD3+ (US FDA)	Ghana	Anti-malarials[21]	Se[a]=100% for analysis based on packaging materials and dosage unit [21], Se[a]=100% for dosage-unit-only analysis[21]	Sp[a]=53% for analysis based on packaging materials and dosage unit [21], Sp[a]=64% for analysis dosage-unit-only analysis [21]	More reliable to conduct side-by-side comparisons with physical authentic samples than using the library images CDAIL[21] - Low skill level required- performances increase with experience
Lateral flow dipstick immunoassay (Unnamed)	Colombia, India, Papua New Guinea, Zambia	Anti-malarials[57]	N/A-No gold standard reported[57] NB: 2-4% cross-reactivity of artemether and artesunate to artemisinin[57]	N/A-No gold standard reported[57]	N/A-No gold standard reported[57] - Low skill level required
Truscan RM (Thermo Scientific)	USA	Erectile dysfunction drug [30]	Testing by unknown number of special agents unfamiliar with instrument and procedure : Acc[c] for identification of the presence/absence of sildenafil (n=14): 91.7% [30]		A sample preparation (extraction, filtration, addition of silver colloid) was performed, the obtained sample solution was then tested in a vial [30] - Training of 20 min considered as sufficient (test by four analysts only) [30]
CBEx (Metrohm Raman)	India, Zimbabwe	Antimalarials, Antibiotics and others (not detailed in the publication) [37]	N/A**		Rugged (instrument dropped accidentally twice with no observed altered functioning; No problem during routine international air transportation and travel by vehicle to various sites; instrument withstood temperatures between room and 40°C temperatures [37] - Less than two weeks training estimated as sufficient to become basic to advanced user [37]
Speedy Breedy (Bactest)	India, Zimbabwe	Antibiotics, Sterile NaCl, Purified water [76]	N/A**		Long time run = power interruption required to restart the run of the sample the next day; Biological waste management required; Carry case not robust enough at the time of study [76] - Less than two weeks training estimated as sufficient to become basic to advanced user [76]

Se, Sensitivity; Sp, specificity;
[a] Against HPLC analysis, [b] Against HPLC and dissolution testing (please note that disintegration testing is not an appropriate proxy for dissolution testing) [c]Against FT-IR
CDAIL, CD3 Authentic Image Library
§ Extreme deviation was defined as a deviation of 20% or more from the declared amount of API as determined by assay, and/or a percentage of active ingredient dissolved 25% or more below the pharmacopoeial limit Q in dissolution testing
*Maximum 10 min for the end user
**Field evaluation aimed at testing the field utility of the device rather than its performance

After applying a sample preparation method, special agents in a mail facility tested 14 samples of Viagra® (12 contained sildenafil), with the Truscan RM with an accuracy of 91.7%

to qualitatively identify the presence/absence of sildenafil (FT-IR analysis as reference technique).[30] Different strengths (simulating 'substandard' medicines) of the same antimalarial APIs and brand could not be reliably distinguished using the match/not-match approach.[19,21] In addition, one in three placebos wrongly passed the identification test *vs.* their full API strength counterpart.[22] In investigations of the p-values (threshold limit for a sample to give a 'pass' or 'fail') obtained by scanning five products containing candesartan with the Truscan RM, it was suggested that the p-value could be set at 0.40 (instead of 0.05) for the device to better discriminate substandard medicines containing less than 50% or more than 150% API from the good quality products.[29] However, these results should be taken with caution considering the small sample size. The First Defender TruScan (superseded by the TruScan RM) determined the amount of APIs to within 1.6–12% of the reference assay for experimental finished products of acetylsalicylic acid, ascorbic acid and caffeine.[31]

The **NanoRam** (B&W Tek) showed 100% sensitivity and 96% specificity (against TLC, with HPLC used to confirm samples which failed TLC) in the investigation of 289 antimalarial samples (including 24 falsified, and 22 experimental 'wrong API fakes' containing paracetamol).[32]

The **Metrohm Raman Instant Analyzer** (MIRA, Metrohm) discriminated between different concentrations of injectable doxorubicin (n=90) and epirubicin (n=90) through glass containers with 100% sensitivity and specificity. Quantitation with a coefficient of determination (R^2) of 0.99 was reported.[33]

The **EZ-Raman-I** (TSI, Inc.) qualitatively confirmed the presence of the stated API in four finished drug products containing amoxicillin, acyclovir and doxycycline,[35] with a Raman binary barcode method using a reference library containing Raman spectra of APIs. [77] On averaging the results of the % of the API claimed on the label of five tablets per sample, predictions by the EZ-Raman-I were within 3% of the HPLC results for three out of four products, and one products showed value 6.0% lower than those obtained by HPLC.

Among the 14 devices based on IR/Mid-IR, the **MicroPhazir** (and its predecessor the Phazir), has been tested on small sample sets of different types of raw or finished pharmaceutical product types in the laboratory.[15,17,23,27,28,31,38,40,78] Spectral data have been successfully acquired through transparent blister packaging using six experimental samples.[23] Quantitation of acetylsalicylic acid, ascorbic acid and caffeine in tablets gave results comparable to a reference benchtop FT-NIR instrument.[31]

The **MicroNIR** (JDSU, then Viavi) and the **TruDefender FT** (Thermo Scientific) have been used for quantitation of API to within 0.1–7.8% of the reference for weight loss and erectile dysfunction medicines, and also for acetylsalicylic acid, ascorbic acid and caffeine.[31,42]

The **SCiO** (Consumer Physics) device showed 100% specificity and sensitivity for the identification of falsified (n=42) *vs*. genuine (n=54) antimalarials, but failed to quantify the amount of amodiaquine in finished products. This device was able to quantify artesunate with 95% certainty in 15 oral products.[46]

The compact benchtop **QDa** single quadrupole mass spectrometer (Waters) correctly identified the ACT artemether+lumefantrine and other compounds, such as chloramphenicol, ciprofloxacin and sugars, in 192 seized falsified antimalarials. The relative intensity of each compound detected could be compared from run to run between tablets and used as a proxy for API quantitation.[72] For quantitation, the handheld **Mini 10 MS** has been demonstrated to produce parts-per-billion detection limits for drugs of abuse in simple samples [71] but has not yet been evaluated for poor quality medicines.

Devices with untested potential to perform quantitative analysis of APIs

Three Raman devices [MiniRam II, (B&W Tek), Raman Rxn1 Microprobe (Kaiser optical), EZ Raman M Analyzer (Enwave Optronics)] [15,34,36] and nine NIR/MIR devices [MultiPurpose Analyzer (Bruker), Luminar 5030 (Brimrose), RxSpec 700Z (ASD), Exoscan

(A2 Technologies), MLp (A2 Technologies), FT/IR-4100 (JASCO), Cary 630 (Agilent), Nicolet iS 10 (Thermo Scientific), Target Blend Analyzer (Thermo Scientific)] were included in small scale laboratory studies.[15,24,27,28,41]

Of note, the **CBEx** (Metrohm Raman) successfully identified the presence of paracetamol, amoxicillin, lumefantrine and pyrazinamide in various APIs/API-combinations but failed to identify other APIs in fixed-drug combinations, (e.g. artemether in artemether-lumefantrine tablets), and furosemide and oxytocin in single API injection samples. [37] A limited set of artificially degraded samples were correctly identified with accuracies depending on the API and the level/type of degradation. A field evaluation of the utility of the device, rather than its performance (**Table 2**), amongst ten operators from the regulatory authorities of India and Zimbabwe with various technical experience, suggested this as a well-functioning device requiring less than two weeks of training. [37]

A prototype **nuclear quadrupole resonance (NQR) device** has been used successfully to identify ampicillin in capsules and paracetamol in tablets through their original packaging. No data on its sensitivity and specificity have yet been reported.[73]

Targeted API Detection Devices

Most devices in this section are semi-quantitative. All techniques require sample destruction and most require sample pre-treatment (e.g. dissolution). Some provide both qualitative and quantitative information and may provide data on other properties (e.g. disintegration characteristics). Others simply qualitatively identify the API.

Quantitative and semi-quantitative Targeted API Detection Devices

The **GPHF-Minilab** (Global Pharma Health Fund) is a ‘lab-in-a-suitcase’ containing the supplies for visual physical inspection of the medicine (both dosage form and packaging),

identification and semi-quantitation of the stated API by TLC, and disintegration testing. It is one of the six field-tested devices identified in this review (**Table 2**).

In a field survey of 84 anti-malarial medicines (including 14 substandard/falsified samples) in Ghana, 100% sensitivity and specificity were reported for Minilab TLC identification against HPLC reference assays.[21] For API identification and semi-quantitation by TLC, sensitivity was 79% with 100% specificity. In Brazil, 14/46 (30%) quinine samples were judged substandard by Minilab TLC with semi-quantitation. However, the seven samples that underwent confirmatory tests were all found to be within specifications [50]. In the same study, all 289 samples collected in Guyana passed TLC with semi-quantitation, but five out of ten samples failed subsequent confirmatory testing. A multi-country survey in Africa found that the Minilab detected 30% of 31 very non-compliant (deviation of $\geq$20% from stated API by HPLC and/or percentage of API dissolved $\geq$25% below the pharmacopeial limit Q in dissolution testing) anti-malarial samples.[51] However, dissolution and disintegration tests measure different aspects of a solid formulation and we would not expect full agreement. TLC testing failed to identify the 77 substandard antimicrobials, among which 76 samples contained %API >80% and <123% of the label claim (specificity of 97%).[53] However, the Minilab is designed to detect samples with API below the 80% threshold. Inter-observer variability was identified as a significant contributor to Minilab semi-quantitative inaccuracy [50,52]. In Tanzania, seven drug inspectors assessed finished products containing four different APIs (antibiotics and anti-malarials) at three different concentrations (0%, 40%, 100%).[52] Twenty-five out of 28 substandard samples with 40% API were incorrectly identified by TLC as acceptable quality. After further training, eight out of 28 samples were still wrongly identified as acceptable quality. All samples with 100% API, zero API, and with wrong API were correctly identified.

The **PharmaChk** is a field-portable microfluidics device, currently limited to artemisinin-based drugs, designed for API quantitation and tablet dissolution testing.[70] Quantitation of

three oral artesunate formulations (mean 5 samples per formulation), showed accuracy to within 0 to 4% of HPLC values.[70]

Single-use **lateral flow immunoassay dipsticks** (resembling rapid malaria diagnostic tests in appearance) use monoclonal antibodies to detect poor quality artemisinin-based anti-malarials [57–59]. Field survey samples (**Table 2**) were not tested against a reference technique and hence sensitivity or specificity cannot be calculated.[57] In laboratory testing, artesunate dipsticks showed 100% specificity for detecting artesunate against other commonly used antimalarials, including other artemisinin derivatives.[59] A semi-quantitative analysis of API content was obtained by sample serial dilutions.[59]

A proof of concept paper describes the adaptation of the Fast Red TR reaction for artesunate detection onto **paper-based microfluidic strips**.[64] The cards could detect the presence and determine relative concentration of artesunate in one genuine sample, and could detect its absence in two formulations containing artemether and dihydroartemisinin. Semi-quantitation accuracy was improved by gray-scale intensity analysis using a smart-phone app.

A battery-powered **capillary electrophoresis** device was able to successfully identify and quantify salbutamol and metoprolol in syrup and tablet formulations. Quantitation accuracy was within 3-13% of results obtained by HPLC.[67]

Paper cards (**aPAD**) have been successfully used for semi-quantitative **iodometric back-titration** of amoxicillin and ampicillin, tests specified in the pharmacopeial analysis of β-lactam antibiotics.[62,63] These cards differentiated between amoxicillin solutions that varied in concentration by 0.15 mg/ml, allowing identification of substandard amoxicillin <83% of labelled API content.[62] The aPADs gave errors of semi-quantitation of 13 % and 5% (compared to HPLC) for 41 samples of amoxicillin and 40 samples of ampicillin collected in Kenya, respectively. [63] In that study, aPADs identified samples containing below/above the USP 90.0% limit of the medicine stated %API, with sensitivities of 73.2% and 80.0% for amoxicillin (n=80) and ampicillin (n=56), respectively (100% specificities). The authors

suggested that artificially degraded samples made for the purpose of the study (thermally stressed) may have led to decreased sensitivities.

By obtaining two-dimensional spectral data of tablets, a **NIR imaging device (D-NIRS)** could evaluate the distribution of different chemical components during tablet dissolution, [44,45] but no sensitivity and specificity data of this device are available.

Purely Qualitative Targeted API Detection Devices

In contrast to the aPADs that enable semi-quantitation based on one chemical reaction (see above), the **paper analytical devices (PADs)** are designed for qualitative screening of APIs and some excipients.[60–62] Separate lanes housing different colorimetric reactions produce a 'colour bar code', which is compared to a reference library of 'standard colour bar code images'. Expert readers can even discriminate different strengths of APIs.[61] In testing of experimental formulations of known concentration, two antibiotics, three anti-tuberculosis medicines and two antimalarials produced sensitivity values of 76-100% (n=9-60), and specificity of 80-100% (n=30-135).[60,61] The identification of APIs in co-formulated samples was more variable. For example, in testing co-formulated tuberculosis (TB) medicine samples, ethambutol was not detected when actually present in 30% and falsely reported as present when absent in 17% of tests.[60] In testing 30 two-API co-formulated TB samples, ethambutol and isoniazid were correctly detected in all samples.[60]

Two **ion mobility spectrometry devices** have been evaluated.[65,66] The **IONSCAN-LS** (Smiths Detection) detected the APIs of erectile dysfunction drugs (EDD) in 26 herbal supplements with 100% sensitivity and specificity, with successful identification of the specific API in 13/15 (87%) of the samples.[66] The **SABRE 4000** (Smiths Detection) showed comparable results to a benchtop ion mobility instrument for detecting sibutramine in dietary supplements.[65]

Devices which primarily examine physical properties

Devices in this section primarily examine physical properties of the sample, such as their visual appearance. They cannot verify the presence or absence of the API. As falsified packaging is the key for identifying falsified medicines they may have an important parallel functionality to chemical analysis devices.

Visual/Colour Inspection

The **Counterfeit Detection Device CD3+** unmasks differences between test and authentic samples (packaging and dosage forms) by allowing the user to compare their appearance under diverse UV-Vis and IR wavelengths.[21,54–56] With this technique, falsified and genuine artesunate blister pack samples (n=203) were identified with sensitivity and specificity of 98.4% and 100%, respectively, with 100% inter-user reliability.[54] In a field study (**Table 2**), 84 artemisinin-based combination therapies were identified with sensitivity of 100% and specificities of 53% (on packaging materials and dosage unit) and 64% (on dosage unit only).[21]

The **X-rite-eye-one** is an optical spectrometer that projects light of wavelengths 380 to 730 nm towards a solid surface, collects the reflected visible spectrum, and digitally records it for comparison with a reference genuine sample.[74] It correctly identified forty out of 41 (98%) samples of erectile dysfunction medicines, among which 35 were falsified. However, on testing genuine samples, 25% of packages and 15% of tablets were wrongly identified as falsified.

Other Physical Properties

Refractometry can be used to quantitatively detect APIs in solution by comparing the measured concentration to a concentration curve constructed from known standards. In testing whether an API was within 80-120% of the stated concentration, the **AR200 digital refractometer** (Leica Microsystems) showed a sensitivity of 83-100%, and specificity of 56-87% for 458 samples of five different poor quality anti-malarials (both tablets and injectables).[75]

The **Counterfeit Drug Indicator** (CoDI) measures the ratio of laser light intensity transmitted and scattered on passing through a tablet, and compares the result from the test sample to that from an authentic tablet. The device correctly discriminated six falsified and 12 authentic artemether-lumefantrine tablets.[55]

The handheld **SOC-410** (Surface Optics Corporation) uses directional hemispherical reflectance to analyse the surface of tablets in the mid- and near-infrared range without need for complex spectral interpretation. It showed 100% accuracy for the identification of one genuine and four falsified Viagra® samples.[68]

A handheld **glossmeter**, based on diffractive optical elements, was developed to analyze differences in the magnitude of specular gloss of the surface of authentic and falsified tablets. The device results showed consistency with the findings from a 2D glossmeter and an optical interference profilometer to screen for two falsified artemether-lumefantrine samples from Ghana. [79]

Microbial contamination detection

The **Speedy Breedy** (Bactest), a portable respirometer that detects pressure changes as a proxy of microbial growth and hence contamination in liquid samples, showed sensitivities from 93.0 to 100% and specificities of 100% to identify microbial contamination by *Escherichia coli* of samples of sterile water for injection that were purposively spiked under various laboratory experimental conditions. Artesunate and oxytocin products for injection were correctly characterized for the presence/absence of microbial contamination with *E. coli* and *Pseudomonas aeruginosa.* Further evaluation of the field utility of the device (rather than its performance) showed that, despite the ability of the device to generate results under uncontrolled field settings (India and Zimbabwe), the requirement for a continuous power source during analysis (that can take more than a day) might be a barrier for its use in remote settings (**Table 2**).[76]

DISCUSSION

The above results demonstrate the huge diversity of technologies and devices becoming available for the field detection and evaluation of medicines.

To maximise the detection and removal of poor quality medicines from the supply chain, a screening device with high sensitivity is required. Specificity is less vital as, although low values would lead to additional work and cost in reference laboratory assays, they would not lead to patient harm. Sensitivity data were found for few devices and were mostly derived from results of laboratory testing on a small number of samples of a few APIs. The median (range) number of APIs that were assessed per device was only 2 (1-20), a very meagre proportion of the ~7,000 global international non-proprietary names of pharmaceutical substances.[80]

The increasing sophistication of falsified medicines requires advanced techniques that detect anomalies of packaging or product not apparent to the naked eye. Of the included devices, the CD3 and the X-rite showed high sensitivity for packaging authenticity evaluation. The low-cost single-use technologies showed promise for qualitative analysis (PADs, lateral flow immunoassay dipsticks) and could be of great interest in the distal pharmaceutical supply chain. Very few devices have been evaluated for their ability to distinguish genuine from substandard medicines with reduced %API. Most devices with the potential to assay API (semi-)quantitatively in finished products require consumables and are destructive (GPHF-Minilab, PharmaChk, aPADs, lateral flow immunoassay dipsticks, paper-based microfluidic strip, capillary electrophoresis), except for spectroscopic devices. However, of the ten spectroscopic devices (Truscan, Nanoram, MIRA, EZ-Raman-I, Microphazir, MicroNIR, TruDefender, SCiO, QDa, Mini10 MS) tested for quantitation, none used automated methods, but required highly trained operators using complex API-specific calibration models, and are therefore not field-ready.

Tablet dissolution characteristics are key determinants of bioavailability and therefore efficacy. No marketed portable devices are currently able to evaluate dissolution, despite the

likely contribution of poor dissolution antimicrobials to antimicrobial resistance.[10] The under-development D-NIRS was the only portable device assessed for its ability to monitor dissolution, and showed promising results, albeit on a limited number of samples. Methods for detecting other quality defects in substandard medicines, such as the presence of impurities or the lack of sterility have received very little attention, except the Speedy Breedy that recently showed promise to identify microbial contamination in liquid samples.[76] The distinction between degraded medicines, which left the factory good quality but deteriorated due to poor storage and transport and those failing due to errors in factory production is vital as the origins and solutions are different. Development of reference and screening API-specific technologies that could distinguish these issues will be of great importance.

Two-third of the devices (27/41, 66%) identified use spectroscopic techniques. Of these, only the TruScan and the NanoRam have been tested on a large number of samples in the laboratory. However, it was not possible to reliably and comprehensively review devices such as the Truscan for their performance, because one of the key publications could not be evaluated, since the APIs contained in the products tested were not detailed.[22] This emphasises the importance of ensuring that the databases of the results of device evaluations are made available to ensure their enduring value. A major advantage in a L/MIC setting of many of the spectroscopic devices is the need for minimal end-user training, provided that the chemometrics analysis steps have already been bundled in user-friendly software. However, there are obstacles to their implementation. Firstly, the purchase cost of most of these devices is high, likely prohibitively so, in L/MIC settings. User-friendly miniaturized low-cost spectrometers such as the SCiO (that can be operated using a smartphone) have recently shown promising performance.[46] Secondly, the need for up-to-date reference specimens, whether as a pre-stored ‘spectral reference library’ or physical samples of quality-assured genuine medicines, adds significant work.[81] ‘In-built’ libraries of raw materials available in some spectrometers are inappropriate for the screening of finished pharmaceutical products, as the

spectra obtained are often influenced by both APIs and excipients and vary between brands. The difficulty of assembling quality-assured comparators and the need for frequent updating of stored spectral signatures may present a barrier to use unless the pharmaceutical industry efficiently and promptly provides updated samples or spectra when manufacturing processes change. Almost 30% (n=114) of anti-malarials collected in one study could not undergo Raman analysis because the authentic comparators could not be obtained by the investigators.[32] Discussion on industry standards for spectra file format and transferability between devices using the same technology will be important.

Each spectroscopic technique has unique advantages and disadvantages. Using a combination of different spectroscopic techniques in parallel may be beneficial. For example, using a Raman spectrometer in combination with an IR spectrometer for tablets containing relatively low quantities of APIs may improve detection.[22,82] Combining a spectroscopic tool with a visual inspection tool may also be synergistic. As far as we are aware there have been no evaluations of combined technologies.

The widely distributed GPHF Minilab (more than 800 units distributed in 95 countries), [83] showed good performance for identification of falsified medicines by TLC in one study and consistently high specificity. Results were user-dependent, underlying the importance of regular good quality training and proficiency testing. Of note, the disintegration testing in the Minilab kit is not an appropriate proxy for dissolution testing. The device showed limited ability to identify substandard medicines. In a recent study in China in which 77 samples were substandard, most being above the 80%API threshold in HPLC testing, 0% sensitivity (97% specificity) was reported.[53] However, vitally, the Minilab does not claim to be able to detect substandard medicines with API content above the 80% limit. Its main function has been to detect zero and wrong API medicines.

There are important limitations to this review. Our search included only scientific databases and only in English. We discounted 29 articles in which the stated aim was to develop, validate

or compare chemometric techniques, rather than to assess the performance of the portable device itself, thereby excluding 13 portable devices (**additional material 7**). This includes the Matrix-F (BrukerOptics), a non-handheld device used in over 300 mobile laboratories in China.[84] Findings of device evaluation performed by non-independent evaluators risk bias and should be interpreted with caution.

Comparison between devices was significantly hindered by the heterogeneity of device evaluation methods and reporting. We found only two studies in which the standards for reporting diagnostic accuracy studies (STARD) were followed.[32,53] Standardized guidance on how to assess and compare the performance of screening devices would be of great benefit. A recent article from United States Pharmacopoeial Convention addresses this.[85] There is an urgent need for international organisations, the device and pharmaceutical industry and regulatory authorities to discuss norms and standards for medicine quality screening devices. In addition, field-testing was conducted for just six devices, leaving a paucity of data on performance in the 'real-world'.

Other key gaps in the literature were identified (**Box 3**). We observed a dire lack of information as to which medicines and formulations can be evaluated with each device. There has been a focus on anti-infective medicines (especially anti-malarials), neglecting other medicine classes.

Box 3. Key gaps in the literature

- Lack of independent evaluation of the majority of devices, particularly in field-settings
- Device performance tested on a very limited subset of available APIs, predominantly anti-infectives
- Very limited testing and comment on the ability of the devices to test through packaging, and the type of packaging that is least obstructive to device use
- Very limited comment on the inability of Raman or IR spectroscopy to test capsules non-destructively, due to the opacity of capsule coating
- Very limited information on the performance of devices to test liquid or parenteral formulations is available with no data on testing of topical formulations
- No studies looking at the effect of tablet coating on device performance
- No information on cost-effectiveness
- No testing or comment on the ability of the devices to distinguish between chiral enantiomers
- Very limited comment on where in the pharmaceutical supply chain which devices are best employed
- Very few studies which comment on training needs for accurate use of the devices

Chemical structures suggest *a priori* that some APIs will be problematic for certain devices. For example, NQR can only detect APIs with quadrupolar nuclei, such as ^{14}N. This is present in over 80% of medicines,[86] but not, for example, the artemisinin derivatives.[65] Similarly, some APIs, such as artesunate and quinine sulphate, have strong fluorescence with weak Raman scattering at 785 nm, impairing the ability of such Raman devices to detect poor quality products labelled as containing these APIs [19,20]. Raman scattering from medicines with relatively low amounts of API(s) is often insufficient [22,82]. Sensitivity of the PADs is also reduced for formulations with a low proportion of API.[61] More than half of pharmaceuticals are chiral compounds, with many enantiomers of racemic drugs showing marked differences in pharmacology. [87,88] No discussion was found on the ability of the reviewed devices to discriminate different enantiomers. Theoretically only NQR would have this capability.

Most of the tested finished products in the included studies were tablets. Certain tablet coatings will likely provide a very difficult barrier to optical spectroscopic examination, as shown in testing of blue-coated dihydroartemisinin with the NanoRam.[47] No data were found

on testing of topical applications (e.g. creams, gels) and little on liquids. It is unclear whether the devices lack the capability to test these formulations, or simply that this has not yet been investigated.

One vital but undiscussed issue is that (with the probable exception of NQR) it will not be possible to non-destructively evaluate capsules unless spectroscopic techniques can be developed that allow the devices to 'see through' the capsule material. Consequently, a very sizeable proportion (in Laos, UK, France and USA, capsules comprise 11.4 % ,[89] 17.7%,[90] 9.7% [91] and 7.7% [92], respectively, of registered oral medicines) of the global medicine supply will not be amenable to non-destructive spectroscopic evaluation. Non-destructive sampling was highlighted by different regulatory authority stakeholders as an ideal feature of a medicine quality screening device in a recent qualitative research paper.[81] The use of transparent capsule shells could greatly expand infrared or Raman devices utility. There are also few data on the ability of devices to accurately assess medicines through packaging (important when sample size is small and samples are required for legal investigations). How spectroscopic device accuracy changes with different types of glass and plastic packaging seems unknown. With such information, blister pack and tablet/capsule/powder/liquid bottle packaging could be designed to facilitate spectroscopic evaluation.

Further key aspects that have received minimal discussion include issues of device maintenance and quality assurance/quality control of the devices performance (including calibration and performance quality checks).

The cost-effectiveness of introducing devices within post-marketing surveillance (PMS) systems, compared to other solutions for strengthening PMS, has not apparently been investigated. Screening technologies should be considered within a broader strategy to reduce the risk of poor quality medicines reaching patients. Given the substantial costs of using most of the devices in L/MICs, investment in devices should be compared with other strategies, such as enhancing inspection of manufacturing sites and evaluation of product dossiers. The public

health effectiveness of detection of poor quality medicines will not be fulfilled unless reference laboratories are accessible and appropriate rapid responsive action is conducted.

How devices can be optimally used in different parts of the pharmaceutical supply has been little discussed, nor their integration into PMS. Their abilities may be over-appreciated and vital routine visual packaging inspection reduced. Non-governmental organizations, procurement agencies and other institutions supplying medicines may also benefit from the use of reliable devices to check the quality of medicines they procure and to identify reliable providers. Because those involved may have diverse educational backgrounds, data are needed to better understand the minimum level of training needed for an appropriate use of the devices.

It seems unlikely, with current technology, that one device will be able to effectively monitor the quality of all medicines and exploration of combinations of devices with different faculties is needed. The synergistic combination of devices with smart phones containing registration, batch number and packaging information for the country's medicines, and alerts of poor quality medicines in the region and to and from WHO holds great promise. As research expands on screening devices for testing different APIs, especially those co-formulated, care will be needed with the public release of these data in order to avoid informing those making poor quality medicines of information that would allow them to circumvent detection of their 'products' by the screening devices.

For a small proportion of the globally available APIs, there is evidence that some devices will reliably detect falsified medicines, often containing zero or wrong API. However, there is much less evidence for their ability to detect substandard medicines, usually containing either too much, too little API or impaired dissolution. If such devices are used, it will be important to recognise this issue and not to regard a pass result as meaning that a medicine is good quality, only that it is not falsified. Clear statements from manufactures and those evaluating these devices on their claimed capabilities and their limitations will be crucial to avoid overconfidence in their abilities.

CONCLUSION

The diversity of devices for medicines quality screening holds great hope for empowering medicine inspectors, making their work more cost-effective and actionable, and protecting patients from the harm of poor quality medicines. However, there is a vitally important lack of independent evaluation of the majority of devices, particularly in field settings. There is currently no device demonstrated to be able to screen the quality of all existing APIs available globally in different formulations and in different settings. Training and costs of implementing screening devices are major concerns, especially in L/MICs, but these considerations have not been explored. Intensive research is needed in order to provide the evidence national medicines regulatory authorities need to determine the optimal choice of device(s) to combat poor quality medicines.

FIGURES AND BOXES LEGENDS

Figure 1. Main characteristics of the included devices by type of analysis, cost at purchase, requirement for consumables and/or reference library. The size of the circles is proportional to the number of devices.

Box 1. Definitions of substandard and falsified medicines

Box 2. Main technologies used in pharmaceutical quality analysis

Box 3. Key gaps in the literature

AUTHOR CONTRIBUTIONS

All the authors were involved in the conceptualisation and methodology of the study. CC, SV and MB designed the data collection tool. CC, SV, SZ and MB were responsible for the formal analysis and investigation. CC, SV and MB were responsible for the original draft preparation.

FMF and PNN were involved in the supervision. All the authors equally contributed to the reviewing and editing of the manuscript.

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COMPETING INTEREST

None declared.

DATA SHARING

No additional data available.

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Supplementary Annex 2 - additional material 1. PRISMA checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction pp4-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, p7; para 1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, p 7; para 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods pp7-8; para 2,3 and 1, respectively
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, p7-8; para 2,3 and 1 respectively
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplementary file 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, p7-8, para 3 and 1,2 respectively

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, pp7-8, para 2 and 1, respectively
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, pp8-10- Key variables and definitions and data analysis
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P10; para 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Qualitative only
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P10; para 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	PRISMA flow diagram, online suppl file 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A see item 12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A see item 12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pp22-25,
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P25, para 2
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P29 and Box 3
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding, p30-31

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Annex 2 - additional material 2. Search terms per search engine

Embase.com, Pubmed and Web of Science

(technology or technique or device or apparatus or instrument or system or detector or method or analyzer) AND (portable or handheld or battery powered or field test or mobile or rapid) AND ("medicine quality" or "drug quality" or "pharmaceutical quality" or counterfeit* OR fake* OR spurious OR substandard* OR falsified OR "falsely labelled" OR "falsely labeled")

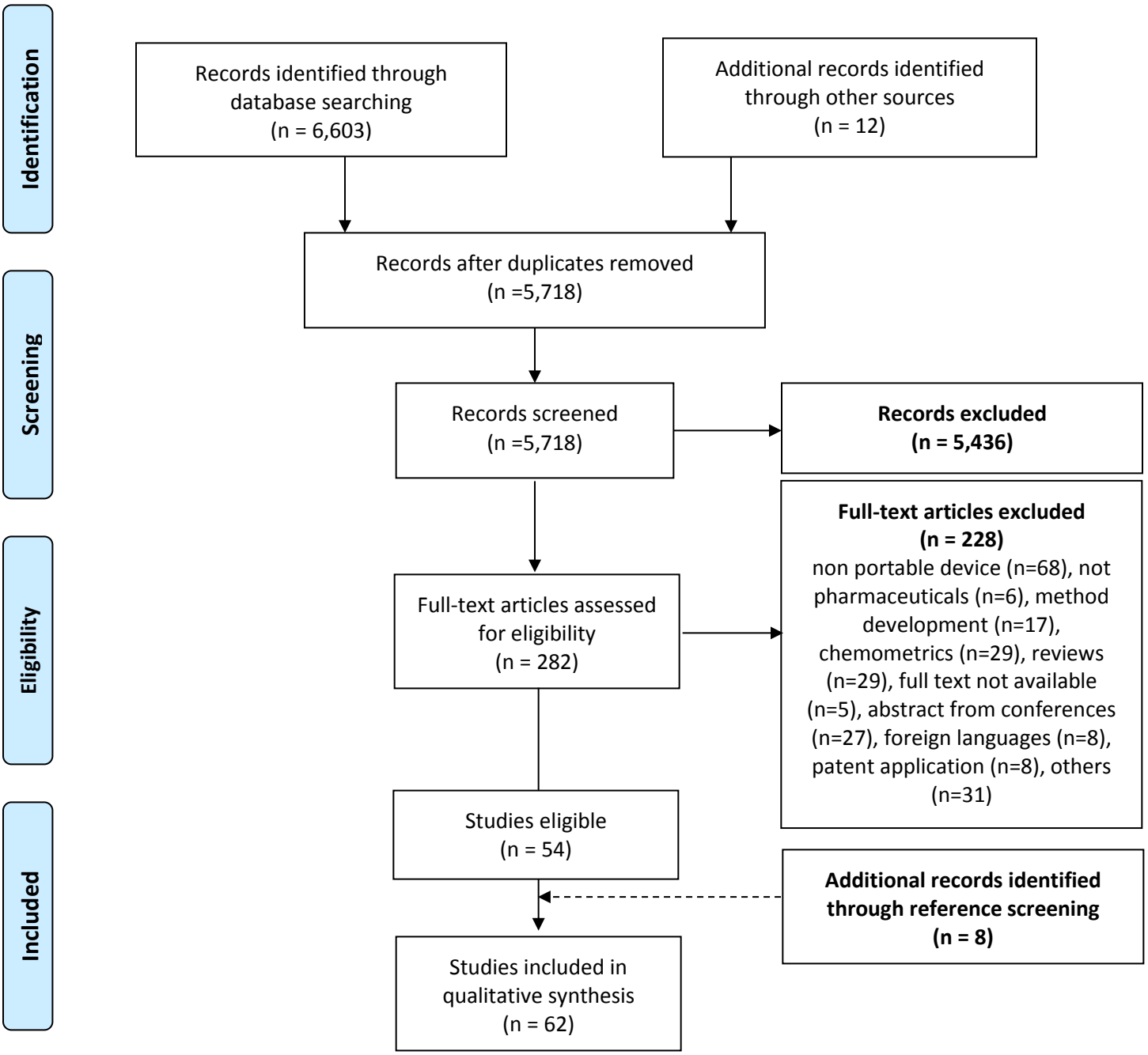
SciFinder

Thirty-six searches were performed in SciFinder, using the main key terms, because all the key terms could not be searched at once.

1. Portable (handheld) device (technique, technology) for medicine quality (drug quality, pharmaceutical quality)
2. Portable (handheld) device (technique, technology) for Falsified medicine (falsified drug, counterfeit medicine)
3. Portable (handheld) device (technique, technology) for fake medicine (substandard medicine)
4. Portable (handheld) device (technique, technology) for fake drug (substandard drug)
5. Portable (handheld) device (technique, technology) for spurious medicine (spurious drug, counterfeit drug)
6. Portable (handheld) device (technique, technology) for falsely labelled medicine (falsely labeled drug)
7. Portable (handheld) instrument (apparatus) for medicine quality (drug quality, pharmaceutical quality)
8. Portable (handheld) instrument (apparatus) for Falsified medicine (falsified drug, counterfeit medicine)
9. Portable (handheld) instrument (apparatus) for fake medicine (substandard medicine)
10. Portable (handheld) instrument (apparatus) for fake drug (substandard drug)
11. Portable (handheld) instrument (apparatus) for spurious medicine (spurious drug, counterfeit drug)
12. Portable (handheld) instrument (apparatus) for falsely labelled medicine (falsely labeled drug)
13. Portable (handheld) detector (analyzer) for medicine quality (drug quality, pharmaceutical quality)
14. Portable (handheld) detector (analyzer) for Falsified medicine (falsified drug, counterfeit medicine)
15. Portable (handheld) detector (analyzer) for fake medicine (substandard medicine)
16. Portable (handheld) detector (analyzer) for fake drug (substandard drug)
17. Portable (handheld) detector (analyzer) for spurious medicine (spurious drug, counterfeit drug)
18. Portable (handheld) detector (analyzer) for falsely labelled medicine (falsely labeled drug)
19. Portable (handheld) method (system) for medicine quality (drug quality, pharmaceutical quality)
20. Portable (handheld) method (system) for Falsified medicine (falsified drug, counterfeit medicine)

21. Portable (handheld) method (system) for fake medicine (substandard medicine)
22. Portable (handheld) method (system) for fake drug (substandard drug)
23. Portable (handheld) method (system) for spurious medicine (spurious drug, counterfeit drug)
24. Portable (handheld) method (system) for falsely labelled medicine (falsely labeled drug)
25. Mobile instrument (mobile apparatus, mobile technology, mobile technique) for medicine quality (drug quality, pharmaceutical quality)
26. Mobile instrument (mobile apparatus, mobile technology, mobile technique) for Falsified medicine (falsified drug, counterfeit medicine)
27. Mobile instrument (mobile apparatus, mobile technology, mobile technique) for fake medicine (substandard medicine)
28. Mobile instrument (mobile apparatus, mobile technology, mobile technique) for fake drug (substandard drug)
29. Mobile instrument (mobile apparatus, mobile technology, mobile technique) for spurious medicine (spurious drug, counterfeit drug)
30. Mobile instrument (mobile apparatus, mobile technology, mobile technique) for falsely labelled medicine (falsely labeled drug)
31. Rapid test (field test) for medicine quality (drug quality, pharmaceutical quality)
32. Rapid test (field test) for Falsified medicine (falsified drug, counterfeit medicine)
33. Rapid test (field test) for fake medicine (substandard medicine)
34. Rapid test (field test) for fake drug (substandard drug)
35. Rapid test (field test) for spurious medicine (spurious drug, counterfeit drug)
36. Rapid test (field test) for falsely labelled medicine (falsely labeled drug)

Supplementary Annex 2 - additional material 3: PRISMA flow-chart



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Supplementary Annex 2 - additional material 4. Reference Requirements per Device

Category	Subcategory	Device	Minimum Reference Required	Pre-recorded	Sample needed for reference
Formulation Screening Devices	*Quantitative*	Select Raman, NIR and MIR spectrometers	Spectral reference library	M	G
		Mass spectrometry	Reference table of values or spectral reference library.	O	R
	Qualitative. Undemonstrated quantitative ability	Select Raman, NIR and MIR spectrometers	Spectral reference library	M	G
		NQR	Reference table of values or spectral reference library.	O	G
Targeted API Detection Devices	*(Semi-)Quantitative*	Minilab	Reference sample (preferably brand specific)	NP	R
		PharmaChk	Reference sample/calibration standard(s) of API.	NP	R
		Lateral Flow Immunoassay Dipsticks	None	N/A	N/A
		Paper-based microfluidic strip	None	N/A	N/A
		Capillary electrophoresis	Genuine brand-specific sample or reference standard	NP	G
		Iodometric back titration	None (positive control needed for performance verification)	N/A	C
		D-NIRS	Genuine sample. (Primarily for	O	G

			dissolution testing purposes).		
	Purely Qualitative	PADs	Library of images	O	R/C
		Ion mobility spectrometry	Genuine sample or reference standard	N/O	G (preferable)
Devices which primarily examine physical properties	*Visual/colour inspection*	CD3	Library of images (dosage form and packaging)	O	G
		X-Rite Eye-One	Spectral reference library (dosage form and packaging)	M	G
	Other physical properties	Refractometry	Reference table of values and at least one known solution.	O	G
		CoDI	Reference table of values.	O	G
		SOC-410	Reference table of values	O	G
		Glossmeter (unnamed)	Gloss value	O	G
Microbial contamination detection		Speedy Breedy	None (negative control needed)	N/A	N/A

G, Genuine brand-specific sample: a quality-assured genuine sample of the medicine under test, from the same manufacturer and at the same dose.
R, Genuine non brand-specific sample: a quality-assured genuine sample of medicine containing the same API and the same dose as the medicine under test, but which is not manufacturer-specific.
C, chemical reference standard: a highly-characterised, quality-assured specimen of the pure API.
N, None: no reference sample is required, but good practice requires use of a reference sample either brand-specific or non brand-specific as a positive control.
'**Pre-loaded**' refers to the ability to acquire the reference data prior to the time of sample testing:

- **M, Mandatory**: the device requires the uploading of pre-recorded reference data prior to use
- **O, Optional**: pre-recorded reference data can be uploaded prior to use if desired, or the genuine sample can be run at the same time as the test sample for comparison.
- **NP, Not Possible** – the device requires a brand/non brand-specific genuine sample to be run at the same time as the test sample.

A **spectral reference library** consists of previously-recorded spectra of genuine samples.
A **reference table of values** consists of values from previous measurement of the reference, and stored either on the instrument or in a separate location.

