World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO Guidance on the Selection and Use of Technologies to Screen and Detect Substandard/Falsified (SF) Medicines

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SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/26.1004:

WHO Guidance on the Selection and Use of Technologies to Screen and Detect Substandard/Falsified (SF) Medicines

Description of Activity	**Date**
Formation of an informal drafting group.	November 2025
Preparation of first draft working document.	December 2025
Review and finalization of the first draft working document with the informal drafting group.	May-June 2026
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	June – July 2026
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	September 2026
Discussion of the feedback received on the working document in a virtual meeting with an informal drafting group.	September 2026
Preparation of a working document for discussion and possible adoption by the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).	September 2026
Presentation to the sixtieth meeting of the ECSPP.	October 2026
Any other follow-up action as required.	

WHO Guidance on the Selection and Use of Technologies to Screen and Detect

Content

Substandard/Falsified (SF) Medicines

Abbreviations

API	active pharmaceutical ingredient
ATR	attenuated total reflection
CoDI	counterfeit drug indicator
DEG/EG	diethylene glycol/ethylene glycol
FPP	finished pharmaceutical products

FT	Fourier transform
GBT	global benchmarking tool
GC	gas chromatography
GC-FID	gas chromatography – flame ionization detection
GMP	good manufacturing practices
HPTLC	high-performance thin-layer chromatography
HPLC	high-performance liquid chromatography
IP	ingress protection
LMIC	low- and middle-income country
MAH	marketing authorization holder
MIR	mid-infrared
MS	mass spectrometry
MSM	member state mechanism on substandard and falsified medical products
NAP	national action plan
NIR	near infrared
NRA	national regulatory authority
NQCL	national quality control laboratories
Ph. Eur.	European Pharmacopoeia
Ph. Int.	International Pharmacopoeia
QA	quality assurance
QC	quality control
SERDS	shifted excitation Raman difference spectroscopy
SF	substandard and falsified
SOP	standard operating procedure
SORS	spatially offset Raman scattering
TLC	thin-layer chromatography
USP	United States Pharmacopoeia
UV	ultraviolet

WHO	World Health Organization
XRF	X-ray fluorescence spectroscopy
XRPD	X-ray powder diffraction

1 Introduction

Substandard and falsified (SF) medicines pose a serious but often underestimated threat to public health. They deprive patients of safe and effective treatment, especially in low- and middle-income countries (LMICs). A 2017 WHO report estimated that around 10% of medicines in LMICs are substandard or falsified *(1)*. Key factors driving the proliferation of SF medicines include limited access to affordable, safe, effective and high-quality medicines; weak technical capacity in national regulatory systems; and poor governance of manufacturing, supply chains and health systems *(2)*.

Regulatory authorities are primarily responsible for preventing, detecting and responding to SF medicines. Ideally, detection is carried out using compendial methods, which rely on validated analytical procedures and often use high-performance liquid chromatography (HPLC) for qualitative and quantitative analysis. These methods provide accurate results but are expensive, time-consuming, and require sophisticated equipment and highly trained staff, which means they must be performed in a laboratory. In low-resource settings, the demand for medicine testing often exceeds available capacity for compendial analysis, causing delays between sample collection and confirmation of poor quality. In the meantime, unsafe medicines may continue to reach patients. Constraints of capacity for compendial testing may also lead to reliance on visual inspection alone, which only detects a small proportion of the SF medicines.

Screening technologies can help address this gap. These methods provide rapid qualitative or quantitative information on the quality of medicines and allow the screening of large numbers of samples in a short time. They cannot replace testing against official specifications, but they are valuable for enabling the analysis of a larger number of samples, quickly identifying suspect SF medicines and protecting patients from possible harm by removing such medicines from circulation, even temporarily through quarantine, and by taking any other appropriate regulatory actions.

Several technologies for medicine quality screening are commercially available, and some of them are already in use in regulatory practice, with others in development or described in scientific studies. The Member State Mechanism (MSM) on substandard and falsified medical products has a working group on detection technologies. In its 2024–2025 workplan, the group prioritized efforts to “improve Member States’ understanding and uptake of technologies to screen and detect SF medical products” *(3)*. In 2025, this MSM working group published survey results from Member States regarding technologies used to screen and detect SF medical products *(4)*. The most frequently reported challenge for Member States in establishing detection systems for SF medicines was the lack of

technical knowledge on this subject. Similarly, a global landscape assessment of screening technologies involving regulators, manufacturers, pharmacies, and distributors reported that "virtually all of the study participants indicated a lack of objective, accessible information on screening technologies to advise them on what technologies would be beneficial for their needs" *(5)*.

To address this gap, the MSM working group recommended the development of a "WHO handbook/guidance on how to select technologies to screen and detect substandard/falsified medical products" *(3)*. The present guidance document was developed in response to that recommendation.

2 Objectives, scope, and intended audience of this guidance

Objectives. The purpose of this guidance is to improve Member States' understanding and uptake of technologies to screen and detect substandard and falsified medicines. It provides an overview of available rapid and low-cost screening technologies and their application in medicine quality screening. The intention is to help decision-makers select and use appropriate technologies and to support their effective and scientifically sound implementation, tailored to national contexts and needs. The use of screening technologies can also help national medicine regulatory agencies in preparing their market surveillance and control activities and fulfil certain indicators of the WHO Global Benchmarking Tool (GBT) for evaluation of regulatory systems of medical products *(6)*.

In addition, this guidance may support international harmonization of good practices in medicine quality monitoring and facilitate mutual recognition of test results. Ultimately, its objective is to support stakeholders in Member States to take quick action to protect patients from harm caused by substandard and falsified medicines, and to promote access to affordable, safe, effective and high-quality medicines.

Scope. This guidance focuses on screening and detection of SF medicines for human use within the supply chain. It does not cover technologies designed specifically for the analysis of biological products, of traditional medicines, of diagnostics or of medical devices. Accordingly, the term "SF medicines" is used in this document instead of "SF medical products".

This guidance covers technologies that allow rapid testing, are affordable, easy to use, and make only moderate demands on laboratory infrastructure and operator training. The covered technologies are readily applicable for medicine quality screening without additional method development or can be applied after only a moderate amount of method development (for example, after developing basic

chemometric models and reference spectra libraries). Any required method development by the user is clearly indicated in the description of these technologies within this guidance.

Screening analysis may be performed in the field, directly at sites where medicines are encountered by inspectors, law enforcement officers, or other authorities. This requires field-portable devices. However, screening analysis may also be performed after samples have been collected and transported to a laboratory, as part of a tiered approach to quality testing. In such a tiered approach, initial screening analysis of large numbers of medicine samples helps decide which samples should be prioritized for confirmatory testing, allowing more efficient use of limited resources for compendial analysis. In this approach, benchtop devices can also be useful for screening analysis and are therefore covered.

This guidance focuses on screening technologies that are currently commercially available and for which sufficient scientific evidence is publicly available to support informed and justified decisions about purchasing and implementing them for medicine quality testing. Additionally, section 7 briefly presents technologies that are not (or not yet) commercially available or for which insufficient evidence is currently available to make well-informed deployment decisions. These technologies may become viable options in the future as more evidence becomes available and commercial products are developed. Section 8 presents some advanced laboratory-based analytical techniques that allow more detailed investigation of suspect samples. Section 11 outlines priority areas for future research on screening technologies to help guide the continued development of this field.

In accordance with WHO rules and regulations, this guidance describes general technology types (for example, Raman spectroscopy) but not individual branded devices. Therefore, it does not aim to provide direct comparisons between different marketed devices. Information on individual devices, including manufacturer names and contacts, price ranges, as well as technical and scientific data, can be found in resources such as the DAFODIL dashboard *(7)*, an interactive website on field-portable devices for medicine quality screening recently established by the Medicine Quality Research Group of the University of Oxford. The DAFODIL website is expected to undergo continuous development. Users may therefore find more information and additional devices on that website than mentioned in this guidance.

If this guidance refers to specific companies, certain manufacturers' products or patented technologies, this does not imply that WHO endorses or recommends them in preference to others of a similar nature that are not mentioned.

Intended audience. The primary intended audience of this guidance includes national medicine regulatory agencies, national medicine quality control laboratories, central medical stores, as well as

customs, law enforcement authorities and other entities such as public health organizations. However, ensuring medicine quality is not the responsibility of regulatory agencies alone. Medicine regulations should promote shared responsibility for assuring the quality, safety, and efficacy of medicines across all parts of the supply chain, including procurement agencies, manufacturers, importers, wholesalers, and retailers of medicines. Marketing authorization holders (MAHs) should be held responsible for the quality of their products on the market. Therefore, this guidance is also addressed to these stakeholders who play important roles in maintaining medicine quality throughout the supply chain.

3 Glossary

The definitions given below apply to the terms used in this document. They have been aligned to the extent possible with the terminology in related WHO guidelines and good practices included in the WHO Quality Assurance of Medicines Terminology Database *(8)* but may have different meanings in other contexts.

Authentic reference / authentic sample. Packaging or sample of a medical product supplied by the authorised manufacturer for comparison purposes.

Available sample. Whatever total quantity of sample materials is available.

Benchtop device. Laboratory instrument designed to be placed and operated on a stable work surface (bench or table). Benchtop devices are typically mains-powered, stationary during operation, and intended for use under controlled laboratory conditions.

Blister. A multi-dose container consisting of two layers, of which one is shaped to contain the individual doses.

Chemometrics. Chemical discipline that uses mathematics, statistics and formal logic, (a) to design or select optimal performance experimental procedures, (b) to provide maximum relevant chemical information by analysing chemical data, and (c) to obtain knowledge about chemical systems. Chemometrics shares mathematical algorithms with related data science domains such as machine learning and data mining.

Colorimetric reaction. Chemical reaction that produces a measurable change in colour or absorbance, where the intensity of the colour is proportional to the concentration of the analyte being measured.

Compendial testing. Analytical evaluation of pharmaceutical products to ensure conformity with established quality, safety, and efficacy specifications promulgated by officially recognized pharmacopoeias. This evaluation verifies identity, assay/potency and impurity testing of

pharmaceutical raw materials and finished dosage forms and may include other specific tests such as dissolution.

False negative. Sample being of poor quality with the test incorrectly giving a pass result.

False positive. Sample being of good quality with the test incorrectly giving a fail result.

Falsified product. A product that has been deliberately and/or fraudulently misrepresented as to its identity, composition or source.

Field-portable device. Device that is intended to be used outside laboratories close to the sample collection site. Field-portable devices encompass transportable, portable, handheld and miniature devices. Under certain circumstances, benchtop devices may also fall within this category, for example, when deployed in mobile laboratories.

Finished pharmaceutical product. A product that has undergone all stages of production, including packaging in its final container and labelling. A finished pharmaceutical product may contain one or more active pharmaceutical ingredients.

Handheld device. A device typically with a volume of less than or equal to 3 dm^3 and weighing between 0.5-3 kg.

Marketing authorization holder. An individual or a corporate entity being in possession of a marketing authorization of a pharmaceutical product.

Miniature device. A device typically with a volume of less than or equal to 0.75 dm^3 and weighing less than 0.5 kg.