Supplementary Annex 2 - additional material 5. Main characteristics of the devices and performance findings in the included publications

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
Raman	MiniRam II (B&W Tek, superseded by the i-Raman B&W Tek)	SR 250-3050 cm-1 (350-1800 cm-1 (17)); excitation laser 785 nm; max laser output power 275 mW; thermoelectrically cooled 2048 pixel CCD detector	8 cm-1	-	Unspecified	No	Yes	Good size, weight, robustness; Very good exportability of data; Very good reference library size;Very Good QA/QC	Not very easy to use; Long pre-heating time; Can't produce an analysis report; Quality of spectrum not good; Quality of the model not good	Any solid forms, not liquids containing proteins	[1]
	Raman Rxn1 Microprobe (Kaiser optical)	SR 200-1800 cm-1, excitation laser 785 nm, 1.7 mm x 1.3 mm sampling area, step size 100 micrometers	4 cm-1	100% Acc to distinguish falsified from genuine samples when k-NN and SIMCA algorithm used (reference method not stated)	Erectile dysfunction (SIL)	Yes (tablets spilt in two)	No	-	-	-	[2]
	TruScan RM* (Thermo Scientific, formerly Ahura)	SR 250 to 2875 cm-1; excitation laser 785 nm; Laser power ~ 250 mW	8 to 10.5 cm-1	Se[c]=79%[3]; Sp[c]=99%[3]; Se[d]=100%[3];Sp[d]=99%[3]; Reliability over time (n=11): 100%[3]; Acc[i]: 100% for falsified and genuines[4]; Acc[i] 67% for placebos[4]; 35% for Generics[4]; Repeatibility : 100% (20 measurements of the same tablets at the same position)[4]; Reproducibility: 100% (changes in position in-between 10 measurements)[4]; Acc[j] 100% when measurement through glass containers or transparent blisterpacks (only tested on 1 product), 0% when through white blister (only tested on 1 product)[4]; Reproducibility 100% (2 different operators, only 2 products tested)[4]; Discovery mode: compositions of only 3 out of 27 falsified samples correctly determined[4]; Good results compared with the benchtop lab instrument although the handheld spectra were much noisier[4];Could not differenciate between a placebo and its genuine containing 0.6% API[4]; Acc: 75 to 100% for identification of genuine medicines depending on the compound [5]; Sp[g] (for different brands of different API) = 100%[5]; Sp[g] (for different lots of the same product) = 100% for AL, CHL,IBU, =2/3 for ZNS[5]; Sp[g] (for different brands of the	Anti-malarials (AMO,AL,ART,AS,DHA,CHL, SP,AL,AS-AMO, AS,SP,CHL,QUI,AL) [9],[3],[5],[10]; Unspecified [6] different formulations produced by La Roche Ltd[4];Lipid modifying agents (ATO)[11]; Antiepileptic (OX)[6]; Anti-tuberculosis[9] (ISO, RIF)[15]; Antibiotics (ERY, CIP,CEF)[9],[12], [15]; Anti-platelet (CLOP) [12]; Cardiovascular medicines (VAL, CAND) [12],[8];Anti-histamine medicines (CET,LOR)[12]; Analgesic and anti-inflammatory medicines (IBU,ASA,PARA) [5]; Minerals/electrolytes (ZNS) [5]; Erectile dysfunction (SIL)[7]	No	Yes (glass vial[13], [4], transparent blister pack[4],[10] [14])	"Very good size, weight, robustness[¥]; Very easy to use[¥]; Good exportability of data[¥]; Quite good analysis report[¥];Very good quality of spectra[¥]; Very good reference library size[¥]; Very Good QA/QC[¥]"[1], 21CFR Part 11 Compliance Documentation[9]; More accurate than the Minilab[9]; Less sensitive to environmental interference than the NIR Phazir[9]; Analyse possible through transparent blister pack[14],[4],[10],[13] (ref [6] showed mixed results-original packaging can interfere) and glass vials[4] (tests on limited number of samples); Discovery mode of the instrument enables to determine the sample chemical composition via a database integrated into the device (more than 8000 references): can sometimes identify the composition in falsified medicines[14],[4]; Instrument software avoids the user to have to perform modeling/chemometrics, making the device user-friendly[4]; The laser did not seem to damage the tablets tested after measures were	High noise and lower signal intensity and resolution compared to a benchtop unit[12],[15],[4] (but good comparative match/fail results in study [4]); ; Slightly less easy to use than the NIR Phazir[9]; Tablet holder not big enough for too large products[4]; Long time needs to be spent for signature measurements[4]; Scanning through white blisterpacks does not give accurate results[4]: High-powered laser component must be registered with the customs authority in some countries[9]; Non standard adaptor required for data transfer[9]; Risk of FP if the intensity of the Raman signal is overwhelming (especially for fixed-dose combinations such as many anti-TB, ARV)[10]	Raman active formulations; Discovery mode may provide information on the chemical composition of the sample (but does not work if compounds not in the integrated reference database and does not work well if mixture of too many compounds)[4]; SP can't be tested because of fluorescence=spectra solely due to SUD[9],[5]; AS[5],[10] and QUI[5] strongly fluorescent but high fluorescence signal suggests their presence, no fluorescence their absence[10]; Unable to detect Raman active species at low concentrations or if tablet thick coating present[12]; Risk of FP if the intensity of the Raman signal is overwhelming (especially for FDC	[1], [3], [4], [5], [6], [7], [8], [9]***, [10]***, [11], , [12], [13], [14],[15], [16], [17], [18]

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
				same API)=100% for AS, IBU, ZNS, ASA, 0% for SP[5];Sp[§] (for different dosages of the same brands of the same API) =0% for ASA and PARA[5];Sp[§] after subjecting the tablets to stress (24h at 70°C and 85% rel humidity)= 100% for AS, CHL, AL and ZNS, 0% for SP[5]Can differentiate medicines from different manufacturers[6]; Potential FN of crushed finished product of ETH if samples are tested against reference spectra from different manufacturers; Laboratory testing by analysts involved in method validation: Acc[k] for identification of the presence/absence of sildenafil using 3 units of Truscan on 117 samples each (same samples): 92.6% (15 instruments errors and 11 user-related errors - improper execution of sample preparation mostly) and 97.4% using Discover mode ; Laboratory, testing by four analysts not involved in method validation, Acc[k] for identification of the presence/absence of sildenafil using 3 units of Truscan on 10 samples (same samples) : 98.3% (2 instrument-relaed errors); 100% using Discover Mode ; Field testing, testing by unknown number of special agents unfamiliar with instrument and procedure : Acc[k] of the presence/absence of sildenafil (n=14) using one unit of the Truscan RM: 91.7% NB: a special sample preparation (extraction, filtration, addition of silver colloid) had to be performed[7]; Peak intensity from the API in a specific spectrum region shown to increase linearly with increase of APIand good repeatability of the p-value using three different lots of authentic products with 10 replicate measurements[8]				repeated 20 times[4]; Decisions = user-independent[14]; Cheap,easily[7] portable,no need for sample preparation,fast,easy to use,no requirement for electric supply, possible to scan through packaging		such as many anti-TB, ARV)[10]	
FirstDefender TruScan* (Thermo Scientific)	SR 250-2900 cm−1; excitation laser 785 nm; Working distance: ~16 mm without nose cone; ~5mm with nose cone	7 to 10.5 cm−1	Lower prediction performance for QAN of API when compared to Phazir NIR and TruDefender FT-MIR	Experimental formulation (non-therapeutic) (ASA/AA/CAF)	Yes	Yes (plastic bag)	Laser focus can be positioned into the sample of interest minimising influence from packaging material -	Poor quantitation of API in powders compared with NIR Phazir device and the Raman TruDefender (Thermo)	-	[19]

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
								successful tests through plastic bags in study			
	MIRA* (Metrohm)	SR 400-2300 cm-1; excitation laser 785 nm; single-mode diode laser - maximum 75 mW on the sample;	12 to 14 cm-1	Using the Metrohm software+specific chemometric approach, the Acc, Se,Sp of discrimination between different concentrations of EPI and DOXO were 100%; QAN: good quantitation prediction with coefficient of determination (R2)= 0.9999, low Se limits the domain of quantification (linearity range 1.26-2.00 mg/ml for DOXO; 0.55-2.00 mg/ml for EPI)	Chemotherapy (DOXO, EPI) (solutions)	No	Yes (glass vial)	-	Only quantitative over limited concentration range (low sensitivity for quantitation)	-	[20]
	NanoRam* (B&W Tek)	SR: 176-2900 cm-1 ; Excitation laser 785 nm; Laser output up to 300 mW; Detector: TE Cooled Linear CCD Array	~9 cm-1 §	For correct identification of API, Se^e=100%, Sp^e=96% [21]; high FP rate for samples with high fluorescence:SP[21]; Cannot detect differences between different batches of the same medicine[21];Cannot discriminate between medicines with the same API from different manufacturers[21]	Anti-malarials [21](AS-AMO,AL,QUI,SP,AS-SP); Analgesics[22] (ASA,PARA); Antibiotics[22] (CIP); Anti-platelet [22] (CLOP); Anti-coagulant [22](WAR); Weight loss medicines [22] (ORL); Cardiovascular medicines [22](PRO, SIM), Erectile dysfunction medicine[22] (VAR)	No	Yes (transparent blister packs[21])	Comes with a library of 110 USP standard pharmaceutical materials [21]; Built-in algorithm with the help of libraries provides an instantaneous answer [22]; Easy-to-use [21], [22]; Tested successfully through transparent blister packs except for tablets with thick blue coating[21]	-	Does not work for tablets with thick blue coating[21]	[21],[22]
	EZ Raman M Analyzer* (Enwave optronics)	SR 250-2000 cm-1; excitation laser 785nm; accumulation time 20s	4-6 cm-1 §	-	Chemotherapy (NEL)	Yes	No	-	-	-	[23]
	CBEx (Metrohm Raman)	Spectral range: 400-2300 cm-1; Laser wavelength: 785nm class 3B laser;"point and shoot' adapter;Vial holder	Can be enhanced with SERS adapter and substrate	Spectra independent of time (day to day variability over 3 consecutive days) and calibration; Cannot reliably distinguish between brands of the same API/co-formulated formulations tested (n=8 API/co-formulated formulations); Different strengths of AL brand could not be distinguished; Spectra not API specific for :coformulated coated intact RHZE tablets (poor quality RHZE may not be correctly identified if one two three API are lacking in the medicine), AMOX intact capsules (but powder analysis API-specific), FUR , OXY; Good agreement of scan through translucent capsule of one PARA brand; SERS substrate analysis did not enhance Raman	Antimalarials (AL); Antituberculosis (IREP, IR); Antibiotics (AMOX); Analgesics (PARA, PASAC); Maternal health medicines (OXY); Cardiovascular medicine (FUR)	Both destroyed and not destroyed	Yes	Easy-to-install and intuitive software; Easy to transfer spectra and libraries between different instruments using microUSB cable; Fast; Small; Marginal instrument to instrument variablility; Does not require electricity; Four-digit code to lock on the instrument (internal timer can be set to lock out a user after a set time period)	Libraries can't be done directly from the instrument (require external computer); Malfunction observed in the field study; Software and hardware only in English; Instrument does not have internet or Bluetooth capabilities	Samples with low API content relatively to excipient and other APIs may be challenging; Co-formulated samples more challenging if one APIs has a strong signal compared to other	[18]

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
				signal of OXY formulations; Degraded products (artificial degradation of genuine sample under different conditions) of AL, AMOX, PARA and RHZE could be identified in some cases as poor quality depending on the level of degradation							
	EZ-Raman-I (TSI, Inc)	Excitation wavelength 785 nm; CCD detector; laser power 400 mW*; tablet holded, vial/cuvette holder		Qualitative correct identification of API in 4 finished products (analysis of intact product, 2 capsules and 2 tablets) using a Raman barcode method; Quantitative predictionc (dissolution of capsules contents and tablets in water; after establishing calibration models using reference standards) of APIs in the four products with % of the label claim being as far as from 0.1% to 12.0% (NB: on average on 5 dosage forms tested for each product predictions results for one acyclovir, one doxycycline and one amoxicillin out of two products were within 3% of HPLC results); Specificities of the quantitative models tested on 6 related APIs (famciclovir, valacyclovir,levofloxacin,erythromycin,cephalexin,penicillin V) showing that the built models are specific of the APIs of interests	Antibiotics (AMOX, DOXY), Antiviral (Acyclovir)	N (for qualitative analysis), Y (for quantitative analysis)	N	Quantitation	-	-	[24]
MIR Fourier Transform	Nicolet iS 10 (Thermo Scientific)	SR 400 - 4000 cm-1	> 0.4 cm-1 §		Unspecified	Yes	No	Quite Good pre-heating time¥; Easy to use: Quite Good¥; Very Good exportability of data; Good analysis report; Good quality of spectra; Very good reference library size; Good quality of the model; Quite Good cost; Very Good QA/QC ¥"	Not Good size, weight, robustness¥	Solid forms and liquids containing proteins¥	[1]
	MLp (A2 technologies)	Not specified	Not specified	-	Unspecified	Unspecified	Unspecified	Very good size, weight, robustness; Very Good pre-heating time; Easy to use: Good; Very Good exportability of data; Good analysis report; Good quality of spectra; Very good reference library size; Quite Good quality of the model; Very Good cost; Good QA/QC ¥	None specified¥	Solid forms and liquids containing proteins ¥	[1]

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
	Exoscan*(A2 technologies - now Agilent technologies; specifications quoted for Exoscan 4100)	SR 650 - 4000 cm-1 §	4 cm-1 §	-	Unspecified	Unspecified	Unspecified	Good size, weight, robustness; Very Good pre-heating time; Easy to use: Good; Very Good exportability of data; Good analysis report ;Good quality of spectra; Very good reference library size; Quite Good quality of the model; Good cost; Good QA/QC¥	Can't produce an analysis report¥	Solid forms and liquids containing proteins ¥	[1]
NIR-Fourier Transform	MicroPhazir* (Thermo Scientific)	SR 4167 - 6250 cm-1 (1600-2400 nm); Probe to depth of 100 micron from tablet surface; Light source: Tungsten lamp	8-12 nm	Potential FN of crushed finished product of ethambutol if the samples are tested against reference spectra from different manufacturers[17]	Unspecified Calcium Channel Blockers [25]; Unspecified [13]; Antiepileptic (OX)[6]; Anti-tuberculosis (ETH)[17]; Antibiotic (CEF)	No	Yes (transparent PVC blister[25])	'More pleasing' and 'slightly easier' to use than the TruScan (Ahura)[9]	May require complex specific chemometric approach depending to the aim of the test[25]	-	[6], [13],[17], [25],
	Phazir RX* (Thermo Scientific)	SR 6266–4173 cm−1; InGaAs photodiode detector; Light source: Tungsten lamp	19 cm−1	QAN of powders: prediction performance of the portable instrument is comparable to the benchtop FT-NIR spectrometer when using calibration models	Experimental formulation (blend of ASA/AA/CAF)	No	No	Phazir has shown slightly higher prediction of quantity of API in powders compared to TruScan and TruDefender	-	-	[19]
	Phazir RX* (Polychromix)	SR 4167-6250 cm-1 (1600 – 2400 nm); PbS solid-state detector; Light source: Tungsten lamp	-	-	Unspecified[1]; Anti-malarials [9] (AMO,AL,ART, AS,DHA, CHL, SP); Antibiotics[9] (ERY, CIP); Anti-tuberculosis drugs[9] (ISO, RIF); Erectile dysfunction (SIL citrate, TAD, VAR hydrochloride trihydrate)[26]; calcium channel blockers (AML)[26];Anti-depressant (CIT)[27]; Analgesic (PARA+CAF)[27]; Weight loss (ORL)[27];	No	Variable (unable to penetrate through some packaging - specifics not given[9])	21CFR Part 11 Compliance Documentation; more accurate than Minilab [9]; In-built reference library of different compounds (can be updated online[9]);According to the authors Phazir slightly ergonomically more pleasing and easier to use than the TruScan[9]; no customs-related issues or regulatory restrictions; Data transfer with Phazir with USB-easier than for the TruScan[9]; Very good size, lightweight, robustness; "Very Good pre-heating time¥; Very easy to use¥;Very Good exportability of data¥; Very Good analysis report¥;Very good quality of spectra¥; Very good reference library size¥; Very Good QA/QC¥"[1]	Must control for humidity changes, sample position and sample tests - or perform multiple tests[9]; Ability to penetrate through various packaging variable[9]	-	[1],[9]***,[26]***,[27]
	Luminar 5030* (Brimrose)	SR options: 9090-16666 cm-1(600-1100 nm), 5880 - 11750 cm-1 (850-1700 nm), 5555-11110 cm-1 (900-1800 nm), 4350 - 9090 cm-1 (1100-2300 nm); sampling area 6mm at 40mm sample distance §	2-10 nm §	-	Unspecified	Unspecified	Unspecified	Good size, weight, robustness; Good pre-heating time; Easy to use: Good; Very Good exportability of data; Very good quality of spectra; Quite Good reference library size; Good quality of the model; Good cost; Quite Good QA/QC	Can't produce an analysis report	Solid forms, not liquids containing proteins	[1]
	Target Blend Analyzer (Thermo Scientific)	SR 7400-5550 cm-1 §	3.5 cm-1 §	-	Unspecified	Unspecified	Unspecified	Quite Good size, weight, robustness; Easy to use: Quite Good; Very Good	Long pre-heating time; High cost	Solid forms, not liquids containing proteins	[1]

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
								exportability of data; Good analysis report; Good quality of spectra; Very Good reference library size; Very Good quality of the model; Very Good QA/QC			
NIR-Dispersive	MicroNIR 1700* (JDSU) superseded by other MicroNIR (Viavi solution)	SR (950-1650 nm) (NB customized wavelength ranges are possible33); 128 pixel InGaAs photodiode array detector; Sample working distance:0–15 mm from window, 3 mm optimal	Optical: <1.25% of center wavelength; Geometric: 6.25nm per pixel; Pixel size/pitch: 30 µm x 250 µm/50 µm	QAL: 6/6 falsified or illegal generic samples correctly identified [28]; QAL: 2 FP out of 22 raw materials tested [28]; QAN: 0.2% (w/w) of error prediction for quantifying ASA,AA,CAF in blends[28]; Acc of 96% for material conformity, Se[b]=98% and Sp[b]=98.5% for mixtures identification of street drugs, promising reproducibility of direct calibration transfer for new serial numbers/models of the device [29]	QAL: 6/6 falsified or illegal generic samples correctly identified[28]; QAL: 2 FP out of 22 raw materials ID[28]; QAN: 0.6% (w/w) error of prediction for quantifying ASA,AA and CAF blends[28]; Accuracy 96% for material conformity, Se[b]=98% and Sp[b]=98.5% for identification of mixtures in street drugs, promising reproducibility of direct calibration transfer for new serial numbers/models of the device[29]	No	Yes (plastic bags [29])	QAN possible –need more investigation[29]	Requires at least 3 different batches of samples to create reference library [28]	Potentially no limitation	[28],[29]
	RxSpec 700Z (ASD)	SR 4000 - 25640 cm-1 (350 - 2500 nm) §	UNK	-	Unspecified	Unspecified	Unspecified	Good size, weight, robustness; Easy to use: Very Good; Good exportability of data; Quite good quality of spectra; Very Good reference library size; Good quality of the model; Very Good QA/QC	Long pre-heating time; Can't produce an analysis report; High cost	Solid forms, not liquids containing proteins	[1]
	SCiO (Consumer Physics)	Small optical integrating attachment similar to an integrating sphere; Spectral range: 740-1,060 nm	UNK	Se[c] and Sp[c]:100% to distinguish between good quality and falsified AS monotherapy and AL combination; QAN: AMO could not be quantified as the spectra of reference standard was not distinguishable in the spectral signature of therapies containing amodiaquine; Quantitation of AS in one brand (AS-AMO co-formulated in separate tablets) : quantitation of AS within ±14.8% with 95% certainty	Anti-malarials (AL,AS, AS-AMO, AS-SUM-PYR, DHA-PIP)	No	No	Potential to quantify API (needs further investigations), Inexpensive; User-friendly	Requires a spectral library of quality-assured medicines	Quantitation may not be possible with some API such as AMO, although a wider wavelength should improve detection of varying amounts of API	[30]
	D-NIRS	SR 6250 - 10000 cm-1 (1000-1600nm); InGaAs-photodiode detector (640 element array); 10 x 10mm incident light area with focus area of 6 x 6 mm; 55mm path length	1nm wavelength resolution, 0.025mm/pixel spatial resolution	-	Experimental sample tablet ((AA, hydroxypropylmethylcellulose) ([31]); (MS, AA, starch, talc) and (talc, MS, lactose, mannitol) ([32]))	No ([32]), Yes ([31] - but specifically to monitor dissolution)	No	Capable of monitoring dissolution characteristics with high Acc; QAN with high Acc	-	-	[31], [32]
Combined NIR/MIR Fourier Transform	TruDefender FT* (Thermo Scientific)	SR 650-4000 cm−1; Michelson interferometer applies the attenuated total reflection (ATR)	4 cm−1	-	Experimental formulation (non-therapeutic) (blend of ASA/AA/CAF)	No	No	-	Slightly lower prediction of quantity of API in powders compared to NIR Phazir RX device (better than Raman	Liquids, powders and solids	[19]

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
		technique for sample presentation							FirstDefender) due to imperfect contact between the diamond reflection element and the powder sample[19][19][19][19][19][19][19]; accessory needed to optimize contact between the samples and the diamond reflection		
	Cary 630 (Agilent)	SR 600 - 5100 cm -1; Michelson interferometer 25mm, 45° §	4 cm-1	Finished products from 2 manufacturers can be differentiated, but different lots within the same manufacturers cannot be distinguished from each other[6]; Rapid detection of finished products containing no APIs[17]	Antiepileptic (OX)[6]; Anti-tuberculosis (ETH)[17]; Antibiotic (CEF)[17]	Yes	No	More effective than Raman/NIR for detecting counterfeits[17]; Possible rapid detection of samples that contain no APIs[17]; Identification of APIs using specific fingerprints in finished products[17]	-	-	[6],[17]
	FT/IR-4100 (JASCO Inc, Tokyo, Japan)	SR 650-4000 cm-1; ATR unit (DuraSampIIR II, Smiths Detection Group, UK) attached	4 cm-1	Able to distinguish between different formulations with same API (i.e. generic versions of branded genuine product)	Lipid-modifying drugs (ATO)	Yes	No	-	-	Crushed tablets	[11]
Reflectance colour measurement	X-rite eye-one* (Regensdorf)	SR 13700-26315 cm-1 (380 nm to 730 nm)	10 nm	Analysis of tablets: 15% FP; analysis of packaging: 25% FP(HPLC ref)	Erectile dysfunction (SIL, VAR, TAD)	No	No	Capable of imaging secondary packaging (i.e. reflectance of carton box measured)	Requires updated reference library of spectra; Significant operator variability (esp with tablets); Ambient light interference if the scanner does not adhere properly = may result in low Acc with convex tablet (i.e Cialis)	Any if reference spectra available	[33]
Low-cost laser absorption/fluorescence	Counterfeit Drug Indicator-CoDI* (Michael D. Green, CDC)	405 nm laser, detection via a Cadmium sulfide photoresistor coupled to a voltmeter; signal measured with and without red filter over photoresistor	N/A	-	Antimalarial (AL,CHL, SP)	No	No	Cheap, portable, battery-powered, Smartphone image analysis application could provide rapid real-time color comparisons of samples	Should be used in combination to other devices: proposed in a three-tiered strategy		[34]
Mass spectrometry	Mini 10 mass spectrometer coupled to ESI and DESI*	Mass range > m/z 500	1 AMU	-	Drugs of abuse (experimental formulation) (blend of methAMPH/COC/heroin), amines (dibutylamine, TRIbutylamine); peptides (non-therapeutic) (bradykinin, synthetic peptide)	Yes	No	DESI allows in-situ sampling	Ionisation method still not miniaturized; rudimentary atmospheric interface	Drugs of abuse, peptides, possibility to extend to small proteins	[35]***
	QDa single quadrupole (Waters) (Single quadrupole (with DART ionization))	Mass range 30-800 m/z, capillary bias 800V, 33V cone voltage, 150C source temperature (for this experiment)	~1 AMU	Low abundance species in samples were not detected (e.g. CLM in falsified samples)	Anti-malarials (AL)	Yes	No	Lower relative energy requirement to other standard MS units	Few settings in voltage and frequency resulting in bias for the collection of ions in to the analyzer; Not user-friendly; Mass accuracy does not allow for confident identification	Samples that can be ionized	[36]

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
									of new compounds; Needs electricity, possibly with a generator; Requires additional gas for testing using solid phase DART ambient ionization		
Nuclear quadrupole resonance (NQR)	Prototype	23 turns on solenoid; 21 micro-H; Q (quality factor) at 3.03 MHz = 76; 3.033 MHz 14N NQR line of AMP and 2.564 MHz 14N NQR line of PARA used; 'pulsed spin locking' data acquisition sequence (pulse width 60 microseconds; pulse separation 422 microseconds (AMP), 1.15 ms (PARA))	N/A	Successful QAN of blister pack of PARA using fixed-pitch RF coil	Analgesic (PARA); antibiotic (AMP capsules)	No	Yes	Accurate in QAN (compared to HPLC)-needs more investigation	Inspection times longer if quadrupolar isotope in low abundance; Requires reference library of spectra	Any containing relatively high abundance of isotope with nuclear spin I > 1/2	[37]
Paper-based devices	Paper test card** (prototype)	12-lane cards ([38], [39])	N/A	Se^g 90-100% for pure API and excipients (drug-dependent[38]; poor Se^g for ETH in combination with RIF; 73% for RIF cut with potato starch); lower Se^g (e.g. 40% for PYR in SP combination) when only small quantity of API[39]); Sp^g 88-100%[38] (drug-dependent; poor SP^g (83%) for ETH in combination with RIF[38])	Antibiotics(AMP[38], AMOX[38]); Anti-tuberculosis drugs[38](RIF, ETH, ISO, PYR) ; common adulterants[38], [39] (PARA, talc, baking soda, chalk, QUI, and DIP); Anti-malarials[39](CHL, DOXY, QUI, SUD, PYR); ASA[39]; CAC	Yes	No	Inexpensive; no consumables required;able to identify wide range of compounds	Interpreting result can be challenging; requires authentic samples	Specifically designed for drugs tested; further development needed to increase range of available APIs	[38],[39]
	aPAD**	Paper test card	N/A	Good differentiation of levels of AMOX that differed by 0.15 mg/ml.[40] ; Semi-QAN analysis^c: AMOX error: 13.0%, systematic bias:11.2%,Inter-device precision (one sample tested 5 times): 0%, AMPI error: 4.7%, systematic bias:3.2%,Inter-device precision (one sample tested 5 times): 2.2%, Inter-reading precision (three analysts): 0.6%; QAL analysis Pass/Fail (identification of samples below or above the USP 90.0% limit of stated API): AMOX Sec:73.2%, Spc:100.0%, AMPI Sec:80.0%, Spc:100.0% NB: authors suggest that artificially degraded samples (thermally stressed) used in the study may have anomalously led to wrong results[41]	Antibiotics (AMOX[40], AMPI)[41]	Yes	No	Inexpensive; semi-QAN	Limited to beta-lactam antibiotics; Destructive, Sample preparation, Slow analysis, Require lab equipment (e.g. balance),non-specific (cannot differentiate beta-lactams from one another)	Beta-lactam antibiotics	[40],[41]

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
	Paper-based microfluidic strip - unnamed**	pH 4 required for AS; Calibrated colour chart guide printed onto device for quantitation; "ColorAssist" iPhone application to improve Acc of quantitation	N/A	Successful identificationg of AS in 3 tablets; LOD:[1] 0.98 mg/ml	Anti-malarial (AS)	Yes	No	Inexpensive; semi-QAN	Specific to AS	AS only	[42]
Lateral flow immunoassay dipstick	Unnamed**	Specific monoclonal antibodies; test line disappears if the concentrations of API are above the LOD	N/A	AS RDT: No cross-reactivity with AS, AMO,PYN,PIP,PRI,PYR,QUI,CHL,LUM at 20,000 ng/ml [43], LOD 40-50 microg/ml [44] and 1000-2000 ng/ml [43] ; LOD 4-8 microg/ml for ART [44]	Antimalarials (AR derivatives: AS, DHA, ART)	Yes	No	Simple sample preparation; Fast ; Inexpensive; Minimal training: RDT known by healthcare providers (e.g for malaria diagnosis); 95% alcohol as solvent -non-toxic for AS and ART; no interference from partner drugs in assays; highly specific	May be difficult to obtain solvents in remote settings; Shelf life under tropical conditions not yet validated; Currently limited to a few API; Single use; Several tests must be run if failed sample [44]	Highly specific to AR derivatives, but antibody method may be possible for other drugs	[43],[44],[45]
Dissolution microfluidics with luminescence detection	PharmaChk beta 1.1	Staggered herringbone chip design; Luminescence measured with photodiode	Not specified	Relative SD < 5%; <4% difference in API quantity compared to HPLC reference standard	Anti-malarial (Lever, Camosunate, Glunate - brand names containing AR)	Yes	No	Can obtain API content and kinetic release profile from dissolving tablet; Cheap; aiming to develop system that could test any drug without extensive reference library	Significant variability in results if wrong solvent used (and solvent choice may be manufacturer-specific); aptamers must be developed for each drug	Currently AR only; hoping to develop system that can test any drug (depending on aptamer availability)	[46]
TLC, colorimetry, disintegration test	GPHF-Minilab (Global Pharma Health Fund E.V.)	N/A	N/A	'Limited' Se[47]; 29% of extremely non-compliant samples§b for both content and dissolution correctly identified by the Minilab [48] ; Se[a] for both ID test and content test=79% , Se[a] for ID test only=100% [3]; Sp[a] for ID test only=100% [3]	Anti-malarials [47],[16],[9],[49],[50],[48],[3],[51],[4] (SP, AMO, MEF, AR monotherapies, ACTs, CHL, QUI, DOXY, TET, PRI, DHA-PIP-TRI); Anti-tuberculosis[52],[9] (RIF, ISO); Antibiotics[9],[49],[51](ERY, CIP, AMOX, AMP, SUL-TRI, MET)	Yes	No	Well established within academic literature, 800 Minilabs distributed across 95 countries; TLC can be used for the related substances (degradation products)/impurities testing; Inexpensive; Wide range of API currently covered (n=85 including non anti-infective compounds)	Many consumables; Time consuming; Training ++; Requires dedicated climate controlled location with potable water and electricity; Rough estimate of API content; Reliability of detection depends on the operator's visual acuity and users attention to detail: proficiency testing required[51]	Wide range of APIs currently covered (n=85 for Minilab, mainly anti-infectives but also includes non anti-infective compounds); Potentially no limitation	,[3],[9]***, [16],[47], [48] [49]***, [50], [51]***, [52],[53]
Refractometry	AR200 digital refractometer* (Leica Microsystems)	Light source: 589nm LED ; refractive index range: 1.3300 - 1.5600 §	Acc +/- 0.0001 nD, +/-0.1% solids, +/-0.2% temperature §	Se[c]: AS: 86%; CHL:83% (250mg tablet); CHL:100% (322.5 mg inj); QUI: 98%; SUL: 97% ; Sp[c]: AS: 87%; CHL:73% (250mg tablet); CHL:86% (322.5 mg inj); QUI: 56%; SUL: 64% (NB: for CHL tab, a adjustment factor for interferences had to be applied)	Antimalarials (AS, CHL,QUI,SP)	Yes-except injection (choroquine)	No	Using refractometry (QAN) and colorimetry (QAL) improves Se and Sp (techniques are complementary)	No QAL	Any soluble drug	[1]***
Reflectance	SOC-410 Directional Hemispherical Reflectometer* (Surface Optics Corporation)	Measure at 2 different angles of incidence (20° and 60°) and for six discrete wavelength bands in the 0.9µm to 12µm; SR: SWIR, NIR, MWIR, LWIR	Unspecified	Statistically significant differences in directional reflectance for the 4 types of falsified medicines against the genuine were identified for 4 out of 6 spectral bands tested - small SD indicating high Se and	Erectile dysfunction medicine (SIL)	No	No	Easy to analyse (no need for chemometrics);Sensitive to chemical composition and physical parameters of the surface of the tablets (e.g. difference of compression force during tableting)	Solid oral dosage forms only(although minor modifications could allow the analysis of other forms)	Solid oral dosage forms	[54]

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Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
				Sp to chemical and physical parameters changes							
	Glossmeter-Unnamed (University of Eastern Finland)	Light source=semiconductor laser	UNK	Data of average gloss obtained consistent with data measured by a 2D glossmeter and the optical profilemeter;NB very limited sample size (n=2)	Antimalarials (AL)	N	N	Fast; Low level of expertise	-	Not liquids	[55]
Capillary electrophoresis	Unnamed	Spellman high voltage unit (UM20*4,12V 200 µA) with safety Perspex cage;Miniaturized high voltage- Contactless conductivity detector (C4D built in-house); Flowcell interface in a Plexiglas Block; Screens for monitoring of voltage and current values;rotary selector;Solenoid valves;Gas pressurized buffer container;Function generator in the surface mount technology format;Pick-up amplifier; Rectifier; Low-noise operational amplifiers;Record of the signals with an ADC-20 data acquisition system connected to the USD-port of a computer	~0.5 ppm	Good agreement with quantitation by HPLC	β-agonists (SAL, MTP)	Yes	No	Robust in day-to-day operation; Small sample volumes compared to automated machines; C4D detector gives better separation efficiencies.	Poor tolerance to changing temperature (drift in migration time)	-	[56]
Ion Mobility Spectrometry	IONSCAN-LS (Smiths Detection, Danbury)	Desorber T°291C (22, 23); MW range 15-1500 AMU (manufacturer)	0.6 ('resolving power', mass resolution not possible to calculate in IMS due to variation in mobility linked to ion size and shape)	-	Weight loss (SIB[57]); erectile dysfunction (SIL, thiomethisoSI, thioSI, homoSI, methesoSI, VAR, piperidenafil, TAD (as adulterant in herbal supplement for erectile dysfunction) [57]	Yes	No	Ultra-fast quantitative analysis; Sub-nanogram Se; selective; low cost per sample §	-	Solids and liquids	[57]***, [58]
	SABRE 4000*(Smiths Detection, Danbury)	Desorber T° 150-210C in 10C increments; scan time 15s	UNK	-	Stimulant (CAF ([58])), vitamin (vitamin B6 ([58]))	Yes	No	-	-	-	[58]
Camera system with various LED sources	CD3/CD3+*(US FDA)	Two charged couple device cameras to capture images and videos (one operates in the UV-Vis; one in the IR spectral region);	Capture of jpeg images at 96 dots per inch resolution (dimensions of image=720x57	Se^c=100% for analysis based on packaging materials and dosage unit [3], Se^c=100% for dosage-unit-only analysis[3]; Sp^c=53% for analysis based on packaging materials and dosage unit [3],	Anti-malarials[3],[59],[34] (AS, AL, AS-AMO), Erectile dysfunction medicines [60] (SIL, TAD), Weight-loss medication [60](ORL)	No	Yes	Screens both packaging and dosage unit (therefore can identify repackaged, degraded drugs); More reliable to conduct side-by-side comparisons with physical	Should be used in combination with other devices such as Raman or FT-IR for better performances [60]	Unlimited	[3], [34],[59] ,[60]

Type of technology	Name of the device (Developer)	Specificities	Resolution	Results of laboratory tests	Therapeutic indication (API tested)	Pharmaceuticals destroyed	Tested through containers ?	Plus	Minus	What medicines could potentially be tested based on chemical structure and specificities of the device	Ref
		digital camera can be used and images analysed using smartphone application; Image analysis software has been integrated in a newer version of the device (the 'CD4')[34]	6 pixels at 24-bit color depth (file size approx 75 Kb))	Sp[c]=64% for analysis dosage-unit-only analysis [3]; Se[a]=98.4% (95% CI=93.8-99.7%) [59] ; Sp[a]=100.0 (95% CI=93.8-100.0%) [59]; Inter-user reliability (3 users)= 100% (K=1)[59]				authentic samples than using the library images CDAIL[3]			
Pressure changes measurement (respirometer system)	Speedy Breedy (Bactest)	Two chambers	N/A	Against incubator and UV-Vis spectrophotometer: laboratory evaluation results on samples of water for injection only[Ω]: Se 100% under condition A and 93.0% under condition B; Against incubator and UV-Vis spectrophotometer: laboratory evaluation on samples of water for injection only[Ω]: Sp 100% under condition A and B	Sterile water, Maternal health medicine 'OXY), Antimalarial (AS) injections	Yes	N/A	Instrument withstood temperatures between ambient and 40°C during transportation; Small; Light; Easy to transport; Technical support by manufacturers prompt and efficient; Easy-to-download and intuitive software; Hardware and software available in English, Chinese, German, Romanian and Spanish.	Power required (power interruption during the study meant the analysis needed to be repeated);At the time of study, cardboard case making the case not robust for travelling (manufacturer in the process of developing a robust travel case); Vessels only available in 50ml volumes (problems for small volumes samples); Long analysis time and reliable power source required; Only two chambers limit the throughput of the instrument	Liquid samples	[61]

UNK, unknown; Acc, Accuracy; AA, Ascorbic acid; ACT, artemisinin combination therapies; AL,Artemether-Lumefantrine; AML, Amlodipine; AMO, Amodiaquine; AMOX, amoxicillin; AMP, Ampicillin; AMPH, Amphetamine; AR, Artemisinin; ART, Artemether; AS, Artesunate; ASA, Acetylsalicylic Acid; ATO, Atorvastatin; CAC, Calcium carbonate; CAF, Caffeine; CEF, Cefuroxime; CET, Cetirizine; CHL, Chloroquine; CI, Confidence Interval; CIP, Ciprofloxacin; CIT, Citalopram; CLM, Chloramphenicol; CLOP, Clopidogrel; COC, Cocaine; DHA, Dihydroartemisinin; DIA, Diazepam; DIL, Diltiazem; DIP, Diphenhydramine; DOXO, Doxorubicin; DOXY, doxycycline; EPI, Epirubicin; ERY, erythromycin; ETH, Ethambutol; FEN, Fenotropil; FDC, Fixed-Dose Combination; FN, False negative; FP, False positive; FUR, Furosemide; IBU, Ibuprofen; ID, Identification; ISO, Isoniazid; LUM, Lumefantrine; LOR, Loratadine; NEL, Nelabrine; OX, Oxcarbazepine; OXY, Oxycodone; PARA, Paracetamol; PASAC, Paracetamol-acetylsalicylic acid-Caffeine PIP, Piperaquine; PIR, Piracetam; PRI, Primaquine; PRO, Propranolol; PYN, Pyronadine; PYR, Pyrimethamine; MEF, Mefloquine; MET, Metronidazole; MS, Magnesium Stearate; MTP, metoprolol; ORL, Orlistat; OXY, Oxytocin; QAN, Quantitative analysis; QAL, Qualitative analysis;

QUI, Quinine; RDT, Rapid Diagnosis Test; RHZE, Rifampicin- Isoniazide-Ethambuthol-Pyrazinamide; RIF, rifampicin; SAL, Salbutamol; Se, sensitivity; SERS, Surface Enhanced Raman Spectroscopy; Sp, specificity; SIB, Sibutramine; SIL, Sildenafil; SIM, Simvastatin; SP, sulfadoxine-pyrimethamine; SR, Spectral Range; SUL, Sulfamethoxazole; SUD, Sulfadoxine; SUM, Sulfamethopyrazine; TAD, Tadalafil; TET, tetracycline; TRI, Trimethoprim; UNK, Unknown; VAL, valsartan; VAR, Vardenafil; WAR, Warfarin; ZNS, Zinc Sulfate

*Handheld, **Handheld- lab-on-a-chip, ***Indicates papers published before 2010

a Against HPLC, Mass spectrometry or Fast Red Dye test assay; b Against Gas chromatography-Mass spectrometry; c Against HPLC API ID and content; d Against HPLC API ID only; e Against TLC (and HPLC for samples failing TLC only), f Against High resolution laboratory grade QTOF mass spectrometer; g No gold standard-tested against known identity of the medicine; h pure reference standards of API (manufacturer supplied) used to benchmark; i One pharmaceutical unit of a medicine was compared to another unit of the same batch; j Unknown reference standard; k Against FTIR or LC-MS

¥The study by Dégardin et al. [1] presents a subjective comparison of multiple devices. Each device feature is described as being 'Very good', 'good', 'quite good' or 'bad' without definition of these NB the final authors' choice of best device per technology is 1:Truscan, 2:Phazir, 3:Mlp

§ Information retrieved from the manufacturer website

Ω the field evaluation was conducted with the aim to determine whether trainees could operate the instrument and whether the instrument could operate in true field-settings;

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Supplementary Annex 2 - additional material 6. Practical characteristics of the devices for use in the field

	Name of the device (Developer)	Weight (kg)/Dimensions (cm)	Calibration and performance maintenance	Operating temperature range	Warm-up time	Tolerance to operational environment changes	Electricity requirements	Consumables requirements	End-user skill level required	Measurement time per sample	Additional equipment required	Other information	Ref
Raman	MiniRam II (B&W Tek)	2.9/25.7x 21.1x11.4 §	UNK	UNK	UNK	UNK	Battery-powered (3 hrs life) §	None	UNK	<5 min	UNK		[1]
	Raman Rxn1 Microprobe (Kaiser optical)	28kg/ 58 x 45 x 20 §	UNK	20-25°C §	20 min §	20-80% humidity §	110-240V, <200W §	None	UNK	30s	Software, computer	One sample per run	[2]
	TruScan RM* (Thermo Scientific, formerly Ahura)	0.9/20.8x10.7x4.3 §	UNK	-20-40°C §	UNK	UNK	Battery-powered (Rechargeable internal lithium ion battery > 3 hrs life) or Mains-powered (100-240 V AC 50/60 Hz)	None	+	Maximum 2 min (+ 5-30 min to create the reference library)[3], [4],[5],[6]	Reference library software; Vial holder, tablet holder	One sample per run	[3],[4] [5], [6],[7] ,[8], , [9],[10], [11]
	TruScan* (Ahura)	<1.8/30x15x7.6 §	Fast and easy calibration[1]¥;[12]; requires reference rods (provided by Ahura)[13]	-20-40°C	Good[1]¥	Less sensitive to external factors than Phazir[12]	Battery-powered (Internal lithium ion battery, >5 hrs life at 25 °C) or Mains-powered (100-240 V AC 50/60 Hz §	None	+	30s to 5 min [12],[14]	Non standard adaptor for data transfer	Safety precautions: high-power laser component[12]- One sample per run	[1], [12]*, [13],[14],[15] , ,[16]*
	FirstDefender TruScan* (Thermo Scientific)	0.8/19.3x10.7x4.4	UNK	-20-50 °C §	UNK	UNK	Battery-powered (lithium ion battery or 123a batteries; > 4 hrs life or Mains-powered (DC Wall Adapter, 12 V 1.25 A) §	None	UNK	UNK	UNK	One sample per run	[17]
	MIRA* (Metrohm)	0.54/12.5×8.5×3.9 §	UNK	-20-40 °C	UNK	UNK	Battery-powered §	None	UNK	< 5 min	UNK	One sample per run	[18]
	NanoRam* (B&W Tek)	1.2kg/22x10x5 §	Calibration following the developer procedures, valid for one year[19]	-20-40°C §	UNK	UNK	Battery-powered (Li-ion, >5 hrs life) or Mains-powered (AC adapter: Output DC 12V, 2A Minimum) §	None	+	15 s (10 for entering data, 5s for scanning the sample) [19]; Reference spectrum created in 3.5 min [19]	Point & Shoot, Vial Holder, Polystyrene Validation Cap, Immersion Probe, Large Bottle Adapter §	One sample per run	[19], [20]
	EZ Raman M Analyzer* (Enwave optronics)	~2.7/10.2x15.9x20.9 §	UNK	10-40°C §	UNK	UNK	Battery-powered-Rechargeable Li battery (5 hrs life) or 90 VAC to 264 VAC §	None	UNK	3 min	PC	One sample per run	[21]
	CBEx (Metrohm Raman)	0.335 /9x7x3.75	Daily calibration (calibration standards provided, 2-years lifetime)	-10-40°C	UNK	Can operate in up to 95% non-condensing humidity (manufacturer). Ambient light can cause instrument response issues; however the referencing function generally alleviates these issues.	2 AA batteries or a micro-USB cable connected to a computer	AA batteries can be used (approx. 3h run in the study before having to change the batteries)	Based on feedback from study participants: a variety of staff with both technical and non-technical backgrounds can become either basic,	Approx 2 min (5 sec to do scan); 20 min to develop a library for one sample	PC useful to compare spectra; Standalone devce do not give matches with Match score below 0.85	One sample per run	[22]

	Name of the device (Developer)	Weight (kg)/Dimensions (cm)	Calibration and performance maintenance	Operating temperature range	War m-up time	Tolerance to operational environment changes	Electricity requirements	Consumables requirements	End-user skill level required	Measureme nt time per sample	Additional equipment required	Other information	Ref
									intermediate or advanced users within approx. two weeks of training				
	EZ-Raman-I (TSI, Inc)	11.3/43.2x33.0x17.8	UNK	UNK	UNK	UNK	Rechargeable lithium battery (4 hours operation); 110/220 V DC power supply	None	UNK	10-40s acquisition times in study	-		[23]
NIR-Dispersive	MicroNIR1700* (JDSU)	0.06/4.5cm diameterx4.2cm height	UNK- NB:Re-zeroing every 15 min in study[24]	-20-40°C	UNK	UNK	USB-powered (<500 mA at 5V)	None	+ with Onsite Software	< 1 min	PC or Tablet; Polyethylene plastic bag with an X heat sealed onto the bag	Bulb life >40,000 hr - One sample per run; Requires polyethylene bag with an X heat sealed onto the bag when the sample is very small [25]	[24],[25]
	SCiO (Consumer Physics)	Smartphone-sized	UNK	UNK	UNK	UNK	UNK	None	+	Acquisition time per spectrum: 2s	Smartphone		[26]
	D-NIRS	< 2/19.1x9.3x12.0	UNK	UNK	UNK	UNK	Mains-powered	None	UNK	3 min (ref [27])	Computer, software		[28], [27]
	RxSpec 700Z (ASD)	UNK/Briefcase-sized'	Very good¥	UNK	Bad¥	UNK	UNK	None	UNK	UNK	UNK		[1]
NIR-Fourier Transform	MicroPhazir* (Thermo Scientific)	1.25/25.4x29.2x15.2 §	UNK	+5-45°C §	UNK	Dust proof,splash proof plastic housing §	Battery-powered (5+ hrs lifetiem, lithium-ion battery pack) or Mains-powered §	None	+	< 5 min	Laptop if more complicated chemometrics approaches are used [29]	One sample per run	[3],[9],[10],[29]
	Phazir RX* (Polychromix)	1.8/25.4x29.2x15.2 §	Very Good[1]¥; Fast and easy[12]	+5-45°C §	Very Good[1]¥	Testing needs to be done in a light controlled environment (results altered if ambient light changed significantly); Sensitive to humidity changes,sample position,sample face for tablets - issues that can be overcome by repeated testing [12]; Dust proof,splash proof plastic housing	Battery-Powered (10 hrs life, quick change battery)	None	+	2-5 s	-	One sample per run	[1],[12]*,[30]*,[31]
	Phazir RX* (Thermo Scientific) newly MicroPhazir?	1.8/25.4x29.2x15.2	UNK	+5-40°C	UNK	UNK	UNK	None	+	UNK	Optional adapter is available that can be attached magnetically to the front of the instrument to optimize sample presentation	One sample per run	[17]
	Luminar 5030* (Brimrose)	UNK	Quite good[1]¥	UNK	Good	UNK	Battery-Powered (2 VDC battery) or Mains-powered (110/220V) §	None	UNK	UNK	PC interface with ethernet connection; Windows-based analytical software for data acquisition §		[1]

	Name of the device (Developer)	Weight (kg)/Dimensions (cm)	Calibration and performance maintenance	Operating temperature range	Warm-up time	Tolerance to operational environment changes	Electricity requirements	Consumables requirements	End-user skill level required	Measurement time per sample	Additional equipment required	Other information	Ref
	Target Blend Analyzer (Thermo Scientific)	9.9/20.8x35.4x30.9 §	Very good¥	UNK	Bad¥	UNK	Battery-powered (3.5 hrs life) §	None	UNK	UNK	PC, software §		[1]
MIR Fourier Transform	MLp (A2 technologies)	UNK	Good¥	UNK	Very good¥	UNK	UNK	None	UNK	UNK	UNK		[1]
	Nicolet iS 10 (Thermo Scientific)	33/25x57x55 §	Very good¥	UNK	Quite good¥	Tightly sealed to resist ambient humidity §	Mains-powered (100-240 V, 50/60 Hz) §	None	UNK	UNK	UNK		[1]
	Exoscan*(A2 technologies - now Agilent technologies; specifications quoted for Exoscan 4100)	3.2/17.1x11.9x22.4 §	Good[1]¥ (built-in 'performance validation' tests for user to run)	0-50°C §	Very good[1]¥ (5 min - from manufacturer)	Tolerates up to 95% humidity; packaged in 'weather-resistant enclosure' designed for outdoor use; altitude up to 2000m §	Battery-Powered (up to 4 hrs life) or Mains-powered (110/220 VAC §	None	UNK	UNK	Comes with handheld PC as standard; can be interfaced to laptop §	One sample per run	[1]
Combined NIR/MIR Fourier Transform	TruDefender FT* (Thermo Scientific)	1.3/19.6x11.2x5.3	UNK	-25-40 °C §	UNK	UNK	Battery-powered (rechargeable lithium ion battery or 123a -ie SureFire™- batteries; >4 hrs life or Mains-powered (Wall plug transformer 100-240 VAC 50/60 Hz §	None	UNK	UNK	Crusher accessory for powders (to press the samples against diamond refelection element)[17]	Little maintenance [17]	[17]
	Cary 630 (Agilent)	3.8/16x31x13 §	UNK	UNK	1hour	UNK	Mains-powered (110 – 240 VAC, 60/50 Hz) §	None	UNK	UNK	UNK		[9],[10]
	FT/IR-4100 (JASCO Inc, Tokyo, Japan)	33/446x64.5x29 §	UNK	UNK	UNK	UNK	Mains-powered	None	UNK	UNK	UNK		[5]
Camera system with various LED sources	CD3/CD3+* (US FDA)	0.3/15.2x7.6	UNK	UNK	UNK	UNK	Battery-Powered (3 to 8 hrs life) or Mains-powered	None	+ Accuracy improves with experience	< 1 min	Digital handheld microscope can be used to examine suspect samples at higher magnifications [32]; Library software [33],[32]		[33],[32],[34],[35]
Low-cost laser absorption/fluorescence	Counterfeit Drug Indicator-CoDI* (Michael D. Green, CDC)	UNK	UNK	UNK	None§	UNK	9V alkaline battery§	Aluminium foil§	+	< 1 min	-	-	[34]
Reflectance	SOC-410 Directional Hemispherical Reflectometer* (Surface Optics Corporation)	29.3x22.9x9.4 §	UNK	0-40°C §	UNK	UNK	Battery-powered §	None	+	5 seconds (measurement at one spectral band and one angle)	UNK	-	[36]
	Glossmeter-Unnamed (University of Eastern Finland)	UNK	UNK	UNK	UNK	UNK	Rechargeable battery	None	+	UNK	UNK	Calibration with a commercial black glass gloss standard in the study	[37]