National Action Plan. Political document where the state formulates the priorities, actions and commitments in relation to the designated topic.

Non-destructive analysis. Analysis that does not affect the physical and chemical properties of the sample being tested.

Non-invasive analysis. Analysis that is performed without opening and damaging the primary packaging of the sample under investigation. A non-invasive analysis is de facto non-destructive.

Portable device. A device typically with a volume of less than or equal to 50 dm^3 and weighing between 3-20 kg.

Post-marketing surveillance of medicines. The activities carried out and measures taken by a national regulatory authority (NRA) to ensure that medicines placed on the market comply with regulations and do not endanger health, safety or any other aspect of public health.

Qualification. Documented evidence that premises, systems or equipment meet the requirements/criteria of the predetermined specifications when properly installed, and/or work correctly and lead to the expected results.

Reference substance (or standard). An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

Reference sample. A collected material that has successfully passed compendial testing.

Sample. A portion of a material collected according to a defined sampling procedure.

Screening technologies. Qualitative and/or semiquantitative technologies that can rapidly acquire the information or analytical data for preliminary identification of suspect medical products in the field.

Sensitivity. Ability of the test to correctly identify a poor quality sample as failing. It is computed as the percentage of true positives over the total of true positives and false negatives. This term should not be confused with the terms detection limit or quantitation limit as defined in ICH Q2(R2) *(9)*.

Specificity. Ability of the test to correctly identify a good quality sample as passing. It is computed as the percentage of true negatives over the total of true negatives and false positives. This term should not be confused with the definition of analytical specificity, as defined in ICH Q2(R2) *(9)*.

Spectrum. Pattern of absorption or emission of radiation produced by a substance when subjected to energy (for example light). In vibrational spectroscopy, a spectrum is a representation of signal intensity (scattered light for Raman or absorbed light for NIR and MIR spectroscopies) as a function of wavelength.

Substandard product. An authorized product that fails to meet either its quality standards or its specifications, or both.

Targeted analysis. Analysis following a hypothesis-driven approach. The objective is to verify the adequacy of the sample against the information provided on the packaging or any other sample-related information. This may include but is not limited to:

- Verifying the stated active pharmaceutical ingredient (API) is present
- Confirming the API concentration matches the label claim

Transportable device. A device typically packaged in suitcases and weighing more than 20 kg, which may typically be transported by car and is used in 'fixed-location mobile laboratories'.

True negative. Sample being good quality with the test correctly giving a pass result.

True positive. Sample being poor quality with the test correctly giving a fail result.

Untargeted analysis. Analysis following an exploratory approach. This approach is envisaged when no reliable sample-related information is available, or when the objective is to discover unexpected deviations, adulterants, or information regarding the sample's composition/nature without prior assumptions about what might be present.

4 Place of screening technologies within the overall quality risk management of medical products

Using screening technologies to detect substandard and falsified medicines should be part of a comprehensive medicine quality risk management system. This system should be described in a National Action Plan (NAP) that addresses prevention, detection, and response strategies for substandard and falsified medical products.

Before developing a strategy for using screening technologies, regulatory authorities should assess:

- The existing capacity for quality assurance/quality control (QA/QC) and post-marketing surveillance of medicines.
- Current knowledge about the local prevalence of substandard and falsified medicines and the public health risks they pose.
- Which governmental, non-governmental, and private stakeholders should be involved.

The use of screening technologies should follow the principles set out by WHO *(10-13)*, the ICH quality guidelines *(14)*, and ISO/IEC 17025 *(15)*. The recent WHO guideline on Good Regulatory Practices for Market Surveillance and Control of Medical Products *(13)* provides detailed guidance on establishing a strategic framework for risk-based market surveillance, as well as on the place of screening technologies within the overall quality risk management of medical products.

Screening technologies can be used in different settings:

- Systematic surveys as part of a post-marketing surveillance programme.
- Spot checks on medicine quality during inspections of pharmaceutical premises, including manufacturers, wholesalers, retailers and pharmacy outlets within health facilities.
- Investigations following incident reports of suspected substandard or falsified medicines, or adverse events reported through pharmacovigilance programmes.
- Routine controls at borders and entry points for medicines, typically through collaboration between national regulatory authorities and border control agencies.
- Incoming goods inspection by central medical stores, health facilities, and commercial medicine suppliers.

Screening technologies can make surveillance more efficient by allowing rapid assessment of larger numbers of samples. This reduces the number of samples that need full testing at quality control laboratories, increases surveillance coverage, and reduces the overall time and cost of surveillance activities. To fully achieve these benefits, a risk-based, tiered approach to testing is recommended as described in *(13, 16)*. For example, a three-level approach may use successive levels of analysis:

1. Visual inspection (including measurement of weight and size)
2. Analysis with screening technologies
3. Full laboratory testing using compendial (pharmacopoeial) or manufacturer methodologies

It is important that national regulations recognize results obtained with screening technologies as sufficient evidence for the NRA to take appropriate regulatory actions (see section 10).

Screening technologies must be embedded within a quality management system (QMS) to ensure their effective and reliable use. Detailed guidance is provided in three WHO documents: the WHO Guideline on the Implementation of QMS for National Regulatory Authorities *(17)*, WHO Good Practices for Pharmaceutical Quality Control Laboratories *(12)*, and WHO Good Regulatory Practices for Market Surveillance and Control of Medical Products *(13)*.

5 Types of substandard and falsified medicines to be detected with screening technologies

Understanding the types of quality problems which may be found in different SF medicines, and the distinction between 'falsified' and 'substandard' medicines, is fundamental to selecting appropriate screening technologies and interpreting their results. In addition to this paragraph, the interested reader may find more information regarding the different aspects of detection, prevention and response to the substandard and falsified medicines scourge in the WHO's Training Toolkit on Substandard and Falsified Medical Products *(18)*.

The World Health Assembly of 2017 adopted the following definitions:

Substandard medical products: Also called "out of specification", these are authorized medical products that fail to meet either their quality standards or their specifications, or both.

Falsified medical products: These are medical products that deliberately/fraudulently misrepresent their identity, composition or source.

In contrast, **unregistered/unlicensed medical products** are medical products that have not undergone evaluation and/or approval by the national or regional regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

The selection of appropriate screening technologies requires careful consideration of the types of defects that need to be detected. Priority should be given to defects that pose the greatest risk to patient health, occur with highest prevalence in the target setting, and/or have significant economic

impact such as waste of health resources or damage to local pharmaceutical industry. The prevalence and types of substandard and falsified medicines vary considerably across geographic regions, healthcare settings, therapeutic categories, and dosage forms.

Medicines not containing the declared API. When medicines do not contain active ingredients, patients receive no therapeutic benefit, leading to treatment failure, disease progression, or even death. Medicines containing incorrect APIs instead of the declared ones may cause adverse effects while failing to provide intended therapeutic benefits. Most medicines with no or incorrect APIs are deliberately falsified, but a few cases have been documented where such medicines resulted from poor manufacturing practice and/or unintended mistakes. Medicines that are SF due to having no APIs or wrong APIs make up only a relatively small fraction of all circulating SF medicines. Many more SF products show other types of deficiencies.

Medicines containing an incorrect enantiomer of the API. A special, rarely encountered challenge is posed by SF medicines which contain the incorrect enantiomer (= optical isomer) of the API, such as levomethorphan instead of dextromethorphan. Different enantiomers often differ substantially in their pharmacology and toxicology, and use of incorrect enantiomers may lead to lack of efficacy and sometimes to severe toxicity.

Medicines containing an incorrect amount of the API(s). These constitute the most frequently reported category of SF medicines in medicine quality studies. Notably, for most of these products there is no evidence for deliberate/fraudulent misrepresentation of their composition, and they represent substandard rather than falsified medicines. Medicine quality studies have shown that most of the detected substandard products still contain more than 80% of the stated API amount(s), a smaller fraction contains between 50 and 80%, and only few contain less than 50%. Medicines with excessive API amounts occur much less frequently than medicines with insufficient amounts, consistent with manufacturers' interests to minimize costs associated with expensive active ingredients. Medicines with insufficient API amounts may not show the expected therapeutic effectiveness, and in case of anti-infectives may contribute to the development of antimicrobial resistance.

Falsified medicines containing the declared APIs in the correct, declared amounts. Some of these products imitate originator products, but some also are labelled as inexpensive generic medicines for which there is a large market in many countries. Although such products may provide therapeutic benefit, they cannot be considered safe due to unknown manufacturing conditions and quality controls. Detection of this type of falsified medicines requires brand identification rather than API analysis (see section 6.2.6).

Solid oral dosage forms with insufficient dissolution of the API. API dissolution constitutes a necessary precondition for bioavailability and therapeutic effectiveness. Substandard medicines with insufficient dissolution produce therapeutic consequences similar to those with insufficient API amounts, including diminished effectiveness and potential contribution to antimicrobial resistance development. Approximately two-thirds of samples failing in dissolution testing pass identity and assay testing, indicating that conducting dissolution testing substantially increases detection of substandard medicines.

Medicines with non-compliant levels of impurities. Dosage form monographs of the International Pharmacopoeia, as well as of other major pharmacopoeias, include tests for impurities, especially to control impurities arising during synthesis of the APIs and impurities resulting from degradation. Compendial testing of impurities requires expensive reference standards and is therefore infrequently included in published medicine quality studies from low- and middle-income countries.

Parenteral dosage forms with microbial or endotoxin contamination. Sterility and absence of bacterial endotoxins or pyrogens represent critical quality criteria for parenteral formulations. These parameters typically require compendial testing methods. Many laboratories have been developing rapid testing approaches. A field-portable device for detecting microbial contamination in sterile liquid samples has been developed *(19)*, but is currently not commercially available.

Medicines containing substandard or falsified excipients. Especially liquid dosage forms contaminated with diethylene glycol or ethylene glycol (DEG/EG) present serious safety concerns due to their toxicity, having caused numerous fatalities in the past. They are therefore an important target for screening technologies (see section 6.2.8).

Substandard and falsified medicines with other defects. Dosage form monographs of the pharmacopoeias include tests for several items. Some of these can be investigated in screening analysis, including uniformity of mass, pH of liquid dosage forms or disintegration of solid dosage forms using simplified test procedures *(20)*. Other parameters are better determined in well-equipped laboratories, such as content uniformity, detection of unexpected contaminants or microbiological contamination.

Substandard and falsified medicines with packaging defects. In addition to physical and chemical defects, many substandard and falsified medicines have been found to have packaging defects. These can affect any aspect of the packaging such as spelling errors, anomalous batch numbers, atypical shelf life, altered manufacturing or expiry dates, and signs of repackaging. Since the packaging information is compromised, such products must be considered unsafe and may lack the expected efficacy.

Another form of packaging alteration involves manufacturers intentionally packing fewer dose units than declared. For example, boxes labelled for 1000 units may systematically contain only 800 to 900 units, thereby affecting inventory accuracy and the quantification of medicine needs.

The first and most important element driving screening technology selection is identifying the target application. A clear understanding of the screening technology's intended use and purpose will help identify evaluation parameters and determine whether multiple screening technologies are needed in a specific context. Target applications may vary by medicine types, anticipated users, geographic locations, supply chain checkpoints, and the public health consequences of poor-quality medicines.