	Name of the device (Developer)	Weight (kg)/Dimensions (cm)	Calibration and performance maintenance	Operating temperature range	Warm-up time	Tolerance to operational environment changes	Electricity requirements	Consumables requirements	End-user skill level required	Measurement time per sample	Additional equipment required	Other information	Ref
Refractometry	AR200 digital refractometer* (Leica Microsystems)	0.41/18x9x3.5 §	Simple calibration system built into machine §	10-45°C;Temperature dependent testing but adding blank and reference standard to confirm the integrity of the assay	UNK	Refractive index is temperature-dependent; max tolerated humidity 50-80% (temperature-dependent; tolerated humidity decreases with increasing ambient temperature), pollution degree 2, altitude up to 2000m	Battery-powered (4xAAA batteries) §	+++ glass vials, enteric coating remover solutions, extraction solvents, reference standards; AAA batteries	UNK	UNK	UNK	>3000 tests before replacing batteries	[38]
Reflectance colour measurement	X-rite eye-one* (Regensdorf)	0.245/15.5x6.6x6.7 §	UNK- NB: Calibration performed every 10 scans in study	10-35°C	UNK	Ambient light interference if the scanner does not adhere perfectly to the tablet surface;Humidity tolerance 0-80% (non-condensing); Dust and Water resistance IP 65; No influence of temperature (20° and 30°C)	USB-powered §	None	+	Few seconds	Laptop computer with USB port		[39]
Lateral flow immunoassay dipsticks	Unnamed**	Few grams	N/A	UNK	None	No significant change in sensitivity when stored at room temperature for 2 weeks [40]; LOD increased after 3 months at 4°C and ambient temperatures for primary made dipsticks targetting all artemisinin derivatives [41] (more investigations are needed for the newer single-API targeted dipsticks)	None	Solvents	+	10 min	Dropper (supplied with plate)	Single use device; Non toxic reagents - Waste management: solvents	[40],[41],[42]
Paper-based devices	Paper-based strip – unnamed**	UNK (likely <0.1)/UNK (4 x 8mm filter paper circles on mounted on chip)	N/A	UNK	N/A	Requires controlled pH	None (if smartphone used to read the cards - battery-powered)	Solvents	UNK	5 min (+ 5 min for semi-quantitative analysis using the smartphone application)	Smartphone (to take digital images and measure gray scale intensity-improves quantitative accuracy)	Single use device	[43]
	Paper analytical device**	UNK (likely < 0.05)/Size of a Playing card	N/A	UNK	None	Majority of reactants stable up to 104 days at 37°C (some reactant lanes degrade within 2-7 days of fabrication[44])	None	Water used as solvent	+	10-20 min	None	Single use device; Non toxic reagents – Waste management: All reagents non-toxic	[44], [45]
	aPAD	UNK Size of a playing card	N/A	UNK	None	UNK	None	Solvents, reagents	+ (Successful tests interpretation by n=1 analyst (unknown qualification) unfamiliar to the aPAD [46]	30-60 minutes	Mortar, Pestle, Analytical balance, Pipet;Can use smartphone camera to analyse results (visual inspection adequate)	Single use device	[47],[46]

	Name of the device (Developer)	Weight (kg)/Dimensions (cm)	Calibration and performance maintenance	Operating temperature range	Warm-up time	Tolerance to operational environment changes	Electricity requirements	Consumables requirements	End-user skill level required	Measurement time per sample	Additional equipment required	Other information	Ref
TLC, colorimetry,disintegration test	GPHF-Minilab (Global Pharma Health Fund E.V.)	~50/83x52x29	Performing TLC on reference APIs and reagents	-	None	TLC requires dedicated climate controlled location; Tropics-compatible but avoiding direct sunlight. No special storage area required for the quantities of chemicals supplied.	Electricity required for UV detectors -can be Battery-Powered 9	Reagents;solvents; reference standards;TLC plates;potable water; NB:2 to 5 years shelf-life for authentic secondary reference standards;5 years shelf-life for reagents and solvents in their original packaging	+++ (Medium Lab Skills - Training of at least one-week;proficiency testing highly recommended	30min -1h30 [48],[49]	Lab glassware	No maintenance[49],[7]; 1000 TLC can be run with available solvents/reagents available at purchase; Safety precautions:some toxic/inflammable solvents/reagents - Waste management: must dispose of TLC solvents	[7],[12],[15],[48],[49]*,[50],[51],[52],[53]*,[54]
Dissolution microfluidics with luminescence detection	PharmaChk beta 1.1	8.2/Pelican briefcase'	Inbuilt calibration; Need new stock solution of reference drug each day	UNK	UNK	UNK	Mains-powered (12V power source from 110/220V	Solvents (Acetylnitrile, NaOH); luminol and hematin porcine probe; Stock solution made with 200-proof ethanol	UNK	5 min	UNK - PC and software should be provided by the company in the kit	Safety precautions:Acetylnitrile solvent is toxic - Waste management: on-board waste container; can run 10-15 samples before emptying	[55]
Mass spectrometry	QDa single quadropole (Waters)	29.4/35.3x20.0x75.0	Internal Calibration performed daily	UNK	10min	UNK	Mains powered 110-240V AC 50/60Hz	Solvents; Gas		Few min for both sample preparation and MS introduction	PC, Software; Ionisation source (some can be transportable but usually requires power and gas)	Needs to remain stationary when in operation.	[56]
Nuclear quadrupole resonance (NQR)	Prototype	UNK/Carry-on luggage	UNK	UNK- NB:Spectra recorded at room temperature	UNK	UNK	Battery-Powered (12V Lithium battery) §	None	UNK (aiming minimal)	UNK	12V Li battery, PC		[57]
Ion mobility spectrometry	SABRE 4000* (Smiths Detection, Danbury)	3.1/36.8 x10.2x11.4	UNK	UNK	10 min §	UNK	Battery-Powered (4hr life) §	Solvents	UNK	< 1 min	Solvent; pipette; centrifuge; scales able to weight ng weights; software	One sample per run	[58]
	IONSCAN-LS (Smiths Detection, Danbury)	42/62x41x88 §	UNK	UNK	UNK	No significant change in ion mobility with humidity (tested at 60% and 90% relative humidity)[58]	Mains-powered (95-265 VAC) §	Solvents;Nitrogen gas	UNK	UNK	Software, nitrogen gas		[58], [59]*
Capillary electrophoresis	Unnamed	UNK	UNK	UNK	UNK	If non-thermostated instrument, measurements can be affected by changing temperatures	Battery-powered (Lithium battery pack (14.8V; 6.6Ah) for electrophoretic and fluidic parts+a pair of Li-ion batteries (2.8 Ah each) for the C4D or Mains-powered	Buffer; Solvents; pH adjusting solutions	UNK	UNK	PC	Safety precautions: safety cage needed for high-voltage components	[60]
Pressure changes measurement (respirometer system)	Speedy Breedy (Bactest)	2.75/13.3x31 x11.2	UNK	UNK	UNK	The device is not waterproof and unshielded, so above normal electromagnetic interference could result in ineffective tests. The instrument is robust but not ruggedized and has not	Local mains AC power supply or 12V DC (car adapter is available) Voltage: Variable (230V / 50Hz – 120V / 60Hz)	Media vessels, sterile plastic water bottles, sterile syringes	Based on feedback from study participants: a variety of staff with both technical	Can exceed 24 hours (each protocol has a different run time that is bacteria specific)	None	None	[61]

Name of the device (Developer)	Weight (kg)/Dimensions (cm)	Calibration and performance maintenance	Operating temperature range	War m-up time	Tolerance to operational environment changes	Electricity requirements	Consumables requirements	End-user skill level required	Measureme nt time per sample	Additional equipment required	Other information	Ref
					been drop tested. However, provided humidity, dust, and vibration changes are not too rapid or severe, the instrument can tolerate fluctuations very well			and non-technical background s can become either basic, intermediate or advanced users within approx. two weeks of training				

LOD, limit of detection; LOQ, limit of quantitation; TLC, Thin-layer chromatography, AL, Artemether-lumefantrine; API, Active Pharmaceutical Ingredient; ASA, acetylsalicylic Acid; HPLC, High Performance Liquid Chromatography,SP, sulfadoxine-pyrimethamine;Se, Sensitivity; Sp, specificity, RDT, Rapid Diagnostic Test, FRTR: Fast Red Dye Reaction; LOD, limit of detection

*Indicates papers published before 2010

¥The study by Dégardin et al. presents a subjective comparison of multiple devices. Each device feature is described as being 'Very good', 'good', 'quite good' or 'bad' without definition of these NB the final authors' choice of best device per technology is 1:TruScan, 2:Phazir, 3:Mlp +: minimal (<2 hours training); ++ : low (2 hours to 1 day of training); +++: high (>1 day of training)

§ Information retrieved from the manufacturer website or from contacts with manufacturer

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Supplementary Annex 2 - additional material 7. Studies and devices (devices with a *) excluded from the review because of the investigation of performances of chemometric techniques rather than the device(s) performances

Name of the device(s) (developer)	Reference
Antaris II FT-NIR Analyzer (ThermoScientific)*/RXN1 (Kaiser Optical)	[1]
Luminar 3070 (Brimrose Corp)*	[2]
ARCspectro FT-NIR (ThermoScientific)*	[3]
Antaris One (ThermoScientific)*/MPA spectrophotometer (Bruker Optics)/FTLA2000-PH60 (ABB-Bomem)*	[4]
Nicolet iS10 FT-IR (ThermoScientific)	[5] [6]
Antaris II FT-NIR Analyzer (ThermoScientific)*	[7]
RXN1 (Kaiser)	[8]
MATRIX-F (Bruker Optik GmbH)	[9]
i-Raman (B & W Tek)	[10]
MATRIX-F (Bruker Optik GmbH)/EQUINOX55 (Bruker Optic GmbH)*	[11]
SCiO (Consumer Physics)/MicroPhazir RX (ThermoScientific)	[13]
MPA spectrophotometer (Bruker Optics)	[14] [16] [23] [24] [29]
EZ-Raman I (Enwave Optronics Inc.)	[15]
Antaris II FT-NIR Analyzer (ThermoScientific)*/Nicolet 6700 FT-IR spectrometer (ThermoScientific)*/Confocal-Micro-Raman spectrometer HR 800 (LabRAM Raman series, Jobin Yvon)*	[17]
MiniRaman II (B & W Tek)	[12] [18] [19]
Sapphire NIR-CI 2450 (Malvern)*	[20]
Alpha Fourier transform infrared - unnamed (Bruker Optics)	[21]
MPA spectrophotometer (Bruker Optics)/RamanStation 400F (Perkin)*	[22]
MicroNIR Pro 1700 (Viavi Solutions Inc)	[25] [27]
RamSpec (Bayspec)*/Miniature Agility*/Xantus-2/Xantus-1/Xantus-Mini(Rigaku)*	[26]
Truscan (ThermoScientific)	[28]

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Supplementary Annex 3. Physical, operational and software characteristics of the devices – laboratory evaluation

Questions	4500a FTIR Single reflection (Agilent)	C-Vue (C-Vue Chromatography)	PharmaChk (Boston University)
Hardware Maintenance require	Cleaning and calibrating only. No user serviceable parts	Yes. Guard filters need eventual replacing when flow gets disrupted. Stationary column cleaning. Occasionally leaks can develop that need to connections to be set back in place. If air bubble gets into the system, need to flush out	Syringe and microfluidic cartridge swaps and cleaning, Maybe a lamp swap eventually
Calibration- specificities	Background scan completed automatically before analysis of the sample; Instrument calibration (laser frequency calibration test, signal to noise performance, stability test). Need a polyethylene standard for the laser test	Calibration Curve of API in question for quantitative analysis	Stick calibration cartridge device, realignment camera, reinserts sampling cartridge (only for amodiaquine). Calibration curve for quantitative analysis done automatically
Calibration frequency	Background done every about every 30min. Instrument calibration should be done weekly or monthly	Daily	Camera realignment should be check daily. Calibration curve for quantitative analysis done for every experiment
Safety hazards	Lithium Ion Batteries; cleaning solution	Chemical Hazards: Flammable, corrosive, reactive.	Chemical Hazards: Flammable, , reactive.
Waste considerations	Kim wipe waste, crushed medicinal samples	Chemical. Mobile phase and sample preparation waste	Solvent waste
Cleaning between samples	After analysis, spray/apply about 5 to 10mL of isopropanol then wipe with a KIM wipe	flush injector port with clean mobile phase or methanol. After day of experiments, clean column and detectors by flushing system with clean mobile phase.	Same API, between experiments, automated. After day of experiments, flow water then air plug through the tubing, will be prompted by the software to clean the device.
Power supply required (Battery or Outlet)	Both	Our set-up was outlet powered, but battery operable available.	Runs on the mains.
Power consumption or battery life	100 to 240 V AC, 3 A, 50 to 60 Hz; (4 hour battery life)	Unknown	Unknown
Sample preparation	Crush medicinal sample in aluminum foil or a piece of weighing paper	Extraction solution needs be created then diluted once or twice before analysis to get to optimal concentration range. Mobile phase needs to also preparation as contains methanol, water, and some case sodium phosphate. See protocol for more details	Extraction of medicine sample and then preparation of instrument reagents. See protocol for more details.
Time per sample analysis	From crushing to spectra, about 3-5 min	Sample Preparation per sample about 10-15min including calibration curve samples. Analysis time is about 10 min per sample which includes injection, elution, and data recording (very API dependent and some sample elute faster or slower than others.) Data analysis time which includes all calibration samples and one questions sample about 10min. Data analysis to extract numbers from one sample after calibration curve done about 1-2min	Experiments: 8min for arteunate IV. If have tablets 20minutes to dissolve tablet in solicitor and run experiment
Reference library	Yes	None needed	None needed
Internet/Bluetooth Capability Features	Bluetooth Capabilities for the Agilent and additional internet/Bluetooth capabilities with the attached computer/phone	Only on the computer controlling the device	Only on the computer controlling the device
Data file format	Unique data format to the Agilent	.csv files	Saved in an excel sheet, and saves photos of analysis also.

Exported data for other analysis	Yes	Yes	Yes
Dimensions of the Device (cm)	22 x 29 x 19 cm (8.5 x 11.5 x 7.5 in)	LC unit alone: 61cm*20cm*21cm Travel Case (with tools, computers, no chemicals): 33cm*86cm*55cm	50cm*42cm*21cm
Languages available	English	English	English
Other accessories/equipment required	Cables for charging and data transfer to the computer	C-Vue kit comes with all the tools and equipment necessary to operate and maintain the device. A scale would be recommended to have to weigh samples.	Filters, Syringes, Supply carrying kit, laptop, vials
Level of training to create the library and software – chemist opinion	Technician level training at a bare minimum. Biggest difficulty is setting up the correct folder and software set up. Experiment to collect spectra as simple as questioned samples analysis	N/A	N/A
Level of training to test a sample only	Medium: Follow the on-screen instructions. Operator needs to know some problems that arise from not having enough sample or the sample is not pressed enough. Problems with Mid-IR analysis should be also known	High: User must be able to prepare chemical solution and understand how to dilute samples (including the mathematics behind it). Must be able to create calibration curves. Ideally understands how a column works and potential troubles with such columns. Must be able to use s spreadsheet like software (Excel) and generate calibration curves and integrate chromatographic peaks.	Medium: Needs ability to prepare all sample solutions and follow on computer instructions
Specific requirements for exporting the technology	Lithium battery export control	N/A	N/A
Accessible user manual	Yes	None	Yes
Barcode reader	Not on the device itself, but could be outfitted to the control computer	Not on the device itself, but could be outfitted to the control computer	Not on the device itself, but could be outfitted to the control computer
Non-destructive (i.e possibility to test the medicine without removing from original packaging)	No	No	No
Additional Comments		Only OFLO, ACA, and SMTM analyzed in this study. LM and P could be detected and quantitated; however, since those medicines are co-formulated and the other API could not be detected, not evaluated. ART, AZITH, AM, and DHA could not be detected even up to the 2000ppm range. Only the Hg detector used because getting no signal response from the Zn, I was getting down to the 5ppm level and getting good signal (OFLO and SMTM)	

General comments/feelings about the device - lab test	Easy to use device, but crushing the sample a downside compared to NIR devices. Device training not bad and relatively easy to use software to sample and generate libraries. Could be more portable using a cell phone (could use Microsoft phone)	Potential improvements could be made in mobile phase and column selection. Fairly robust device and very little troubleshooting needed to be done besides in mobile phase selection development. With two detectors, a two computer set-up was required (one for each detector) for simultaneous data collection. Detector improvements could help detect the other APIs (different wavelength sources). Due the devices build, should be easy to swap detectors for new ones. Separation and resolution not as good as HPLC, but being powered by a hand cranked syringe pump is still good.	The software crashed once and the optics mis-selected the proper lanes for analysis from the cartridge. Mis-selected lanes could be later fixed with Mat Lab because images saved. Waste accumulation from PharmaChk equivalent to that of liquid chromatography experiments.

Questions	Rapid Diagnostic Tests (Penn University)	Progeny (Rigaku)	NeoSpectra 2.5 (Si-ware)	MicroPHAZIR RX (Thermo Fisher)	Truscan RM (Thermo Fisher)
Hardware Maintenance require	No	No	Might need to change the light sources light bulb after a year or two of continuous use (1000 hour bulb life)	The tungsten light bulb in the device may need to be swapped out if the bulb burns out.	No, but it is required a computer to create methods and use other tools
Calibration-specificities	N/A	Benzonitrile standard is use to calibrate	Dial/every time the instrument turns off: place white felective tile on the fiber optic sampling probe and click "background" in NeoSpectra 2.5 software. Monthly: place white felective tile on the fiber optic sampling probe and click "Add Optical Gain Settings" in Neo Spectra Software and save.	Two Types: 1.) Self-Test, no sample needed 2.) Calibrate References, standard provided by Thermo Needed	A polistyrene sample could be used to calibrate.
Calibration frequency	N/A	Performance Verification (PV) should be done daily. Instrument Calibration when PV fails.	see above	1.) Weekly 2.) yearly or any time the device undergoes significant vibration or maintenance	Daily Self-Test recommended using polystyrene sample. More intense instrument check using sample provided by Thermo recommended yearly.
Safety hazards	Solvent hazards from the alcohol	Lithium Ion Batteries. Class 3b laser product.	High intensity light source (not a laser)	Lithium Ion batteries. High intensity light source (not a laser)	Lithium Ion Batteries. Class 3b laser product.
Waste considerations	spent RDTs, spent droppers, medicine solution waste	Wipe sampling surface with clean tissue	Wipe sampling surface with clean tissue	Wipe sampling surface with clean tissue	Wipe sampling surface with clean tissue
Cleaning between samples	N/A	Wipe sampling surface with clean tissue	wipe fiber optic sampling probe with Kim wipe	wipe sampling surface with a tissue	A wipe is used between every measurement
Power supply required (Battery or Outlet)	N/A	Lithium Ion battery	Outlet for the light source (AVALIGHT-HAL-MINI). USB power and data transfer for the Nespectra detector unit	Lithium Ion battery	Lithium Ion battery
Power consumption or battery life	N/A	Several Hours of Operation >6 hours	12 VDC / 2.08A (light source);	about 5 to 6 hours	3-4 hours

Sample preparation	solution preparations, crush tablet	Place sample (powder, tablet, or blister) onto sample probe.	Place sample (powder, tablet, or blister) onto sample probe.	Place sample (powder, tablet, or blister) onto sample probe.	Place sample (powder, tablet, or blister) onto sample probe.
Time per sample analysis	Sample preparation (12min), Test (5 min), data analysis (1 min) -->does not include replicates when necessary due substandard reading	25-50 seconds	<1 min to record spectra; for operator to open prerecorded spectra of known to compare to and evaluate, about 2 to 5min depending on where on hard drive operator saved the spectra	10 to 15 seconds	Different timing. During the method creation the measures ranged between 10s and up to 5 min. Once the method is created, the measures took between 10-1 min (depends on the result: coincidence corresponds to 10-15 s and fail 1-2 min
Reference library	N/A	Yes	No, user compares experimental spectra to previously recorded known spectra	Yes	Yes
Internet/Bluetooth Capability Features	N/A	Yes	Limited to the attached computer	No	No
Data file format	N/A	CSV raw spectra and image of scan report (.jpg)	Neospecta	Thermo proprietary files, PDF Report	Thermo proprietary files, PDF Report
Exported data for other analysis	N/A	Yes	Yes	Unknown	Unknown
Dimensions of the Device (cm)	7cm*2cm*0.5cm	Rigaku (8cm*34cm*7cm),	150 x 78 x 37 mm (light source), fiber optic cable and probe (6.35mm*1m),	10cm*23cm*25cm	21cm*11cm*5cm
Languages available	Protocol in English	Chinese, Turkish, Russian, Japanese, French, Spanish, English, Czech, Bulgarian and Arabic	English	Unknown	Unknown
Other accessories/equipment required	N/A	Sample analysis adapter	Many, for strictly tablet analysis: light source (AVALIGHT-HAL-MINI) with high intensity dongle, white reflective tile (Avantes WS-2), Thor Lab fiber optic probe holder (RPH), Thor Labs fiber optical cable and sampling Probe (FG550LEC-YCABLE-SP), data transfer and power cables (seperate for detector and light source)	Reference Sample Holder, extra battery, screwdrivers to take apart front nose cone	Different sample analysis adapters
Level of training to create the library and software – chemist opinion	scale/balance (not included)	A library could be create by any user	Basic computer knowledge needed for software operation	Significant training and assistance needed to set-up computer. High level of training need to create library, specifically in converting the initial signatures (spectra) and developing a method for each medicine when testing.	A computer software knowledge is required to create the methods and also to connect the instrument and the computer
Level of training to test a sample only	Low: Only ability needed to prepare extractions and dilutions.	Medium: Needs to be able to conduct calibration check and understand how to conduct experiments. Device analyzes spectra.	Medium/High: Needs to be able to conduct calibration check and understand how to conduct experiments. User spectra interpretation required	Medium: Needs to be able to conduct calibration check and understand how to conduct experiments.	Medium: Needs to be able to conduct calibration check and understand how to conduct experiments. . Device analyzes spectra.

Specific requirements for exporting the technology	None known	Potential Regulation of the Lasers. Lithium battery export control	none known	Lithium battery export control	Potential Regulation of the Lasers. Lithium battery export control
Accessible user manual	Yes	Yes	Yes, available in the flash drive where the software installation is	Yes	Yes
Barcode reader	No	Yes	Not on the device itself, but could be outfitted to the control computer	Yes	Yes
Non-destructive (i.e possibility to test the medicine without removing from original packaging)	N/A	Yes, through transparent blister packs. Artesun powder cannot be analyze directly from the bottle; these samples were analyzed using a plastic bag.	Yes	Yes	Yes, through transparent blister packs. Artesun powder cannot be analyze directly from the bottle; these samples were analyzed using a plastic bag.
Additional Comments		When the pills have oval shape, the position where you do the analysis could have influence during the identification	Sample probe configuration: the sample probe was inserted into the probe holder. The probe and holder was mounted to a clamp. The probe sampling window was parallel with the floor/table and facing up. The samples rested on top of the sampling interface to ensure pressure uniformity between samples.		
General comments/feelings about the device - lab test	Need more of the devices than expected. The protocol dictates that samples that register as "falsified ir substandard" on the first trial should be retested with a new RDT to confirm results. Lots of consumables for a screening test. Artemether RDT test do not work.	The time it takes to complete a scan depends on the sample. Some take longer than others. The graphical user interface is like a smartphone. Everything including library creation could be done on the device itself.	Needs data processing software. Relatively easy to set-up and operate. Experimental set-up can be configured in many ways and spectra can be recorded rapidly.	When generating the methods, the manufacturer representative recommended taking 25scans per method (or 5 signature acquisitions). When exporting the signatures for the method development, initial simplified method development would not create the methods because many of the spectra were too similar. Found a way around it by going into the advanced method development mode. See method report document. Importing, exporting, and configuring the MicroPhazir RX not really straight forward and requires a few hoops to jump through like need to activate the device for either sync or configuration modes before connecting to a computer.	Bad spectra were obtained for samples as AMK, Augmentin with oval shapes; the detected RAMAN spectra has a background noise that difficult the identification of potential unique peaks for the samples. During the method spectra acquisition the flatter the samples the faster the analysis. Easy to use buttons, and library creation needs an external computer. Initial set-up the most difficult part because of the computer set-up

Questions	Minilab TLC Kit (GPHF)	NIRScan (Young Green Energy)	Paper Analytical Decices (Notre Dame University)
Hardware Maintenance require	Change batteries in UV lights, may need replace bulbs at one point.	None user serviceable it seems	N/A
Calibration- specificities	Not applicable. TLC plates standardized and calibration solutions run along with samples	Calibration files load automatically to the NIR device when library file selected.	N/A
Calibration frequency	N/A	N/A	N/A
Safety hazards	Chemical Hazards: Flammable, corrosive, reactive, inhalation hazard. Minimize exposure to the UV lamp	Lithion Ion Batteries	None
Waste considerations	Chemical Waste from all the solvents used in the Minilab. Spent TLC plates and capillaries.	No	Used card and water
Cleaning between samples	After removing chemical hazards, soap and water to clean glassware to reuse.	Wipe sampling surface with clean tissue if necessary	Change water in between PADs.
Power supply required (Battery or Outlet)	Batteries (AA) just needed for the UV lamps	Battery Operated	None
Power consumption or battery life	AA battery dependent, but about 12 hours of continuous use	Several Hours of Operation >5 hours	N/A (excluding a device to take photos if necessary)
Sample preparation	API dependent. Briefly, two working standards needed to be prepped, a 100% and a 80% of the correct API concentration. Both samples and standard preparation included at least one extraction solution and then a dilution. Many others required a second dilution after the first one	None	Crushing and grinding tablet
Time per sample analysis	Assuming analyzing just one sample with one API (only one TLC plate), technician skills dependent. Standard Preparation for both 100% and 80% about 15 min. Sample Preparation about 7 minutes. TLC spotting about 3 minutes. TLC development about 15 minutes. TLC analysis using UV lamps about 1 min. TLC analysis using chemical staining about 10 minutes.	4-5 second scan, 1-2 minute set up from opening the app	10 min (2 min crushing + 2 min spreading the powder + 3 minutes color development in water + 3 min reading)
Reference library	Reference photos of what the TLC plate should look like at the end of the analysis	Yes	Library of the color codes for each API or combination of API - provided with the devices
Internet/Bluetooth Capability Features	N/A	Yes	N/A
Data file format	N/A	.csv	N/A

Exported data for other analysis	N/A	Yes	No
Dimensions of the Device (cm)	Entire kit not including chemicals	NIR instrument (8cm*6cm*4cm), Android Phone for data collection (15cm*7.5cm*0.5cm)	11cm*7cm*0.1cm
Languages available	English	English	Protocol and Reference Photos in English
Other accessories/equipment required		Phone charger, power outlet adapter	Mortar; Pestle (could also crush in wax paper to avoid mortar) ;2 Containers for water migration (one for the test card, one for the negative control); Spatula
Level of training to create the library and software – chemist opinion	N/A	Must be done by software developer	N/A
Level of training to test a sample only	Medium/High: User must be trained in the safe handling of the chemicals. Brief explanation of TLC and how to best spot and develop plates recommended	Low: Must be capable of operating smart phone and apps	Low: Manufacturer Developed
Specific requirements for exporting the technology	None known	Lithium battery export control	None known
Accessible user manual	Yes	yes	yes
Barcode reader	No	No, unless you get an app for the cell phone	No
Non-destructive (i.e possibility to test the medicine without removing from original packaging)	No	Yes through blister packs and glass, but only for pre-selected medicines and clear packaging	None
Additional Comments	Protocol for Piperaquine extraction states to add methanol to hydrochloric acid (HCl). I would recommend adding HCl to methanol instead for chemical safety to dilute the HCl more slowly as it can be reactive.		

General comments/feelings about the device - lab test	Basic TLC experiments. Although all the physical equipment necessary in a single kit, all the chemicals necessary to conduct the experiments can hinder portability due to volume and safety hazards. Protocols were very thorough for preparation and analysis. Distinction between 100% and 80% standards sometimes difficult to distinguish, primarily for acid staining detections.	Very easy-to-use device, if one understands how to use a smartphone. Initial library reference spectra errors for a few of the samples, but could be fixed remotely by the developer.	Simple device to utilize. Biggest struggle is to apply the sample powder to the PAD in a consistent manner. Colors can be hard to analyze sometimes.

Supplementary Annex 4. 4500a FTIR Single - Protocols

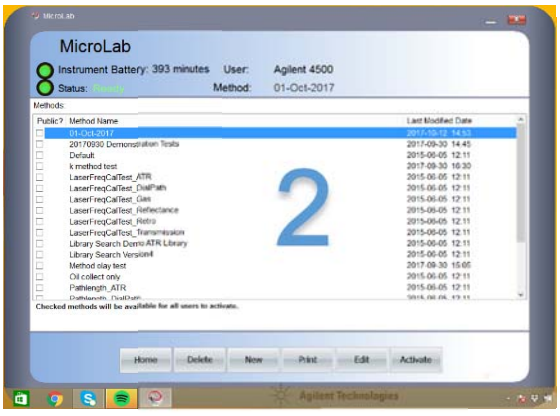
Overview of the operating procedures

The Agilent 4500a Series FTIR consisted in two dependent instruments; an Agilent 4500a FTIR device and a laptop computer with an installation of MicroLab software. The software requires a 'Professional' Edition of a Windows Operating System at least as new as Windows XP.

The Agilent 4500a Series FTIR device contains all the hardware for sampling (Infrared light source, the diamond Attenuated Total Reflectance (ATR) crystal sampling surface, sample press and detector) and operates with a laptop computer. The Sony VAIO SVT131A11M, Window 8.1 Pro laptop computer, acted as the unit's user graphical interface, as well as the command module for the sampling unit, generating spectra and storing data. Cable connection was used as a communication between the sampling unit and the laptop computer.

Basic Operation

Once both devices are fully-powered, the user must activate the software "MicroLab PC" on the laptop **(1)**. From the main menu on the screen choose methods and activate **(2)**. The user must then clean the sampling window; a green light demonstrates that the sampling window is clean enough and ready for analysis **(3)**. The system is configured to collect a background spectrum before analysis of each sample. This provides a baseline profile of the system conditions with no sample loaded on the instrument **(4)**. The user places the sample onto the sampling window, and closes the sample holder. A graph of the sample should then appear on-screen for the user to ensure that the sample has well-covered the sampling window **(5)**. The user then starts the analysis via the operating window on the laptop screen. The experimental spectra displayed with all the matched spectra in the selected method **(6)**.



Agilent 4500a FTIR reference library features overview

The Agilent allows user to create a reference library by collecting one good spectrum of the sample. The collected spectrum needs to be added to an appropriate library folder within the software (new 'libraries' – folders of spectra – can be created by the user). Therefore, the library has to be applied to the desired library folder in which the instrument will search.

Agilent 4500a FTIR Library Spectra/Calibration/Troubleshooting Protocol Generation:

Generating Libraries

1. **Method Generation**
    a. Your method not only defines how the instrument will conduct its experiments, but will also define the library that the instrument will search through after your experiment is complete. You need to collect your library spectra with the same method you use for your questioned samples to ensure that the spectra are consistent
        i. From the main menu of the software, select "Methods"
        ii. To generate a new method, select "New" at the bottom of the screen
            1. To edit a previous method, highlight the method you would like to edit and select "Edit" at the bottom

iii. The parameters of the experiments can be altered by the user; however, many of the default parameters work well for pharmaceutical analysis. Ensure the following parameters are set for quick and optimal analysis:
    1. **optional**In the "Type" tab, analysis time can be reduced by selecting "Background Valid time limit" and set the value to 30 minutes so you do not have to do a background scan after every sample
    2. In the "Instrument" tab, for the sampling technology, select from the drop-down menu "ATR"
    3. The "Libraries" tab is where you will link your method to the library you want to analyze (after generating your reference spectrum).
        a. Remember, you will record your new library spectra with this method, then add them to this new method for consistent sampling
iv. After the parameters have been set, select "Save As" to save and name the method

2. Library Generation

i. To generate the library, from the main menu, select "Advanced Features"
ii. Select "Library Management"
iii. To generate a new library, select "New Library"
    1. To edit previous libraries, highlight the library name in the scroll down menu
iv. When you select "New Library", a window should pop-up. Name the library in the "Library Name" line and ensure the box is checked for "ATR Spectra" Select "Create" when ready
    1. To access this menu on old libraries, highlight the library and select "Properties"
v. Ensure the library you want to edit is highlighted in the scroll down menu and select "Add to Library" to add spectra in the library, and to remove spectra, highlight the spectra in the spectra scroll down menu and the select "Delete From Lib"

3. Library Spectra Generation

i. In order to select the method you would like to make the library spectra with, select "Methods" from the main menu
ii. Highlight the method you would like to use, the select "Activate"
    1. When back in the main menu, ensure the correct method if selected by look at the top of the window next to "Method:"
iii. Select "Start" from the main menu
iv. Clean the sampling crystal thoroughly with a wipe and solvent before clicking "Next", the instrument will then do a check crystal check and then a background check.
v. Load the sample on the sample window and apply pressure with the sample press **be finger tight with the press**, then click "Next"
vi. Type out the same of the sample in the "(optional) Sample ID" line ***not optional***
    1. Include at least this information in the following order with a "_" in between each:
        a. YearMonthDate (Ex. 20170927)

b. Brand Name
c. Active Ingredient(s)
d. Batch Number
e. ***Optional*** User Initials to determine who made the library

vii. Feel free to type in any relevant information in the "(optional) Comments:" section.
viii. In the real-time spectra window in below the comment section, look for peaks
1. If the spectra is completely flat, apply more pressure to the press until the signal stops increasing ***finger tight only***
2. See troubleshooting guide if you see no signal if you still don't see spectra
ix. Select "Next" when ready
x. After the sample is measured/recorded,
1. Select "Details" to look at the spectra to ensure quality
2. Select "Data Handling", then "Add to Library…" to add the spectra to a library that was generated previously
a. Change the "Match Text:" to desired name when conducting questioned sample analysis
i. Include at least this information in the following order with a "_" in between each:
1. YearMonthDate (Ex. 20170927)
2. Brand Name
3. Active Ingredient(s)
4. Batch Number
5. ***Optional*** User Initials to determine who made the spectra
b. Select the library you would like to add the spectra to by either selecting from the "Select from Method Libraries" or by clicking the "…" button after the "Library Name:" line.
c. Select "Add to Library" when done.
3. Select "Done" to continue with experiments
4. Select "Home" to return to the main menu

b. You can add previously collect spectra by accessing the "Previous Results" from the main menu, selecting the spectra you would like to use, and the following the same steps as above.

Library Files Location on the Sony PC

C:\Users\Public\Documents\Agilent\Microlab\Libraries

- Simple copy and paste when you need to upload or download libraries

Calibration:

- All calibrations are done from the "Systems Check Menu" located in the "Advanced Features" menu in the main menu
  - Weekly Calibration

1. Ensure the "Performance (Signal-to-noise)" is selected and only this test,
    - Also set the "Number of Tests:" to 5 so speed analysis
2. Select "Next", Follow the on-screen instructions
    - You do not need any sample for this calibration
3. After the test is complete, select the "Laser Frequency Calibration Check" and only this test
    - Set the "Number of Runs:" to 5 and that the "Check value only" box is selected
4. Select "Next", Follow the on-screen instructions
    - You will need the polystyrene card that comes in the box with the instrument
5. After these tests, you are ready for experiments

- Monthly (or at least a few times a year)
    1. Ensure all the possible tests are selected
        - If you do not have toluene, do not do the "Pathlength Calibration Check"
        - Ensure all the number of test, minutes, and runs are set to their default
            - 15 tests
            - 30 minutes
            - 15 runs
            - 5 runs
    2. Select "Next", Follow the on-screen instructions
        - I have had problems where the instrument would not proceed to the next calibration after the first test, just select the calibrations that were not performed and continue.

Trouble Shooting Protocol:

1. Ensure that the crystal was clean during the background scan
    a. Although there is a crystal clean check, do not assume it is perfect and clean with tissues and solvent (isopropanol is ideal)
2. Ensure there is enough powdered sample and pressure on the ATR diamond crystal
    a. Release the sample press and transfer more powder onto the sample if necessary
    b. Ensure the sample press is finger tight, do not be afraid to add a little pressure, but monitor the real-time signal (the part of the software where you also write down the sample name and comments before recording the spectra to save)
3. Ensure the battery is more than 1/3 charged (just in case it is a power issue) or that the instrument is hooked up to the mains
4. When in doubt, restart the device and computer
    a. Ensure after restart that before you open up the "MicroLab PC" software, the FTIR is fully on and plugges into the computer or else the software will not open
5. Conduct the weekly calibration to ensure it's not an instrument problem
    a. If the weekly calibration passes, most likely it is a sampling issue
6. If you believe it is an issue with the clean check, you can reset the check by the following

    a. From the main menu, select “Advanced Features” and then select “Diagnostics
    b. To reset the instrument what the instrument thinks is a clean ATR, select “Reset Clean Validity”
        i. ***Ensure the sampling crystal and press are as clean as possible***
7. If the weekly calibration FAILS, perform a monthly calibration
8. If the monthly calibration FAILS, restart the device and computer
    a. You may way to unplug the instrument from the mains and wait for the battery to discharge to simulate removing the battery
9. Perform another daily calibration, then monthly calibration
10. If it fails again, contact the experts
    a. From the main menu, select “Advanced Features” and then select “Diagnostics”
    b. This information may be relevant to understanding the cause of the problem.

Downloading the Microlab PC Software to a Computer

- The software downloads are no more difficult than any other program (lots of hitting “Next” and Accept”); however, the software is currently only registered to Serena’s Sony laptop and the Lenovo QDa desktop at Georgia Tech. Only these computers have full functionality for the software.

4500a FTIR Single Reflection – Training

PRACTICE MEDICINES

LOMWRU Codes	Brand	API	Dosage	Manufacturer
LA16/115	AMK	Amoxicillin – Clavulanic acid	1000 mg	RX Manufacturing
G113 G373 G399	Metronidazol	Metronidazole	250 mg	CBF Pharmaceutical Factory
G414 G491	Clarithro 500	Clarithromycin	500 mg	VIDIPHA, Vietnam
G313 G329 G431 G471	Erythro-500	Erythromycin	500 mg	Codupha-Lao Pharma Factory
G416 G494	Norfloxyl 400	Norfloxacin	400 mg	Bangkok Lab & Cosmetic
G339 G355 G377	Penicillin V	Penicillin V	400000 IU	Codupha-Lao Pharma Factory
G458 G493 G522	Roxithroxyl	Roxithromycin	150 mg	Bangkok Lab & Cosmetic

INTENSIVE TRAINING

I. Training equipment
- Agilent 4500FTIR
- Laptop Computer
- Medicines practice sample
- Alcohol
- Cleaning tissue
- Brush
- Paper
- Pestle

II. Training procedures:

1. General Information
   - Give study document to each inspector (5 minutes)
   - Introduction (presentation): overview of project objectives, general information about the devices
   - Show them the device and all supplementary items in packing case, with explanation of function.
2. Practice
   Allow them to practice step by step
   - Connect USB cable with laptop computer
   - Switch ON and login the device
   - Experiment with samples (2 samples)
   - Explain process step-by-step at the same time as demonstrating until get the result
3. Presentation: background theory
   - Recap basic operating procedure(set-up and basic use of the device)
   - Overview of basic theory of FTIR (1 slide)
4. Practice (2)
   - Each inspector given opportunity to test three different samples for each (one inspector practised with only one sample (inspector decision))
   - Explain how to record result in to the record sheet.
5. Presentation: common problems with FTIR and how to fix them

RUDIMENTARY TRAINING

- SOP document given to inspector (inspector left alone for 5 minutes to read)
- Show device and explain how to setup and how to use
- Give them three samples to practice with, alongside trainer (most of them were choose just 3 samples for practices)
- Explain the result and how to record onto record sheet
- Opportunity for question and answer

Common questions from the inspectors:

- Can it scan all types of medicines?
- Can we create and add library by ourselves?
- How many library entries can the device save?
- Can we export the data from the device?
- How much does the device cost?

Other comment:

- Some inspectors made mistakes in practice (e.g. forgetting to clean the crystal window; forgetting to rename sample

4500a FTIR Single Reflection – Quick guides

Quick guide of operating procedures used in the field evaluation

1. Connect the Agilent 4500a FTIR with a laptop computer via cable.
2. Open the “Microlab PC” program.
3. Before using, the user needs to calibrate the device at least once a week (Other chemical or instrument are unneeded).
4. On main menu, select “Methods” and choose the desired method, then click “Activate”.
5. On main screen, select “Start” to run an analysis.
6. Clean the crystal sampling window then click “Next”. The status light turns green means it is ready to analyze.
7. Place a sample the middle of the sampling window. Close the press then click “Next”
8. The graph of sample will appear. Name the sample then click “Next”.
9. The experimental spectrum compared to the library spectra will appear with the number of quality.

Supplementary Annex 5. C-Vue - Protocols

1. **Questioned Sample Preparation**
    - 1.1. All samples were extracted in powder form. Tablets were crushed into a fine powder by wrapping the sample in weighing paper and crushing it with a pestle. Samples that were already in powder form (ART) were not further modified.
    - 1.2. A sampling of the medicinal powder (between 10-25mg) was placed into a clean vial and extracted using 5 mL of an extraction solution
        - 1.2.1. Sulfamethoxazole/Trimethoprim – methanol
        - 1.2.2. Amoxicillin/Clavulanic Acid – methanol
        - 1.2.3. Ofloxacin – 4.9mL of water: 0.1mL of glacial acetic acid
    - 1.3. Based on this extraction, the concentration of active ingredient was calculated based on the reported values issued by the manufacturer.
    - 1.4. These extractions were then diluted to the working concentration required for the C-Vue using the mobile phase utilized by each API specific LC protocol.
        - 1.4.1. SMTM- 100ppm SM and 20 ppm TM
            - 1.4.1.1. In 30:70 methanol: water with 0.1M Disodium Phosphate
        - 1.4.2. ACA- 100ppm for A resulting with either
            - 1.4.2.1.1. 14ppm CA with 875mg A formulations or
            - 1.4.2.1.2. 25ppm CA with 500mg formulations
            - 1.4.2.2. in 5:95 methanol: water with 0.1M Disodium Phosphate
        - 1.4.3. OFLO – 100ppm OFLO
            - 1.4.3.1. In 30:70 methanol: water with 0.1M Disodium Phosphate
    - 1.5. Samples were stored in a 4°C refrigerator when not in use

2. **Calibration Curve Preparation**
    - 2.1. Extractions and dilutions were carried out in the same protocol following 1.2 to 1.4 with the following exceptions:
        - 2.1.1. The API was derived from a pure stock of only the API (stocks from TCI Chemical and Sigma Aldrich)
        - 2.1.2. A range of concentrations were prepared in which both APIs were present in the same calibration solution for binary medicines and listed below:
            - 2.1.2.1. SMTM - 30/6 ppm, 60/12 ppm, 90/18 ppm, 120/25 ppm
            - 2.1.2.2. ACA – 30/4 ppm, 60/15 ppm, 90/25 ppm, 120/35 ppm
            - 2.1.2.3. OFLO- 30 ppm, 60 ppm, 90 ppm, 120 ppm
3. **C-Vue LC Preparations**
    - 3.1. From a dry pump or when switching mobile phases, ensure the column is disconnected from the six-port injector
    - 3.2. Fill the 60mL mobile phase syringe with the desired mobile phase solution
        - 3.2.1. To prevent gas bubbles from entering the LC system, hook the filled mobile phase syringe to an empty 60mL syringe
        - 3.2.2. Secure the mobile phase syringe’s plunger to prevent movement

3.2.3. Pull on the plunger of the empty syringe to generate a vacuum within both syringes until the empty syringe's plunger reaches its maximum distance before removing the plunger from the syringe

3.2.4. Tap the mobile phase syringe until the bubbles in the solution subside

3.2.5. Release the vacuum and remove he mobile phase syringe and push out any remaining air in the syringe

3.3. Load the mobile phase syringe into the C-Vue

3.4. Purge the injector by adding some pressure to the pump spring

3.5. Capture the mobile phase in a a container coming out of the injector until no air bubbles are present

3.6. Connect the injector and the column together.

3.7. Connect the column to the detector(s) and plumb the lines from the detector(s) to a waste container

3.8. Flow mobile phase through the LC system at a pump spring compression of 30mm for about 30min

3.9. At the same time, turn the detectors to allow them to warm -up.

3.9.1. The detectors are warmed up when you go into the C-Vue software, monitor the signal from the detectors, and noticed that the signal has reached a steady flat baseline

3.10. During experiments, ensure the pump spring is set to 50mm prior to injection and recording. (See 4. And 5. For those)

4. Sample/Calibration Injection Protocol

4.1. Ensure the six-port injector is in the load position

4.2. Using a 1mL syringe, flow 1mL of a blank mobile phase to clean the injector

4.3. After cleaning, fill a 1mL syringe with at least 0.8mL of sample solution

4.4. Flow 0.5mL of sample solution through the syringe to clean the injector and subsequently the 0.3mL to load the sample

4.4.1. For subsequent injections of the sample, the 0.5mL injection does not need to be repeated

4.5. To inject the sample into the system, the injector should be rapidly switched to the "Inject" position at the same time as hitting "Run" (this will begin recording data, see 5.5 to 5.6 to stop& save) in the C-Vue software and remain there for the duration of the run.

4.6. To load the next sample, switch the injector back to the "Load" position and repeat steps 4.2 to 4.5 for brand new samples or 4.4 to 4.5 for the same sample

5. C-Vue Software Set-up and Recording

5.1. Turn on the computer

5.2. Start the C-Vue software

5.3. Ensure signal appears in the C-Vue software window

5.4. Follow steps 4.4 to 4.6 for sampling

5.5. After recording the necessary data, click "STOP" to stop recording

5.6. The file explorer window should pop up, save the file to a designated folder with a filename

6. C-Vue Software Data Analysis

6.1. In the "Analysis" tab of the software, press the open button

6.2. Select "Raw Data .csv"

6.3. Open the file that was saved.

6.4. Integrate the peaks

6.4.1. Press the "Manual Integrate button"

6.4.2. From left side to the right side of the chromatogram, right click the beginning and end of the peak

6.4.2.1. For multiple peaks, continue marking the beginning and end of the peak

6.4.3. Once all the peaks have been marked, left click

6.5. Collect the Area information to compile calibration curves through linear regression analysis and determine the concentration of the sample tested

Table 1. Experimental details for the laboratory evaluation

Active Ingredient	Ofloxacin	Sulfamethoxazole/ Trimethoprim	Amoxicillin/Clavulanic Acid
Mobile Phase*	30:70 Methanol:Water	30:70 Methanol:Water	5:95 Methanol:Water
Pump Spring Load at start (mm)	50	50	50
Retention Time (min)	4.8	4.6/3.5	4.4/3.1
API Extraction Solvent	98:2 Water: Glacial Acetic Acid	Methanol	Methanol
Dilution Solvent*	30:70 Methanol:Water	30:70 Methanol:Water	5:95 Methanol:Water
Final Sample API Target Concertation (ppm)	100	100/20	1.) 100/14.3 for 875mg/125mg ACA formulation 2.) 100/25.2 for 500mg/125mg ACA formulations
Target Calibration Curve Point Concentrations (ppm)	30 60 90 120	30/6 60/12 90/18 120/24	30/5 60/15 90/25 120/35

*Solvent contains 0.1 M Disodium Phosphate as a buffer

For the C-Vue analysis, there two major types of solutions that needed to be prepared. First were the calibrations samples that were extracted from pure API stock (TCI Chemical or Sigma Aldrich). Four-point calibration curves were created at the concentrations specified in **Table 1** Each point was tested three times from the same dilution sample. Second were the samples tested that were extracted and diluted to an API concentration that is also specified in **Table 1** based on the manufacture's reported value(s). Both calibration and experimental samples were extracted and diluted with the same solutions to maintain consistency. Each sample in the study was extracted and diluted once and tested 3 times.