6 Well-established screening technologies

This section presents technologies which have been used quite widely in the screening for SF medicines, and for which sufficient evidence is available to allow a well-informed decision on their deployment for medicine quality testing.

6.1 Overview

Most technologies discussed in this section are described in various pharmacopoeial chapters. Readers are encouraged to consult the general chapters addressing theoretical concepts and analytical instrument qualification in pharmacopoeias. In addition to method-specific chapters, readers should also refer to pharmacopoeial chapters on analytical instrument qualification, analytical procedure validation, design of experiments, chemometrics, and related topics.

6.1.1 Visual inspection and instrumental packaging/labelling analysis

The visual inspection of dosage forms, labels, patient leaflets, and packaging is a WHO-recognized essential component of medicine quality surveys and should precede advanced screening technologies *(10)*. Visually detected irregularities — on the packaging (for examples see section 5) or on the dosage form itself (such as product discoloration, oral liquid caking, presence of visible particulate matter) — must be reported. Overreliance on technological methods (for example spectroscopy) may undermine attention to visual inspection; this can be mitigated by using standardized, comprehensive checklists *(21-23)*. Such visual inspection does not require input from the genuine manufacturer or marketing authorization holder.

Analytical screening tools (such as reflectance, fluorescence, optical microscopy, infrared/Raman spectroscopy, X-ray fluorescence (XRF), scanning electron microscope (SEM), micro-computed

tomography (CT)) may support packaging analysis but depend on comparison with reference samples or manufacturer-supplied data.

6.1.2 Uniformity of mass for single-dose preparations

Uniformity of mass serves as a rapid, non-destructive surrogate test and requires only a qualified analytical balance. While this test provides no information on the identity or content of the active ingredient, it remains a reliable indicator of manufacturing deficiencies.

Applicable procedures and acceptance criteria are defined in the relevant pharmacopoeial monographs.

6.1.3 Thin-layer chromatography (TLC)

Of the different technologies for medicine quality screening in LMICs, TLC is probably the longest established one. TLC analysis involves dissolving the medicine in a suitable solvent (such as methanol), then manually applying defined volumes of the sample and the reference standard to a start line on a TLC plate using glass capillaries. The plate—coated with an adsorbent stationary phase on an inert backing—is placed vertically in a chamber containing an organic mobile phase, which ascends by capillary action, separating compounds based on their chemical properties and phase interactions. When the solvent front nears the top, the plate is removed, dried, and spots are visualized under UV light or via chemical staining. For the analyte of interest, the spot in the sample and the reference standard must show the same retardation factor (Rf), indicating that they have travelled the same distance from the start line, if the analyte in the sample is chemically identical to the one in the reference. Spot intensity allows semiquantitative assessment. Results can be documented photographically, e.g. using a smartphone *(24)*.

TLC requires only standard lab glassware and materials which can be purchased from laboratory suppliers or in form of a kit (see section 9.2.1).

High-performance thin-layer chromatography (HPTLC) is an advanced form of TLC which enables precise qualitative and quantitative analysis and requires more costly instrumentation. For this reason, it is not covered in this guidance.

6.1.4 Colorimetric paper analytical devices (PADs)

Colorimetric paper analytical devices (PADs) are paper-based devices that identify chemical entities through specific colorimetric reactions *(25, 26)*. PADs are produced by wax printing on fast-flow chromatography paper, creating several separate reaction lanes containing trace quantities of chemical reagents that produce colour changes in response to different chemical functional groups. The chemical reagents are preloaded on the PAD, and all procedures that would normally be

performed by a lab worker—sequential reagent additions, pH neutralizations, and mixing—are performed automatically in the lanes when the PAD is activated.

Sample analysis requires the substance to be in powder form (crushed tablets or powder removed from capsules or vials). The sample is spread across the several lanes, and the bottom of the PAD is then placed in 1 cm of water and kept upright. Once the water reaches the top of the PAD, the PAD is removed from water and laid flat for 3 minutes. The developed colours constitute a "barcode" of the API which is compared by eye with expected colours (depending on the API), or users may employ a specifically developed mobile application *(25)*.

The most commonly used type of PADs is only available for 19 single APIs and one fixed-dose combination at the time of writing this guidance *(25)*.

6.1.5 Vibrational spectroscopy

6.1.5.1 Raman spectroscopy

Raman spectroscopy analyses pharmaceutical products by directing a laser onto the sample and capturing backscattered light to generate a spectrum (intensity vs. Raman shift, cm^{-1}). Built-in software typically delivers "PASS/FAIL" results and identifies active ingredients by matching spectra against a database. Quantitative analysis is possible but requires advanced chemometrics and expertise and is rarely embedded in field-portable devices.

As a vibrational technique, Raman detects energy shifts from molecular vibrations during laser-matter interaction. Though the Raman signal is extremely weak (<0.00001% of incident light), it yields a unique "fingerprint" per compound—reflecting chemical bonds, molecular environment, and physical state (including polymorphs)—enabling both identification and quantification (intensity correlates with concentration). Spectra are wavelength-independent, allowing cross-instrument comparison and shared databases.

Main types of devices. Raman spectrometers are available in benchtop, portable, handheld, and miniature configurations. Originally designed for raw materials, most modern handheld devices now support analysis of finished pharmaceutical products (FPPs) like tablets and capsules via specialized accessories and software. The most common devices for medicine quality screening are handheld 785 nm laser spectrometers operating in backscattering mode. Advanced variants offer specialized techniques for specific challenges:

- **Spatially Offset Raman Scattering (SORS)** enables non-invasive analysis through packaging (for example paper, plastic, amber bottles, coloured containers). It acquires two spectra—one

at the surface and one offset (a few mm away)—and subtracts the surface signal to isolate the subsurface medicine spectrum.

- **Sequentially Shifted Excitation (SSE) / SERDS** mitigates fluorescence interference by using two closely spaced laser wavelengths. Raman peaks shift with wavelength, while fluorescence remains stable, allowing background subtraction and recovery of a clean Raman spectrum.

6.1.5.2 Near-infrared spectroscopy

Near-infrared (NIR) spectroscopy analysis of pharmaceutical solid dosage forms starts with measuring a background reference, followed by sample placement on the sensor window. The sample is illuminated by infrared light, and reflected radiation is collected, processed into a NIR absorbance spectrum, then compared to a database to generate "PASS/FAIL" or quantitative results. NIR spectroscopy measures light absorption in the 800–2500 nm (12,500–4,000 cm^{-1}) range, where IR-active molecules with C–H, N–H, O–H, and S–H bonds absorb energy at characteristic wavelengths through overtones and combination bands, producing broad, overlapping spectral bands requiring chemometric interpretation.

Two measurement modes are commonly used for medicines analysis:

- **Transmission mode on sample solutions:** The sample is placed in a glass cuvette (1–2 mm path length for liquids) or specific accessories (for solid samples) within the light beam. Transmittance (T) is measured relative to a background (air or empty cell). This mode ensures representative sampling of dose proportional formulations or multilayer tablets and may result in accurate quantitative measurements. For aqueous solutions, small path lengths avoid signal saturation at water absorption bands (1950 and 1450 nm).
- **Diffuse reflectance mode:** The light that has penetrated and re-emerged from the sample is measured. This is the most common measurement mode for solid samples. Reflectance (R) is computed using a highly reflective reference material (such as PTFE, gold, or ceramics). Measurements are performed directly on the device's sensor or using fibre-optic probes.

Transmittance and reflectance are classically converted to absorbance: $A = -\log_{10}(T)$ and $A = \log_{10}(1/R)$ that may be plotted against wavelength (λ, nm) or wavenumber ($\tilde{\nu} = 1/\lambda$, cm^{-1}) to constitute a spectrum.

Main types of devices. NIR spectrophotometers contain three main components: a light source, a light processing element, and a detector. Instruments fall into two categories: (i) Fourier transform (FT) spectrophotometers use an interferometer to convert incoming light into modulated light, which interacts with the sample and is detected as an interferogram then converted into a spectrum via

Fourier transform. (ii) Dispersive spectrophotometers use filters, gratings, or prisms to physically separate light into component wavelengths. FT spectrophotometers offer higher signal-to-noise ratios (enabling faster measurements), superior wavelength accuracy, and linear wavelength scales for more precise calibration.

NIR spectrophotometers are available as benchtop, portable, handheld, and miniature devices. Most benchtop instruments use FT technology and measure across the complete NIR range, whilst most portable and handheld devices use dispersive technology and cover only partial NIR ranges. When using portable or handheld devices, operators must verify that the instrument covers wavelengths where medicines of interest show characteristic absorption patterns, either through published literature or initial testing with a full-range benchtop device. Modern miniature NIR devices are increasingly used due to their excellent analytical performance relative to cost.

6.1.5.3 Mid-infrared spectroscopy

Mid-infrared (MIR) spectroscopy is based on the same light absorption principle as near-infrared spectroscopy but covers 2.5–25 µm (4000–400 cm^{-1}). Absorption arises mainly from fundamental transitions, producing sharp spectral features characteristic of functional groups (functional bands; above 1500 cm^{-1}) or the molecule as a whole (fingerprint bands; below 1500 cm^{-1}).

Major MIR measurement approaches in pharmaceutical analysis are:

- Transmission: Solid samples are powdered and mixed with an alkali halide (such as KBr) at 1:100–400 ratio, pressed into a disc, and placed in the light beam. Non-aqueous liquids are placed between two alkali halide discs. Background measurements using pure alkali halide discs remove ambient air interference (mostly CO_2 and H_2O). Other procedures may be used to acquire transmission spectra (such as mulls, compression cells, transmission cells).
- Attenuated Total Reflection (ATR) spectroscopy: ATR-IR enables simpler, faster collection of IR spectra from solid or liquid samples without preparation. Light passes through an internal reflection element (IRE) (made of diamond, ZnSe, Ge, or Si), generating an evanescent wave that penetrates a few microns into the sample before reaching the detector. The sample is pressed onto the IRE to ensure close, uniform contact. ATR-IR spectra are typically limited to 4000–650 cm^{-1} due to IRE cut-off. Background is measured using air and a clean IRE.

Main types of devices:

MIR spectrophotometers are available in three main formats: benchtop, portable, and handheld devices. Most MIR instruments are FT spectrophotometers, with handheld devices typically being ATR-based instruments with fixed spectral resolution.

6.1.5.4 Vibrational spectroscopy specific considerations

This section provides guidance on implementing reflection vibrational spectroscopic methods for pharmaceutical solid dosage form analysis. It aims to help practitioners select among Raman, NIR, and MIR spectroscopy based on application requirements and technical limitations.

Limit of detection

The limit of detection for APIs using Raman, NIR, or MIR reflection spectroscopy typically ranges from 1-2% (w/w) of the total formulation, though this varies with the specific API and formulation composition. Surface-Enhanced Raman Scattering (SERS) improves sensitivity by increasing the API signal. SERS can be performed with most instruments that accommodate glass vials but requires sample destruction (grinding) and mixing with silver or gold nanoparticle substrates and is limited to qualitative use due to reproducibility issues.