Prior to the calibration and questioned sample injection, the C-Vue must be prepared for analysis. The mobile phase was degassed, loaded, and fed through the injector, column, and detectors on the C-Vue for about 15-minutes. While the system was flushing, the detectors were turned on and warmed up until they registered a flat baseline seen in the C-Vue's software window. Once the C-Vue was ready, each injection of a sample was recorded independently. For injection preparation, the injector was kept in the "Load" position and the sample loop was cleaned with the mobile phase of the instrument (1mL). Then, the loop was additionally flushed with the next sample to be tested (0.8 mL). Flushing with both blank and sample only occured between different samples. For back to back trials of the same sample, only 0.3mL of sample was loaded to ensure the 0.1mL sample loop was completely full. The calibrations samples would be run prior to the questioned samples. When injecting, the six-port injector and the software were independently operated; however, they needed to be started simultaneously with one hand on the injector and the other on the computer with only one operator. After all the samples were recorded, the user would hit stop and save the file to the user's selected folder. The peak areas for each chromatogram were later measured using the C-Vue's software and recorded into a spreadsheet to process the calibration samples into a linear regression plot and to calculate the percentage concentrations of API in the questioned samples. For a sample to be registered as good quality, the percentage concentration must fall between the specified thresholds described in the main report of this project.

Supplementary Annex 6. MicroPHAZIR RX – Protocols

Overview of the operating procedures

After turning on the device **(**Figure 1**,** picture **1)**, the user logs into their credentials **(**Figure 1**,** picture **2)**. The tungsten lamp (infrared source for the device) must then warm up and go through a self-test (run-time ~10 minutes, performed daily) to ensure optimal performance. A more rigorous calibration is required annually with reference samples specifically purchased from Thermo-Fisher Scientific (see below).

After a successful self-test, the user goes to the "Run" function, and from the Methods tab, should select the comparator library spectrum for the sample they wish to test. The user is then prompted to input the filename and batch number of the sample.

Three sampling techniques were employed:

a. For tablets tested out of blister packaging, the MicroPHAZIR is placed on a

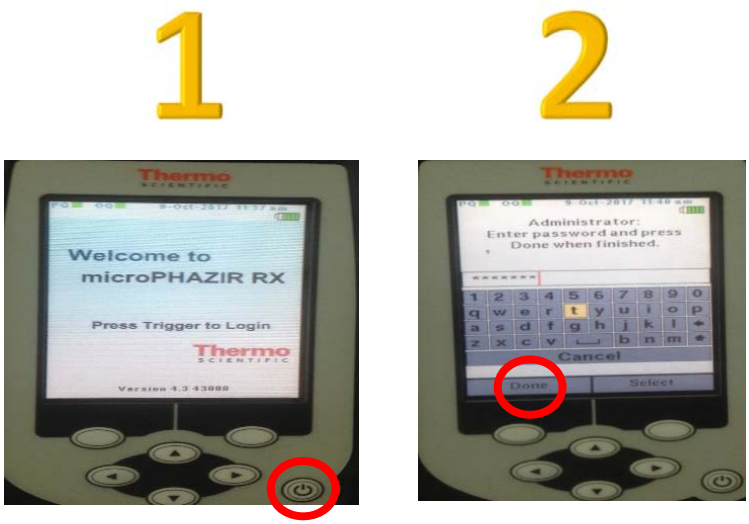


Figure 1: Start-up screen for MicroPHAZIR

table surface so that the sampling window is parallel to the table. The tablets are then rested on the sampling window and the home-made sample holder added if necessary (**Figure 2**).

b. For tablets tested inside the blister packaging, the MicroPhazir would be held in one of the user's hands and the other hand would hold the blister pack sample flush against the sampling window (**Figure 3**).
c. For the ART samples (API powder in vial), the artesunate vial would first be tapped several times against a hard surface to shake the powder to the bottom of the vial. The vial was then placed on its base on top of the sampling window.

Once the sample was appropriately positioned, the user either pulls the device trigger or presses ‘go’ on the device screen, starting the sample scan. After the scan is complete, a ‘Pass’ or ‘Fail’ results is displayed (see Quick guide below).

Figure 2. MicroPHAZIR sampling of tablet

Figure 3. MicroPHAZIR sampling of tablet through blister

MicroPhazir reference library features overview

When generating reference library spectra, the MicroPhazir guides the user to collect five spectra of the same sample, allowing the user to introduce some variability into reference collection like batch variation or sample position to have an average spectrum to compare to. The collected spectra are labelled ‘signatures’. After spectra collection, the data must be uploaded to a computer for processing. On the computer, all the signatures desired in a library must be uploaded to the same workspace, the user selects the mathematical functions desired, and the software then outputs a single library file that contains all the selected spectra to be uploaded to the MicroPhazir. Libraries that are generated by the software cannot be edited afterward, thus new libraries must be generated for minor or major edits. Communication between the MicroPhazir and computer requires downloading two software packages to the computer. When the user is ready to connect the instrument to the computer (via USB cable),

you must activate the sync function on the MicroPhazir. There are two separate sync functions for uploading experimental data and uploading/downloading reference signatures and libraries.

MicroPhazir RX Library Spectra/Calibration/Troubleshooting Protocol Generation:

The user first needs to Sign In to the Main Menu using:

- Username: Administrator
- Password: default

1. **Generating Signatures on the MicroPhazir <u>(defined as Methods)</u>**
    i. From the main menu, select "Tools"
    ii. Select "Acquire Signature"
    iii. Highlight and select "Method:"
    iv. Scroll up and then to the left to highlight the "New" tab.
    v. Press select to add a new signature entry to the device
    vi. Type in the method file name
        1. Include at least this information in the following order with a "-" in between each:
            a. YearMonthDate (Ex. 20170927)
            b. Brand Name
            c. Active Ingredient(s)
            d. Batch Number
            e. ***Optional*** User Initials to determine who made the library
    vii. Press "Done"
    viii. Highlight and select "Batch:"
    ix. Scroll up and then to the left to highlight the "New" tab.
        1. If you are taking another signature of the same batch, scroll through the options to find the correct batch number, skip the next steps until you get to the sample number
    x. Press select to add a new signature entry to the device
    xi. Type in the batch number of the sample.
    xii. Press "Done"
    xiii. The "Sample:" line should autofill,
        1. If not, highlight and repeat the same steps as creating a new batch or selecting an old one.
    xiv. Once you confirm that the samples information is correct, highlight and select 'Continue to Start Run"
    xv. Follow the on screen instructions:
        1. Place the sample on the sampling window (or vice versa)
            a. If the tablets are smaller than the sampling window, place cover over the sample and sampling interface to prevent ambient light from entering the detector
        2. Pull the device trigger or press "Select" to scan
            a. Look at the resulting spectra
                i. If the spectra look good (not completely flat, but with broad peaks and valleys), continue to the next scan

ii. If the spectra looks bad, press “Esc” to repeat the experiment

3. Continue until you have 5 spectra that overlap each other well.

xvi. If the resulting spectra overlaps well, highlight and select “Save Current Signature and Continue”

1. Bad overlap, select “Cancel without Saving” and repeat the experiment

xvii. Repeat the process to add more signatures to your library.

2. Uploading the Signatures to the computer

a. In this study, the software to process the signatures to make libraries is on was uploaded to a desktop computer (Dell Optiplex 3020 MM_338)

i. From the main menu, select “Sync”

ii. Connect a Mini-USB to the MicroPhazir, and the USB end to the computer.

a. **Uploads and downloads from the device and compute take a while take a while, be patient**

iii. If file syncing was successful, a message from computer should pop-up.

1. To check if data and signatures was uploaded successfully
   a. Go to the computers file explorer
   b. Access the “Local Disk (C:)”
   c. Access the ‘Thermo” folder
   d. Access the “data” folder
   e. Access the “Archive” Folder
   f. Look for the folder with the day the the device was synced and access it
   g. Ensure the data you collected is in that folder

iv. Access the “Method Generator” desktop app

1. To ensure full software capabilities, click on the “Model” tab and ensure the “Advanced Modeling” is enabled

v. To access the data, click on the “File” tab, click “Open Data File” and use the file explorer to find the signatures

1. Access the “Local Disk (C:)”
2. Access the ‘Thermo” folder
3. Access the “data” folder
4. Access the “Archive” Folder
5. Look for the folder with the day the the device was synced and access it
6. Acess the “Data” folder on the time stamped folder
7. Select the Signature file that was created the day they were acquired

Note-you can process multiple different spectra at the same time.**Ensure that the software can recognize the samples between different sample acquisitions

vi. In the list adjacent to the “1. Read Data File” button highlighted in green, ensure that the signatures you would like to make a method with are highlighted in blue.

vii. Once selection is highlighted, click the “2. Pre-Process” button highlighted in green

1. The spectral window should change if below the pre-process: step 1 was “S. Golay”, step 2 was “Normalize Range”, and the rest were skips (these are the default processing standards)

viii. Once selection is highlighted, click the “3. Spectral-Match-knn” button highlighted in green
   1. The window below this button should spit out results showing how well different spectra can distinguish themselves from one another
   2. If samples cannot correctly identify themselves,
      a. Either isolate out the bad spectra in near the “1. Read Data File” button highlighted in green
      b. **ADVANCED** Attempt to adjust the pre-processing parameters
      c. This step can be overridden by continuing onto the next step **be aware** your library searches may not give you the correct result because it may identify the mismatched spectra

ix. Once satisfied with the results from

x. “3. Spectral-Match-knn” button highlighted in green, then press the “4. Creating SM-KNN Application” button highlighted in green

xi. A window should pop up
   1. Ensure that the experiment is set to “Verification (pass/fail)
   2. All of the other parameters are default and work well.

xii. Click ”OK”

xiii. Save and name the method file in the following folder:
   1. Local Disk (C:)/Thermo/Data/Method Generator/Applications
      a. Include at least this information in the following order with a “-” in between each:
         i. YearMonthDate (Ex. 20170927)
         ii. Brand Name
         iii. Active Ingredient(s)
         iv. Batch Number
         v. ***Optional*** User Initials to determine who made the library

xiv. Remove the data USB cable from the MicroPhazir if you have not done so already

3. Uploading the Methods back to the MicroPhazir

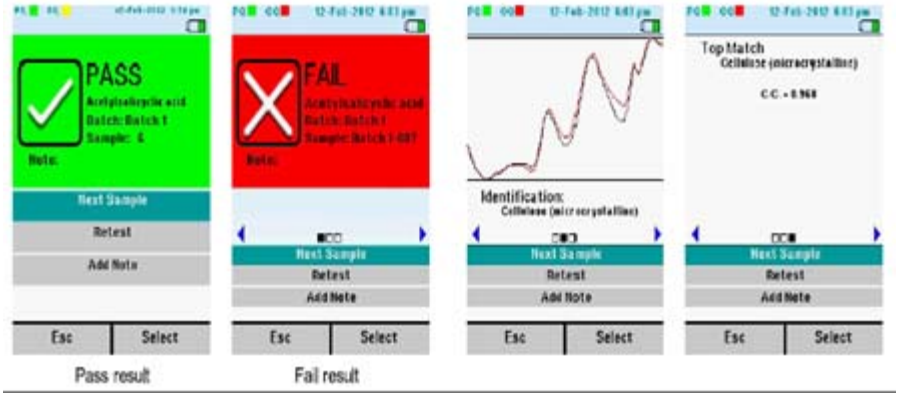
a. From the MicroPhazir’s main menu, select “Tools”
b. Select “Configure microPHAZIR”
c. Select “Configure with Libraries”
d. Connect the USB to the MicroPhazir and the computer
e. Access the “microPhazir Admin” desktop app on the computer
   i. **Uploads, downloads, and opening up the software for the device and computer take a while take a while, be patient**
   ii. Don’ t be afraid to click on the desktop app a few times
f. The methods you created should be in the right-hand column under the ‘Local PC Libraries and Methods”
   i. This is in the Methods “tab” just in case the software opens up to the wrong tab

g. Highlight the method you would like to add to the MicroPhazir and press the "Copy to Active" button
h. Once uploaded, close the software and remove the USB cable and you should be ready for analysis.

Calibration:

- **Daily/Weekly Calibration (Self Test)**
  1. From the main menu, select "Self Test"

  2. Select "Start Scan"
     - If a lamp warm-up warning appears, wait the allotted time for proper warm up.
  3. The device should automatically start its own test.
  4. The result of the performance qualification should pop up
     - If pass, select "Return to Main Screen" and continue with



experimentation
     - If fails, see troubleshooting protocol

- **Annual Calibration (Calibrate Reference)**
  1. From the main menu, select "Tools"
  2. Select "Configure microPHAZIR"
  3. Select "Calibrate Reference"
  4. Place the sample holder on top of the sample interface (Part 810-0139)
     - It's the black piece of plastic we use as a tablet cover, remove the electrical tape

5. Place the "microPHAZIR Reference Standard" (barcode 990200017088) in the sample holder,
    - Have the blank white side of the of the reference standard flush with the sample interface
    - You should see the "WR"side of the reference standard stick out of the sample holder
6. Press "Select" to start the calibration
7. The results of the experiment should pop up
    - If successful, press "OK" and continue with experiments
    - If failure, follow troubleshooting protocol

Trouble Shooting Protocol:

11. Ensure the sample is properly secured or being held in front of the sampling interface or vial holder
    a. Minimize and potential ambient light from entering the device
    b. Hold the sample in one position and do not move
12. Ensure the battery is more than 1/3 charged (just in case it is a power issue)
13. When in doubt, restart the device
    a. Remove the battery after shutdown to ensure the device completely turns off
14. Conduct a Self Test to ensure it's not an instrument problem
    a. If the self test passes, most likely it is a sampling issue
15. If the self test FAILS, perform a Calibrate Reference
16. If the calibrate reference FAILS, restart the device and remove the battery
    a. Allow the instrument to sit without the battery for 5 minutes to ensure no charge remains in the instrument
17. Perform another calibrate reference
18. If it fails again, contact the experts
    a. May need to do an "Operational Qualification" test (In the "Tools" menu), but requires the reference standards recommended by Thermo that were not included
    b. In the meantime:
        i. In the "Configure mciroPHAZIR" menu (link found in the "Tools" menu", select "Get Diagnostics"
    i. Connect the Connect the USB to the MicroPhazir and the computer
    j. Access the "microPhazir Admin" desktop app on the computer
        i. **Uploads, downloads, and opening up the software for the device and computer take a while take a while, be patient**
        ii. Don' t be afraid to click on the desktop app a few times
        iii. The diagnostic data could be critical to determine the source of the error.

Downloading the Thermo MicroPhazir Software to a Computer

- The software downloads are no more difficult than any other program (lots of hitting "Next" and Accept"); however, you need to ensure that both the "Method Generator" and "microPHAZIR Admin" software packages are downloaded for full capabilities prior to experimentation.

MicroPHAZIR RX – Training

PRACTICE MEDICINES

LOMWRU Codes	Brand	API	Dosage	Manufacturer
LA16/115	AMK	Amoxicillin – Clavulanic acid	1000 mg	RX Manufacturing
G113 G373 G399	Metronidazol	Metronidazole	250 mg	CBF Pharmaceutical Factory
G414 G491	Clarithro 500	Clarithromycin	500 mg	VIDIPHA, Vietnam
G313 G329 G431 G471	Erythro-500	Erythromycin	500 mg	Codupha-Lao Pharma Factory
G416 G494	Norfloxyl 400	Norfloxacin	400 mg	Bangkok Lab & Cosmetic
G339 G355 G377	Penicillin V	Penicillin V	400000 IU	Codupha-Lao Pharma Factory
G458 G493 G522	Roxithroxyl	Roxithromycin	150 mg	Bangkok Lab & Cosmetic

INTENSIVE TRAINING

- Training Materials
  - ✓ MicroPHAZIR quick start guide

- ✓ MicroPHAZIR device plus accessories (battery, charger, sample cover (sample holder supplied with device, customized by laboratory team to act as sample cover))
- ✓ Practice medicines (see table above)
- ✓ Inspector record sheet (identical to that supplied for recording results in evaluation pharmacy)
- ✓ Handout with presentation slides

- Training session
  1. Presentation: Device overview and basic operating procedure
     - Give basic overview of device, including how to run a simple scan/calibration.
     - Introduction to NIR spectroscopy (1 slide).
  2. Opportunity to practise
     - Each inspector allowed to run one sample each on the device
  3. Presentation: explanation of how the device works, including how it makes the pass/fail decision; types of medicine (dosage forms) it can analyse; how to review results; additional features (e.g. interrogating 'fail' result in order to find the closest matching spectrum)
     - During the training, inspectors were free to ask any questions
  4. Thirty minutes to practise using the device
     - Seven different APIs provided (see table with 'Practice Medicines' above)
     - Asked to record results on recording sheet (same as will be used during inspection).
  5. Presentation:
     - Possible sampling problems with solutions (general to NIR; one slide)
     - Brief explanation of how to upload data to computer (no demonstration or practice)
- Time spend on training
  1 – 2 hours
- Scans performed per inspector during training
  30 – 40 scans

RUDIMENTARY TRAINING

- Training Materials
  - ✓ MicroPHAZIR quick start guide
  - ✓ MicroPHAZIR device plus accessories (battery, charger, sample cover (sample holder supplied with device, customized by laboratory team to act as sample cover))
  - ✓ Inspector record sheet
- Training session
  - o Quick guide SOP given to inspector; left for 5 minutes to read through SOP
  - o Trainer returns. MicroPHAZIR with accessories in packing case given to inspector
  - o Trainer demonstrates how to calibrate and run a sample, and how to record appropriately on the
  - o Inspector allowed to perform 1-3 scans on up to 3 samples
  - o Inspector escorted to pharmacy for inspection.
- Time spent on training
  15 minutes

- Scan performed per training
  3 - 6 scans

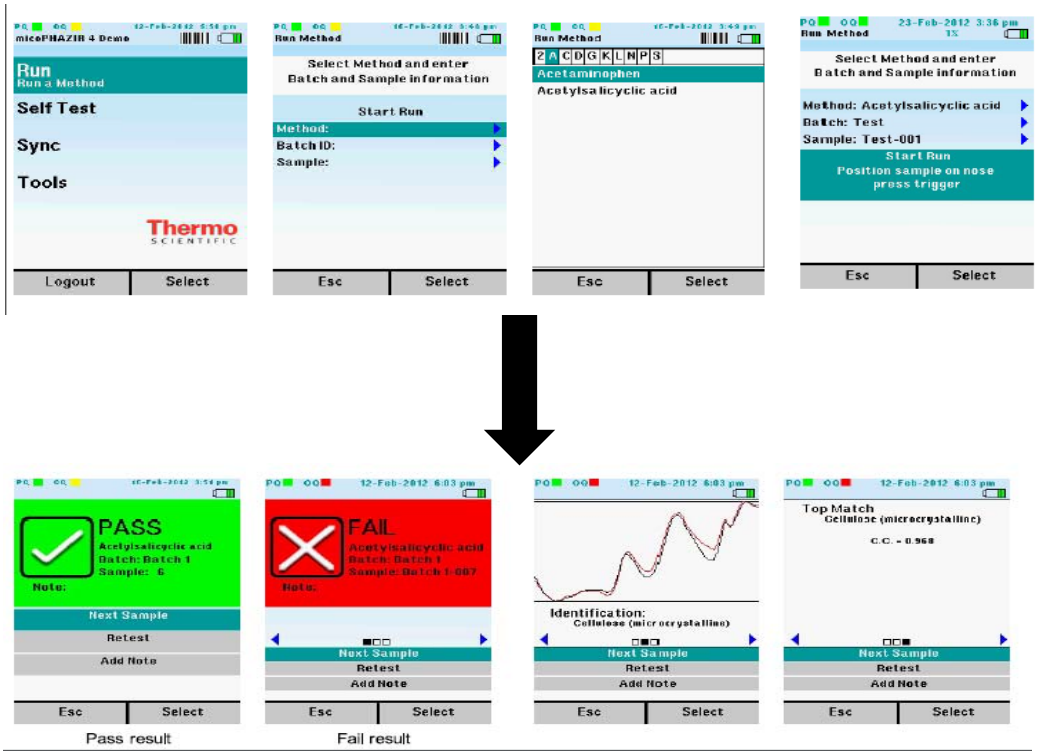
Training summary

- Particular difficulties noted by inspectors during training
  - Difficult to hold the sample still on the sampling window while scanning
- Common question
  - Does the percentage displayed indicate the percentage API content? (the percentage displayed was the percentage to which the sampling window was covered)
  - What kind of file can be extracted from the device?
- Comment
  - It would be easier to use if there was a sample holder

MicroPHAZIR RX – Quick guides

Quick guide of operating procedures used in the field evaluation

1. Press and hold the power button on the MicroPhazir until the screen begins to turn on. Wait a few minutes for the software to load properly.
2. Once at the login screen, press and release the trigger to the "Select User" screen
3. Select "Administrator" by highlighting the selection and hitting the "Select" button (top right tab button)
4. Type in the password is "default" and then hit done.
5. Before testing medicine, highlight and select the "Self-Test" option and click "START SCAN".
   a. If warning message pops up, the lamp on the device is warming up, so wait the allotted time mentioned on the screen and after the time is over, the device will run its own test. Leave the instrument alone until the scan is complete
6. If the scan registers as a "PASS", proceed to step 9.
7. If the scan registers as a "FAIL", turn the instrument off and restart.
8. Repeat steps 1 through 7 again. Contact technician if it fails again.
9. Select "Run"
10. Select "Method:" and scroll down and select the medicine you would like to analyze
11. Select the batch if there is one (for a simple analysis just select "1")
12. OPTIONAL: You can also select the sample number the same way you would a batch in step #10 except in the "Sample:" selection (for simple analysis, keep the sample as "1-001", the number will adjust for every new sample you do)
13. Once this menu has been complete, place the medicine on the glowing sample window.
14. Once the medicine is ready, select "Start Run"



Pass result

Fail result

Supplementary Annex 7. Minilab – Protocols

6.65 Amoxicillin (as trihydrate incl. potassium clavulanate co-formulations)

Primary Screening via Physical Inspection and Disintegration Test

I. PHYSICAL INSPECTION

Search for deficiencies on labelling, packaging and dosage forms as described in the opening chapters on general methods and operations of the main manual. Write down all product particulars using the reporting form as a guide. Each tablet or capsule usually contains amoxicillin trihydrate translating into the final dosage strengths of 250, 500, 750, 875 and 1000 mg of anhydrous amoxicillin. Frequently, amoxicillin 500 and 875 mg tablets are combined with a 125 mg of clavulanic acid in form of its potassium salt. Other dosage strengths for amoxicillin and clavulanic acid in single and fixed-dose combinations are known to exist.

II. DISINTEGRATION TEST

Whether or not combined with potassium clavulanate, all quick release amoxicillin tablets and capsules must pass the disintegration test as described in the opening chapters on general methods and operations of the main manual. They should disintegrate in water at 37 °C in less than 30 minutes. It's a major defect if a drug product doesn't pass this test.

III. RESULTS & ACTIONS TO BE TAKEN

Drug products from unusually cheap sources, drug products with missing or incorrect accompanying documents and drug products with defective dosage forms, packaging or with incomplete, damaged or missing labels or with labels written in a foreign language should be subjected to a thin layer chromatographic test.

Verification of Drug Identity and Content via Thin Layer Chromatography

I. PRINCIPLE

Whether or not combined with potassium clavulanate, amoxicillin is extracted from tablets and capsules with diluted ammonia solution and determined by TLC with reference to an authentic secondary standard. For a rapid drug quality verification of the clavulanic acid fraction consult the appropriate protocol shown in this supplement.

II. EQUIPMENT AND REAGENTS

1) Pestle
2) Aluminium foil
3) Funnel
4) Label tape
5) Marker pen
6) Pencil and ruler
7) 10-ml vials
8) Set of straight pipettes (1 to 25 ml)
9) Set of laboratory glass bottles (25 to 100 ml)
10) Merck TLC aluminium plates precoated with silica gel 60 F_{254}, size 5x10 cm
11) Glass microcapillaries (2-µl filling capacity)
12) TLC developing chamber (500-ml jar)
13) Hot plate
14) Filter paper
15) Pair of scissors
16) Pair of tweezers
17) UV light of 254 nm
18) TLC dipping chamber (250-ml beaker)
19) Iodine chamber
20) Ammonia solution 25%
21) Ethyl acetate
22) Glacial acetic acid
23) Methanol
24) Ninhydrin
25) Water
26) Secondary reference standard, for example tablets containing 500 mg of amoxicillin with or without potassium clavulanate

III. PREPARATION OF THE STOCK STANDARD SOLUTION

The preparation of the stock standard solution requires an authentic drug product for reference purposes, for example, tablets containing 500 mg of amoxicillin with or without potassium clavulanate. Wrap up one reference tablet into aluminium foil and crush it down to a fine powder using a pestle. Carefully empty the aluminium foil over a 100-ml laboratory glass bottle and wash down all residual solids with 45 ml of water followed by 5 ml of concentrated ammonia solution using appropriate straight pipettes. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid. The solution obtained should contain 10 mg of total amoxicillin per ml and be labelled as *'Amoxicillin Stock Standard Solution'*. Freshly prepare this solution for each test. Continue to work with the hazy supernatant liquid.

IV. PREPARATION OF THE WORKING STANDARD SOLUTION 100% (UPPER WORKING LIMIT)

Pipette 1 ml of the stock standard solution into a 10-ml vial and add 3 ml of methanol. Close and shake the vial. The solution obtained should contain 2.5 mg of total amoxicillin per ml and be labelled as *'Amoxicillin Working Standard Solution 100%'*.

This higher working standard solution represents a drug product of good quality containing 100 % of amoxicillin.

V. PREPARATION OF THE WORKING STANDARD SOLUTION 80% (LOWER WORKING LIMIT)

Pipette 1 ml of the stock standard solution into a 10-ml vial and add 4 ml of methanol. Close and shake the vial. The solution obtained should contain 2.0 mg of total amoxicillin per ml and be labelled as *'Amoxicillin Working Standard Solution 80%'*.

This lower working standard solution represents a drug product of poor quality containing just 80% of the amount of amoxicillin as stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

VI. PREPARATION OF THE STOCK SAMPLE SOLUTION FROM A PRODUCT CLAIMING TO CONTAIN 250 MG OF AMOXICILLIN PER UNIT

Take one whole tablet or capsule from a correspondent drug product sampled in the field. As usual, tablets are wrapped up into aluminium foil and crushed down to a fine powder. Transfer all the powder obtained into an appropriately sized laboratory glass bottle. Powder obtained from a sample capsule should be transferred directly into the bottle adding the cap and body shells last. For extraction, add 22.5 ml of water followed by 2.5 ml concentrated ammonia solution using appropriate straight pipettes. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

500 MG OF AMOXICILLIN PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 45 ml of water plus 5 ml of concentrated ammonia solution. Continue to work as above.

750 MG OF AMOXICILLIN PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 67.5 ml of water plus 7.5 ml of concentrated ammonia solution. Continue to work as above.

875 MG OF AMOXICILLIN PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 79 ml of water plus 8.5 ml of concentrated ammonia solution. Continue to work as above.

1000 MG OF AMOXICILLIN PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 90 ml of water plus 10 ml of concentrated ammonia solution. Continue to work as above.

Whether or not combined with clavulanic acid, all stock sample solutions produced should finally contain 10 mg of amoxicillin per ml and be labelled as *'Amoxicillin Stock Sample Solution'*. Freshly prepare these solutions for each test. Continue to work with the clear or hazy supernatant liquids.

VII. PREPARATION OF THE WORKING SAMPLE SOLUTION

Pipette 1 ml of the stock sample solution into a 10-ml vial and add 3 ml of methanol. Close and shake the vial and label as *'Amoxicillin Working Sample Solution'*.

The expected concentration of amoxicillin in this working sample solution is 2.5 mg per ml and should match the concentration of amoxicillin of the higher working standard solution produced above.

VIII. SPOTTING

Mark an origin line parallel to and about 1.5 cm from the bottom edge of the chromatoplate and apply 2 µl of each test and standard solution prepared as shown in the picture opposite using the microcapillary pipettes supplied.

Up to five spots can be placed on a plate. Check the uniformity of all spots using UV light of 254 nm. All spots should be circular in shape and equally spaced across the origin line. Although their intensities might differ, their diameters never should. Different intensities are due to residual amounts of tablet and capsule excipients or different drug concentrations in the sample solutions. A difference in spot size, however, relates to poor spotting. Repeat this step if homogeneous spotting is not achieved first time.

Note that the filling of the microcapillary pipettes might take some time when handling aqueous sample solutions. As traces of water are causing blurred spots and tailing, completely dry off all extraction solvent before chromatoplate development using the hot plate supplied.

IX. DEVELOPMENT

Pipette 15 ml of ethyl acetate, 5 ml of glacial acetic acid and 5 ml of water into the jar being used as TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes thus ensuring saturation of the chamber with solvent vapour. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate until the solvent front has moved about three-quarters of the length of the plate, the developing time being about 30 minutes. Remove the plate from the chamber, mark the solvent front and allow any excess solvent to evaporate using a hot plate if necessary.

X. DETECTION

Dry off all residual solvent and observe the chromatoplate under UV light of 254 nm before and after iodine staining. Use these methods of detection for amoxicillin identification and quantification purposes.

A further verification of amoxicillin's identity and content can be achieved when observing a second plate at daylight after ninhydrin staining. It would also indicate the presence of any potassium clavulanate. For this, dissolve 3 g of ninhydrin (about 10 times a well filled spatula) in a mixture of a 150 ml of methanol and 30 ml of glacial acetic acid. Use the plastic beaker supplied to accommodate the staining solution. This will allow dipping the chromatoplate into the solution using a pair of tweezers. Instantly remove the plate from the beaker, let all surplus solution run down onto paper tissue and finally dry the back of the plate using paper tissue again. Continue to dry off all staining solution on a hot plate and observe how the spots for amoxicillin and, in case of fixed-dose combinations, the spots for potassium clavulanate are gradually becoming visible.

The ninhydrin staining process is illustrated in full on page 26 of the main manual issued 2008. Note that the staining with ninhydrin will make it impossible to further observe spots previously made visible at UV light of 254 nm. Also note that skin contaminated with ninhydrin solution will be stained as well. However, this is not dangerous to health and the violet spots will disappear after about a day or two.

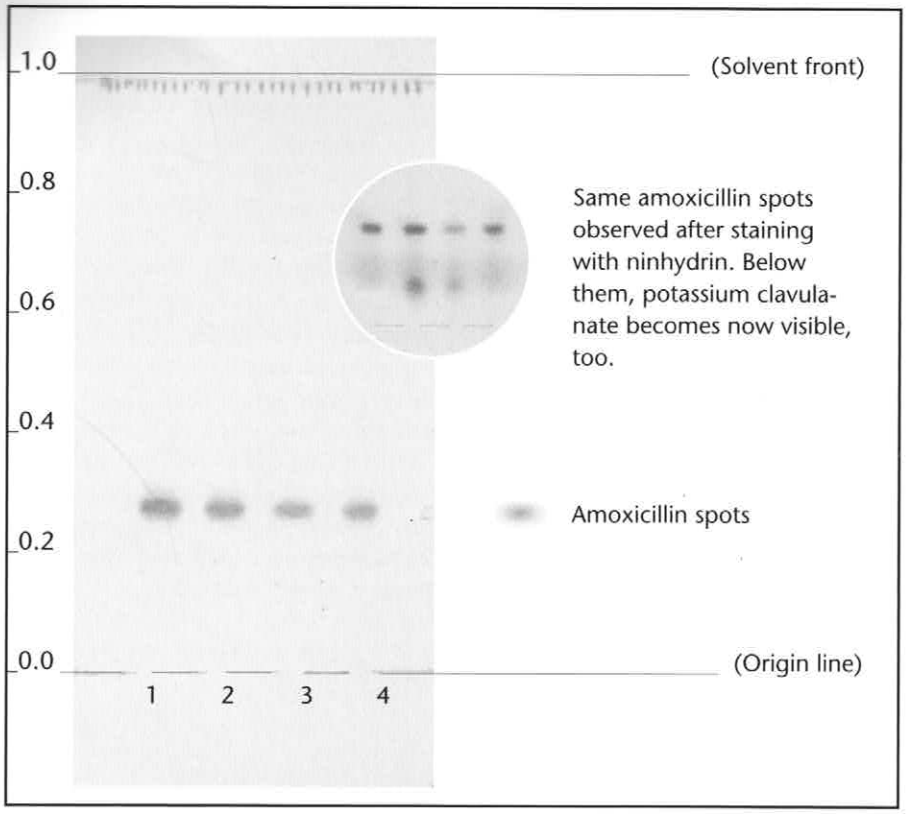
XI. CHROMATOPLATE OBSERVED AT DAYLIGHT AFTER IODINE STAINING

Run No.1:
Upper working standard representing 100% of total amoxicillin

Run No.2:
A product of good quality with acceptable amoxicillin content

Run No.3:
A product of poor quality with unacceptable low amoxicillin content

Run No.4:
Lower working standard representing 80% of total amoxicillin



XII. OBSERVATIONS MADE AT 254 NM

Any potassium clavulanate would stay invisible here and a weak bluish spot at a travel distance of about 0.27 indicates the presence of amoxicillin in the test solution.

XIII. OBSERVATIONS MADE AT DAYLIGHT AFTER IODINE STAINING

All amoxicillin spots already observed at 254 nm are now turning yellowish brown and any potassium clavulanate would again stay invisible. Still observe the plate when iodine evaporates already. Spots reflecting poor quality products will disappear first gradually followed by the reference spots representing a drug content of an 80 and 100 percent, respectively.

XIV. OBSERVATIONS MADE AT 254 NM AFTER IODINE STAINING

All amoxicillin spots already observed before iodine staining are becoming much more pronounced now and any potassium clavulanate would stay invisible here again. Additional strong spots generated by the test solution would point at other drugs or amoxicillin degradation, the latter case being more likely when associated with a smaller principal spot. Auxiliary agents incorporated in the different tablet or capsule formulations might cause some fainter spots emerging near or on the origin line.

XV. OBSERVATIONS MADE AT DAYLIGHT AFTER NINHYDRIN STAINING

All amoxicillin spots previously observed before and after iodine staining are now turning deep orange gradually becoming red. Spots emerging at a travel distance of about 0.15 would now indicate the presence of potassium clavulanate, too. For a further verification of clavulanic acid identity and content in amoxicillin co-formulations follow the protocol 6.69 on page 20 of this supplement.

XVI. RESULTS & ACTIONS TO BE TAKEN

The spot for amoxicillin in the chromatogram obtained with the test solution must correspond in terms of colour, size, intensity, shape and travel distance to that in the chromatogram obtained with the lower and higher standard solution. This result must be obtained for each method of detection. If this is not achieved, repeat the run from scratch with a second sample. Reject the batch if the drug content cannot be verified in a third run. For a second opinion, refer additional samples to a fully-fledged drug quality control laboratory. Retain samples and put the batch on quarantine until a final decision on rejection or release has been taken. For documentation purposes, take pictures of all the readings with a digital camera turning off the flash first.

6.66 Artemether (in lumefantrine tablets, dispersible tablets and dry syrups)

Primary Screening via Physical Inspection and Disintegration Test

I. PHYSICAL INSPECTION

Search for deficiencies on labelling, packaging and dosage forms as described in the opening chapters on general methods and operations of the main manual. Write down all product particulars using the reporting form as a guide. Each tablet and dispersible tablet usually contains 20 mg of artemether combined with a 120 mg of lumefantrine. Frequently, co-formulated products are also presented as dry powder for oral suspensions usually containing 180 or 360 mg of artemether and 1080 or 2160 mg of lumefantrine, respectively. Independent from the concentration of active ingredients in the dry powder, each 5 ml of the ready suspension should finally contain 15 mg of artemether and 90 mg of lumefantrine.

II. DISINTEGRATION TEST

The disintegration test is not applicable for fixed-dose combination medicines presented as powder for oral suspensions. However, all quick release artemether/lumefantrine tablet formulations must pass this test as described in the opening chapters on general methods and operations of the main manual. They should disintegrate in water at 37 °C in less than 30 minutes. It's a major defect if a drug product doesn't pass this test.

III. RESULTS & ACTIONS TO BE TAKEN

Drug products from unusually cheap sources, drug products with missing or incorrect accompanying documents and drug products with defective dosage forms, packaging or with incomplete, damaged or missing labels or with labels written in a foreign language should be subjected to a thin layer chromatographic test.

Verification of Drug Identity and Content via Thin Layer Chromatography

I. PRINCIPLE

Artemether is extracted from lumefantrine fixed-dose combination tablets, dispersible tablets and powder for oral suspensions with methanolic glacial acetic acid solution and determined by TLC with reference to an authentic secondary standard. For a rapid drug quality verification of the lumefantrine fraction consult the appropriate protocol shown in this supplement.

II. EQUIPMENT AND REAGENTS

1) Pestle
2) Aluminium foil
3) Funnel
4) Label tape
5) Marker pen
6) Pencil and ruler
7) 10-ml vials
8) Set of straight pipettes (1 to 25 ml)
9) Set of laboratory glass bottles (25 to 100 ml)
10) Merck TLC aluminium plates pre-coated with silica gel 60 F_{254}, size 5x10 cm
11) Glass microcapillaries (2-µl filling capacity)
12) TLC developing chamber (500-ml jar)
13) Hot plate
14) Filter paper
15) Pair of scissors
16) Pair of tweezers
17) UV light of 254 nm
18) UV light of 366 nm
19) TLC dipping chamber (250-ml beaker)
20) Sulphuric acid solution 96%
21) Ethyl acetate
22) Glacial acetic acid
23) Methanol
24) Toluene
25) Secondary reference standard, for example, fixed-dose combination tablets containing 20 mg of artemether and a 120 mg of lumefantrine

III. PREPARATION OF THE STOCK STANDARD SOLUTION

The preparation of the stock standard solution requires an authentic drug product for reference purposes, for example, tablets containing 20 mg of artemether combined with a 120 mg of lumefantrine. Wrap up one reference tablet into aluminium foil and crush it down to a fine powder using a pestle. Carefully empty the aluminium foil over a 25-ml laboratory glass bottle and wash down all residual solids with 9 ml of methanol followed by 1 ml of glacial acetic acid using appropriate straight pipettes. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid. Next to lumefantrine, the solution obtained should contain 2 mg of total artemether per ml and be labelled as *'Artemether Stock Standard Solution'*. Freshly prepare this solution for each test. Continue to work with the clear or hazy supernatant liquid.

V. PREPARATION OF THE WORKING STANDARD SOLUTION 100% (UPPER WORKING LIMIT)

The stock standard solution requires no further dilution. It already represents the final working concentration of 2 mg of total artemether per ml. Just for more convenient handling, some of the supernatant liquid may want to be transferred into a 10-ml vial.

This higher working standard solution represents a drug product of good quality containing 100 % of artemether.

PREPARATION OF THE WORKING STANDARD SOLUTION 80% (LOWER WORKING LIMIT)

Pipette 4 ml of the stock standard solution into a 10-ml vial and add 1 ml of methanol. Close and shake the vial. The solution obtained should contain 1.6 mg of total artemether per ml and be labelled as *'Artemether Working Standard Solution 80%'*.

This lower working standard solution represents a drug product of poor quality containing just 80% of the amount of artemether as stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

PREPARATION OF THE STOCK SAMPLE SOLUTION FROM A TABLET CLAIMING TO CONTAIN 20 MG OF ARTEMETHER PER UNIT

Take one whole tablet from an appropriate drug product sampled in the field. As usual, wrap up the tablet into aluminium foil and crush it down to a fine powder. Transfer all the powder obtained into a 25-ml laboratory glass bottle. For extraction, add 5 ml of methanol followed by 0.55 ml of glacial acetic acid using a set of appropriate straight pipettes. Close the lab bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

POWDER FOR ORAL SUSPENSION CLAIMING TO CONTAIN 180 MG OF ARTEMETHER PER BOTTLE

Take one whole bottle from a corresponding drug product sampled in the field. For extraction, add to the dry powder still sitting in the original container 45 ml of methanol followed by 5 ml of glacial acetic acid using a set of appropriate straight pipettes. Close the sample bottle and thoroughly shake for about three minutes. Allow the mix to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

POWDER FOR ORAL SUSPENSION CLAIMING TO CONTAIN 360 MG OF ARTEMETHER PER BOTTLE

Take one whole sample bottle and add to the dry powder still sitting in the original container 90 ml of methanol followed by 10 ml of glacial acetic acid using a set of appropriate straight pipettes. Close the sample container and thoroughly shake for about three minutes. Allow the mix to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

Next to lumefantrine all stock sample solutions produced should finally contain 3.6 mg of total artemether per ml and be labelled as *'Artemether Stock Sample Solution'*. Freshly prepare these solutions for each test. Continue to work with the clear or hazy supernatant liquids.

VII. PREPARATION OF THE WORKING SAMPLE SOLUTION

Pipette 2.5 ml of the stock sample solution into a 10-ml vial and add 2 ml of methanol. Close and shake the vial and label as *'Artemether Working Sample Solution'*.

The expected concentration of artemether in this working sample solution is 2 mg per ml and should match the concentration of artemether of the higher working standard solution produced above.

VIII. SPOTTING

Mark an origin line parallel to and about 1.5 cm from the bottom edge of the chromatoplate and apply 2 µl of each test and standard solution prepared as shown in the picture opposite using the microcapillary pipettes supplied.

Up to five spots can be placed on a plate. Check the uniformity of all spots using UV light of 254 nm. Even if artemether itself stays invisible, excipients and other drug compounds will show up to facilitate verification. All spots should be circular in shape and equally spaced across the origin line. Although their intensities might differ, their diameters never should. Different intensities are due to residual amounts of excipients or different drug concentrations in the sample solutions. A difference in spot size, however, relates to poor spotting. Repeat this step if homogeneous spotting is not achieved first time.

IX. DEVELOPMENT

Pipette 18 ml of toluene, 4 ml of ethyl acetate and 2 ml of glacial acetic acid into the jar being used as TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes thus ensuring saturation of the chamber with solvent vapour. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate until the solvent front has moved about three-quarters of the length of the plate, the developing time being about 10 minutes. Remove the plate from the chamber, mark the solvent front and allow any excess solvent to evaporate using a hot plate if necessary.

X. DETECTION

When working on this type of fixed-dose combination medicines, it is best to check the presence of lumefantrine before that of artemether. For this, expose the dried chromatoplate first to UV light of 254 nm using the battery-driven lamp supplied.

For the detection of the artemether fraction, expose the chromatoplate to sulphuric acid staining. For this, fill the 250-ml plastic beaker supplied with a 190 ml of methanol followed by 10 ml of concentrated sulphuric acid solution and mix gently. Allow the mix to cool down and submerge the chromatoplate upside down into the staining solution using a pair of tweezers. Instantly remove the plate again from the solution and let all surplus liquid run down onto paper tissue. Wipe off residual liquid from the back of the plate and continue to dry off all staining solution on the hot plate supplied. During heating, all artemether spots are gradually becoming visible at daylight. Use this method of detection for both, artemether identification and quantification purposes. Note that the staining operation performed with sulphuric acid solution is very similar to that with ninhydrin illustrated on page 26 of the main manual.

After sulphuric acid staining and chromatoplate reading at daylight, a further verification of artemether identity and content can be achieved when subjecting the chromatoplate to UV light of 366 nm in a dark room.

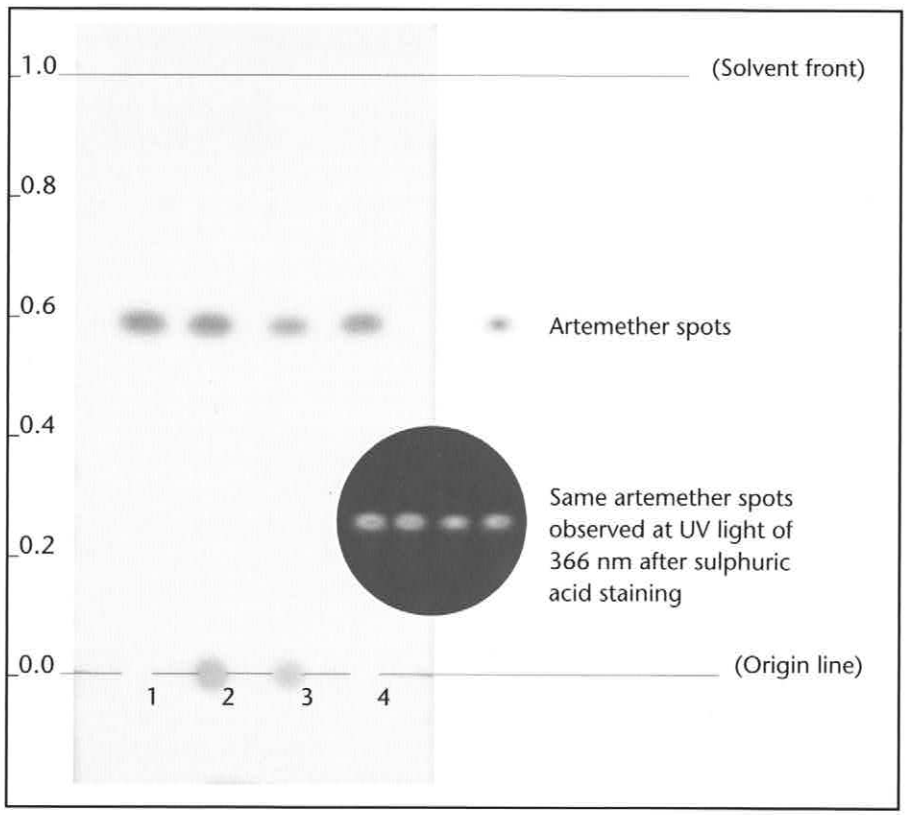
XI. CHROMATOPLATE OBSERVED AT DAYLIGHT AFTER SULPHURIC ACID STAINING

Run No.1:
Upper working standard representing 100% of total artemether

Run No.2:
A product of good quality with acceptable artemether content

Run No.3:
A product of poor quality with un-acceptable low artemether content

Run No.4:
Lower working standard representing 80% of total artemether



XII. OBSERVATIONS MADE AT 254 NM BEFORE STAINING

Artemether itself stays invisible and no other spots should be detected unless the medicine under investigation is presented as a co-formulated product. In the latter case, a strong violet spot at a travel distance of about 0.16 indicates the presence of lumefantrine and, in case of dry powders for oral suspensions, a second strong spot between a travel distance of 0.40 and 0.50 the presence of a preservative either from the benzoate or paraben family. Saccharin sodium as sweetener in dispersible tablets would settle at about 0.20 but stays below its limit of detection due to strong dilutions during sample preparation. For a better identification of the lumefantrine fraction go to page 28 of this supplement.