Sample positioning

Consistent sample positioning is critical for reproducible NIR and Raman measurements. While straightforward for liquid samples in vials or bulk powders, positioning becomes challenging when measuring through packaging (for example blister packs) or analysing hard capsules. Handheld devices offer various sample presentation accessories, and some benchtop instruments incorporate autofocus features to maintain consistent positioning. MIR-ATR circumvents this issue, as samples are usually powdered and pressed directly onto the instrument's internal reflection element to ensure intimate contact.

Measurement representativeness

Reflection spectroscopy interrogates only the sample surface, with penetration depth varying by technique: NIR penetrates hundreds of microns to several millimetres, Raman spectroscopy reaches several dozen microns, and MIR-ATR probes only a few microns below the surface. To improve NIR and Raman representativeness, measure both sides of multiple units per sample. For MIR-ATR, grind multiple tablets and measure several aliquots of the resulting powder. Additional sampling considerations are discussed in Chapter 10.

Pharmaceutical tablets present specific challenges for spectroscopic techniques. When focused on the surface, coating materials (such as titanium dioxide, TiO_2) may dominate the Raman spectrum and obscure signals from the underlying API. NIR spectroscopy is less affected by coatings due to its greater penetration depth, although certain coating materials (notably iron oxides) can reduce signal quality.

To address this, compare spectra from intact tablets (using different lenses if available) with spectra from tablet cores (obtained after coating removal, cutting, or grinding). Select the least invasive

measurement configuration that still provides representative information about the sample's core. Sugar coatings may block core signal entirely, requiring sample destruction.

Capsule shells contain water, with concentrations that vary depending on sample age and storage conditions. This introduces unwanted spectral variability in MIR measurements. Furthermore, the low powder density within capsules reduces light scattering efficiency, resulting in decreased signal-to-noise ratios for both NIR and Raman spectroscopy. These factors may necessitate alternative sampling strategies, such as opening capsules and analysing the contents directly as bulk powder.

Coloured samples

Coloured samples (coatings, capsules, herbal/dietary products) may fluoresce, overwhelming Raman signals. SERDS, SSE, SORS, or longer laser wavelengths (1064 nm) can mitigate this. The colour of the sample generally does not interfere with NIR or MIR measurements.

Weak or noisy signals may require longer exposure or higher laser power, risking thermal damage (melting, burning). 1064 nm lasers pose higher risk due to inherently weaker signals and higher power needs. Mitigation strategies include reducing power, raster scanning, or increasing spot size to distribute energy. Neither NIR nor MIR spectroscopy are affected by local heating of the sample.

Measurement through packaging

Transparent packaging (plastic bags, glass vials, clear blisters, gel capsules) generally permits Raman measurement. Opaque or thick packaging may block signals; alternatives include unpacking, SORS, or specialized optics. Through-packaging analysis may experience issues when packaging has degraded (such as blister packs exposed to UV light). Such alteration of packaging's properties can compromise the analysis of the sample signal or introduce spectral variability that is not linked to sample's quality.

When analysing ground samples, container selection depends on the technique: glass vials are suitable for NIR measurements, whilst thin polyethylene bags are preferable for Raman spectroscopy. Due to its shallow penetration depth, MIR-ATR cannot analyse samples through packaging.

Ambient light protection

Raman spectrometers require protection from ambient light during measurement; most include covers, nose cones, or tablet holders to shield the detector. NIR reflection measurements are considerably less sensitive to ambient light interference and typically require no special protection measures. However, measurements under direct sunlight should be avoided.

6.2 Analytical performance of screening technologies

The following comparison of the analytical performance of different screening technologies is based primarily on recent reviews by Zambrzycki et al. *(27)*, Caillet et al. *(28)* and Sacré et al. *(29)*.

Table 1 summarizes the performances of each screening technology to facilitate a quick comparison. A more detailed explanation of each scoring is provided in the text.

Table 1: Estimate of the performance of different analytical technologies for different purposes in the analysis of SF medicines.

●●●●● signifies the most desirable score for the respective criterion. The exact performance of each technology depends on the specific experimental task, the specific device used, and the experimental protocol followed.

	Visual inspection and instrumental packaging analysis	Thin-layer chromatography	Raman spectroscopy	Near-infrared spectroscopy (reflection mode)	Near-infrared spectroscopy (transmission mode on sample solutions)	Mid-infrared spectroscopy	Paper-analytical devices	HPLC-UV	HPLC-Mass spectrometry
Confirmation of declared API (= identity testing)	○○○○○	●●●●○[1]	●●●●●	●●●◐○	●●○○	●●●●○	●●●○○	●●●●◐[1]	●●●●●
Quantification of API amount (= assay testing)	○○○○○	●●○○○	●●○○○	●●●○○	●●●●○	●●●○○	●○○○○	●●●●●	●●●●◐
Dissolution testing	○○○○○	○○○○○	○○○○○	○○○○○	○○○○○	○○○○○	○○○○○	●●●●●[2]	○○○○○
Identification of unknown APIs	○○○○○	●◐○○○[1]	●●●●○	●○○○○	●○○○○	●●●●○	○○○○○	●●●○○[1]	●●●●●
Impurity testing	○○○○○	●○○○○	◐○○○○	◐○○○○	◐○○○○	◐○○○○	○○○○○	●●●●●	●●●●●
Differentiation between brands with identical API composition	●●●●○	○○○○○	●●○○○	●●●●●	○○○○○	●●●○○[3]	◐○○○○[3]	○○○○○	●●○○○[3]
Detection of manipulated expiry dates	●●●●○	○○○○○	○○○○○	○○○○○	○○○○○	○○○○○	○○○○○	○○○○○	○○○○○
Detection of contamination with DEG/EG	○○○○○	●●●●○	◐○○○○	○○○○○	○○○○○	○○○○○	○○○○○	●●●●○[4]	●●●●○

[1] Reference standards for the declared API (or for the unknown API) are required.