XIII. OBSERVATIONS MADE AT DAYLIGHT AFTER SULPHURIC ACID STAINING

A dark brown spot at a travel distance of about 0.59 indicates the presence of artemether in the test solution. Auxiliary agents incorporated in the different tablet and powder formulations may cause further spots near or on the origin line. Beyond this, no other spots should be visible even if artemether is combined with lumefantrine. Additional strong spots generated by the test solution would point at other drugs or artemether degradation, the latter case being more likely when associated with a smaller principal spot.

XIV. OBSERVATIONS MADE AT 366 NM AFTER SULPHURIC ACID STAINING

When exposing the chromatoplate to UV light of 366 nm after heating with sulphuric acid, all brown artemether spots previously observed at daylight are now showing an off-white fluorescence.

XV. RESULTS & ACTIONS TO BE TAKEN

The artemether spot in the chromatogram obtained with the test solution must correspond in terms of colour, size, intensity, shape and travel distance to that in the chromatogram obtained with the lower and higher standard solution. This result must be obtained for each method of detection. If this is not achieved, repeat the run from scratch with a second sample. Reject the batch if the drug content cannot be verified in a third run. For a second opinion, refer additional samples to a fully-fledged drug quality control laboratory. Retain some samples and put the batch on quarantine until a final decision on rejection or release has been taken. For documentation purposes, take pictures of all the readings with a digital camera turning off the flash first.

6.71 Lumefantrine (in artemether tablets, dispersible tablets and dry syrups)

Primary Screening via Physical Inspection and Disintegration Test

I. PHYSICAL INSPECTION

Search for deficiencies on labelling, packaging and dosage forms as described in the opening chapters on general methods and operations of the main manual. Write down all product particulars using the reporting form as a guide. Each tablet and dispersible tablet usually contains a 120 mg of lumefantrine combined with 20 mg of artemether. Frequently, co-formulated products are also presented as dry powder for oral suspensions usually containing 1080 or 2160 mg of lumefantrine and 180 or 360 mg of artemether, respectively. Independent from the concentration of active ingredients in the dry powder, each 5 ml of the ready suspension should finally contain 90 mg of lumefantrine and 15 mg of artemether.

II. DISINTEGRATION TEST

The disintegration test is not applicable for fixed-dose combination medicines presented as a powder for oral suspensions. However, all quick release lumefantrine/artemether tablet formulations must pass this test as described in the opening chapters on general methods and operations of the main manual. They should disintegrate in water at 37 °C in less than 30 minutes. It's a major defect if a drug product doesn't pass this test.

III. RESULTS & ACTIONS TO BE TAKEN

Drug products from unusually cheap sources, drug products with missing or incorrect accompanying documents and drug products with defective dosage forms, packaging or with incomplete, damaged or missing labels or with labels written in a foreign language should be subjected to a thin layer chromatographic test.

Verification of Drug Identity and Content via Thin Layer Chromatography

I. PRINCIPLE

Lumefantrine is extracted from artemether fixed-dose combination tablets, dispersible tablets and powder for oral suspensions with methanolic glacial acetic acid solution and determined by TLC with reference to an authentic secondary standard. For a rapid drug quality verification of the artemether fraction consult the appropriate protocol shown in this supplement.

II. EQUIPMENT AND REAGENTS

1) Pestle
2) Aluminium foil
3) Funnel
4) Label tape
5) Marker pen
6) Pencil and ruler
7) 10-ml vials
8) Set of straight pipettes (1 to 25 ml)
9) Set of laboratory glass bottles (25 to 100 ml)
10) Merck TLC aluminium plates pre-coated with silica gel 60 F_{254}, size 5x10 cm
11) Glass microcapillaries (2-µl filling capacity)
12) TLC developing chamber (500-ml jar)
13) Hot plate
14) Filter paper
15) Pair of scissors
16) Pair of tweezers
17) UV light of 254 nm
18) Iodine chamber
19) Ethyl acetate
20) Glacial acetic acid
21) Methanol
22) Secondary reference standard, for example, fixed-dose combination tablets containing a 120 mg of lumefantrine and 20 mg of artemether

III. PREPARATION OF THE STOCK STANDARD SOLUTION

The preparation of the stock standard solution requires an authentic drug product for reference purposes, for example, tablets containing a 120 mg of lumefantrine combined with 20 mg of artemether. Wrap up one reference tablet into aluminium foil and crush it down to a fine powder using a pestle. Carefully empty the aluminium foil over a 100-ml laboratory glass bottle and wash down all residual solids with 45 ml of methanol followed by 5 ml of glacial acetic acid using a set of appropriate straight pipettes. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid. Next to artemether, the solution obtained should contain 2.4 mg of total lumefantrine per ml and be labelled as *'Lumefantrine Stock Standard Solution'*. Freshly prepare this solution for each test. Continue to work with the clear or hazy supernatant liquid.

IV. PREPARATION OF THE WORKING STANDARD SOLUTION 100% (UPPER WORKING LIMIT)

Pipette 1 ml of the stock standard solution into a 10-ml vial and add 2 ml of methanol. Close and shake the vial. The solution obtained should contain 0.8 mg of total lumefantrine per ml and be labelled as *'Lumefantrine Working Standard Solution 100%'*.

This higher working standard solution represents a drug product of good quality containing 100 % of lumefantrine.

V. PREPARATION OF THE WORKING STANDARD SOLUTION 80% (LOWER WORKING LIMIT)

Pipette 4 ml of the stock standard solution into a 25-ml vial and add 11 ml of methanol. Close and shake the vial. The solution obtained should contain 0.64 mg of total lumefantrine per ml and be labelled as *'Lumefantrine Working Standard Solution 80%'*.

This lower working standard solution represents a drug product of poor quality containing just 80% of the amount of lumefantrine as stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

VI. PREPARATION OF THE STOCK SAMPLE SOLUTION FROM A TABLET CLAIMING TO CONTAIN 120 MG OF LUMEFANTRINE PER UNIT

Take one whole tablet from an appropriate drug product sampled in the field. As usual, wrap up the tablet into aluminium foil and crush it down to a fine powder. Transfer all the powder obtained into a 25-ml laboratory glass bottle. For extraction, add 5 ml of methanol followed by 0.55 ml of glacial acetic acid using a set of appropriate straight pipettes. Close the lab bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

POWDER FOR ORAL SUSPENSION CLAIMING TO CONTAIN 1080 MG OF LUMEFANTRINE PER BOTTLE

Take one whole bottle from a corresponding drug product sampled in the field. For extraction, add to the dry powder still sitting in the original container 45 ml of methanol followed by 5 ml of glacial acetic acid using a set of appropriate straight pipettes. Close the sample bottle and thoroughly shake for about three minutes. Allow the mix to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

POWDER FOR ORAL SUSPENSION CLAIMING TO CONTAIN 2160 MG OF LUMEFANTRINE PER BOTTLE

Take one whole sample bottle and add to the dry powder still sitting in the original container 90 ml of methanol followed by 10 ml of glacial acetic acid using a set of appropriate straight pipettes. Close the sample container and thoroughly shake for about three minutes. Allow the mix to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

Next to artemether all stock sample solutions produced should finally contain 21.6 mg of total lumefantrine per ml and be labelled as *'Lumefantrine Stock Sample Solution'*. Freshly prepare these solutions for each test. Continue to work with the clear or hazy supernatant liquid.

VII. PREPARATION OF THE WORKING SAMPLE SOLUTION

Pipette 1 ml of the stock sample solution into a 40-ml vial and add 23.5 ml of methanol followed by 2.5 ml of glacial acetic acid. Close and shake the vial and label as *'Lumefantrine Working Sample Solution'*.

The expected concentration of lumefantrine in this working sample solution is 0.8 mg per ml and should match the concentration of lumefantrine of the higher working standard solution produced above.

VIII. SPOTTING

Mark an origin line parallel to and about 1.5 cm from the bottom edge of the chromatoplate and apply 2 µl of each test and standard solution prepared as shown in the picture opposite using the microcapillary pipettes supplied.

Up to five spots can be placed on a plate. Check the uniformity of all spots using UV light of 254 nm. All spots should be circular in shape and equally spaced across the origin line. Although their intensities might differ, their diameters never should. Different intensities are due to residual amounts excipients or different drug concentrations in the sample solutions. A difference in spot size, however, relates to poor spotting. Repeat this step if homogeneous spotting is not achieved first time.

IX. DEVELOPMENT

Pipette 18 ml of ethyl acetate, 4 ml of methanol and 2 ml glacial acetic acid into the jar being used as TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes thus ensuring saturation of the chamber with solvent vapour. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate until the solvent front has moved about three-quarters of the length of the plate, the developing time being about 10 minutes. Remove the plate from the chamber, mark the solvent front and allow any excess solvent to evaporate using a hot plate if necessary.

X. DETECTION

Dry off all residual solvent and observe the chromatoplate under UV light of 254 nm using the battery-driven lamp supplied. Use this method of detection for both, lumefantrine identification and quantification purposes. Further verification of lumefantrine identity and content can be achieved when observing the plate at daylight after iodine staining. Complete staining may take about 5 to 10 minutes.

After the presence of lumefantrine has been verified, the chromatoplate can be exposed to sulphuric acid staining for the detection of residual artemether extracted alongside the lumefantrine fraction. This can even be done after the chromatoplate has been exposed to iodine vapour already. Go to page 10 of this supplement to see how to perform the staining process and observe the plate at daylight. After that, a further detection of residual artemether is possible when exposing the stained chromatoplate to UV light of 366 nm in a dark room.

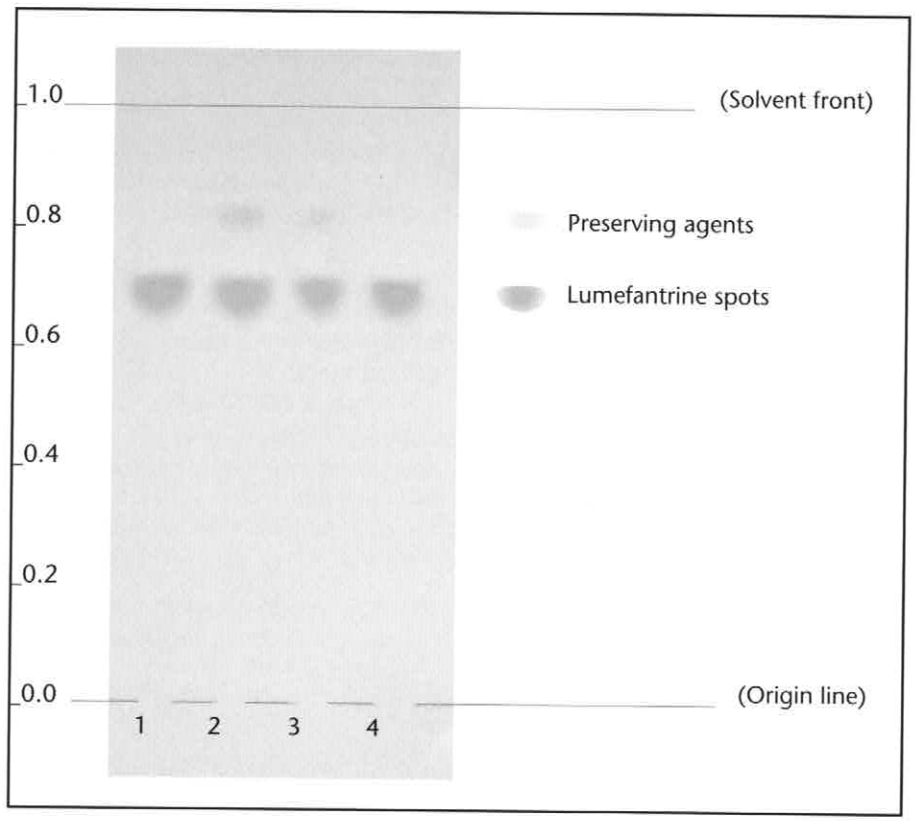
XI. CHROMATOPLATE OBSERVED UNDER UV LIGHT OF 254 NM

Run No.1:
Upper working standard representing 100% of total lumefantrine

Run No.2:
A product of good quality with acceptable lumefantrine content

Run No.3:
A product of poor quality with unacceptable low lumefantrine content

Run No.4:
Lower working standard representing 80% of total lumefantrine



XII. OBSERVATIONS MADE AT 254 NM

A strong blue-violet spot at a travel distance of about 0.69 indicates the presence of lumefantrine in the test solution. No other spots are visible except for a faint spot of a preserving agent from the benzoate or paraben family at a travel distance around 0.81 and of other additives, for example, sucrose below a relative retention factor of 0.20 near or on the origin line when working with dry powders for oral suspensions. Saccharin sodium as sweetener in dispersible tablets would settle at about 0.45 but stays below its limit of detection due to strong dilutions during sample preparation. Any other strong spots generated by the test solution would point at other drugs or lumefantrine degradation, the latter case being more likely when associated with a smaller principal spot. The artemether fraction settling near the solvent front at a travel distance of about 0.85 stays invisible at this point. For the identification of this component, go to page 8 of this supplement.

XIII. OBSERVATIONS MADE AT DAY-LIGHT AFTER IODINE STAINING

When exposing the chromatoplate to iodine vapour, all lumefantrine spots already observed at 254 nm are slowly turning yellowish now. Still observe the plate when iodine evaporates already. Spots reflecting poor quality products will disappear first gradually followed by the reference spots representing a drug content of an 80 and 100 percent, respectively.

XIV. RESULTS & ACTIONS TO BE TAKEN

The lumefantrine spot in the chromatogram obtained with the test solution must correspond in terms of colour, size, intensity, shape and travel distance to that in the chromatogram obtained with the lower and higher standard solution. This result must be obtained for each method of detection. If this is not achieved, repeat the run from scratch with a second sample. Reject the batch if the drug content cannot be verified in a third run. For a second opinion, refer additional samples to a fully-fledged drug quality control laboratory. Retain some samples and put the batch on quarantine until a final decision on rejection or release has been taken. For documentation purposes, take pictures of all the readings with a digital camera turning off the flash first.

6.72 Ofloxacin (as single formulation tablet and capsule)

Primary Screening via Visual Inspection and Disintegration Test

I. VISUAL & PHYSICAL INSPECTION

Search for deficiencies on labelling, packaging and dosage forms as described in the opening chapters on general methods and operations of the main manual. Write down all product particulars using the reporting form as a guide. Each tablet or capsule usually contains a 100 to 400 mg of ofloxacin free base.

II. DISINTEGRATION TEST

All quick release ofloxacin tablets and capsules must pass the disintegration test as described in the opening chapters on general methods and operations of the main manual. They should disintegrate in water at 37 °C in less than 30 minutes. It's a major defect if a drug product doesn't pass this test.

III. RESULTS & ACTIONS TO BE TAKEN

Drug products from unusually cheap sources, drug products with missing or incorrect accompanying documents and drug products with defective dosage forms, packaging or with incomplete, damaged or missing labels or with labels written in a foreign language should be subjected to a thin layer chromatographic test.

Verification of Drug Identity and Content via Thin Layer Chromatography

I. PRINCIPLE

Ofloxacin tablets and capsules are extracted with aqueous acetic acid soution and determined by TLC with reference to an authentic secondary standard.

II. EQUIPMENT AND REAGENTS

1) Pestle
2) Aluminium foil
3) Funnel
4) Label tape
5) Marker pen
6) Pencil and ruler
7) 10-ml vials
8) Set of straight pipettes (1 to 25 ml)
9) Set of laboratory glass bottles (25 to 100 ml)
10) Merck TLC aluminium plates pre-coated with silica gel 60 F 254, size 5x10 cm
11) Glass microcapillaries (2-µl filling capacity)
12) TLC developing chamber (500-ml jar)
13) Hot plate
14) Filter paper
15) Pair of scissors
16) Pair of tweezers
17) UV light of 254 nm
18) UV light of 366 nm
19) Iodine chamber
20) Glacial acetic acid
21) Methanol
22) Water
23) Ammonia solution 25%
24) Secondary reference standard, for example, tablets containing 200 mg of ofloxacin free base

III. PREPARATION OF THE STOCK STANDARD SOLUTION

The preparation of the stock standard solution requires an authentic drug product for reference purposes, for example, tablets containing 200 mg of ofloxacin free base. Wrap up one reference tablet into aluminium foil and crush it down to a fine powder using a pestle. Carefully empty the aluminium foil over a 40-ml laboratory glass bottle and wash down all residual solids with 19.6 ml of water followed by 0.4 ml of glacial acetic acid using appropriate straight pipettes. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid. The solution obtained should contain 10 mg of total drug per ml and be labelled as *'Ofloxacin Stock Standard Solution'*. Freshly prepare this solution for each test. Continue to work with the clear or hazy supernatant liquid.

IV. PREPARATION OF THE WORKING STANDARD SOLUTION 100% (UPPER WORKING LIMIT)

Pipette 1 ml of the stock standard solution into a 10-ml vial and add 7 ml of methanol. Close and shake the vial. The solution obtained should contain 1.25 mg of total drug per ml and be labelled as *'Ofloxacin Working Standard Solution 100%'*.

This higher working standard solution represents a drug product of good quality containing 100 % of ofloxacin free base.

V. PREPARATION OF THE WORKING STANDARD SOLUTION 80% (LOWER WORKING LIMIT)

Pipette 1 ml of the stock standard solution into a 10-ml vial and add 9 ml of methanol. Close and shake the vial. The solution obtained should contain 1 mg of total drug per ml and be labelled as *'Ofloxacin Working Standard Solution 80%'*.

This lower working standard solution represents a drug product of poor quality containing just 80% of the amount of ofloxacin free base as stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

VI. PREPARATION OF THE STOCK SAMPLE SOLUTION FROM A PRODUCT CLAIMING TO CONTAIN 100 MG OF OFLOXACIN PER UNIT

Take one whole tablet or capsule from an appropriate drug product sampled in the field. As usual, tablets are wrapped up into aluminium foil and crushed down to a fine powder. Transfer all the powder obtained into a 25-ml laboratory glass bottle. Powder obtained from a sample capsule should be transferred directly into the bottle adding the cap and body shells last. For extraction, add 9.8 ml of water followed by 0.2 ml of glacial acetic acid using appropriate straight pipettes, close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

200 MG OF OFLOXACIN PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 19.6 ml of water followed by 0.4 ml of glacial acetic acid using appropriate straight pipettes and a 25-ml laboratory glass bottle as sample container. Continue to work as above.

400 MG OF OFLOXACIN PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 39.2 ml of water followed by 0.8 ml of glacial acetic acid using appropriate straight pipettes and a 40-ml laboratory glass bottle as sample container. Continue to work as above.

All stock sample solutions produced should finally contain 10 mg of total drug per ml and be labelled as *'Ofloxacin Stock Sample Solution'*. Freshly prepare these solutions for each test. Continue to work with the clear or hazy supernatant liquids.

VII. PREPARATION OF THE WORKING SAMPLE SOLUTION

Pipette 1 ml of the stock sample solution into a 10-ml vial and add 7 ml of methanol. Close and shake the vial and label as *'Ofloxacin Working Sample Solution'*.

The expected concentration of ofloxacin free base in this working sample solution is 1.25 mg per ml and should match the concentration of ofloxacin of the higher working standard solution produced above.

VIII. SPOTTING

Mark an origin line parallel to and about 1.5 cm from the bottom edge of the chromatoplate and apply 2 µl of each test and standard solution as shown in the picture opposite using the microcapillary pipettes supplied.

Up to five spots can be placed on a plate. Check the uniformity of all spots using UV light of 254 nm. All spots should be circular in shape and equally spaced across the origin line. Although their intensities might differ, their diameters never should. Different intensities are due to residual amounts of tablet and capsule excipients or different drug concentrations in the sample solutions. A difference in spot size, however, relates to poor spotting. Repeat this step if homogeneous spotting is not achieved first time.

Note that the filling of the microcapillary pipettes might take some time when handling aqueous sample solutions. As traces of water are causing blurred spots and tailing, completely dry off all extraction solvent before chromatoplate development using the hot plate supplied.

IX. DEVELOPMENT

Pipette 14 ml of methanol, 4 ml of concentrated ammonia solution and 2 ml of water into the jar being used as TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes thus ensuring saturation of the chamber with solvent vapour. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate until the solvent front has moved about three-quarters of the length of the plate, the developing time being about 30 minutes. Remove the plate from the chamber, mark the solvent front and allow any excess solvent to evaporate using a hot plate if necessary.

X. DETECTION

Dry off all residual solvent and observe the chromatoplate under UV light of 254 and 366 nm using the battery-driven lamps supplied. Use these methods of detection for both, identification and quantification purposes. Make sure that the work place is really dark with little or no ambient light when operating the UV lamp of 366 nm. Further verification of drug identity and content can be achieved when observing the plate at daylight after iodine staining.

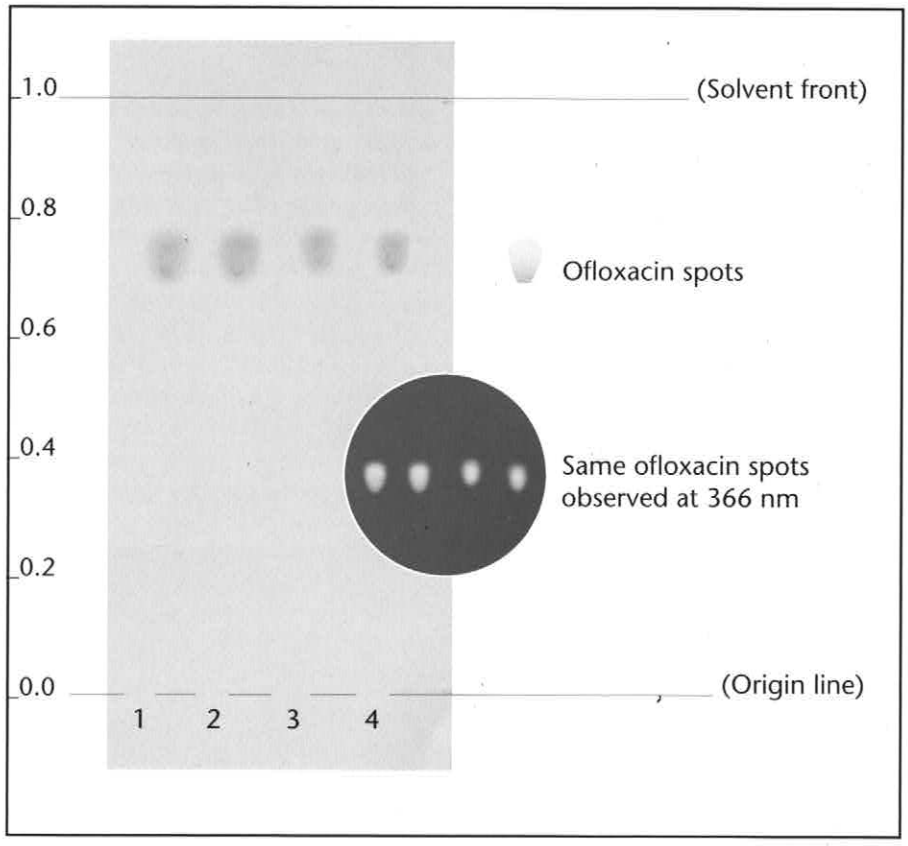
XI. CHROMATOPLATES OBSERVED UNDER UV LIGHT OF 254 NM

Run No.1:
Upper working standard representing 100% of total ofloxacin

Run No.2:
A product of good quality with acceptable ofloxacin content

Run No.3:
A product of poor quality with unacceptable low ofloxacin content

Run No.4:
Lower working standard representing 80% of total ofloxacin



XII. OBSERVATIONS MADE AT 254 NM

A blue-violet spot at a travel distance of about 0.71 indicates the presence of ofloxacin in the test solution. Additional strong spots generated by the test solution would point at other drugs or ofloxacin degradation, the latter case being more likely when associated with a smaller principal spot. Auxiliary agents incorporated in the different tablet or capsule formulations might cause some fainter spots emerging near or on the origin line.

XIII. OBSERVATIONS MADE AT 366 NM

When exposing the chromatoplate to UV light of 366 nm in a dark room, all ofloxacin spots already observed at 254 nm must now show an intense yellowish-blue fluorescence. Bear in mind that the colour shown here can be indicative only. The actual shade of the reference spot on the plate will be valid for decision making.

XIV. OBSERVATIONS MADE AT DAYLIGHT AFTER IODINE STAINING

When exposing the chromatoplate to iodine vapour, all ofloxacin spots already observed at 254 and 366 nm are now turning yellowish brown. Still observe the plate when iodine evaporates already. Spots reflecting poor quality products will disappear first gradually followed by the reference spots representing a drug content of 80 and 100 percent, respectively.

XV. RESULTS & ACTIONS TO BE TAKEN

The ofloxacin spot in the chromatogram obtained with the test solution must correspond in terms of colour, size, intensity, shape and travel distance to that in the chromatogram obtained with the lower and higher standard solution. This result must be obtained for each method of detection. If this is not achieved, repeat the run from scratch with a second sample. Reject the batch if the drug content cannot be verified in a third run. For a second opinion, refer additional samples to a fully-fledged drug quality control laboratory. Retain some samples and put the batch on quarantine until a final decision on rejection or release has been taken. For documentation purposes, take pictures of all the readings with a digital camera turning off the flash first.

6.85 Artesunate (for oral and parenteral use incl. frequent co-formulations)

Primary Screening via Physical Inspection and Disintegration Test

I. PHYSICAL INSPECTION

Search for deficiencies on labelling, packaging and dosage forms as described in the opening chapters on general methods and operations of the main manual. Write down all product particulars using the reporting form as a guide. Formulations for oral use are generally co-formulated consisting of artesunate on one side and either amodiaquine, mefloquine, pyronaridine, pyrimethamine, sulfadoxine or sulfamethoxypyrazine on the other; the artesunate fraction usually being presented in dosage strengths between a 25 and 200 mg then. Formulations for parenteral use are coming as powder for injection each vial usually containing 30, 60 or 120 mg of anhydrous artesunate.

II. DISINTEGRATION TEST

All quick release artesunate tablets and capsules must pass the disintegration test as described in the opening chapters on general methods and operations of the main manual. They should disintegrate in water at 37 °C in less than 30 minutes. It's a major defect if a drug product doesn't pass this test.

III. RESULTS & ACTIONS TO BE TAKEN

Drug products from unusually cheap sources, drug products with missing or incorrect accompanying documents and drug products with defective dosage forms, packaging or with incomplete, damaged or missing labels or with labels written in a foreign language should be subjected to a thin layer chromatographic test.

Verification of Drug Identity and Content via Thin Layer Chromatography

I. PRINCIPLE

Whether or not combined with other antimalarials, artesunate is extracted from tablets, capsules and powder for injection with methanol and determined by TLC with reference to an appropriate secondary standard. All procedures presented in this protocol are also fit for the detection of artesunate in co-formulated products either containing amodiaquine, mefloquine, pyronaridine, pyrimethamine, sulfadoxine or sulfamethoxypyrazine. For the detection of these antimalarials consult the corresponding protocols issued in the previous supplements.

II. EQUIPMENT AND REAGENTS

1) Pestle
2) Aluminium foil
3) Funnel
4) Label tape
5) Marker pen
6) Pencil and ruler
7) 10-ml vials
8) Set of straight pipettes (1 to 25 ml)
9) Set of laboratory glass bottles (25 to 100 ml)
10) Merck TLC aluminium plates pre-coated with silica gel 60 F_{254}, size 5x10 cm
11) Glass microcapillaries (2-µl filling capacity)
12) TLC developing chamber (500-ml jar)
13) Hot plate
14) Filter paper
15) Pair of scissors
16) Pair of tweezers
17) UV light of 254 nm
18) TLC dipping chamber (250-ml beaker)
19) Sulphuric acid solution 96%
20) Acetone
21) Ethyl acetate
22) Glacial acetic acid
23) Methanol
24) Reference standard, for example artesunate 50 mg tablets

III. PREPARATION OF THE STOCK STANDARD SOLUTION

The preparation of the stock standard solution requires an authentic drug product for reference purposes, for example, tablets containing 50 mg of artesunate. Wrap up one reference tablet into aluminium foil and crush it down to a fine powder using a pestle. Carefully empty the aluminium foil over a 25-ml laboratory glass bottle and wash down all residual solids with 10 ml of methanol using a straight pipette. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid. The solution obtained should contain 5 mg of total arte-

sunate per ml and be labelled as *'Artesunate Stock Standard Solution'*. Freshly prepare this solution for each test. Continue to work with the clear or hazy supernatant liquid.

PREPARATION OF THE WORKING STANDARD SOLUTION 100% (UPPER WORKING LIMIT)

The artesunate stock standard solution requires no further dilution. It already represents the final working concentration of 5 mg of total drug per ml. Just for more convenient handling, some of the supernatant liquid may want to be transferred into a 10-ml vial and be labelled as *'Artesunate Working Standard Solution 100%'*.

This higher working standard solution represents a drug product of good quality containing 100 % of artesunate.

PREPARATION OF THE WORKING STANDARD SOLUTION 80% (LOWER WORKING LIMIT)

Pipette 4 ml of the stock standard solution into a 10-ml vial and add 1 ml of methanol. Close and shake the vial. The solution obtained should contain 4 mg of total artesunate per ml and be labelled as *'Artesunate Working Standard Solution 80%'*.

This lower working standard solution represents a drug product of poor quality containing just 80% of the amount of artesunate as stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

PREPARATION OF THE STOCK SAMPLE SOLUTION FROM A PRODUCT CLAIMING TO CONTAIN 25 MG OF ARTESUNATE PER UNIT FOR ORAL USE

Take one whole tablet or capsule from an appropriate drug product sampled in the field. As usual, tablets are wrapped up into aluminium foil and crushed down to a fine powder. Transfer all the powder obtained into a 25-ml laboratory glass bottle. Powder obtained from a sample capsule should be transferred directly into the bottle adding the cap and body shells last. For extraction, add 5 ml of methanol using a straight pipette, close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

30 MG OF ARTESUNATE PER UNIT FOR PARENTERAL USE

Take one sealed vial from an appropriate drug product sampled in the field. Open the vial and dissolve its content with 6 ml of methanol using a straight pipette. For complete dissolution, use the rubber stopper from the cap to close the vial and shake thoroughly till all solids are dissolved and the solution is clear or almost clear. In case the vial is too small to accommodate 6 ml of solution, break down the dissolution process into several steps and combine the solutions from each step into a 25-ml laboratory glass bottle.

50 MG OF ARTESUNATE PER UNIT FOR ORAL USE

Take one whole sample tablet or capsule and extract the powder obtained with 10 ml of methanol following the procedure for oral formulations as described above.

60 MG OF ARTESUNATE PER UNIT FOR PARENTERAL USE

Take one vial and dissolve the powder obtained in 12 ml of methanol following the procedure for parenteral formulations described above.

60 MG OF ARTESUNATE PER UNIT FOR ORAL USE

Take one whole sample tablet or capsule and extract the powder obtained with 12 ml of methanol following the procedure for oral formulations as described above.

100 MG OF ARTESUNATE PER UNIT FOR ORAL USE

Take one whole sample tablet or capsule and extract the powder obtained with 20 ml of methanol following the procedure for oral formulations as described above.

120 MG OF ARTESUNATE PER UNIT FOR PARENTERAL USE

Take one vial and dissolve the powder obtained in 24 ml of methanol following the procedure for parenteral formulations as described above.

200 MG OF ARTESUNATE PER UNIT FOR ORAL USE

Take one whole sample tablet or capsule and extract the powder obtained with 40 ml of methanol following the procedure for oral formulations as described above but using a 100-ml lab bottle for sample extraction.

Whether or not combined with other antimalarials, all stock sample solutions produced should finally contain 5 mg of total artesunate per ml and be labelled as *'Artesunate Stock Sample Solution'*. Freshly prepare these solutions for each test. Continue to work with the clear or hazy supernatant liquids.

VII. PREPARATION OF THE WORKING SAMPLE SOLUTION

Artesunate stock sample solutions require no further dilution. They already represent the final working concentration of 5 mg of total artesunate per ml. If prepared from a high quality product, the sample solution should match the concentration of artesunate of the higher working standard solution produced above.

VIII. SPOTTING

Mark an origin line parallel to and about 1.5 cm from the bottom edge of the chromatoplate and apply 2 µl of each test and standard solution prepared as shown in the picture opposite using the microcapillary pipettes supplied.

Up to five spots can be placed on a plate. Check the uniformity of all spots using UV light of 254 nm. Even if artesunate itself stays invisible, excipients and other drug compounds will show up to facilitate verification. All spots should be circular in shape and equally spaced across the origin line. Although their intensities might differ, their diameters never should. Different intensities are due to residual amounts of excipients, different drug concentrations or combinations in the sample solutions. A difference in spot size, however, relates to poor spotting. Repeat this step if homogeneous spotting is not achieved first time.

IX. DEVELOPMENT

Pipette 18 ml of ethyl acetate, 4 ml of acetone and precisely 0.1 ml of glacial acetic acid into the jar being used as TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes thus ensuring saturation of the chamber with solvent vapour. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate until the solvent front has moved about three-quarters of the length of the plate, the developing time being about 10 minutes. Remove the plate from the chamber, mark the solvent front and allow any excess solvent to evaporate using a hot plate if necessary.

X. DETECTION

When working on fixed-dose combination medicines, it is best to check the presence of other drugs before that of artesunate. For this, expose the dried chromatoplate first to UV light of 254 nm using the battery-driven lamp supplied.

After the presence or absence of other drug compounds has been verified, the chromatoplate can be exposed to sulphuric acid staining for the detection of artesunate. For this, fill the 250-ml plastic beaker supplied with a 190 ml of methanol followed by 10 ml of concentrated sulphuric acid solution and mix gently. Allow the mix to cool down and submerge the chromatoplate into the staining solution using a pair of tweezers. Instantly remove the plate and let all surplus solution run down onto paper tissue. Wait a further fifteen seconds, wipe off any residual liquid from the back of the plate and continue to dry off all staining solution on the hot plate supplied. During heating, all artesunate spots are gradually becoming visible at daylight. Use this method of detection for both, artesunate identification and quantification purposes. Note that the staining process is illustrated on page 26 of the main manual issued 2008.

After staining with sulphuric acid plus heat, a detection of other drugs in co-formulated artesunate products is possible when subjecting the chromatoplate to UV light of 366 nm in a dark room.

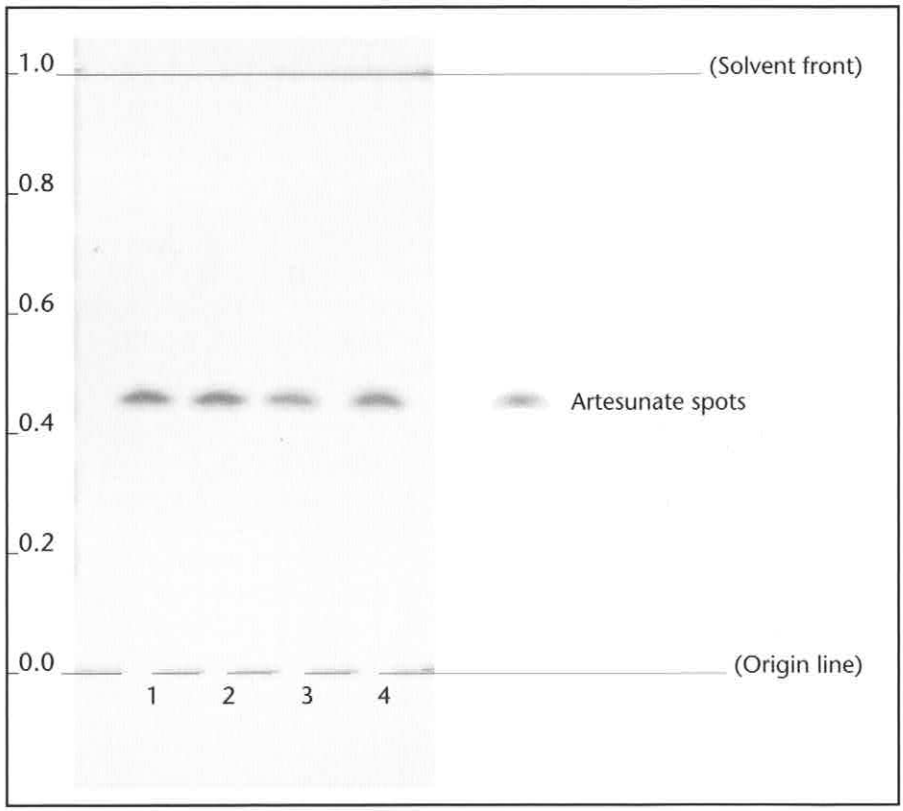
I. CHROMATOPLATE OBSERVED AT DAYLIGHT AFTER EXPOSURE TO SULPHURIC ACID AND HEAT

un No.1:
pper working standard
presenting 100% of total
tesunate

un No.2:
product of good quality with
ceptable artesunate content

un No.3:
product of poor quality with
nacceptable low artesunate content

un No.4:
wer working standard
presenting 80% of total
tesunate



II. OBSERVATIONS MADE AT 254 NM BEFORE STAINING

Artesunate stays invisible and no other spots should be detected unless the sample under investigation comes as co-formulated product containing also UV visible drugs, for example sulfadoxine and sulfamethoxypyrazine, both having very similar travel distances around 0.57. Other drugs arising from co-formulations (amodiaquine, mefloquine, pyronaridine, pyrimethamine) and excipients might cause some spots emerging near or on the origin line.

III. OBSERVATIONS MADE AT DAYLIGHT AFTER SULPHURIC ACID STAINING

A brown spot at a travel distance of about 0.46 indicates the presence of artesunate in the test solution. No other drugs should show up at this stage. Additional strong spots generated by the test solution would point to other drugs or artesunate degradation, the latter case being more likely when associated with a smaller principal spot. A smaller principal spot from the test solution may also indicate a poor artesunate content and no spot at all complete artesunate absence. Other accessory drugs arising from co-formulations, for example, amodiaquine and mefloquine or excipients might cause some spots emerging near or on the origin line.

IV. RESULTS & ACTIONS TO BE TAKEN

The artesunate spot in the chromatogram obtained with the test solution must correspond in terms of colour, size, intensity, shape and travel distance to that in the chromatogram obtained with the lower and higher standard solution. This result must be obtained for each method of detection. If this is not achieved, repeat the run from scratch with a second sample. Reject the batch if the drug content cannot be verified in a third run. For a second opinion, refer additional samples to a fully-fledged drug quality control laboratory. Retain samples and put the batch on quarantine until a final decision on rejection or release has been taken. For documentation purposes, take pictures of all the readings with a digital camera turning off the flash first.

6.52 Azithromycin (including powder for oral suspensions)

Primary Screening via Physical Inspection and Disintegration Test

I. PHYSICAL INSPECTION

Search for deficiencies on labelling, packaging and dosage forms as described in the opening chapters on general methods and operations of the main manual. Write down all product particulars using the reporting form as a guide. Each tablet or capsule usually contains 250 or 500 mg of azithromycin. Other dosage strengths are known to exist. Also, azithromycin is frequently presented as powder for oral suspensions usually containing 200 mg of active ingredient per 5 ml of ready mix.

II. DISINTEGRATION TEST

All quick release azithromycin tablets and capsules must pass the disintegration test as described in the opening chapters on general methods and operations of the main manual. They should disintegrate in water at 37 °C in less than 30 minutes. It's a major defect if a drug product doesn't pass this test.

III. RESULTS & ACTIONS TO BE TAKEN

Drug products from unusually cheap sources, drug products with missing or incorrect accompanying documents and drug products with defective dosage forms, packaging or with incomplete, damaged or missing labels or with labels written in a foreign language should be subjected to a thin layer chromatographic test.

Verification of Drug Identity and Content via Thin Layer Chromatography

I. PRINCIPLE

Azithromycin tablets and capsules are extracted and aqueous suspensions are diluted with methanol and determined by TLC with reference to an authentic secondary standard.

II. EQUIPMENT AND REAGENTS

1) Pestle
2) Aluminium foil
3) Funnel
4) Label tape
5) Marker pen
6) Pencil and ruler
7) 10-ml vials
8) Set of straight pipettes (1 to 25 ml)
9) Set of laboratory glass bottles (25 to 100 ml)
10) Merck TLC aluminium plates precoated with silica gel 60 F_{254}, size 5x10 cm
11) Glass microcapillaries (2-µl filling capacity)
12) TLC developing chamber (500-ml jar)
13) Hot plate
14) Filter paper
15) Pair of scissors
16) Pair of tweezers
17) UV light of 254 nm
18) Iodine chamber
19) TLC dipping chamber (250-ml beaker)
20) Sulphuric acid solution 96%
21) Ethyl acetate
22) Glacial acetic acid
23) Methanol
24) Ammonia solution 25%
25) Authentic reference standard, for example, azithromycin 250 mg tablets

III. PREPARATION OF THE STOCK STANDARD SOLUTION

The preparation of the stock standard solution requires an authentic drug product for reference purposes, for example, tablets containing 250 mg of azithromycin. Wrap up one reference tablet into aluminium foil and crush it down to a fine powder using a pestle. Carefully empty the aluminium foil over a 40-ml laboratory glass bottle and wash down all residual solids with 25 ml of methanol using a straight pipette. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid. The solution obtained should contain 10 mg of total drug per ml and be labelled as *'Azithromycin Stock Standard Solution'*. Freshly prepare this solution for each test. Continue to work with the clear or hazy supernatant liquid.

IV. PREPARATION OF THE WORKING STANDARD SOLUTION 100% (UPPER WORKING LIMIT)

Pipette 2 ml of the stock standard solution into a 10-ml vial and add 2 ml of methanol. Close and shake the vial. The solution obtained should contain 5 mg of total drug per ml and be labelled as *'Azithromycin Working Standard Solution 100%'*.

This higher working standard solution represents a drug product of good quality containing 100 % of azithromycin.

V. PREPARATION OF THE WORKING STANDARD SOLUTION 80% (LOWER WORKING LIMIT)

Pipette 2 ml of the stock standard solution into a 10-ml vial and add 3 ml of methanol. Close and shake the vial. The solution obtained should contain 4 mg of total drug per ml and be labelled as *'Azithromycin Working Standard Solution 80%'*.

This lower working standard solution represents a drug product of poor quality containing just 80% of the amount of azithromycin as stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

VI. PREPARATION OF THE STOCK SAMPLE SOLUTION FROM SINGLE SOLID DOSAGE FORMS CLAIMING TO CONTAIN 200 MG OF AZITHROMYCIN PER UNIT

Take one whole tablet or capsule from an appropriate drug product sampled in the field. As usual, tablets are wrapped up into aluminium foil and crushed down to a fine powder. Transfer all the powder obtained into a 25-ml laboratory glass bottle. Powder obtained from a sample capsule should be transferred directly into the bottle adding the cap and body shells last. For extraction, add 20 ml of methanol using a straight pipette, close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

SINGLE SOLID DOSAGE FORMS CLAIMING TO CONTAIN 250 MG OF AZITHROMYCIN PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 25 ml of methanol using a straight pipette and a 40-ml laboratory glass bottle as sample container. Continue to work as above.

SINGLE SOLID DOSAGE FORMS CLAIMING TO CONTAIN 500 MG OF AZITHROMYCIN PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 50 ml of methanol using a straight pipette and a 100-ml laboratory glass bottle as sample container. Continue to work as above.

POWDER FOR ORAL SUSPENSIONS CLAIMING TO CONTAIN 200 MG OF AZITHROMYCIN PER 5 ML

As directed by the manufacturer, suspend the powder in the bottle with water using the given mark. Shake well. Transfer 5 ml of the suspension obtained into a 25-ml laboratory glass bottle and dilute with 15 ml of methanol using each time appropriate straight pipettes.

All stock sample solutions produced should finally contain 10 mg of total drug per ml and be labelled as 'Azithromycin Stock Sample Solution'. Freshly prepare these solutions for each test. Continue to work with the clear or hazy supernatant liquids.

VII. PREPARATION OF THE WORKING SAMPLE SOLUTION

Pipette 2 ml of the stock sample solution into a 10-ml vial and add 2 ml of methanol. Close and shake the vial and label as *'Azithromycin Working Sample Solution 100%'.*

The expected concentration of azithromycin in this working sample solution is 5 mg of total drug per ml and should match the concentration of azithromycin of the higher working standard solution produced above.

VIII. SPOTTING

Mark an origin line parallel to and about 1.5 cm from the bottom edge of the chromatoplate and apply 2 µl of each test and standard solution prepared as shown in the picture opposite using the microcapillary pipettes supplied.

Up to five spots can be placed on a plate. Check the uniformity of all spots using UV light of 254 nm. Even if azithromycin itself stays invisible, some excipients will show up to facilitate verification. All spots should be circular in shape and equally spaced across the origin line. Although their intensities might differ, their diameters never should. Different intensities are due to residual amounts of tablet and capsule excipients or different drug concentrations in the sample solutions. A difference in spot size, however, relates to poor spotting. Repeat this step if homogeneous spotting is not achieved first time.

IX. DEVELOPMENT

A) Azithromycin drug content verification: pipette 20 ml of methanol, 5 ml of ethyl acetate and 0.5 ml of concentrated ammonia solution into the jar being used as TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes thus ensuring saturation of the chamber with solvent vapour. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate until the solvent front has moved about three-quarters of the length of the plate, the developing time being about 15 minutes. Remove the plate from the chamber, mark the solvent front and allow any excess solvent to evaporate using a hot plate if necessary.

B) Azithromycin versus erythromycin: in order to make the difference in travel distances between both drug compounds more pronounce, reverse the pH of the mobile from above with 1 ml of glacial acetic acid and perform a second run with a new plate. Use the pH indicator paper supplied to verify acidity of the mobile phase after thorough shaking. The yellow paper should turn to pale red at least and any smell of ammonia should have disappeared.

X. DETECTION

Dry off all residual solvent and expose the chromatoplate to iodine vapour for about one minute. Remove the plate from the iodine chamber and observe the plate at daylight. Use this method of detection for identification and quantification purposes of both, azithromycin and erythromycin. Further verification of drug identity and content can be achieved when immersing the plate in methanolic sulphuric acid solution shortly after the iodine staining. For this, fill the 250-ml plastic beaker supplied with a 190 ml of methanol followed by 10 ml of concentrated sulphuric acid solution and mix gently. Allow the mix to cool down and submerge the chromatoplate into the staining solution using a pair of tweezers. Instantly remove the plate and let all surplus solution run down onto paper tissue. Wipe off residual liquid from the back of the plate and continue to dry off all staining solution on the hot plate supplied. During heating, all azithromycin and erythromycin spots are gradually becoming visible at daylight.

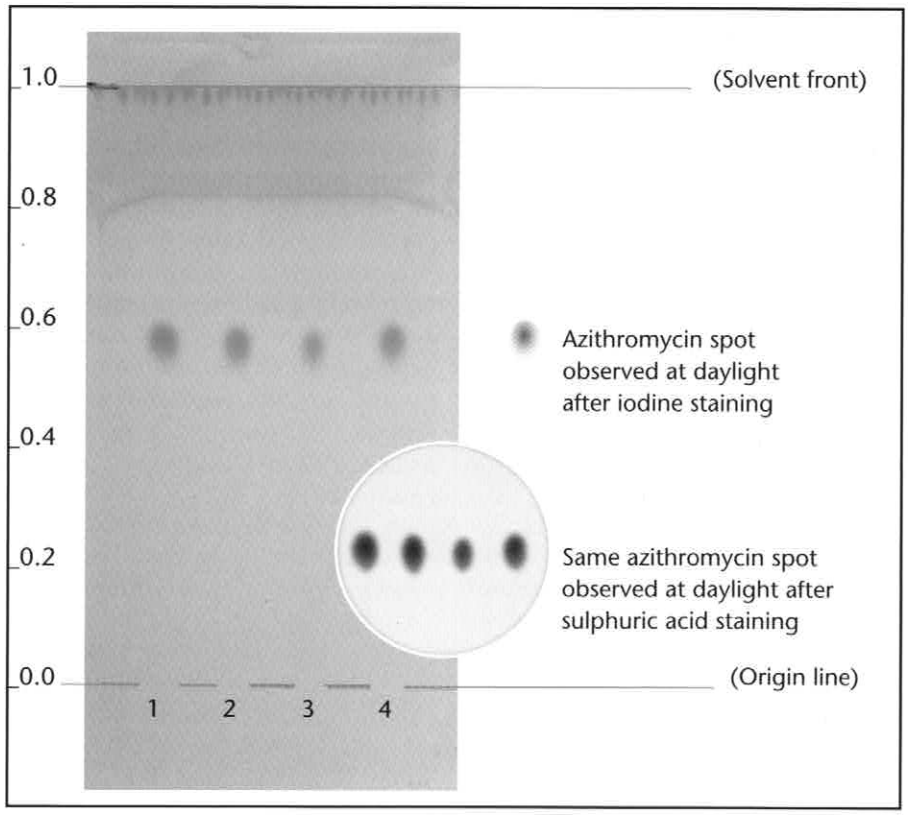
XI. CHROMATOPLATE FROM MOBILE PHASE A OBSERVED AT DAYLIGHT AFTER IODINE AND SULPHURIC ACID STAINING

Run No.1:
Upper working standard representing 100% of total azithromycin

Run No.2:
A drug product of good quality with acceptable drug content

Run No.3:
A drug product of poor quality with unacceptable low drug content

Run No.4:
Lower working standard representing 80% of total azithromycin



XII. OBSERVATIONS MADE AT DAYLIGHT AFTER IODINE STAINING

Mobile phase A: a strong orange-brown spot at a travel distance of about 0.58 indicates the presence of azithromycin in the test solution. Additional strong spots generated by the test solution would point at other drugs or azithromycin degradation, the latter case being more likely when associated with a smaller principal spot. Auxiliary agents incorporated in the different tablet or capsule formulations might cause some fainter spots either travelling alongside the solvent front or emerging near or on the origin line. Still observe the plate when iodine evaporates already. Spots reflecting poor quality products will disappear first gradually followed by the reference spots representing a drug content of an 80 and 100 percent, respectively.

Mobile phase B: erythromycin spots are running in the front settling at a travel distance of about 0.38 followed by spots from azithromycin with a relative retention factor of about 0.28. Spots from both compounds are showing a distinct shape and tailing assisting in identification.

XIII. OBSERVATIONS MADE AT DAYLIGHT AFTER SULPHURIC ACID STAINING

Mobile phase A and B: all azithromycin spots already observed after iodine staining are now turning dark brown. The same happens to all erythromycin spots.

XIV. RESULTS & ACTIONS TO BE TAKEN

The azithromycin spot in the chromatogram obtained with the test solution must correspond in terms of colour, size, intensity, shape and travel distance to that in the chromatogram obtained with the lower and higher standard solution. This result must be obtained for each method of detection. If this is not achieved, repeat the run from scratch with a second sample. Reject the batch if the drug content cannot be verified in a third run. For a second opinion, refer additional samples to a fully-fledged drug quality control laboratory. Retain samples and put the batch on quarantine until a final decision on rejection or release has been taken. For documentation purposes, take pictures of all the readings with a digital camera turning off the flash first.

6.54 Dihydroartemisinin (incl. piperaquine phosphate co-formulations)

Primary Screening via Physical Inspection and Disintegration Test

I. PHYSICAL INSPECTION

Search for deficiencies on labelling, packaging and dosage forms as described in the opening chapters on general methods and operations of the main manual. Write down all product particulars using the reporting form as a guide. Each tablet or capsule usually contains 20, 60 or 80 mg of dihydroartemisinin. More recently, single drug formulations for monotherapy are replaced by fixed-dose combination medicines consisting of a 40 mg of dihydroartemisinin and 320 mg of piperaquine tetraphosphate.

II. DISINTEGRATION TEST

All quick release dihydroartemisinin single dose and fixed-dose combination tablets and capsules must pass the disintegration test as described in the opening chapters on general methods and operations of the main manual. They should disintegrate in water at 37 °C in less than 30 minutes. It's a major defect if a drug product doesn't pass this test.

III. RESULTS & ACTIONS TO BE TAKEN

Drug products from unusually cheap sources, drug products with missing or incorrect accompanying documents and drug products with defective dosage forms, packaging or with incomplete, damaged or missing labels or with labels written in a foreign language should be subjected to a thin layer chromatographic test.

Verification of Drug Identity and Content via Thin Layer Chromatography

I. PRINCIPLE

Dihydroartemisinin is extracted from tablets and capsules with methanol and determined by TLC with reference to an authentic secondary standard. For a verification of piperaquine phosphate in fixed-dose combination medicines go to page 28 of this supplement.

II. EQUIPMENT AND REAGENTS

1) Pestle
2) Aluminium foil
3) Funnel
4) Label tape
5) Marker pen
6) Pencil and ruler
7) 10-ml vials
8) Set of straight pipettes (1 to 25 ml)
9) Set of laboratory glass bottles (25 to 100 ml)
10) Merck TLC aluminium plates precoated with silica gel 60 F_{254}, size 5x10 cm
11) Glass microcapillaries (2-µl filling capacity)
12) TLC developing chamber (500-ml jar)
13) Hot plate
14) Filter paper
15) Pair of scissors
16) Pair of tweezers
17) UV light of 254 nm
18) TLC dipping chamber (250-ml beaker)
19) Sulphuric acid solution 96%
20) Ethyl acetate
21) Methanol
22) Ammonia solution 25%
23) Authentic reference standard, for example, fixed-dose combination tablets containing 40 mg of dihydroartemisinin and 320 mg of piperaquine phosphate

PREPARATION OF THE STOCK STANDARD SOLUTION

The preparation of the stock standard solution requires an authentic drug product for reference purposes, for example, tablets containing 40 mg of dihydroartemisinin combined with 320 mg of piperaquine phosphate. Wrap up one reference tablet into aluminium foil and crush it down to a fine powder using a pestle. Carefully empty the aluminium foil over a 40-ml laboratory glass bottle and wash down all residual solids with 20 ml of methanol using a straight pipette. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid. The solution obtained should contain 2 mg of total dihydroartemisinin per ml and be labelled as *'Dihydroartemisinin Stock Standard Solution'*. Freshly prepare this solution for each test. Continue to work with the clear or hazy supernatant liquid.

PREPARATION OF THE WORKING STANDARD SOLUTION 100% (UPPER WORKING LIMIT)

The stock standard solution requires no further dilution. It already represents the final working concentration of 2 mg of total dihydroartemisinin per ml. Just for more convenient handling, some of the supernatant liquid may want to be transferred into a 10-ml vial.

This higher working standard solution represents a drug product of good quality containing 100 % of dihydroartemisinin.

PREPARATION OF THE WORKING STANDARD SOLUTION 80% (LOWER WORKING LIMIT)

Pipette 4 ml of the stock standard solution into a 10-ml vial and add 1 ml of methanol. Close and shake the vial. The solution obtained should contain 1.6 mg of total dihydroartemisinin per ml and be labelled as *'Dihydroartemisinin Working Standard Solution 80%'*.

This lower working standard solution represents a drug product of poor quality containing just 80% of the amount of dihydroartemisinin as stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

PREPARATION OF THE STOCK SAMPLE SOLUTION FROM A PRODUCT CLAIMING TO CONTAIN 20 MG OF DIHYDROARTEMISININ PER UNIT

Take one whole tablet or capsule from an appropriate drug product sampled in the field. As usual, tablets are wrapped up into aluminium foil and crushed down to a fine powder. Transfer all the powder obtained into an appropriate laboratory glass bottle. Powder obtained from a sample capsule should be transferred directly into the bottle adding the cap and body shells last. For extraction, add 10 ml of methanol using a straight pipette, close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

40 MG OF DIHYDROARTEMISININ PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 20 ml of methanol following the procedure described above.

60 MG OF DIHYDROARTEMISININ PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 30 ml of methanol following the procedure described above.

80 MG OF DIHYDROARTEMISININ PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 40 ml of methanol following the procedure described above.

All stock sample solutions produced should finally contain 2 mg of total dihydroartemisinin per ml and be labelled as *'Dihydroartemisinin Stock Sample Solution'*. Freshly prepare these solutions for each test. Continue to work with the clear or hazy supernatant liquids.

VII. PREPARATION OF THE WORKING SAMPLE SOLUTION

Dihydroartemisinin stock sample solutions require no further dilution. They already represent the final working concentration of 2 mg of total dihydroartemisinin per ml. If prepared from a high quality product, the sample solution should match the concentration of dihydroartemisinin of the higher working standard solution produced above.

VIII. SPOTTING

Mark an origin line parallel to and about 1.5 cm from the bottom edge of the chromatoplate and apply 2 µl of each test and standard solution prepared as shown in the picture opposite using the microcapillary pipettes supplied.

Up to five spots can be placed on a plate. Check the uniformity of all spots using UV light of 254 nm. Even if dihydroartemisinin itself stays invisible, excipients and other drug compounds will show up to facilitate verification. All spots should be circular in shape and equally spaced across the origin line. Although their intensities might differ, their diameters never should. Different intensities are due to residual amounts of tablet and capsule excipients or different drug concentrations in the sample solutions. A difference in spot size, however, relates to poor spotting. Repeat this step if homogeneous spotting is not achieved first time.

IX. DEVELOPMENT

Pipette 16 ml of ethyl acetate, 4 ml of methanol and 3 ml of concentrated ammonia solution into the jar being used as TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes thus ensuring saturation of the chamber with solvent vapour. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate until the solvent front has moved about three-quarters of the length of the plate, the developing time being about 15 minutes. Remove the plate from the chamber, mark the solvent front and allow any excess solvent to evaporate using a hot plate if necessary.

X. DETECTION

When working on fixed-dose combination medicines, it is best to check the presence of piperaquine phosphate before that of dihydroartemisinin. For this, expose the dried chromatoplate first to UV light of 254 nm using the battery-driven lamp supplied.

After the presence or absence of piperaquine has been verified, the chromatoplate can be exposed to sulphuric acid staining for the detection of dihydroartemisinin. For this, fill the 250-ml plastic beaker supplied with a 190 ml of methanol followed by 10 ml of concentrated sulphuric acid solution and mix gently. Allow the mix to cool down and submerge the chromatoplate upside down into the staining solution using a pair of tweezers. Instantly remove the plate and let all surplus solution run down onto paper tissue. Wipe off residual liquid from the back of the plate and continue to dry off all staining solution on the hot plate supplied. During heating, all dihydroartemisinin spots are gradually becoming visible at daylight. Use this method of detection for both, dihydroartemisinin identification and quantification purposes.

After staining with sulphuric acid and heat, a further detection of dihydroartemisinin and piperaquine is possible when exposing the dyed chromatoplate to UV light of 366 nm in a dark room.

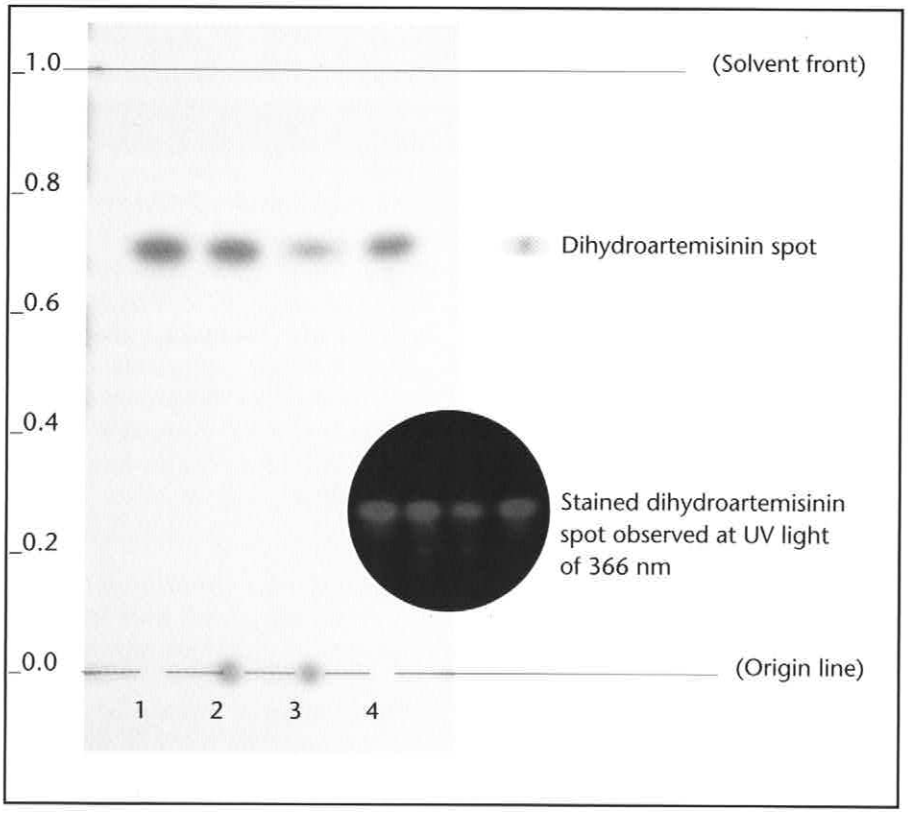
XI. CHROMATOPLATE OBSERVED AT DAYLIGHT AND UNDER UV LIGHT OF 366 NM AFTER SULPHURIC ACID STAINING

Run No.1:
Upper working standard representing 100% of total dihydroartemisinin

Run No.2:
A drug product of good quality with acceptable drug content

Run No.3:
A drug product of poor quality with unacceptable low drug content

Run No.4:
Lower working standard representing 80% of total dihydroartemisinin



XII. OBSERVATIONS MADE AT 254 NM BEFORE STAINING

Dihydroartemisinin stays invisible and no other spots should be detected unless the sample under investigation comes as fixed-dose combination medicines containing also piperaquine phosphate. In case of co-formulations, a spot representing piperaquine will become visible at a travel distance of about 0.54. Weak spots observed here are due to the low solubility of piperaquine phosphate in methanol used for sample extraction. Other spots generated by the test solution would point to other drugs.

XIII. OBSERVATIONS MADE AT DAYLIGHT AFTER SULPHURIC ACID STAINING

A brown spot at a travel distance of about 0.69 indicates the presence of dihydroartemisinin in the test solution. No other spots should be visible even if dihydroartemisinin is combined with piperaquine phosphate. Additional strong spots generated by the test solution would point at other drugs or dihydroartemisinin degradation, the latter case being more likely when associated with a smaller principal spot. Auxiliary agents incorporated in the different tablet or capsule formulations might cause some fainter spots either travelling alongside the solvent front or emerging near or on the origin line.

XIV. OBSERVATIONS MADE AT 366 NM AFTER SULPHURIC ACID STAINING

Both spots, the one for dihydroartemisinin and piperaquine, previously observed step by step with different detection methods are now becoming visible simultaneously; the spot for dihydroartemisinin showing an off-white and the one for piperaquine a light blue fluorescence.

XV. RESULTS & ACTIONS TO BE TAKEN

The dihydroartemisinin spot in the chromatogram obtained with the test solution must correspond in terms of colour, size, intensity, shape and travel distance to that in the chromatogram obtained with the lower and higher standard solution. This result must be obtained for each method of detection. If this is not achieved, repeat the run from scratch with a second sample. Reject the batch if the drug content cannot be verified in a third run. For a second opinion, refer additional samples to a fully-fledged drug quality control laboratory. Retain samples and put the batch on quarantine until a final decision on rejection or release has been taken. For documentation purposes, take pictures of all the readings with a digital camera turning off the flash first.

6.39 Sulfamethoxazole (including cotrimoxazole formulations)

Primary Screening via Visual Inspection and Disintegration Test

I. VISUAL INSPECTION

Search for deficiencies on labelling, packaging and dosage forms as described in the opening chapters on general methods and operations. Write down all product particulars using the reporting form as a guide. Each tablet or capsule usually contains a 100 or 400 mg of sulfamethoxazole combined with a 20 or 80 mg of trimethoprim, respectively. Other strengths are known to exist. The term cotrimoxazole commonly refers to appropriate fixed-dose combination products.

II. DISINTEGRATION TEST

All quick release cotrimoxazole tablets and capsules must pass the disintegration test as described in the opening chapters on general methods and operations. They should disintegrate in water at 37 °C in less than 30 minutes. It is a major defect if a drug product does not pass this test.

III. RESULTS & ACTIONS TO BE TAKEN

Drug products from unusually cheap sources, drug products with missing or incorrect accompanying documents and drug products with defective dosage forms, packaging or with incomplete, damaged or missing labels or with labels written in a foreign language should be subjected to a thin layer chromatographic test.

Verification of Drug Identity and Content via Thin Layer Chromatography

I. PRINCIPLE

Sulfamethoxazole and trimethoprim are extracted from tablets and capsules with methanol and determined by TLC with reference to an authentic secondary standard.

II. EQUIPMENT AND REAGENTS

1) Pestle
2) Aluminium foil
3) Funnel
4) Label tape
5) Marker pen
6) Pencil
7) 10-ml vials
8) Set of straight pipettes (1 to 25 ml)
9) Set of laboratory glass bottles (25 to 100 ml)
10) Merck TLC aluminium plates pre-coated with silica gel 60 F 254, size 5x10 cm
11) Glass microcapillaries (2-µl filling capacity)
12) TLC developing chamber (500-ml jar)
13) Hot plate
14) Filter paper
15) Pair of scissors
16) Pair of tweezers
17) UV light of 254 nm
18) Iodine chamber
19) Ethyl acetate
20) Methanol
21) Secondary reference standard, for example, sulfamethoxazole/trimethoprim 100/20 mg tablets

PREPARATION OF THE STOCK STANDARD SOLUTION

The preparation of the stock standard solution requires an authentic drug product for reference purposes, for example, tablets containing 100 mg of sulfamethoxazole combined with 20 mg of trimethoprim. Wrap up one reference tablet into aluminium foil and crush it down to a fine powder using a pestle. Carefully empty the aluminium foil over a 25-ml laboratory glass bottle and wash down all residual solids with 10 ml of methanol using a straight pipette. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid. The solution obtained should contain 10 mg of sulfamethoxazole and 2 mg of trimethoprim per ml and be labelled as *'Cotrimoxazole Stock Standard Solution'*. Freshly prepare this solution for each test. Continue to work with the clear or hazy supernatant liquid.

PREPARATION OF THE WORKING STANDARD SOLUTION 100% (UPPER WORKING LIMIT)

Pipette 2 ml of the stock standard solution into a 10-ml vial and add 2 ml of methanol. Close and shake the vial. The solution obtained should contain 5 mg of sulfamethoxazole and 1 mg of trimethoprim per ml and be labelled as *'Cotrimoxazole Working Standard Solution 100%'*.

This higher working standard solution represents a drug product of good quality containing 100 % of sulfamethoxazole and trimethoprim.

PREPARATION OF THE WORKING STANDARD SOLUTION 80% (LOWER WORKING LIMIT)

Pipette 2 ml of the stock standard solution into a 10-ml vial and add 3 ml of methanol. Close and shake the vial. The solution obtained should contain 4 mg of sulfamethoxazole and 0.8 mg of trimethoprim per ml and be labelled as *'Cotrimoxazole Working Standard Solution 80%'*.

This lower working standard solution represents a drug product of poor quality containing just 80% of the amount of sulfamethoxazole and trimethoprim as stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

PREPARATION OF THE STOCK SAMPLE SOLUTION FROM A PRODUCT CLAIMING TO CONTAIN 100 MG OF SULFAMETHOXAZOLE AND 20 MG OF TRIMETHOPRIM PER UNIT

Take one whole tablet or capsule from an appropriate drug product sampled in the field. As usual, tablets are wrapped up into aluminium foil and crushed down to a fine powder. Transfer all the powder obtained into a 25-ml laboratory glass bottle. Powder obtained from a sample capsule should be transferred directly into the bottle adding the cap and body shells last. For extraction, add 10 ml of methanol using a straight pipette, close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

400 MG OF SULFAMETHOXAZOLE AND 80 MG OF TRIMETHOPRIM PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 40 ml of methanol using a straight pipette and a 100-ml laboratory glass bottle as sample container. Continue to work as shown above.

All stock sample solutions produced should finally contain 10 mg of sulfamethoxazole and 2 mg of trimethoprim per ml and be labelled as *'Cotrimoxazole Stock Sample Solution'*. Freshly prepare these solutions for each test. Continue to work with the clear or hazy supernatant liquids.

VII. PREPARATION OF THE WORKING SAMPLE SOLUTION

Pipette 2 ml of the stock sample solution into a 10-ml vial and add 2 ml of methanol. Close and shake the vial and label as *'Cotrimoxazole Working Sample Solution'*.

The expected concentration of sulfamethoxazole in the working sample solution is 5 mg and that of trimethoprim 1 mg per ml and each of them should match the concentration of its appropriate counterpart in the higher working standard solution produced above.

VIII. SPOTTING

Mark an origin line parallel to and about 1.5 cm from the bottom edge of the chromatoplate and apply 2 µl of each test and standard solution as shown in the picture opposite using the microcapillary pipettes supplied.

Up to five spots can be placed on a plate. Check the uniformity of all spots using UV light of 254 nm. All spots should be circular in shape and equally spaced across the origin line. Although their intensities might differ, their diameters never should. Different intensities are due to residual amounts of tablet and capsule excipients or different drug concentrations in the sample solutions. A difference in spot size, however, relates to poor spotting. Repeat this step if homogeneous spotting is not achieved first time.

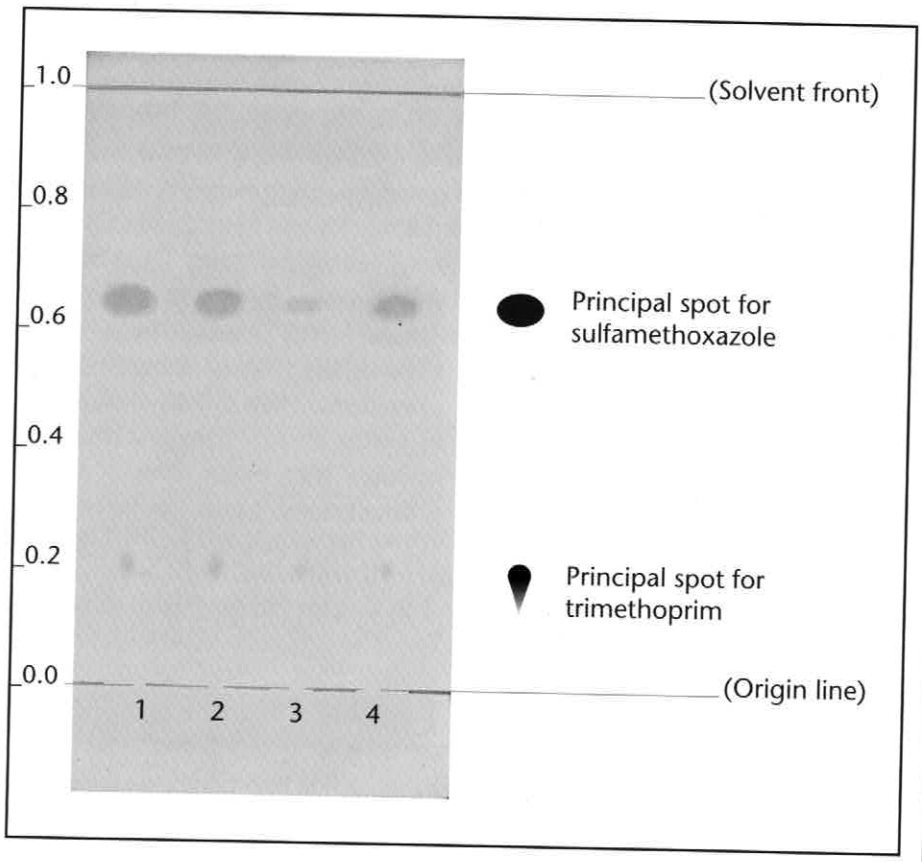
IX. DEVELOPMENT

Pipette 15 ml of ethyl acetate and 5 ml of methanol into the jar being used as TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes thus ensuring saturation of the chamber with solvent vapour. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate until the solvent front has moved about three-quarters of the length of the plate, the developing time being about 15 minutes. Remove the plate from the chamber, mark the solvent front and allow any excess solvent to evaporate using a hot plate if necessary.

X. DETECTION

Dry off all residual solvent and observe the chromatoplate under UV light of 254 nm using the battery-driven lamp supplied. Use this method of detection for both, identification and quantification purposes. Further verification of drug identity and content can be achieved when observing the plate at daylight after iodine staining.

XI. CHROMATOPLATE OBSERVED UNDER UV LIGHT OF 254 NM



Run No.1:
Cotrimoxazole's upper working limit representing 100 % of total drug.

Run No.2:
A drug product of good quality.

Run No.3:
A drug product of poor quality.

Run No.4:
Cotrimoxazole's lower working limit representing 80 % of total drug.

XII. OBSERVATIONS MADE AT 254 NM

A strong blue-violet spot at a travel distance of about 0.65 indicates the presence of sulfamethoxazole and a second smaller spot at about 0.24 that of trimethoprim in the test solution. Both spots must be there when presented as fixed-dose combination product. Additional strong spots generated by the test solution would point at other drugs or degradation of cotrimoxazole actives, the latter case being more likely when associated with smaller principal spots. Auxiliary agents incorporated in the different tablet or capsule formulations might cause some fainter spots emerging near or on the origin line.

XIII. OBSERVATIONS MADE AT DAYLIGHT AFTER IODINE STAINING

When exposing the chromatoplate to iodine vapour, all sulfamethoxazole and trimethoprim spots already observed at 254 nm are now turning yellowish brown. Still observe the plate when iodine evaporates already. Spots reflecting poor quality products will disappear first gradually followed by the reference spots representing a drug content of an 80 and 100 percent, respectively.

XIV. RESULTS & ACTIONS TO BE TAKEN

Both, the sulfamethoxazole and trimethoprim spot in the chromatogram obtained with the test solution, must correspond in terms of colour, size, intensity, shape and travel distance to that in the chromatogram obtained with the lower and higher standard solution. This result must be obtained for each method of detection. If this is not achieved, repeat the run from scratch with a second sample. Reject the batch if the drug content cannot be verified in a third run. For a second opinion, refer additional samples to a fully-fledged drug quality control laboratory. Retain samples and put the batch on quarantine until a final decision on rejection or release has been taken.

Supplementary Annex 8. Neospectra 2.5 - Protocols

Assembly/Disassembly of the device

a. For the light source, remove the AVALIGHT-HALM-MINI light source from its box along with the power supply and the dongle labeled with the word “HIGH”
    i. Attach the power supply to the mains electricity and then the power supply to the light source.
    ii. Attach the dongle to the back of the light source and secure it with the screws embedded in the dongle.
    iii. Remove the cap on the light output of the source, but do not turn on the light source at this step.
b. For the Neospectra 2.5 detector unit, remove the detector and USB cable from the box.
    i. Attach the USB cable from the computer to the detector unit.
    ii. Remove cap from the light input for the detector
c. For the fiber optic cable and probe, remove from it from the box. ***NOTE: Although the fiber optic cable is flexible, the user can bend the cable too far and break the internal optical fiber and make the cable unusable. Be careful and allow the cable to freely move and bend, never force the cable into a position. ***
    i. Remove the cap from the end of the cable that has a flower pattern of five dots printed on it (this will be the smallest screw connection of the two on the cable) Screw this end into the light source.
    ii. Remove the cap from the end of the cable that has a the “THORLABS” logo on it (this will be the largest screw connection of the two on the cable). Screw this end into the Neospectra 2.5 detector unit.
    iii. Depending on how the user would like to conduct experiments on medicine tablets and powders, the user can set up the probe in two different ways:
        1. The user can use the probe without any further modification from the above-mentioned set-up. The probe can freely move around and be used like pen to sample the surface of the samples is question.
        2. The user can attach the end of the probe to a probe holder in order to not hold by hand either the sample or probe while conducting experiments (the way the instrument was tested in this study).
            a. Insert the probe in the probe holder until the end of the probe is flush with the largest flat side of the probe holder.
            b. Tighten the set screw to secure the probe in place.
            c. Attach the probe holder to a clamp. Allow sampling window of the probe and flat face of the probe holder be parallel to the floor and face them towards the ceiling. This allows the user to place sample on top of the probe to sample without having to hold it by hand.
d. To disassemble the device, follow the protocol in reverse order.

Software Download (to install on computer)

a. Included with the Neospectra 2.5 detector is flash drive that contains the software that controls the detector.
b. Access the flash drive and open the "SpectroMOST6.1_Setup" file. Follow the onscreen instructions to install.
c. Towards the end of the software installation, the software will tell you to connect the detector to the computer to finish the configuration.

Device Operational protocol

a. Turn on the light source and allow the source to warm up for 10 to 15 minutes so the lamp is outputting a consistent amount of light.
b. While the lamp in the light source is warming up, connect the Neospectra to the computer if not done so already
    i. Open the "SpectroMOST" software on the computer.
    ii. At the bottom of the window, the "Status" should eventually become green with "NeoSpectra module is Ready!" to ensure the detector is communicating with the master computer.
    iii. The detector settings can also be set-up including the "Scan Time", "Resolution", and "Optical Gain Settings". For this study:
        1. Scan Time = 10 s
        2. Resolution = 8 nm @ 1550 nm
        3. Optical Gain Setting = Reflection
c. Once the lamp is warm, the instrument can undergo further set-up.
    iv. Remove the cover from the white reference tile and place the white side of the sample flush against the sampling window of the sampling probe.
    v. In the software, then click "Background" to acquire a background scan to tune the device.
d. The device should be ready to begin scanning samples.
    vi. Clean the sampling window with a delicate task wipe and if necessary, some isopropanol (or other light organic solvent) if the probe is especially dirty.
    vii. Place the sample in question flush against the sampling window.
        1. For powdered samples, ensure that there is as thick of accumulation of the powder over the sampling window to get the best results.
    viii. When the sample is ready, hit the "Scan" button in the software window.
    ix. If the quality of the spectra looks acceptable, press the "Save" button in the software window to save it in the user's desired folder. ***NOTES:
        1. The spectra does not autosave after scanning unless the "Auto-save" is checked and enabled.
        2. Ever subsequent scan will overlay with the previous scan(s). When saving, each spectra will be saved with a single filename set by user and then automatically numbered in order from the first to last scan.
            a. To clear the spectrum window, click "Clear" button.

2. Data Analysis

a. Samples that were used for reference spectra were tested in the above-mentioned protocol and saved in a specified reference folder. The filenames also stated that the samples were reference spectra.
b. The questioned samples are scanned as stated in the above-mentioned protocol and saved in a separate sample scan folder.
c. The reference spectra can then be overlaid on top of the questioned sample spectra.
    i. With the questioned sample spectra in the window, click the "Load" button in the software window.
    ii. Open the reference file spectra that relate the sample in question.
    iii. The reference spectra will be loaded into the window as subsequent scans.
    iv. Additional sample spectra can be added to window following the same process as with the reference spectra.
d. The data then can be directly analyzed and compared in that window, or a screenshot of the window can be used to export the spectral analysis to a different computer.
e. If the user would like to export the raw spectral data for third party data processing software, the spectra files saved by the SpectroMOST software can be opened in basic text file (ex. Notepad) or spreadsheet software (ex. Excel)

Calibration

a. At a minimum, conduct a new background test with the white reference tile every 2 hours. The more often the better to minimize any chance of detector drift that may happen.
b. Monthly, a "Wavelength & Wavenumber Correction" test is recommended. See section 6.h for how to conduct the correction.

Trouble Shooting

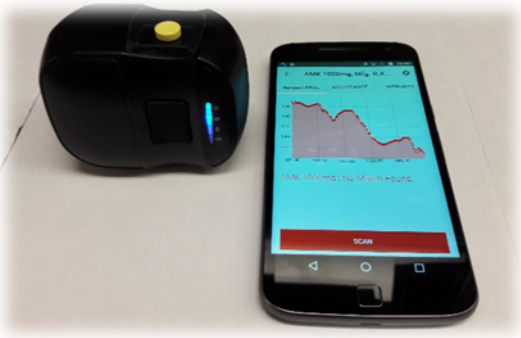
a. Ensure the detector is connected to the computer
    i. See if the status of the detector is ready at the bottom of the software window.
    ii. If not, unplug the USB cable and plug the USB back into the computer. Check the status.
    iii. Restart the software and later the computer if subsequent attempts could not connect the detector to the computer.
    iv. Contact the developers if the detector to the computer connection issue persists.
b. Ensure all the connections to the fiber optic cable from the light source and detector are tight.
c. Ensure the light source is on and the high intensity dongle is fully plugged into the light source.
d. Reclean the sampling window and probe.
e. If using the probe holder, ensure that the probe is flush with the flat surface of the probe holder.
    v. If not, a gap may have been created that allowed ambient light to enter the detector or the reflected light from the sample could not reflect as well.
f. Ensure all detector parameters are set appropriately.

g. Conduct another background scan with the white reflectance tile and then rescan the sample.
h. If the problem of poor quality spectra persists, select the “Wavelength & Wavenumber Correction” at the bottom of the software window.
    vi. Attempt a “Self-Correction” first using the white reference tile and then click proceed. Scan the while reference tile as you would when doing a background scan.
    vii. When the instrument is operating properly, the user can also develop additional correction tests with different samples to ensure reliability. The user needs to ensure the following when selecting a reference material for a new wavelength/wavenumber correction test:
        1. Easily accessible and plentiful
        2. Does not degrade (or very minimally)
        3. Available in high purity easily
        4. Generates spectral features
i. Potential issue with the fiber optic cable:
    viii. If the light from the light source to the probe seems darker than usual or light is absent when the source is on at the end of the probe, there might be a break in the fiber optic cable between the light source and probe.
    ix. Unplug the fiber optic cable from the detector and then shine a light onto the sampling window of the probe. If no light appears at the end that connects to the detector, the fiber optic cable is broken from the probe to the detector
    x. Replace if necessarily, but contact an expert to ensure, especially if the cable had been bent too far.
j. Contact the developers if a problem persists.

Supplementary Annex 9. NIRscan (Beta version) – Protocols

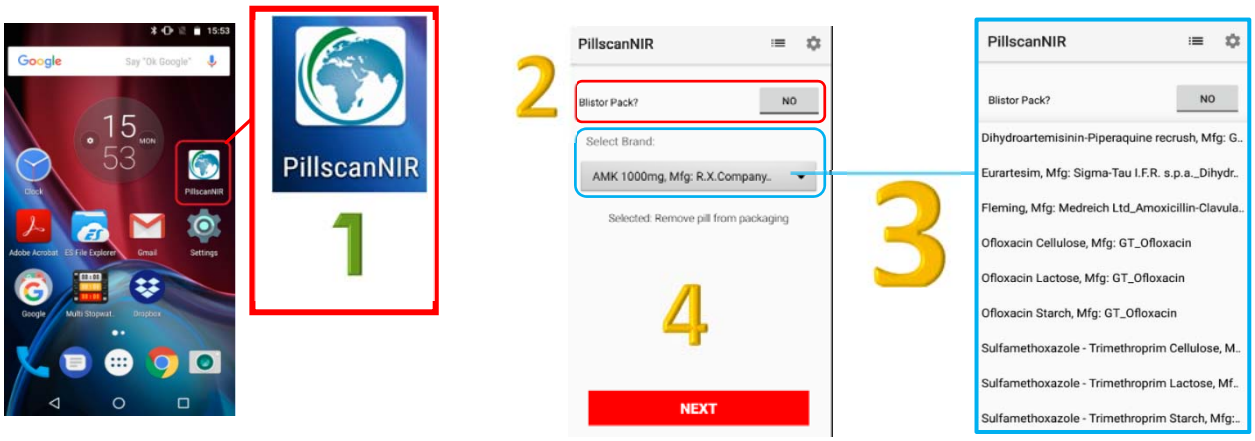
Operating procedures

The NIRscan used in this work consisted of two separate devices; a near-infrared sampling unit and a smartphone that runs an Android® based operating system.



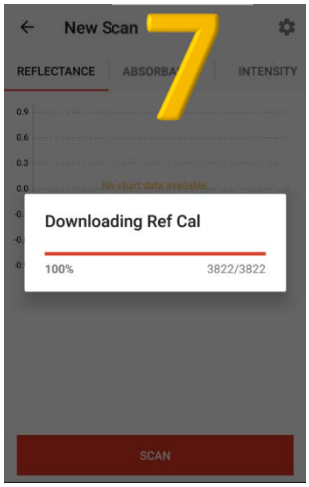
The near infrared sampling unit contains all the hardware necessary for sampling the target (light source, sampling window, optics, and detector) and operates cooperatively with the smartphone. The smartphone, a Motorola G4 Plus-Android version 7.0, acts as the unit's user graphical interface, command module for the sampling unit, and data storage for the device. Communication between the sampling unit and smartphone is achieved using Bluetooth® wireless technology. Both the sampling unit and smartphone are powered by internal lithium ion batteries and can be recharged using the same micro-USB cable.

To operate the NIRscan, once both devices are fully powered the user must activate the "PillScanNIR" application on the smartphone **(1)**. From the main menu of the app, the user selects the type of analysis desired (i.e through blister pack or not) **(2)**. The library spectrum that the sampling unit will compare its experimental results to is then selected by the user from a list of available spectra of medicines sorted by brand names of medicines **(3)**.



After library spectrum selection, the phone uploads the sampling and calibration protocol to the sampling unit.

Tablets are rested on top of the sampling window (blistered samples are placed and held flush against the sampling window) **(5)**. Using either the phone or a button on the sampling unit **(6)**, a scan is initiated on the sample of interest. The spectral data is then uploaded from the sampling unit to the smartphone and computationally analyzed. After a few seconds **(7)** The smartphone then displays whether the experimentally collected spectra successfully matched the selected library spectra **(8)**.



NIRScan reference library operating details

The reference library spectra was generated by Intellectual Ventures laboratory, the developer of the Android application because the device was not ready for user based reference library generation at the time of the study. Reference genuine samples were shipped to Intellectual Ventures laboratory where the library and processing would be generated and uploaded to the smartphone application.

NIRScan – Training

PRACTICE MEDICINES

Table 1. Samples used for practice by inspectors during intensive and basic trainings

LOMWRU Sample Codes	Brand	API	Dosage	Manufacturer
LA16/115	AMK	Amoxicillin – Clavulanic acid	1000 mg	RX Manufacturing
G113;G373;G399	Metronidazol	Metronidazole	250 mg	CBF Pharmaceutical Factory
G414;G491	Clarithro 500	Clarithromycin	500 mg	VIDIPHA, Vietnam
G313;G329;G431;G471	Erythro-500	Erythromycin	500 mg	Codupha-Lao Pharma Factory
G416;G494	Norfloxyl 400	Norfloxacin	400 mg	Bangkok Lab & Cosmetic
G339;G355;G377	Penicillin V	Penicillin V	400000 IU	Codupha-Lao Pharma Factory
G458;G493;G522	Roxithroxyl	Roxithromycin	150 mg	Bangkok Lab & Cosmetic

INTENSIVE TRAINING

Time spent: 1 - 2 hour including practice

1. Trainer briefly presents the different pieces of the device: NIR unit, smartphone and smartphone application

2. Presentation: the trainees were given hard copies of the slides of the oral presentation and one sheet with details of operating procedures (see 'Quick Guide', below) .

2.1. Intention and purpose of the training

- All of the devices used in this study are designed to assist in the search for poor quality medicines on-site during drug inspection
- The NIRscan device uses infrared technology to assess the quality of the medicines
- The device may be able to distinguish genuine from falsified medicines and has variable ability to distinguish genuine from substandard medicines

2.2. Device composition

- Device: Signal lights and scan button.
- Application: Pillscan application on mobile phone main screen

2.3. Demonstration of device in use by the trainer

2.4. Processing steps (see above)

2.5. Practice

While inspectors are practising, the trainers explained more about how the NIRScan works (e.g where the light is coming from, what is displayed on the smartphone screen). Each trainee tested 3 to 5 medicines (different brands, **Table 1**).

2.6. Data extraction: Written on sheet with a brief explanation but no verbal training

RUDIMENTARY TRAINING

Time spent: 5 - 10 minutes including practice

1. Trainers showing the NIR unit, smartphone and application
2. Processing & Practice: The trainee practiced on 1 to 3 different medicines (different brands, **Table 1**)

QUESTIONS ASKED AND COMMENTS GIVEN BY THE DRUG INSPECTORS DURING THE TRAININGS

Questions:

- Can the NIRScan assess the quality of creams and gels?
- How is the reference library creation done with this device?
- What is the reliability of the reference library?

Other comments:

- NIRScan reference library doesn't contain many references
-

NIRScan – Quick guides

Quick guide of operating procedures used in the field evaluation

1. Turn on the phone by pressing and holding the bottom at the top right side.

2. Turn on the NIRscan by flipping the switch on button on the bottom of the device. Check that the light on the front of the device turn on
3. On the phone, sign in using the code “5555”
4. Click on the application Icon “PillscanNIR”
5. For the “Blister Pack?” box on the right hand of the screen (define whether the sample you want to analyze is in a transparent pack or not) type “Yes or No” option.
6. Select the appropriate brand/sample you want to analyze in the “Select Brand” scroll down window

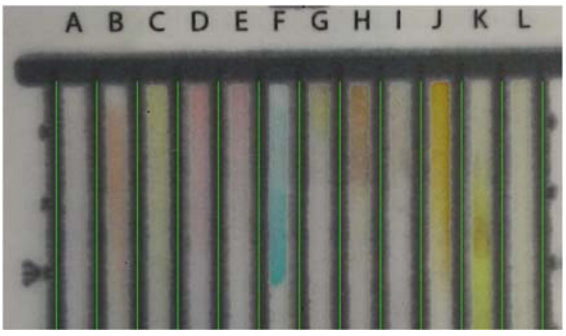
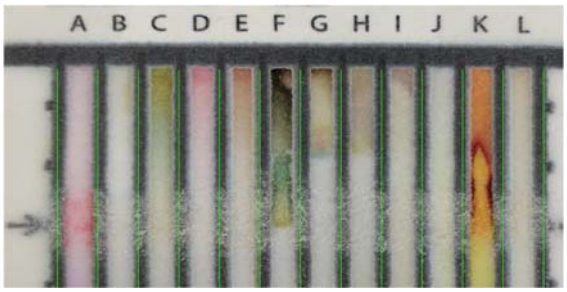
   At this point, the Bluetooth light on the NIRscan device should be solid blue. If not, turn the NIRscan on and off and restart to step 5.
7. Click the “NEXT” button. The Bluetooth light on the NIRScan should now be flashing.
8. Once the phone has uploaded the calibration file (done automatically) to the NIRscan (on mobile screen a blank chart of a new scan would appear), place the medicine on the sampling window of the device (small rectangle glass window on the device)
9. Either press “SCAN” on the phone or press and release the black rubber button adjacent to the lights on the NIRScan device. **LEAVE the tablet on the sampling window or CONTINUE to hold the blister on the window until the phone tells you the scan is done.
10. Interprete the analysis, briefly wipe the sampling window with a clean cloth, and run the next sample:
    a. If looking at the same medicine, just press the “SCAN” button again on the phone or press and release the rubber button on the NIRscan device
    b. If looking at a different medicine, hit the “←” button on the phone’s app and repeat steps 6-10.
11. Turn off the NIRScan and phone

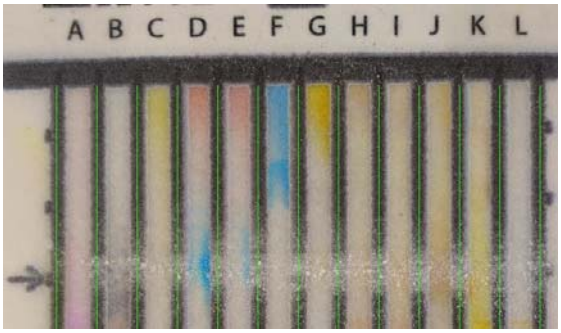
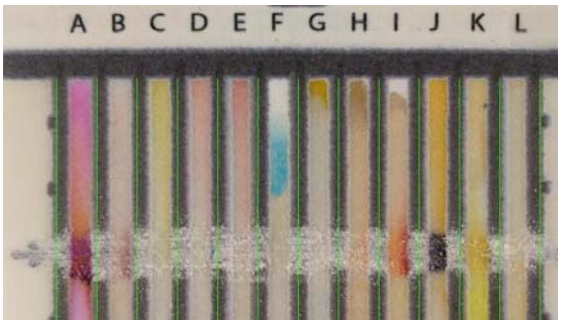
Supplementary Annex 10. Paper Analytical Devices – Protocols

Overview of the operating procedures

The sample must be crushed into a fine powder. The powder is then applied to the PAD by taking a several milligrams and depositing a line of the sample in the middle of the card where the arrows designate. This line of sample powder is perpendicular and across all the lanes. Using any spatula like tool like a popsicle or stirring stick, the line of powder is then compressed into the card to ensure the sample sticks and is embedded into the card. Once the card has been prepared, the bottom of the card is placed into a few millimeters of water and allowed to develop. The water is pulled through the PAD through capillary action and the water travels up the card. The water interacts with the deposited reagents to dissolve them and then the reagents infused with the water interacts with the chemicals that are in the sample as the pass the deposit line. As the water reaches the top of the card, the reagents have time to react with the samples and the resulting reaction product or lack of a product is captured at the top of the card. The card can be read after about 3 minutes.

PADs reference library photos

Water (negative control)		To be compared to the other API
Amoxicillin – clavulanic acid		C: Green (may range from yellow-green to brown-green) F: Dark green (lane often gets "stuck" K: Cherry red

Azithromycin		D: Turquoise/blue color at swipe line F: Purple color at swipe line
Dihydroartemisinin - Piperaquine		D: Blue at swipe (fades quick) E: Blue at swipe (less intense than D)
Ofloxacin		D: Blue (fades quickly) J: Many dosage forms contain starch, giving black at swipe line L: Orange
Sulfamethoxazole - Trimethoprim		A: Red/purple I: Orange/red at swipe line J: Black at swipe line in dosage forms that contain starch

Paper Analytical Devices – Training

PRACTICE MEDICINES

LOMWRU Codes	Brand	API	Manufacturer
G426	Ofloxin 200	Ofloxacin 200 mg	CBF Pharmaceutical Factory
G553	STRIM-SIDE	Sulfamethoxazole 400 mg – Trimethoprim 80 mg	KPN Pharma
G314 G432 G556	Vactrim	Sulfamethoxazole 400 mg – Trimethoprim 80 mg	Codupha-Lao Pharma Factory

INTENSIVE TRAINING

- Training Materials
  - ✓ Quick guide
  - ✓ PAD papers
  - ✓ Stick
  - ✓ Pestle
  - ✓ A4 papers
  - ✓ Bowl
  - ✓ A bottle of water
  - ✓ Seven different samples/APIs
  - ✓ Record sheets
  - ✓ Presentation sheet
  - ✓ Mobile phone(Standard and photos taking)

- Training session
  - o Presentation: overview of background to the device, including how to run a calibration (negative control) and basic principles of device technology (each lane contains a unique colour reaction to identify different functional groups on drug molecules).
  - o Practice: each inspector given opportunity to practice with medicines from the practice set (see above).
  - o At the same time as the inspectors are running samples, the trainer also explained the different colorimetric reactions (using reference slides) and how to interpret the colour barcode to arrive at a pass/fail decision
  - o Range of APIs and dosage forms able to be tested with the device was also detailed to the inspectors.
  - o During the training, inspectors were encouraged to questions

    - After this initial talk-through, the inspectors were given approximately 1 hour to test further samples and record the result on the recording sheet (identical to that which would be supplied during the evaluation pharmacy inspection).
    - At the end of the training, trainers gave a brief overview of how to upload data out of the mobile phone (photos of the completed PADs)
    - An overview was also given of possible problems that might occur during the sampling procedure and potential solutions (1 slide).
- The interval between intensive training and evaluation pharmacy inspection was at least 1 week.

- Time spend on training
  2 – 3 hours
- Scan performed per trainer
  5 – 10 scans

RUDIMENTARY TRAINING

- Training materials supplied as above ('Intensive Training').
- Trainer demonstrates how to calibrate (negative control) and demonstrates one sample test, including how to interpret the colour barcode and how to record on the record sheet.
- Inspector was then permitted to run 1-2 samples before being escorted to the evaluation pharmacy to start inspection.
- Time spend on training
  20 minutes
- Scan performed per training
  1-2 scans

For both trainings, the inspectors were reminded to make sure that the water was not visibly contaminated by the samples (e.g. visible powder residue). If the water was visibly contaminated, they were advised to change.

Paper Analytical Devices – Quick guides

Quick guide of operating procedures used in the field evaluation

1. Crush the sample if it is in tablet form.
2. Apply the powder to card and firmly press so it sticks to each lane.
3. Dip card in water for three minutes.
4. Take card off the water. Colors develop in three minutes.
5. Lay the card flat and take a photo from straight overhead, make sure the whole card appears in the photo.

6. Compare the tested card to the reference photo. Reference photo can be in print or an electronic image.

Supplementary Annex 11 PharmaChk – Protocols

PharmaChk

User Manual

PharmaChk v2.0

December 2016

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Overview

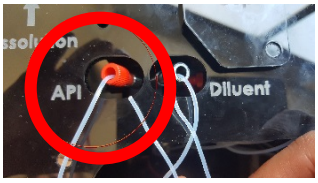
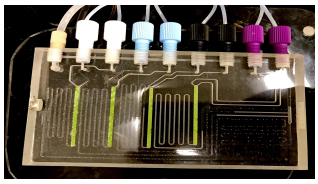
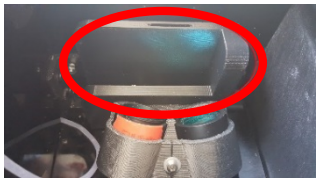
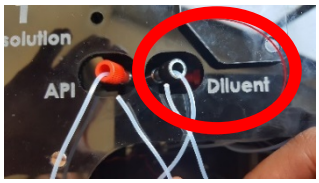
PharmaChk is a user-friendly, accurate, and portable system that screens for poor quality medicines by quantifying active pharmaceutical ingredient (API) content. Using a quantitative, light-based platform, PharmaChk provides users with:

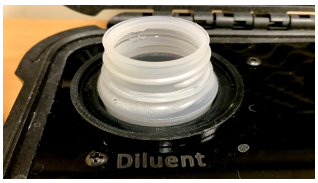
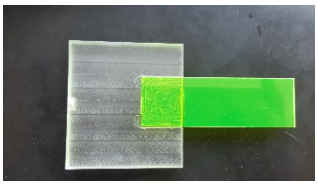
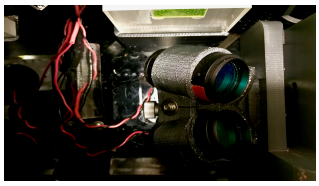
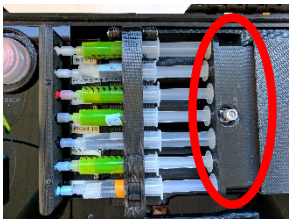
- Direct quantification of API with high specificity
- Point-of-care design requiring minimal user training
- Substantial increase in testing throughput
- Minimal resource usage
- Greater accuracy, robustness, and portability than MiniLab™

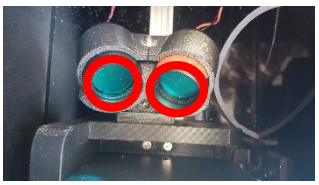
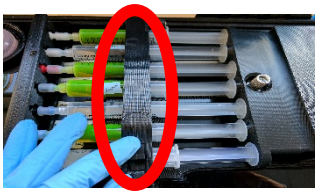
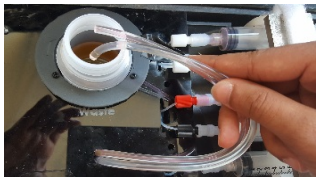
The purpose of the PharmaChk User Manual is to provide step-by-step instructions to operators on sample testing and device maintenance.

Glossary

The following section defines components referred to throughout this manual in alphabetical order.

Component	Image
API tube	
Cartridge	
Cartridge lid	
Cartridge nest	
Diluent tube	

Diluent cup	
Dissolution vessel	
Dissolution filter	
Flat-fielding cartridge	
Focus Knob	
Probe holder	
Pump bar	

LED and Filters Wavelengths (λ): 490, 515 nm	
Sonicator probe	
Syringe cradle	
Syringe	
Syringe cradle latch	
Touchscreen laptop	
Waste cup	

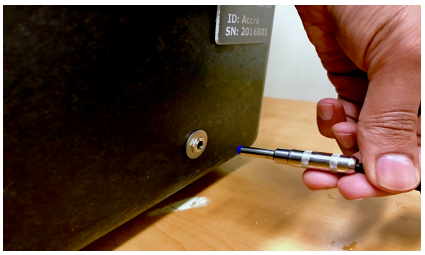
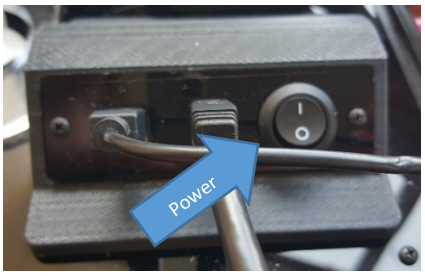
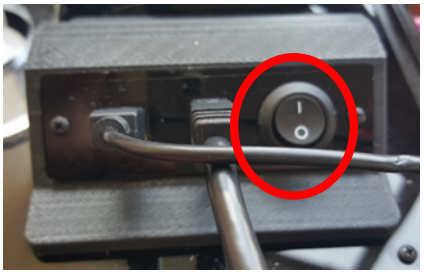
Sample Preparation

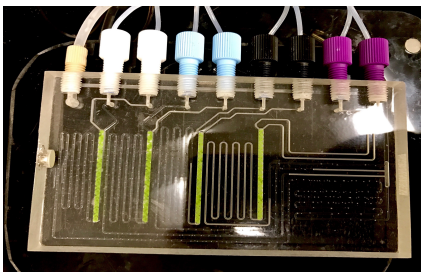
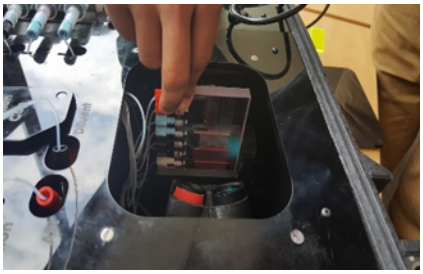
- For artesunate tests, probe and reference standards must be prepared **immediately** prior to testing
- For amodiaquine tests, probe and reference standards can be prepared **up to 3 days** prior to testing.

Materials
• Artesunate Reference Powder
• Amodiaquine Reference Powder
• Eosin Y
• 50 mg/mL Fluorescein + Luminol in DMSO
• 0.4 mg/mL hematin in 0.1 M NaOH
• Distilled water
• 0.1 M NaOH
• 50 mL conical tubes
• Serological pipettes (50 mL, 10 mL, 5 mL) and controller
Probe preparation
Amodiaquine Assay
1. Prepare 500 mL of 0.1 mM Eosin Y by weighing out 35 mg to 500 mL of distilled water.
Artesunate Assay
1. Prepare a 0.4 mg/mL hematin solution by weighing out 20 mg hematin and adding to 50 mL 0.1 M NaOH. Use PharmaChk instrument to sonicate solution for 3 minutes to fully dissolve hematin.
2. Add 5 mL of 0.4 mg/mL hematin solution to 45 mL 0.1 M NaOH in a 50 mL conical tube.
3. Add 80 µL of 50 mg/mL Fluorescein + Luminol solution to solution prepared in step 2. Mix solution.
Reference standard preparation
Amodiaquine Assay
1. Prepare a 0.027 mg/mL solution of amodiaquine in distilled water by weighing 27 mg of amodiaquine and adding to 1 L of water.
2. Prepared the 100% reference standard in a 50 mL conical by transferring 10 mL of the 0.027 mg/mL amodiaquine solution.
3. Prepare the 50% reference standard in a 50 mL conical tube by adding 5 mL of the 0.027 mg/mL solution to 5 mL of distilled water.
4. Prepare the 10% reference standard in a 50 mL conical tube by adding 1 mL of the 0.027 mg/mL solution to 9 mL of distilled water.
Artesunate Assay

1. Prepare a 2.0 mg/mL solution of artesunate in 0.1 M NaOH by weighing 34 mg of artesunate and adding to 17 mL 0.1 M NaOH. This is the 100% reference solution to be used in artesunate tests.
2. Prepare the 50% reference standard in a 50 mL conical tube by adding 5 mL of the 2.0 mg/mL artesunate solution to 5 mL 0.1 M NaOH.
3. Prepare the 10% reference standard in a 50 mL conical by adding 1 mL of the 2.0 mg/mL artesunate solution to 9 mL 0.1 M NaOH.
Loading syringes
1. Attach the labeled syringe needle to the appropriate syringe and uncap
2. Slowly draw up 10 ml of reagent into the appropriately labeled syringe
3. Remove any excess air from syringes.
4. Cap needle and detach from syringe

Testing Protocol

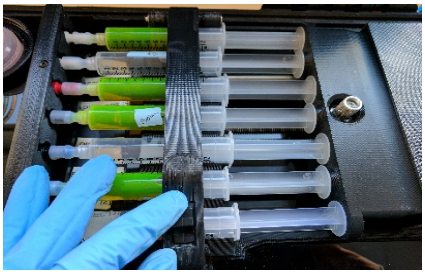
1. Plug in the power cable to the instrument	
2. Plug in two USB cables into the outlets near the power button	
3. Plug in the other ends of the two USB cables into the touchscreen laptop	
4. Turn on the instrument	

5. Open PharmaChk program on laptop and wait for start up	
Follow instructions on user interface to select API and Brand	
Follow instructions on user interface to set up testing cartridge. *If inserting a new cartridge, follow steps 6-8 below. Otherwise, press "Skip".*	
6. If inserting a new cartridge, connect tubing to cartridge by screwing in each tube into its corresponding input <u>NOTE</u> When the cartridge is placed upright with the inputs running down the left side, tube (1) will be connected to the top input, with subsequent inputs connected in the following order: (2), (3), (4), (6), (7), (8), (5), (9)	
7. Insert cartridge into cartridge nest with tube connections facing towards the inside of the device	
8. Replace cartridge lid and ensure it is securely closed	

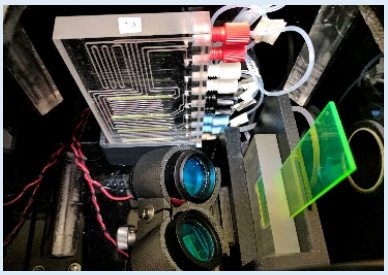
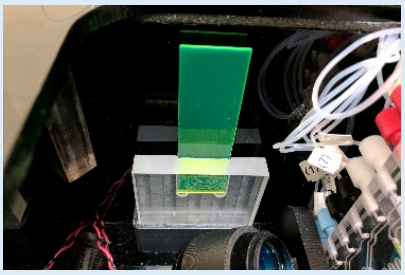
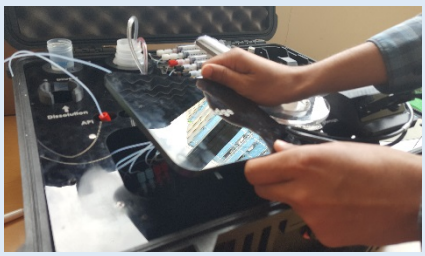
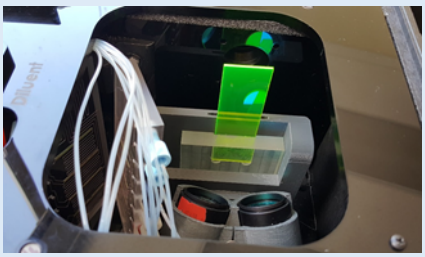
Follow instructions on user interface to set up reagent syringes.

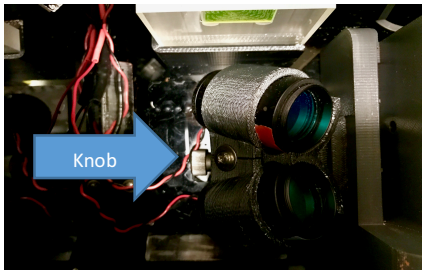
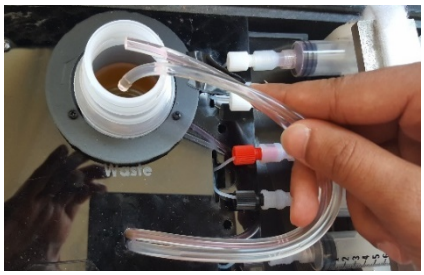
If inserting new syringes, press "Load" and follow steps 9-10 below. Otherwise press "Skip" if more than 1 mL of solution remains in each syringe.

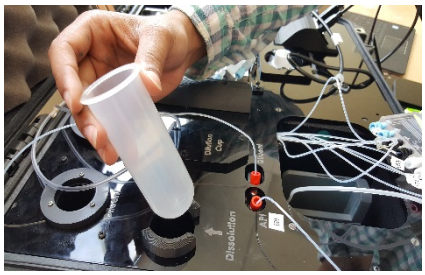
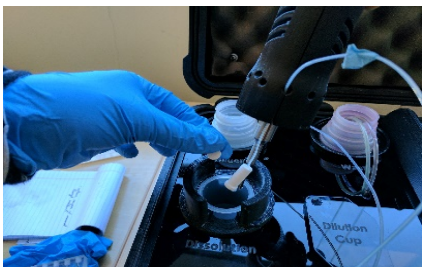
ARTESUNATE TESTING ONLY

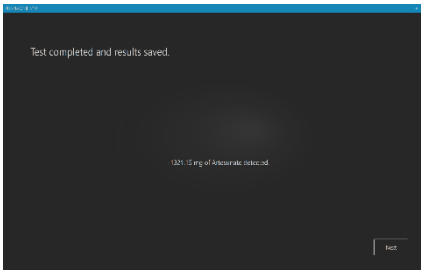
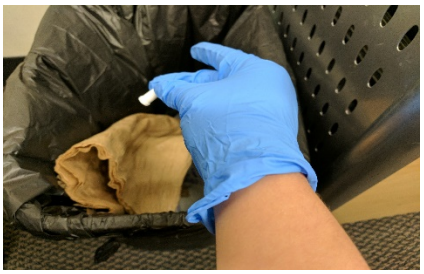
Put on safety goggles and gloves if performing a test on Artesunate	⚠ Artesunate testing requires the use of sodium hydroxide (NaOH), a basic chemical that is corrosive and can burn skin with prolonged exposure
9. Connect each syringe with the corresponding tube (color coded) by screwing the tip of the syringe into end of the tube	
10. Lay the syringe cradle bar across all syringes and secure latch	

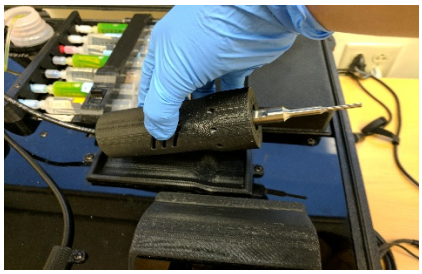
Follow instructions on user interface to proceed to the next step.

Follow steps 11-14 for AMODIAQUINE TESTING ONLY	
11. Open cartridge lid and ensure cartridge nest is empty NOTE If a cartridge is already in the cartridge nest, leave cartridge tubing connected, remove flat field slide from its location and place the cartridge in the slot where the flat field slide is stored	
12. Insert flat fielding cartridge into cartridge nest with the green slide touching the back wall of the cartridge nest NOTE Handle the flat fielding cartridge by the base and not by the green glass slide	
13. Replace cartridge lid and ensure it is securely closed	
Follow instructions on user interface	
14. Lift cartridge lid, remove flat field slide from cartridge nest and put back into flat field nest NOTE Handle the flat fielding cartridge by the base and not by the green glass slide	
Follow instructions on user interface to proceed to the next step	

15. If cartridge requires focus adjustment, turn the focus knob on cartridge nest until image is in focus, otherwise proceed to next step	
Follow instructions on user interface to proceed to the next step	
16. Ensure empty waste vessel is placed in opening labeled WASTE and tubing is inserted to bottom of vessel NOTE Empty waste into chemical waste receptacle if vessel is more than half full of liquid	
17. Insert diluent cup filled to top with distilled water	
18. Insert diluent tube into diluent cup NOTE Ensure the tube touches the bottom of the diluent vessel	

19. Fill dissolution vessel with 50 ml of solvent and insert into opening labeled DISSOLUTION Artesunate – insert 50ml SODIUM HYDROXIDE (NaOH) solvent Amodiaquine - insert 50 ml WATER solvent	
Press "Confirm" on user interface	
20. Insert API tube through small hole in base of the probe holder and feed all the way through to the other side up until the stopper	
21. Insert tip of API tubing into open end of dissolution filter	
22. Drop tablet into dissolution vessel and quickly proceed to next step.	
Press "Confirm" on the user interface	

23. Submerge sonication probe and dissolution filter into dissolution vessel, ensuring that API tubing is still inserted up to the stopper NOTE Never touch the tip of the sonicator when it has been turned on Never turn the sonicator on unless the tip is submerged in liquid	
Press "Confirm" on the user interface and then "Next"	
Press "Begin" to start test	
24. View test results and touch **Next** after testing is complete NOTE Do not exit the program or turn off the instrument while cleaning is still being performed	
25. Remove dissolution filter and throw in the trash	
26. Wipe down the sonicator probe	

27. Place the sonicator onto storage cradle	
28. Properly dispose of sample and solvent in dissolution vessel, and waste in waste vessel NOTE Dissolution vessel must be properly cleaned and dried before being used for further testing if reusing	
Follow instructions on the user interface to proceed *Press "Yes" to repeat a new test of the same API, starting again at step 6. Otherwise press "No" to proceed to system cleaning (refer to next section).*	

System Cleaning

Always perform full cleaning cycle

- before starting a test on a different API
- after two Amodiaquine tests have been completed
- once syringes are empty
- before taking a prolonged break or immediately after completing testing for the day

1. Disconnect each of the reference and probe syringes from its corresponding tubing and remove from syringe cradle
2. Connect seven syringes loaded with 10 ml of water to the tubing by screwing the tip of the syringe into end of the tube
3. Lay each syringe filled with water into the syringe cradle, place the cradle bar across all syringes and latch
4. Ensure the base of each syringe is vertically aligned and not overlapping the base with neighboring syringes
5. Confirm water syringes have been connected on laptop and wait for cycle to complete
6. Unlatch syringe cradle, disconnect each of the seven empty syringes from its corresponding tubing and remove from syringe cradle
7. Connect seven syringes loaded with 10 ml of air to the tubing by screwing the tip of the syringe into end of the tube
8. Lay each syringe filled with air into the syringe cradle, place the cradle bar across all syringes and latch
9. Ensure the base of each syringe is vertically aligned and not overlapping the base with neighboring syringes

10. Confirm air syringes have been connected on laptop and wait for cycle to complete
11. Unlatch syringe cradle, disconnect each of the seven empty syringes from its corresponding tubing and remove from syringe cradle
12. Repeat Full cleaning cycle: steps 2 - 11
13. Dispose of waste in waste cup

Waste Disposal

Waste disposal should be performed:

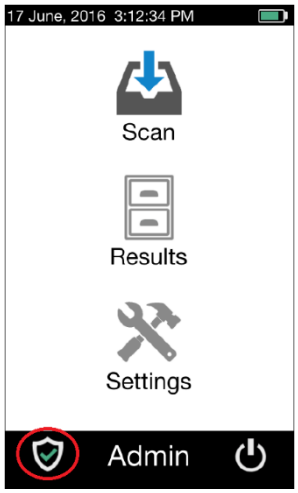
- after a full set of syringes have been pumped through the cartridge (e.g. reagents or water)
- at the end of the day

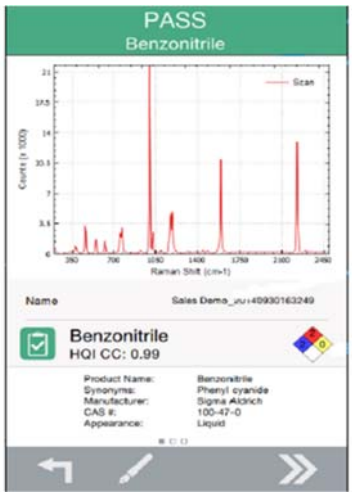
1. Put on safety glasses and gloves
2. Pour liquid from waste cup into designated hazardous chemical receptacle
3. Return waste cup into holder
4. Pour liquid from dissolution vessel into designated hazardous chemical receptacle
5. Dispose of empty dissolution vessel into trash or wash to reuse

Supplementary Annex 12 Progeny – Protocols

Overview of the operating procedures

After turning on the device and logging in, the instrument verification test is recommended prior to scanning materials. Performance verification is a daily test done to ensure that the instrument is performing within acceptable specification. The user press on shield icon on the left bottom on screen and select the standard material which and run the sample analysis. The given results were pass or fail. After a successful test, the user goes to "Scan" function which contained three analysis modes: application, batch and analyse modes. The progeny basically operates two modes- *Analyze* and *Application*.





On the analyse mode, the instrument compares the detected data to its "Master Library" of spectral profiles and then calculated a correlation coefficient (CC) value for each profile. The instrument identified the substance named in the spectral profile with the top match. Match or No Match will be returned as a result. It is most useful for identifying samples of unknown substances.

For the application mode, the instrument collected the spectral data using a specified collection of pre-set instrument settings and custom libraries which means the sample is compared only the *sub-library* of spectral profiles to calculate the correlation value. Pass or Fail will be returned as a result. It is useful for either identifying or verifying samples from known collections of substances.

Rigaku Progeny reference library features overview

To create a reference library spectra of the progeny, the user needs only one good spectrum of the sample. Processing by analyze mode the same operation as scanning a sample.

Once the spectrum was collected, the user chose to add in the master library or the sub-library with a specific sett-up. The user is able to include or update the sample's information.

Rigaku Progeny Library Spectra/Calibration/Troubleshooting Protocol

Generation/Sync results:

Sub-Libraries

- All library spectra generated are saved to the Master Library. For example, therefore pharmaceutical samples will be mixed with food spectra during normal analysis. Sub-libraries are used so the user can define what samples that are being samples and what sub-set of libraries to focus the device on.
    1.) From the main menu, press "Settings"
    2.) Press "Library"
    3.) Press the "Add Library Symbol" button on the bottom right hand of the screen.
    4.) Enter the desired name of the Sub-Library and press the check mark button
    5.) You created a new Sub-library.
    6.) To add previously acquired spectra, select the desired library
    7.) Press the "Add Spectra Symbol" button (looks like an EKG) on the bottom right of the screen
    8.) You can write the name of the spectra, or immediately press the check mark to scroll through the entire master library
    9.) Select one or multiple spectra by double pressing each selection and when done, press the check mark.
    10.) To generate new spectra, see protocol below:

Generating New Library Spectra

1.) Ensure the device is turned on and that proper sample holder/space is attached to the instrument
    a. For tablet, use the tablet holder that attaches to the spacer
    b. For blister pack samples, just use the spacer:
2.) Have the sample in the proper position in front of the sampling interface
3.) Press the "Scan" button in the main menu
4.) Press the "Analyze" Button
5.) Press "Arm Laser" to prepare the instrument for analysis
6.) Pres "Scan" on the instrument to complete the experiment

7.) Look at spectra and determine if suitable for library.

a. See if the spectra has sharp peaks, the baseline is fairly flat, and the signal is in the thousands (ideal, but lower ones acceptable if and only peaks are well defined, not just on big hump)

Figure 18. Analyze Scan Results Screen

8.) Press the "Add Library Button" if the spectra looks acceptable

9.) Type in the name of the sample in the "Enter Material Name" and once cone press the check mark

a. Include at least this information in the following order with a "_" in between each:

i. YearMonthDate (Ex. 20170927)

ii. Brand Name

iii. Active Ingredient(s)

iv. Batch Number

v. ***Optional*** User Initials to determine who made the library

10.) Add the spectra to the desired library

a. "Master Library" contains every library spectra that was collected by the instrument

b. Other results are user generated libraries no narrow down the samples you want to analyze known as a “sub-library”
    i. Each “sub-library” has defined experimental conditions that the user can set.

11.) The library spectra is ready for use.

Application Development Protocol

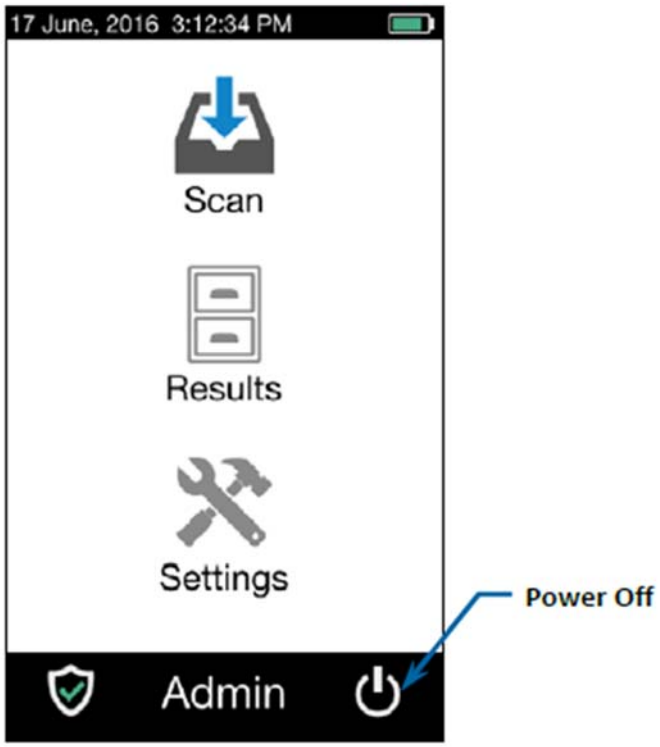
- Applications are used to in order for the user to pre-select a library spectra to find out if the experimental sample matches the library spectra. The device will look at other spectra in the master library, but only if the samples fails. The user can define in applications what the pass threshold for pass or failures to ensure a certain percentage of confidence. How to make an application:

1.) Press the “Settings” button from the main menu
2.) Press the “Applications” button
3.) Press the “Add Application Symbol” button on the bottom right of the screen
4.) Type in the name of the application and press the check mark
5.) Select the application you just named
6.) Adjust the parameters to desired settings
    a. For pharmaceutical analysis, most of the default parameters should work fine. You can select a sub-library your created specific to the types of samples you are analyzing. You can also adjust the “Pass Threshold” to define at which point a sample passes or fails based on the closeness of the match.
7.) Press the check mark when done
8.) Application should have Saved

Instrument Calibration Protocol

- Daily/Weekly Calibration (Performance Verification)

Figure 6. Progeny Main Screen with No Login



1.) Press the "Shield Symbol" on the bottom left hand corner of the main menu.
2.) Select "Performance Verification"
3.) Select the sample you have from the defined list (the one that came with the instrument is the best)
4.) Attach the correct sampling interface (use the vial holder for the benzonitrile sample)
5.) Press "Arm Laser" to prep the sample
6.) Press "Scan" when ready to conduct the experiment
7.) The Result window should pop up.
    - If pass, add comments if you would like by pressing the "Pen Symbol" at the bottom of the screen. Go to the home menu and conduct experiments.
    - If failure:
        - Restart the device and re-test

        - remove the battery after shutdown to ensure the device completely turns off
    - If failure again:
        - Conduct an instrument calibration

- Monthly/Every Couple Month Calibration (Instrument Calibration)
    1.) Press the "Shield Symbol" on the bottom left hand corner of the main menu.
    2.) Select "Instrument Calibration"
    3.) Select "Benzonitrile"
    4.) Attach the vial holder to the instrument and insert the benzonitrile vial.
    5.) Press "Arm Laser"
    6.) Press "Scan" when ready to conduct the experiment
    7.) The result window should pop up:
        - If pass, add comments if you would like by pressing the "Pen Symbol" at the bottom of the screen. Go to the home menu and conduct experiments.
        - If failure:
            - See Troubleshooting protocol

Trouble Shooting Protocol:

1.) Ensure the sample is properly secured or being held in front of the sampling interface or vial holder
    a. Minimize and potential ambient light from entering the device
    b. Hold the sample in one position and do not move
2.) Ensure the battery is more than 1/3 charged (just in case it is a power issue)
    a. You can charge and use the device at the same time using the instrument holder
3.) When in doubt, restart the device
    a. Remove the battery after shutdown to ensure the device completely turns off
4.) Conduct a performance verification to ensure it's not an instrument problem
    a. If the performance verification passes, most likely it is a sampling issue
5.) If the performance verification FAILS, perform an Instrument Calibration
6.) If the instrument calibration FAILS, restart the device and remove the battery
    a. Allow the instrument to sit without the battery for 5 minutes to ensure no charge remains in the instrument
7.) Perform another instrument calibration
8.) If it fails again, contact the experts

Sync Results to Computer:

1) Connect Progeny to USB port on PC with provided min-USB to USB cable.
2) Wait for PC to recognize the new USB connection
3) Type http://Progeny into the website browser.
4) Select and download the desired file name or all files.

The file would be in PDF form in the zipped file.

Progeny – Training

PRACTICES MEDICINES

LOMWRU Codes	Brand	API	Dosage	Manufacturer
G279 G352	Ciprofloxacin-DNA	Ciprofloxacin	500 mg	DNA Pharma, Vietnam
G113 G373 G399	Metronidazol	Metronidazole	250 mg	CBF Pharmaceutical Factory
G414 G491	Clarithro 500	Clarithromycin	500 mg	VIDIPHA, Vietnam
G313 G329 G431 G471	Erythro-500	Erythromycin	500 mg	Codupha-Lao Pharma Factory

G416 G494	Norfloxyl 400	Norfloxacin	400 mg	Bangkok Lab & Cosmetic
G339 G355 G377	Penicillin V	Penicillin V	400000 IU	Codupha-Lao Pharma Factory
G458 G493 G522	Roxithroxyl	Roxithromycin	150 mg	Bangkok Lab & Cosmetic

INTENSIVE TRAINING

Time spent: Approx. 1 - 2 hours including Practice

1. Showing the device: The device, along with the accessories, was shown to the inspectors with an explanation of its function.
2. Presentation: A handout including presentation slides (1 sheet) and SOP (1 sheet) was given to each inspector. Oral presentation given on:

   2.1. The intention and purpose of training and the technology used by the device:

   - All of the devices used in this study can be used to help in the search for poor quality medicines
   - Progeny uses RAMAN technology to examine medicines and decide if they are genuine
   - The device should be able to distinguish genuine from fake medicines (stated API vs no API) and but has variable ability to find substandard medicines
   - The device should be able to be used on-site during an inspection.

2.2. Device composition:

- Device structure: Main screen, use of touchscreen for navigation and typing.
- Extra equipment: Tablet holder, cones for packaging and vial holder for calibration.

2.3. Testing: The inspectors were given time to practice with the pre-prepared practice medicines. As they practised, they were talked through:

- How to log-in to the device
- How to calibrate the device
- Operation & Interpretation: basic introduction to Raman spectroscopy (1 slide) plus how to interpret the result. Each inspector tested 3 to 5 different brands.

(*A set of practice medicines were assembled and used in training; none of the brands or APIs in the practice set were used in either the mock pharmacy or sample set testing)

- Inspectors were advised about the two modes of testing:
  - 2.3.1. Analyse mode: the device obtains a scan of the sample and then compares to all entries in the reference library of thedevice. Result given as ‘Match’ or ‘No Match’ (‘Match’ states the closest matching spectrum in the reference library to the scanned sample spectrum; ‘no match’ indicates that no reference library spectrum matches the scanned sample spectrum with a correlation coefficient > 0.9).
  - 2.3.2. Application mode: prior to scanning the sample, the user selects the reference library entry with which the device should compare the sample spectrum. Result given as ‘Pass’ (sample spectrum matches selected reference spectrum with correlation coefficient > 0.9) or ‘Fail’ (sample spectrum does not match selected reference spectrum with correlation coefficient > 0.9).

2.4. Data extraction: written instructions on how to upload data from the device to a computer were provided but no verbal training given. No inspectors practised this.

RUDIMENTARY TRAINING

Time spent: Approx. 5 - 10 minutes

1. The device, along with the accessories, was shown to the inspectors with an explanation of its function.
2. Practice testing: Each inspector was given the opportunity to test1 to 3 different brands from the practice medicine set using both analysis modes: 'Analyse' and 'Application'. (*A set of practice medicines were assembled and used in training; none of the brands or APIs in the practice set were used in either the mock pharmacy or sample set testing)

Common Questions asked by the inspectors to trainers during training:

- Is it possible to scan medicines in other dosage forms (e.g. paste, cream).
- Can the device scan through yellow-brown glass or bottle?
- What is the difference between Analyze and Application mode?
- How accurate and reliable are the reference library entries?

Other comments:

- Progeny is quite a big, heavy device with a hard-to-press touchscreen.
- Analysis time feels long.
- It is difficult to put the tablet in the tablet holder.

Progeny – Quick guides

Quick guide of operating procedures used in the field evaluation

Power on the Progeny, then log in with an administrator or default account. Run a performance verification as part of the daily performance qualification to ensure that the instrument is performing within acceptable specifications.

Performance qualification

1) From main screen, select (**Calibration**) from the left of the action bar to display the "Select Method" screen with the calibration options.
2) Select "Performance Verification" to display the verification screen with a list of the calibration samples.
3) Choose the "Benzonitrile" material from the list to display a confirmation screen.
4) Place the benzonitrile standard into a vial cone and place to the Progeny.
5) Select "Arm Laser" soft key to display the "Performance Verification" scan screen.
6) Select the "Scan" soft key to start the sample-analysis cycle.
7) If the result is "Pass", select "cancel/back" to return to the main screen.
8) If "Fail", calibrate the instrument.

Performing Scans

1. **Scanning with *Analyze***

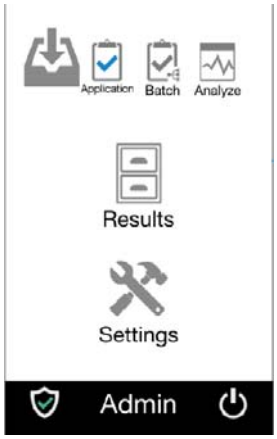
    1) From main screen, select "Scan" to display the scan options.
    2) Select "Analyze" to display the analyse confirmation screen with the laser warning.
    3) Select "OK/Arm Laser"
    4) Place the sample in the spacer
        a. If sample is a tablet, place with the tablet holder
        b. If scan through packaging, place with the nose cone.
    5) Select "Scan" to start the sample analysis.
    6) When the sample analysis completes the scan results screen displays as Match or No Match.
    7) Change the file name of the sample test.

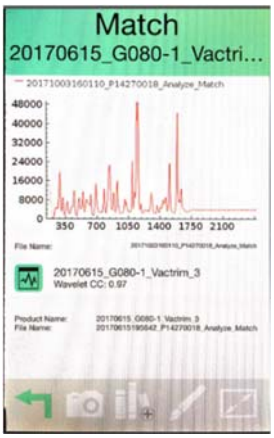
    *Optional: press the camera icon to take a picture of the sample; press the books with plus icons to add the current spectrum to a library.

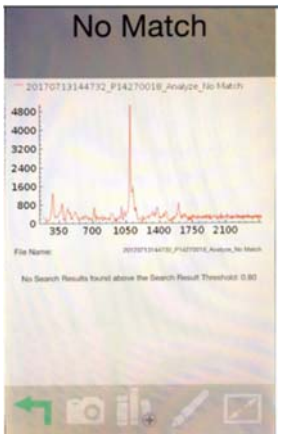
2. **Scanning with *Application***

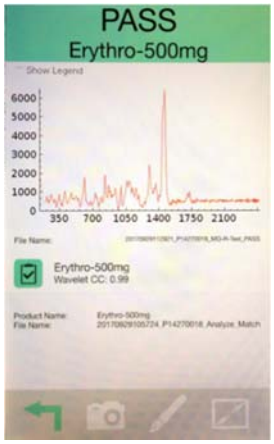
‘Application’ mode was selected when the initial scan of the sample in ‘analyse’ mode displayed as no match or matched with the wrong brand name or material.

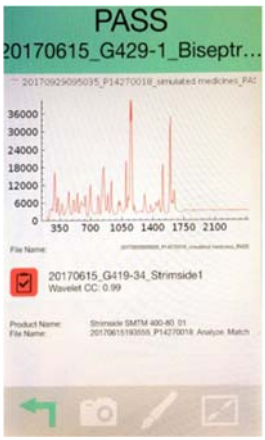
1) From main screen, select “Scan” to display the scan options.
2) Select “Application” then select he desired application.
3) Select the brand name of the sample to test from the list of material.
4) Select “OK/Arm Laser”
5) Place the sample in the spacer
    a. If sample is a tablet, place with the tablet holder
    b. If scan through packaging, place with the nose cone.
6) Select “Scan” to start the sample analysis.
7) When the sample analysis completes the scan results screen displays as Pass or Fail.
8) Change the file name of the sample test.

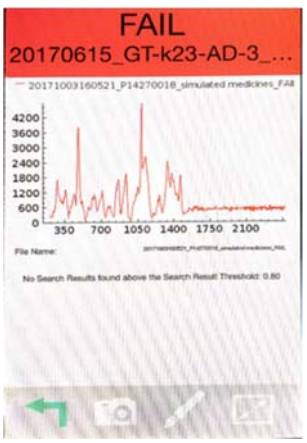












Supplementary Annex 13. Rapid diagnostic test – Protocols

Artemether Dipstick Test

Materials provided in the Artemether Dipstick Test

Lot number	Item	Quantity
	Artemether Dipstick	1
	Dropper	1
	Desiccant	1
	Instructions	1

It is recommended the above items be stored at 4° C.

Use by: 12 months after production.

1. Extraction

Crush the drug tablet in a folded piece of paper to a fine powder. Then transfer the powder to ≥95% alcohol to produce a content of 2 mg/ml based on the labelled content of the commercial drug and mix well (See Table 1). Discard the paper. Do not reuse the paper for the next test to avoid contamination. For artemether soft capsules and artemether injection, directly dissolve the drug to ≥95% alcohol to produce a content of 2 mg/ml and shake well.

2. Dilution

Using the dropper, to transfer one drop of the solution prepared in step one, into 5ml water in a cup. The diluted concentration is approximately 10 μg/ml of Artemether in theory , Then transfer one drop of the 10 μg/ml solution to 5ml water in another cup. The theoretical concentration is approximately 50 ng/ml (The indicator range is 50 ng/mL for artemether)

Table 1. Sample Extraction

Content of Artemether (mg/tablet) (mg/capsule) (mg/tube)	Volume of Alcohol (mL)	Theoretical Concentration (mg/mL)
10	5	2
20	10	2
50	25	2
80	40	2

3. Dipstick analysis

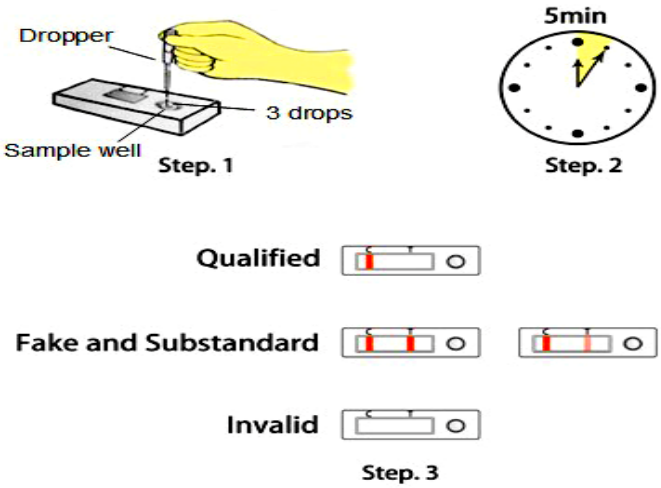
Rinse the dropper in 95% alcohol at least 3 times to avoid contamination. Using the dropper to add 3 drops of the 50 ng/ml diluted drug into the sample well of the dipstick. The color of the test and control line should be visually observed within 15 minutes (See Figure 1).

4. Result interpretation

If the test line shows no color, it means the drug is qualified. If the test line shows dark or faint color, it means that the drug is fake or substandard. We suggest that the drug needs to be tested at a higher concentration to confirm the finding.

Rinse the dropper in 95% alcohol at least 3 times to avoid contamination. Using the dropper to add 3 drops of 10 μg/ml diluted drug into the sample well of the dipstick. The color of the test and control line should be visually observed within 5 minutes (See Figure 1).

If the test line shows no color, it means the drug is substandard. If the test line shows color, it means the drug is fake.



Artesunate Dipstick Test

Materials provided in the Artesunate Dipstick Test

Lot number	Item	Quantity
	Artesunate Dipstick	1
	Dropper	1
	Desiccant	1
	Instructions	1

It is recommended the above items be stored at 4° C.

Use by: 12 months after production.

5. Extraction

Crush the drug tablet in a folded piece of paper to a fine powder. Then transfer the powder to ≥95% alcohol to produce a content of 2 mg/ml based on the labelled content of the commercial drug and mix well (See Table 1). Discard the paper. Do not reuse the paper for the next test to avoid contamination. For artesunate injection, directly dissolve the drug to ≥95% alcohol to produce a content of 2 mg/ml and shake well.

6. Dilution

Using the dropper, to transfer one drop of the solution prepared in step one, into 5 ml water in a cup. The diluted concentration is approximately 10 μg/ml of Artesunate in theory.Then transfer one drop of the 10 μg/ml solution to 5ml water in another cup. The theoretical concentration is approximately 50 ng/ml (The indicator range is 50 ng/mL for artesunater).

Table 1. Sample Extraction

Content of Artesunate (mg/tablet) (mg/tube)	Volume of Alcohol (mL)	Theoretical Concentration (mg/mL)
10	5	2
20	10	2
50	25	2
80	40	2

7. Dipstick analysis

Rinse the dropper in 95% alcohol at least 3 times to avoid contamination. Using the dropper to add 3 drops of the 50 ng/ml dilute drug into the sample well of the dipstick. The color of the test and control line should be visually observed within 5 minutes (See Figure 1).

8. Result interpretation

If the test line shows no color, it means the drug is qualified. If the test line shows dark or faint color, it means that the drug is fake or substandard. We suggest that the drug needs to be tested at a higher concentration to confirm the finding.

Rinse the dropper in 95% alcohol at least 3 times to avoid contamination. Using the dropper to add 3 drops of the 10μg/ml diluted drug into the sample well of the dipstick. The color of the test and control line should be visually observed within 5 minutes (See Figure 1).

If the test line shows color, it means the drug is fake. If the test line shows no color, it means the drug is substandard.

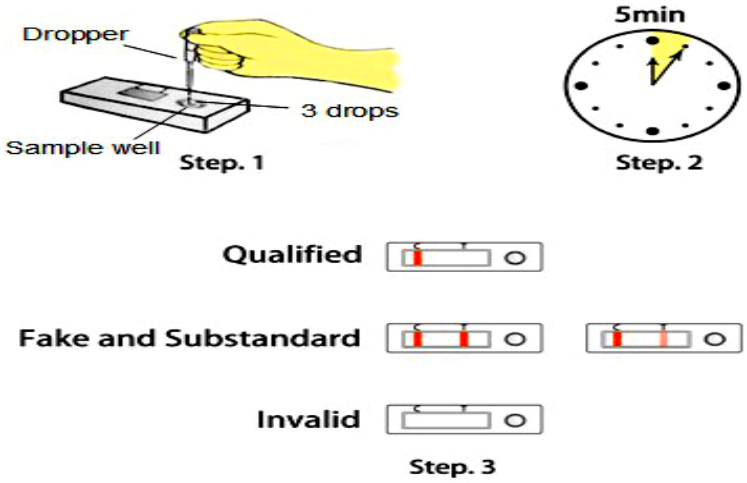


Figure 1. A schematic of the assay steps.

Dihydroartemisinin Dipstick Test

Materials provided in the Artesunate Dipstick Test

Lot number	Item	Quantity
	Dihydroartemisinin Dipstick	1
	Dropper	1
	Desiccant	1
	Instructions	1

It is recommended the above items be stored at 4° C.

Use by: 12 months after production.

9. Extraction

Crush the drug tablet in a folded piece of paper to a fine powder. Then transfer the powder to ≥95% alcohol to produce a content of 2 mg/ml based on the labelled content of the commercial drug and mix well. Discard the paper. Do not reuse the paper for the next test to avoid contamination. For injection, directly dissolve the drug to ≥95% alcohol to produce a content of 2 mg/ml and shake well.

10. Dilution

Using the dropper, to transfer one drop of the solution prepared in step one, into 2.5 ml water in a cup. The theoretical concentration is approximately 20μg/ml. Then transfer one drop of the 20 μg/ml solution to 2.5ml water in another cup. The theoretical concentration is approximately 200 ng/ml (The indicator range is 200 ng/mL for dihydroartemisinin).

11. Dipstick analysis

Rinse the dropper in 95% alcohol at least 3 times to avoid contamination. Using the dropper to add 3 drops of the 200 ng/ml diluted drug (theoretical concentration) into the sample well of the dipstick. The color of the test and control line should be visually observed within 5 minutes (See Figure 1).

12. Result interpretation

If the test line shows no color, it means the drug is qualified. If the test line shows dark or faint color, it means that the drug is fake or substandard. We suggest that the drug needs to be tested at a higher concentration to confirm the finding.

Rinse the dropper in 95% alcohol at least 3 times to avoid contamination. Using the dropper to add 3 drops of 20 μg/ml drug (theoretical concentration) into the sample well of

the dipstick. The color of the test and control line should be visually observed within 5 minutes (See Figure 1).

If the test line shows color, it means the drug is fake. If the test line shows no color, it means the drug is substandard.

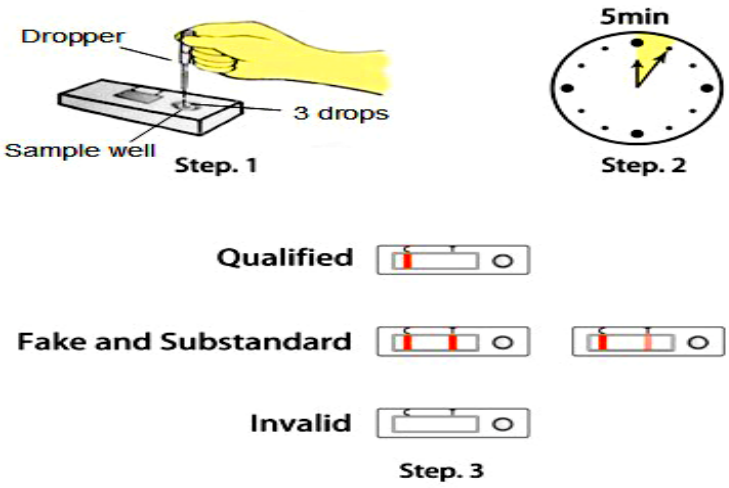
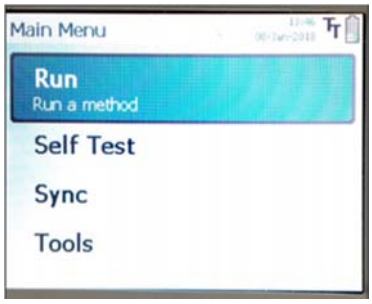


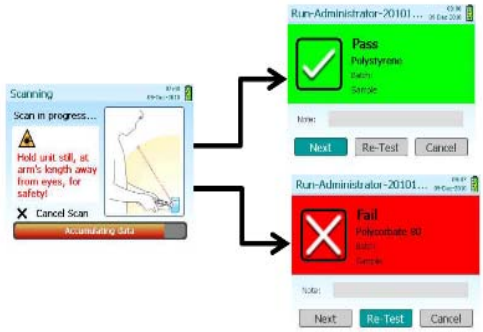
Figure 1. A schematic of the assay steps.

Supplementary Annex 14. Truscan RM – Protocols

Overview of the operating procedures

After turning on the device, the user logs into their credentials and goes through a self-test daily to ensure optimal performance. The user selects “Self-Test” and places the standard vial into the vial holder; after a few seconds the screen produces a pass or a fail. After a successful test, the user goes to the “Run” function, selects the library spectra defined as ‘Methods’ that they would like to compare to, and the user inputs the filename of the sample. To sampling tablets out of the packaging, the user placed the tablet into the tablet holder and a nose cone for through packaging. The user would then started scan and “Pass” or “Fail” would displayed as results.





TruScan reference library features overview

When generating reference library spectra on the TruScan, the user would collect one good spectrum of the sample. Once the spectrum is collected, known as signatures by the company/instrument, they would be in inactive mode and must be activate on the computer. The software installation is required. When the user is ready to connect the instrument to the

computer (via Ethernet cable), by sync test in network diagnostics function. After the successful sync test, access to the web browser with the specific IP address and activate the signatures. Add the activated signatures to the library, known as method or create a new method. Signatures and methods are able to be edited afterward.

Thermo Truscan RM Library Spectra/Calibration/Troubleshooting Protocol

Generation/Sync results:

Device Sign In to the Main Menu (assuming that has not been changed)

- Username: Administrator
- Password: default

Generating Libraries (defined as Methods)

1. **Generating Signatures on the TruScan**
    i. From the main menu, select "Tools"
    ii. Select "Acquire Signature"
    iii. Position the sample in front of the sampling interface
        - Using the vial holder for small vials
        - Using the tablet holder for pills and tablets
        - Using the nose cone for bulky samples
    iv. Select "Start Scan"
    v. After the analysis, confirm the spectra looks good
        - Sharp peaks, flat baseline, no big humps
    vi. Highlight and select the "Name" row.
    vii. Include at least this information in the following order with a "-" in between each:
        - YearMonthDate (Ex. 20170927)
        - Brand Name
        - Active Ingredient(s)
        - Batch Number
        - ***Optional*** User Initials to determine who made the library

viii. After the name has of signature has been written, highlight and select "Save"

ix. Repeat the steps to collect other signatures for other samples

2. <u>Uploading the Signatures to the computer</u>

b. Currently the software to process the signatures to make libraries is on the ASUS laptop (LOMWRU-17)

i. Ensure the TruScan is on and that you are signed on into the main menu

ii. Open the bottom cover of the TruScan, but DO NOT open the compartment with the library

iii. Insert the mini-USD to ethernet cable adapter to the TruScan

1. The connection is just above the battery compartment

iv. Connect an ethernet cable from the adapter to the computer

v. Access "Internet Explorer" on the computer

vi. On the "Address" bar, type in the following IP address if it has not been saved: (192.168.99.100)

vii. Sign in to the "Web Admin Login" with the same credentials as the device sign in

viii. Select and press the "Signatures" tab on the browser

ix. In the dropdown box (top left corner of the browser under "Methods" and "Signatures"), select "Inactive Signatures

x. Select the inactive signatures that you would like to use in the eventual library and then press "Activate Selected"

xi. To generate a new library entry, select "Add Method"

1. If you just want to add signatures to an old method, just select the old method from the "Methods" menu and add them

xii. Fill in the "Method Name" line

xiii. Include at least this information in the following order with a "-" in between each:

1. YearMonthDate (Ex. 20170927)
2. Brand Name
3. Active Ingredient(s)
4. Batch Number

5. ***Optional*** User Initials to determine who made the library

xiv. At the bottom of the webpage in the "Unattahced Signatures" box, highlight the spectra(s) you would like to use for the method

xv. Click the "←" button and this should add the signatures to the method.

1. ***You can add multiple spectra to on method***
    a. Ex. Different batches of the same sample

xvi. Once selected the appropriate signatures, click "Add Method" button on the bottom

xvii. To ensure the method has been appropriately uploaded, go back to the TruScan

1. From the main menu, select "Run"
2. Highlight and select method
3. Ensure the method you created in the computer browser is there

xviii. Un plug the adapters and cables and you should be ready to go.

Calibration:

- Daily/Weekly Calibration (Self Test)

1. From the main menu, select "Self Test"
2. Attach the vial holder to the sample interface and insert the polystyrene sample from the case into the holder
    - Ensure the label on the sample is placed on the opposite side of the instrument sample interface/LCD screen
3. Highlight the sample ID, hit enter, and type in the following information:
    - Include at least this information in the following order with a "-" in between each:
        - YearMonthDate (Ex. 20170927)
        - User Initials to determine who made the calibration
4. Highlight "Start Test" and hit enter

5. The Result window should pop up.
    - If pass, go to the home menu and conduct experiments.
    - If failure:
        - Repeat the test
        - If fails again, restart the device and re-test
            - remove the battery after shutdown to ensure the device completely turns off
        - If failure again:
            - Conduct an instrument certification

- <u>Annual Calibration (Instrument Certification)</u>
    - This certification calibrates the instrument up factory grade specifications, only needs to be done once a year to achieve "Good Manufacturing Practice

1. From the main menu, select "Tools"
2. Highlight and select "Instrument Certification"
3. Attach the vial holder to the sample interface and insert the polystyrene sample from the case into the holder
    - Ensure the label on the sample is placed on the opposite side of the instrument sample interface/LCD screen
4. Highlight the sample ID, hit enter, and type in the following information:
    i. Include at least this information in the following order with a "-" in between each:
        1. YearMonthDate (Ex. 20170927)
        2. Sample Initials (PS)
        3. User Initials to determine who made the calibration

b. Highlight “Start Test” and hit enter
c. Replace the polystyrene sample with a vial of cyclohexane
d. Highlight the sample ID, hit enter, and type in the following information:
    i. Include at least this information in the following order with a “-” in between each:
        1. YearMonthDate (Ex. 20170927)
        2. Sample Initials (CH)
        3. User Initials to determine who made the calibration
e. Highlight “Start Test” and hit enter
f. Replace the cyclohexane sample with a vial of acetaminophen
g. Highlight the sample ID, hit enter, and type in the following information:
    i. Include at least this information in the following order with a “-” in between each:
        1. YearMonthDate (Ex. 20170927)
        2. Sample Initials (ACET)
        3. User Initials to determine who made the calibration
h. Highlight “Start Test” and hit enter
i. The Result window should pop up.
    i. If pass, go to the home menu and conduct experiments.
    ii. If failure:
        1. Consult troubleshooting protocol

Trouble Shooting Protocol:

1. Ensure the sample is properly secured or being held in front of the sampling interface or vial holder
    a. Minimize and potential ambient light from entering the device
    b. Hold the sample in one position and do not move
2. Ensure the battery is more than 1/3 charged (just in case it is a power issue)
    a. You can charge and use the device at the same time using the instrument holder
3. When in doubt, restart the device
    a. Remove the battery after shutdown to ensure the device completely turns off
4. Conduct a Self Test to ensure it's not an instrument problem
    a. If the self test passes, most likely it is a sampling issue
5. If the self test FAILS, perform an Instrument Certification
6. If the instrument certification FAILS, restart the device and remove the battery
    a. Allow the instrument to sit without the battery for 5 minutes to ensure no charge remains in the instrument
7. Perform another instrument certification
8. If it fails again, contact the experts

Downloading the Thermo TruScan Software to a Computer

- The instruction manual that comes with the software is descriptive to set the software for the computer, just a bit out of order for my tastes, so below I have a list and order you should get for setting the instrument and software up.
    - Setting up the TurScan RM for the network (since you are using an ethernet cable)
        1. Login to the analyzer:
        2. Select Tools > press the Enter key > System Settings > press the Enter key.
        3. Select Network > press the Enter key > select Use DHCP > use the arrow key to set
        4. Use DHCP to No.
        5. Select IP Address > press the Enter key. Using the keypad, enter 192.168.99.100,
        6. Select Done.
        7. In the Netmask field, enter 255.255.255.0.
        8. Delete values in the Subnet, Gateway, and DNS fields.
        9. Press the Esc key and Save the settings.

10. Press the Esc key again to return to the Main menu.

- Setting the Computer for the TruScan network (windows 7 or XP ***Pro***)
    1. From Control Panel, select Network and Sharing Center
    2. Select Change adapter settings.
    3. Select Local Area Network. Right click for Properties.
    4. Select Internet Protocol Version 4
    5. If this network card will be used exclusively to connect to the TruScan RM analyzer, select the General tab > select Use the following IP address > set the IP address to 192.168.99.99. The subnet mask field will self-populate (255.255.255.0). Leave all other fields blank.
    6. Click okay
- Opening the Firewall to the TruScan
    1. On a designated sync server, open Windows Firewall settings by clicking Start > Control Panel.
    2. Double-click Windows Firewall.
    3. If Windows Firewall is currently turned OFF, you may skip the rest of this procedure. If Windows Firewall is turned ON, click the Exceptions tab, and then click Add Port.
    4. In the Name field, enter a descriptive name (we recommend TruScanSyncServer), and enter 8083 in the Port Number box. Click OK.
    5. Repeat step 3 and step 4 until ports 8083, 8084, 8085, 8086, 8087, 8088, 8089, 8090, 8091, and 8092 have each been added. You will add a total of 10 ports.
    6. Click OK to complete the settings.
- Setting up software to export data from the TruScan RM to the computer
    1. Ensure the TruScan is on and that you are signed on into the main menu
    2. Open the bottom cover of the TruScan, but DO NOT open the compartment with the library
    3. Insert the mini-USD to ethernet cable adapter to the TruScan
        - The connection is just above the battery compartment
    4. Connect an ethernet cable from the adapter to the computer
    5. Access “Internet Explorer” on the computer
    6. On the “Address” bar, type in the following IP address if it has not been saved: (192.168.99.100)
    7. Sign in to the “Web Admin Login” with the same credentials as the device sign in
    8. Click the Archives tab
    9. Click Download the SyncServer Installation Kit.
    10. In the File Download - Security Warning dialog, click Run.
    11. In the TruScan SyncServer Setup Wizard, click Next.
    12. Select an Installation folder > click Next.

13. In the Config Settings dialog, set path folders > click Continue.
14. Let the installer complete, including the novaPDF 7 printer setup
15. In the Installation Complete dialog, click Close.
16. Go to Control Panel > Devices and Printers.
17. Go to novaPDF Properties > Advanced tab.
18. Select Print directly to the printer. Click Apply, then click OK.

- Run a Sync Test to ensure proper connectivity between the TruScan and Computer
    1. Form the main menu of the TruScan, Select Tools > press the Enter key > select System Settings > press the Enter key.
    2. Select Network > press the Enter key > select Diagnostics > press the Enter key.
    3. Select Sync Test > press the Enter key.
    4. If the TruScan passes, you should be all set
        - If failure, look again through the protocol above.
            - Also reference the TruScan manual.
            - Keep in mind, home editions of Microsoft Windows will not work, windows 7 an XP should work (Pro Only)

Sync results:

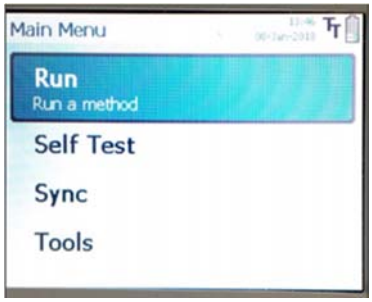
1. Connect the TruScan to the computer via Ethernet cable.
2. In main screen of device, select sync then go.
3. When it completely synced, the items to send would be 0.
4. The folder located in the archive folder where the software was installed.
5. The folder named by the date of synchronization and the files would be in PDF form.

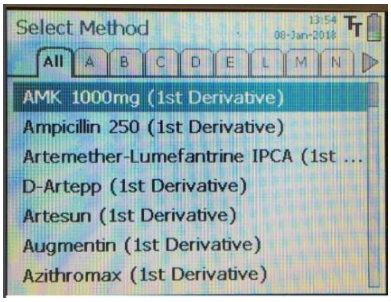
Truscan RM – Quick guides

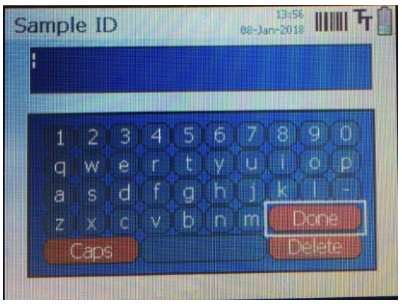
Quick guide of operating procedures used in the field evaluation

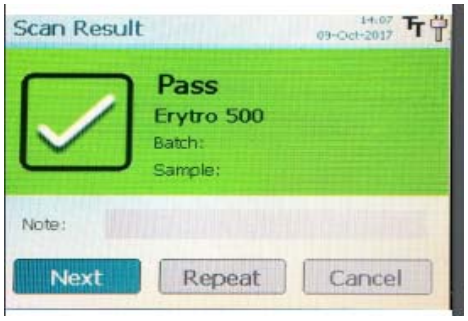
1. Power on the TruScan on power up unit and wait until the device completely initializes the database.
2. Press the key icon and select the username and enter the password.
3. From main screen, select “Self-Test” to calibrate.
4. Attach the vial holder and insert the test standard.
5. Name the sample ID (optional)
6. Press “Start Test” and “Pass” or “Fail” screen appear and return to the main menu.
7. Retest again if it fails.
8. In the main screen, highlight and press “Run”.
9. Select “Method” which the sample would compares.
10. Enter the sample ID.

11. Place the sample material in position.
12. Select “Start Run” to analyse.
13. The analysis completes when the “Pass” or “Fail” appears.









Truscan RM - Training

LOMWRU Codes	Brand	API	Dosage	Manufacturer
G279 G352	Ciprofloxacin-DNA	Ciprofloxacin	500 mg	DNA Pharma, Vietnam
G113 G373 G399	Metronidazol	Metronidazole	250 mg	CBF Pharmaceutical Factory
G414 G491	Clarithro 500	Clarithromycin	500 mg	VIDIPHA, Vietnam
G313 G329 G431 G471	Erythro-500	Erythromycin	500 mg	Codupha-Lao Pharma Factory
G416 G494	Norfloxyl 400	Norfloxacin	400 mg	Bangkok Lab & Cosmetic
G339 G355 G377	Penicillin V	Penicillin V	400000 IU	Codupha-Lao Pharma Factory
G458 G493 G522	Roxithroxyl	Roxithromycin	150 mg	Bangkok Lab & Cosmetic

INTENSIVE TRAINING

Time spent: Approx. 1 - 2 hours including Practice

1. Introducing the device: The device, along with accessories, was shown to the inspector and a brief description given of its function.
2. Presentation: The inspector was given a handout with the presentation slides (1 page) and SOP (1 page). Presentation:
   2.1. Overview of purpose of training and device:
   - All of the devices in the study can be used to help in the search for poor quality medicines

- TruScan uses RAMAN spectroscopy to examine medicines and decide if they are genuine
- They should all be able to distinguish genuine from fake medicines (stated API vs no API) and have variable ability to find substandard medicines
- All of them should be able to be used on-site during an inspection.

2.2. Device structure:

- Device: Main screen, using buttons to navigate for control and typing.
- Extra equipment: Tablet holder, cones for packaging and vial holder for calibration.

2.3. Processing: opportunity for inspector to practise with practice medicines provided: each inspector tested 3 to 5 different brands. While practising, they were talked through:

- Logging into the device
- How to calibrate
- Operation: brief overview of the chemistry underlying Raman spectroscopy (one slide)

(*Practice medicines were assembled from APIs and brands which were not stocked in the mock pharmacy or used in the sample sets)

- Result: simple interpretation (Pass/Fail) with top matches if there are any.

2.4. Data extraction: Inspectors were given written instructions on how to upload data from the device to a computer, but had no verbal training in this and did not practice the procedure.

RUDIMENTARY TRAINING

Time spent: Approx. 5 - 10 minutes

1. Introducing the device: The device, along with accessories, was shown to the inspector and a brief description given of its function.
2. The written 'quick start operating guide' was provided alongside the device.

Practice: Each inspector have tested 1 to 3 different brands from the practice medicine set (*Practice medicines were assembled from APIs and brands which were not stocked in the mock pharmacy or used in the sample sets)

Common questions asked by inspectors to trainer during training:

- Is it possible to scan medicines in other dosage forms (e.g. paste, cream)?
- How accurate and reliable are the reference library entries in the device?

Other comments:

- TruScan is quite a big and heavy device.
- It takes quite a long time to perform the analysis and has many set-up steps .
- It is difficult to change the tablet holder.

Supplementary Annex 15. UPLC confirmatory methods protocols

Active Ingredient(s)	Mobile Phase A	Gradient	Detector	Column Type	Flow Rate (mL/min)
Amoxicillin/ Clavulanic Acid	Water: 10 mM NaH_2PO_4, adjust with H_3PO_4 or 10 n NaOH to pH 4.4	Isocratic: 98% A, 2% B	220 nm (both APIs)	X	0.450
Artemether	Water: 10 mM NaH_2PO_4, adjust with H3PO4 to pH 3.0	Isocratic: 35% A, 65% B	210 nm	X	0.500
Artesunate	Water: KH_2PO_4, 10 mM, pH 3.0	Isocratic:50% A, 50% B	215 nm	X	0.500
Azithromycin	Water: KH_2PO_4, 33 mM, pH 8.5	Isocratic:20% A, 80% B	220 nm	X	0.500
Dihydroartemisinin	Water: 10 mM KH_2PO_4, adjust with H3PO4 to pH 3.0	Isocratic:45% A, 55% B	210 nm	X	0.500
Lumefantrine	Water: 10 mM NaH_2PO_4, adjust with H_3PO_4 to pH 3.0	Isocratic: 25% A, 75% B	300 nm	X	0.500
Ofloxacin	Water: 10 mM KH_2PO_4, adjust with H_3PO_4 to pH 3.0	Isocratic: 90% A, 10% B	294 nm	Y	0.500
Piperaquine	Water: 50 mM perchlorate, adjust to pH 2.0 - 2.1 with 1 N HCl	Gradient: 0 min 95% A/5% B; 0.2 min 95% A/5% B; 2.0 min 20%A/80%B; 2.25 min 95% A/5% B; 2.5 min 95% A/5% B	240 nm	Y	0.500
Sulfamethoxazole/ Trimethoprim	Water: with 0.1% Triethylamine adjust tp pH 5.9 with Acetic Acid/0.2 N NaOH	Isocratic:82% A, 18% B	270 nm (SM); 240 nm (TM)	X	0.500

X = C18: Phenomenex Luna Omega 1.6 µm C18 100A, 2.1x100 mm (PN: 00D-4742-AN)

Y = C18: Waters Cortecs C18 2.7 µm 100A, 2.1x50 mm (PN:186007365)

For all methods: Mobile Phase B is Acetonitrile; Column Temperature is 40°C; Injection Volume is 2.00 µL

Summary of changes made to adapt HPLC methods to UPLC

Overview

Pharmacopeial methods utilizing HPLC were adapted for UPLC primarily by using columns with smaller particle sizes and dimensions. This resulted in lower flow rates, smaller injection volumes and significantly shortened cycle times, while maintaining the required quality of separations. With the exception of sulfamethoxazole and trimethoprim, the C18 column chemistry specified in the pharmacopeial methods was used. Separations by UPLC provided the additional benefit of significant reductions in solvent use.

Pharmacopeial protocols called for isocratic elution for all actives except artemether/lumefantrine. The UPLC methods used isocratic separations for all adapted pharmacopeial methods. Proportions of mobile phases A and B were modified to improve separations and reduce cycle times. Unless noted below, mobile phases and detection wavelengths were the same or modified slightly. When detection wavelengths were altered, two actives with different absorbance spectra were being analyzed (e.g. sulfamethoxazole and trimethoprim), and the changes improved measurements.

In most instances the solvents used for extractions were the same as used in the pharmacopeial methods. When these were altered, it simplified the solvents while ensuring the solubility of the active ingredients. Whereas pharmacopeial methods often specify the extraction of multiple tablets, in this study samples were analyzed on a per tablet basis, often sampling a fraction of the ground tablet.

A pharmacopeial method was not available for dihydroartemisinin/piperaquine and an HPLC method from the literature was adapted as described below.

Comments on Specific Methods

The following provides references to pharmacopeial methods that formed the basis of the adapted methods and highlights adaptations of significance.

1. Amoxicillin and Clavulanate
    a. The analysis of Amoxicillin and Clavulanate was adapted from the USP Monographs, 2017, pp 2792-3. The NaH_2PO_4 buffer was reduced from 65mM to 10 mM.
2. Artemether and Lumefantrine
    a. The analysis of artemether and lumefantrine was adapted from The Int. Pharmacopoeia Sixth Ed., 2016. Artemether was dissolved using a simplified solvent containing KH_2PO_4 buffer and acetonitrile (50:50), in which lumefantrine is sparingly soluble. This enhanced the signal from artemether relative to lumefantrine. Lumefantrine was dissolved in dimethyl sulfoxide. Artemether and lumefantrine were measured from separate injections using different isocratic conditions. Detection of lumefantrine was changed to 300 nm.

3. Artesunate
    a. The analysis of artesunate followed the method in The Int. Pharmacopoeia Sixth Ed., 2016. The only changes made were those related to the column used for UPLC.
4. Azithromycin
    a. The analysis of azithromycin was adapted from the method published in 2010 in The United States Pharmacopeial Convention. The extraction solvent was changed to 30% 33 mM KH_2PO_4, pH 8.5, 70% methanol and octanesulfonate was removed from the mobile phase.
5. Dihydroartemisinin and Piperaquine
    a. A pharmacopeial method for dihydroartemisinin and piperaquine was unavailable and a method was adapted from Peterson et.al., PLOS One. 2017, https://doi.org/10.1371/journal.pone.0184165 September 6, 2017 pp 1-22. Dihydroartemisinin was dissolved in acetonitrile and mobile phase A was 10 mM KH_2PO_4, pH 3.0. For Piperaquine analysis, a gradient was used in place of isocratic conditions and the detection wavelength was changed to 240 nm.
6. Ofloxacin
    a. The analysis of ofloxacin was adapted was adapted from the USP Monographs, 2017, pp 5413-4. Standards and extracts were prepared with water.
7. Sulfamethoxazole and Trimethoprim
    a. The analysis was adapted from the USP Monographs, 2017, pp 6272-3. A Waters BEH-phenyl column was used. Mobile phase A was water with 0.2% acetic acid. Detection wavelengths were optimized for sulfamethoxazole (270 nm) and trimethoprim (240 nm).

Standard and Sample Preparations

Amoxicillin/Clavulanic Acid

- Standards: Make a combined Amoxicillin and Clavulanate Standard
    1. Weigh 9 - 11 mg Potassium clavulanate into a 12 mL vial.
    2. Add 10 ml water and sonicate 5 min.
    3. Weigh 23 - 27 mg Amoxicillin trihydrate into a 25 ml volumetric flask
    4. Add 10 - 15 ml water and mix.
    5. Add 4.000 ml of the clavulanate stock and sonicate 5 min.
    6. Bring to volume and mix thoroughly.
    7. Dilute as needed to be in sample range.
- Sample Prep
    1. Record tablet mass.
    2. Divide tablet into 4 quarters. Store in a vial at RT away from light.
    3. Weigh one of the tablet quarters, record mass and transfer to a flask
    4. Add 150 - 300 ml water (so that amoxicillin is approx. 0.8 mg/ml. Record the ml of water added.
    5. Sonicate for 5 min.

6. Mix with stir bar for 15 - 30 min.
7. Centrifuge 1.6 mL of sample in a microfuge at high speed for 4 min.
8. Transfer 1 mL of clear sample to UPLC vial for analysis.

- Notes
    1. Tablet extractions have been stable for both amoxicillin and clavulanate for at least 24 hours.
    2. Clavulanate Standards may be used for up to 24 hr.
    3. Amoxicillin is stable for at least 2 days.

Artemether

- Standards
    - Artemether
        1. Dissolve 8 - 10 mg in 10 ml of 50% A, 50% B.
        2. Sonicate 5 min.
        3. Use as standard.
- Sample Prep
    - Artemether
        1. Weigh out 1/6 to 1/5 of tablet weight into an 11 ml glass vial. Sonicate 5 min.
        2. Add 5 ml of 50% A, 50%B.
        3. Sonicate 5 min.
        4. Measure as soon as possible and no later than 5 hour after dissolving
    - Lumefantrine
        1. Weigh out 1/10 of tablet weight into a 25 ml volumetric flask.
        2. Add approx. 20 ml dimethyl sulfoxide.
        3. Sonicate 5 min and bring to volume with dimethyl sulfoxide.
        4. Combine 100 µl extract with 3.000 ml 35% 10 mM KH_2PO_4, pH 3.0/65% acetonitrile
    - Notes
        1. Protect APIs from light
        2. Tablet extractions for both Artemether and Lumefantrine have been stable

Artesunate

- Standard Prep
    1. Weigh approx. 100 mg into a 25 ml volumetric flask. Record mass.
    2. Fill flask approx. 90% with acetonitrile, sonicate 5 min and bring to volume with acetonitrile.
    3. Dilute to obtain standards ranging from approx. 4 to 1 mg/ml.
- Sample Prep
    1. Open top of vial and add 10 ml acetonitrile. Swirl to dissolve contents.
    2. Transfer to a 25 ml volumetric flask
    3. Repeat transfer from the vial to the volumetric flask with two 5 ml washes
    4. Sonicate 2 min and bring to volume.

Azithromycin

- Standard Prep
    1. Dissolve 25 mg in 25 ml mobile phase
    2. Dilute 10-fold for approximately 100 ug/ml, or as needed for a calibration curve
- Sample Prep
    1. Record weight of tablet
    2. Crush tablet into a fine powder using a mortar and pestle, store in 11 ml vial
    3. Transfer 1/10 to 1/5 of tablet to 25 ml of mobile phase
    4. Dilute 10-fold in mobile phase for approx. 100 ug/ml

Dihydroartemisinin

- Standard Prep
    1. Weigh 9 - 11 mg dihydroartemesinin.
    2. Dissolve in 10 ml acetonitrile
    3. Sonicate 5 minutes.
    4. Dilute 75%, 50% and 25% for a set of calibration standards
- Sample Prep
    1. Record tablet mass.
    2. Grind to a fine powder.
    3. Weigh out approximately 1/10 of tablet mass to a 15 ml high speed centrifuge tube. Record mass.
    4. Add 5.00 ml acetonitrile.
    5. Sonicate for 5 min.
    6. Centrifuge 12,000 x G for 5 min.
    7. Measure extract without further dilution.
- Notes
    1. Standards stable for at least 1 days (at room temp).
    2. Tablet extractions stable for at least 24 hr.
    3. This method separates the alpha and beta epimers, combine peak areas from both peaks for quantitation.

Lumefantrine

- Standard Prep
    1. Dissolve 10 -14 mg into 25 ml of dimethyl sulfoxide
    2. Sonicate 5 min.
    3. Dilute as needed in 50%water/50% acetonitrile to obtain a standard at 15 -20 ug/ml.
- Sample Prep
    1. Weigh out 1/10 of tablet weight into a 25 ml volumetric flask.
    2. Add approx. 20 ml dimethyl sulfoxide.
    3. Sonicate 5 min and bring to volume with dimethyl sulfoxide.

4. Combine 100 µl extract with 3.000 ml 35% 10 mM KH_2PO_4, pH 3.0/65% acetonitrile

- Notes
    1. Protect APIs from light
    2. Tablet extractions for both Artemether and Lumefantrine have been stable
    3.

Ofloxacin

- Standard Prep
    1. Weigh 19 - 21 mg ofloxacin into a 40 ml extraction vial.
    2. Add 20 ml water using a 10 ml glass pipet.
    3. Sonicate 5-10 min or until the ofloxacin is completely dissolved.
    4. Dilute 500 ul of the stock with 24.500 ml water using a 25 ml volumetric flask for a standard at approx. 20 µg/ml.
- Sample Prep
    1. Record tablet mass.
    2. Cut tablet in half using a tablet cutter.
    3. Weigh one of the tablet halves and record mass.
    4. Place the half tablet into a 250 flask. Add 200 ml water - record volume of water.
    5. Sonicate 5 min or until the tablet is completely broken apart.
    6. Mix on stir plate for 15 min.
    7. Transfer 1.8 ml to a 2 ml microfuge tube and centrifuge at high speed for 4 min.
    8. Dilute 1000 ul of the spun extract with 24.000 ml water using a 25 ml VF.
- Notes
    1. Standards and extracts stable for at least 4 days (at RT).
    2. Do not filter through polyethersulfone

Piperaquine

- Standard Prep
    1. Weigh 9 - 11 mg Piperaquine tetraphosphate tetrahydrate in to 50 ml VF.
    2. Add approximately 40 ml 0.01 N hydrochloric acid
    3. Sonicate 5 minutes.
    4. Bring to volume and mix thoroughly. Use as calibration standard (approx. 200 µg/ml).
- Sample Prep
    1. Record tablet mass.
    2. Grind to a fine powder.
    3. Weigh out approximately 1/5 of tablet mass to a 250 ml flask. Record mass.
    4. Add 100 ml 0.01 N hydrochloric acid. Record the ml of water added. (PIP at approx. 640 µg/ml).
    5. Sonicate for 5 min.

6. Mix with stir bar for 15 - 30 min.
7. Centrifuge 1.6 ml of sample in a microfuge at high speed for 4 min.
8. Add 1.00 ml water to UPLC vials. Add 500 µl of extract to vial and mix.

- Notes
  1. Standards stable for at least 4 days (at RT).
  2. Tablet extractions stable for at least 2 days.

Sulfamethoxazole/Trimethoprim

- Standard Prep
  1. Weigh 28 - 32 mg Sulfamethoxazole into a 25 ml volumetric flask.
  2. Weigh 9 - 11 mg Trimethoprim into the same flask.
  3. Add 20 mL methanol and sonicate 5 min.
  4. Bring to volume
  5. Dilute as needed to be in sample range.
- Sample Prep
  1. Record tablet mass.
  2. Grind tablet to a fine powder using a mortar/pestle. Store in a vial at RT away from light.
  3. Transfer 1/10 - 1/4 of tablet mass to a vial or volumetric flask.
  4. Record the mass to be extracted.
  5. Dissolve in 10, 20 or 25 ml methanol, depending on mg extracted.
  6. Sonicate 5 min.
  7. Centrifuge 4 ml of sample in at 13,000 x g for 4 min.
  8. Dilute 100 µl of clear sample with 5.00 ml methanol. Transfer to UPLC vial for analysis.
- Notes
  1. Protect APIs from light
  2. Stability of tablet extractions: At least 48 hr

Supplementary Annex 16. Field evaluation (laboratory technicians) – Minilab results

Technician	Study Sample Code	LOMWRU sample Code	Brand	API/strength	Dosage form	Study phase	TLC result (Rf%)		Disintegration test	
							Spot 1	Spot 2	Result	time
Tech 1	EP48	G576-8	Oflocee	Ofloxacin 200 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	4 min
	EP58	G557-9	Ofloxacin	Ofloxacin 200 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	6 min
	EP57	G557-9	Ofloxacin	Ofloxacin 200 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	4 min
	EP63	G322-2	Ofloxin	Ofloxacin 200 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3:51 min
	EP151	LA16/169--3	Ofloxin	Ofloxacin 200 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3 min
	EP64	G582-9	Ofloxin	Ofloxacin 200 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3:51 min
	EP81	G566-5	Di-Flo	Ofloxacin 200 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3:52 min
	EP76	G555-9	Di-Flo	Ofloxacin 200 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3:45 min
	EP133	LA17/06-20	Oralzicin	Azithromycin 250 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	5 min
	EP132	LA17/06-16	Oralzicin	Azithromycin 250 mg	Tablet	EP	Pass (3.22)	Pass (0.00)	Pass	2:48 min
	EP131	LA17/06-4	Oralzicin	Azithromycin 250 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	5 min
	EP135	LA17/06-06	Oralzicin	Azithromycin 250 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3 min
	EP134	LA17/06-2	Oralzicin	Azithromycin 250 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	4 min
	EP144	LA16/150-2	Azithromax	Azithromycin 250 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	1 min
	EP145	LA16/175-1	Azithromax	Azithromycin 250 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	2 min
	EP142	G567-1	Azithromax	Azithromycin 250 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3 min
	SPS 02	Simulated No API (0%)	Tested as Vactrim (SMTM)	Sulphamethoxazole 80 mg	Tablet	SS	Fail (not found)	Fail (not found)	Pass	1:30 min
				Trimethoprim 400 mg		SS	Fail (not found)	Fail (not found)	Pass	
	SPS 03	Simulated 100%	Tested as Biseptrim (SMTM)	Sulphamethoxazole 80 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Fail	>30 min
				Trimethoprim 400 mg		SS	Pass (1.18)	Pass (1.18)	Fail	
	SPS 04	Simulated 50%	Tested as Biseptrim (SMTM)	Sulphamethoxazole 80 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	3:44 min
				Trimethoprim 400 mg		SS	Pass (0.00)	Pass (0.00)	Pass	
	SPS 16	G558-3	Diabeta (glibenclamide) Tested as SMTM	Sulphamethoxazole 80 mg	Tablet	SS	Fail (not found)	Fail (not found)	Pass	20 min
				Trimethoprim 400 mg		SS	Fail (not found)	Fail (not found)	Pass	
	SPS 20	G269-3	Sulfatrim	Sulphamethoxazole 80 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	15 min
				Trimethoprim 400 mg		SS	Pass (0.00)	Pass (0.00)	Pass	

Technician	Study Sample Code	LOMWRU sample Code	Brand	API/strength	Dosage form	Study phase	TLC result (Rf%)		Disintegration test	
							Spot 1	Spot 2	Result	time
	SPS 21	G541-3	Sulfatrim	Sulphamethoxazole 80 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	16 min
				Trimethoprim 400 mg		SS	Pass (0.00)	Pass (0.00)	Pass	
Tech 2	EP022	G572-9	D-Artepp	Dihydroartemisinin 40 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	13 min
				Piperaquine 320 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP023	G572-9	D-Artepp	Dihydroartemisinin 40 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3:04 min
				Piperaquine 320 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP024	G552-4	D-Artepp	Dihydroartemisinin 40 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	1:50 min
				Piperaquine 320 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP025	G572-10	D-Artepp	Dihydroartemisinin 40 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	2:50 min
				Piperaquine 320 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP026	G572-10	D-Artepp	Dihydroartemisinin 40 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	1:11 min
				Piperaquine 320 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP027	G572-10	D-Artepp	Dihydroartemisinin 40 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	4:08 min
				Piperaquine 320 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP084	G568-21	Vactrim	Sulphamethoxazole 80 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	5:48 min
				Trimethoprim 400 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP101	G568-21	Vactrim	Sulphamethoxazole 80 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	5:05 min
				Trimethoprim 400 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP109	G553-31	Strimside	Sulphamethoxazole 80 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3:56 min
				Trimethoprim 400 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP102	G553-31	Strimside	Sulphamethoxazole 80 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	6 min
				Trimethoprim 400 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP113	G540-13	Biseptrim	Sulphamethoxazole 80 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3:33 min
				Trimethoprim 400 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP129	G571-6	Sulfatrim	Sulphamethoxazole 80 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	5 min
				Trimethoprim 400 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	SPS 06	MM17/01-1	Artemether-Lumefantrine IPCA	Artemether 20 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	1 min
				Lumefantrine 120 mg		SS	Pass (0.00)	Pass (0.00)	Pass	
	SPS 22	G592-1	Co-artem	Artemether 20 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	2 min
				Lumefantrine 120 mg		SS	Pass (0.00)	Pass (0.00)	Pass	

Technician	Study Sample Code	LOMWRU sample Code	Brand	API/strength	Dosage form	Study phase	TLC result (Rf%)		Disintegration test	
							Spot 1	Spot 2	Result	time
	SPS 09	G593-2	Co-artem	Artemether 20 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	2 min
				Lumefantrine 120 mg		SS	Pass (0.00)	Pass (0.00)	Pass	
	SPS 10	LC6	Co-artem	Artemether 20 mg	Tablet	SS	Fail (Not found)	Fail (not found)	Pass	2 min
				Lumefantrine 120 mg		SS	Fail (not found)	Fail (not found)	Pass	
	SPS11	LC10	Co-artem	Artemether 20 mg	Tablet	SS	Fail (not found)	Fail (not found)	Pass	2 min
				Lumefantrine 120 mg		SS	Fail (not found)	Fail (not found)	Pass	
	SPS 07	SS0044	Artemether-Lumefantrine IPCA	Artemether 20 mg	Tablet	SS	Fail (not found)	Fail (not found)	Pass	2 min
				Lumefantrine 120 mg		SS	Fail (not found)	Fail (not found)	Pass	
Tech 3	EP28	G593-1	Co-artem	Artemether 20 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	2 min
				Lumefantrine 120 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP34	N37	Co-artem	Artemether 20 mg	Tablet	EP	Fail (not found)	Fail (not found)	Pass	1:30 min
				Lumefantrine 120 mg		EP	Fail (not found)	Fail (not found)	Pass	
	EP35	G592-5	Co-artem	Artemether 20 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	2 min
				Lumefantrine 120 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP41	N20	Co-artem	Artemether 20 mg	Tablet	EP	Fail (not found)	Fail (not found)	Pass	7:25 min
				Lumefantrine 120 mg		EP	Fail (not found)	Fail (not found)	Pass	
	EP37	G592-5	Co-artem	Artemether 20 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	1 min
				Lumefantrine 120 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP42	N35	Co-artem	Artemether 20 mg	Tablet	EP	Fail (not found)	Fail (not found)	Pass	1:36 min
				Lumefantrine 120 mg		EP	Fail (not found)	Fail (not found)	Pass	
	EP38	G592-5	Co-artem	Artemether 20 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	2 min
				Lumefantrine 120 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP36	G592-5	Co-artem	Artemether 20 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	2 min
				Lumefantrine 120 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP40	G593-1	Co-artem	Artemether 20 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	2 min
				Lumefantrine 120 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP014	G573-12/G573-19	Artesun	Artesunate 60mg	Injection	EP	Pass (0.00)	Pass (0.00)	N/A	N/A

Technician	Study Sample Code	LOMWRU sample Code	Brand	API/strength	Dosage form	Study phase	TLC result (Rf%)		Disintegration test	
							Spot 1	Spot 2	Result	time
	EP017	G573-11/G573-16	Artesun	Artesunate 60mg	Injection	EP	Pass (0.00)	Pass (0.00)	N/A	N/A
	EP019	G573-15/G573-20	Artesun	Artesunate 60mg	Injection	EP	Pass (0.00)	Pass (0.00)	N/A	N/A
	EP016	G573-17/G573-18	Artesun	Artesunate 60mg	Injection	EP	Pass (0.00)	Pass (0.00)	N/A	N/A
	EP001	G583-1-2	Augmentin	Amoxycillin 500 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3:45 min
				Clavulanic acid 125 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP004	G583-1-2	Augmentin	Amoxycillin 500 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	2:56 min
				Clavulanic acid 125 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP006	G461-1	Augmentin	Amoxycillin 500 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3 min
				Clavulanic acid 125 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP007	G461-3	Augmentin	Amoxycillin 500 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	4 min
				Clavulanic acid 125 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	EP008	G488	Augmentin	Amoxycillin 500 mg	Tablet	EP	Pass (0.00)	Pass (0.00)	Pass	3.33 min
				Clavulanic acid 125 mg		EP	Pass (0.00)	Pass (0.00)	Pass	
	SPS 05	Simulated 100%	Tested as Ofloxacin CDP (OFLO)	Ofloxacin 200 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	13 min
	SPS 14	G569-10	Oflocee	Ofloxacin 200 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	3:04 min
	SPS 01	Simulated 50%	Tested as Ofloxacin CDP (OFLO)	Ofloxacin 200 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	1:50 min
	SPS 02	Simulated No API (0%)	Tested as Ofloxacin CDP (OFLO)	Ofloxacin 200 mg	Tablet	SS	Fail (not found)	Fail (not found)	Pass	19 min
	SPS 13	G555-6	Di-flo	Ofloxacin 200 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	1:11 min
	SPS 15	G557-8	Ofloxacin	Ofloxacin 200 mg	Tablet	SS	Pass (0.00)	Pass (0.00)	Pass	4:08 min

API= Active Pharmaceutical Ingredient;ACA, amoxicillin-clavulanic acid; AMLM, artemether-lumefantrine; ART, artesunate; AZITH, azithromycin; DHAP, dihydroartemisinin-piperaquine; EP, Evaluation Pharmacy; OFLO, Ofloxacin; SMTM, sulfamethoxazole-trimethoprim; SS= sample set