[2] In combination with a dissolution testing apparatus.
[3] If the different brands contain different excipients.
[4] After chemical derivatisation.

6.2.1 Confirmation of declared API (= identity testing)

Confirming the presence of the declared active pharmaceutical ingredient is a primary objective of screening technologies. Visual inspection cannot detect chemical composition and is therefore unsuitable for API confirmation.

HPLC, with adequate detection device, offers the highest specificity and sensitivity for API identification in finished pharmaceutical products (FPPs).

Raman spectroscopy is particularly well suited for targeted API identification, being rapid, non-destructive, and simple to perform. For most APIs in tablets, detection relies on comparing measured spectra against pre-built databases of chemical reference standards, which are commercially available for thousands of compounds. However, the technique requires sufficient API concentration and may suffer from interference by fluorescence, packaging materials, and coloured coatings.

TLC and PADs are highly effective but have distinct limitations. Both require sample destruction. TLC is time-consuming and necessitates parallel analysis with reference standards; if spraying reagents are used for detection, this demands laboratory facilities with fume hoods. PADs are very simple to use, and their interpretation can be facilitated through a mobile application. However, they lack specificity; different APIs with similar functional groups may produce confounded results in PAD analysis, while they are usually well separated in TLC analysis. Currently, PADs are available for only approximately 20 APIs, while TLC analysis protocols are available for many more APIs. Both TLC and PADs offer the advantage of not requiring pre-calibration, allowing trained users to analyse samples directly.

Mid-infrared spectroscopy (MIR) offers specificity comparable to Raman spectroscopy and is unaffected by fluorescence or coating interference. However, MIR requires sample destruction through pulverisation and is unsuitable for aqueous media or hygroscopic powders due to water interference.

Near-infrared spectroscopy (NIR) in diffuse reflectance mode is rapid, non-destructive, and easy to apply but requires comprehensive spectral databases of FPPs. Chemometric analysis is also required due to the lack of sharp spectral features and sensitivity to physical properties. These requirements, notably the absence of comprehensive spectral database of FPPs, complicate its implementation as a screening technology. NIR transmission mode after sample dissolution may overcome some limitations but still requires sample destruction and extensive calibration standards preparation for chemometric modelling, whilst solvent signals may obscure API signatures.

Current screening technologies, along with most compendial methods, fail to distinguish between enantiomers (optical isomers) of a given API, making the presence of an incorrect enantiomer, or of a racemate instead of a pure enantiomer, particularly difficult to detect.

6.2.2 Quantitation of API amount (= assay testing)

After confirming API identity, determining the correct amount is essential, as incorrect API content is the most reported quality defect in substandard and falsified medicines (see section 5). Some screening technologies provide quantitative or semiquantitative results on API content, though typically with lower accuracy and precision than compendial methods. Unfortunately, most screening technologies fail to detect samples containing 80% of the declared API as non-compliant, and even samples containing only 50% of the declared API are often wrongly classified as compliant *(27)*.

HPLC is recognized as the gold standard for API quantitation due to its versatility, sensitivity, and specificity. The most effective analytical combination uses HPLC separation with mass spectrometry detection for compound identification and ultraviolet (UV) detection for quantitative performance and linearity.

Vibrational spectroscopic techniques can provide comparable quantitative performance under specific conditions. Benchtop transmission equipment using NIR or Raman spectroscopy for liquid or solid samples can achieve results comparable to HPLC in some cases. However, diffuse reflectance modes (benchtop or handheld) measure only sample surfaces, limiting accuracy for non-homogeneous samples or multi-layer tablets. Mid-infrared spectroscopy circumvents this through sample pulverisation, ensuring representative sampling. Non-destructive reflectance analysis of hard capsules is particularly challenging due to spectral distortions from poor measurement reproducibility of encapsulated powders.

A major limitation of vibrational spectroscopy for API quantification is the requirement for chemometric modelling. Calibration is time-consuming, resource-intensive, and requires specialized expertise in chemometrics and data analysis *(30, 31)*, typically involving preparation and measurement of numerous reference samples with known API concentrations. Once calibrated and validated, routine analysis becomes rapid, straightforward, and potentially non-destructive. Consequently, these methods are typically employed only when large numbers of similar samples require routine analysis, reducing chromatographic workload. This approach suits manufacturing quality control environments better than regulatory screening laboratories where sample types vary considerably.

TLC provides quantitative information through spot intensity, typically estimated by visual comparison with standard solutions at different concentrations. However, this visual estimation lacks precision and detects only large quantitative deviations *(20)*. High-performance TLC (HPTLC) may

provide competitive alternatives to HPLC but requires more advanced laboratory equipment than simple TLC.

PADs with visual assessment provide primarily qualitative results. Semiquantitative PAD evaluation can be carried out with mobile applications but remains very imprecise.

6.2.3 Dissolution testing

Compendial dissolution testing uses standardized dissolution apparatuses and typically HPLC-UV to quantify the dissolved API. Testing requires significant time and large numbers of dosage units that may be difficult to obtain in field studies. A small-scale dissolution method using fewer dosage units has been reported *(32)*, but it still relies on the same compendial technology. Currently, there is no commercial field-portable device which allows testing of the dissolution of FPPs in a rapid, easy-to-use manner.

6.2.4 Identification of unknown APIs

This section refers to the untargeted API identification in a suspect sample — a task inherently more complex than targeted identification, as it must proceed in the absence of, or in the presence of misleading, prior information regarding the nature or identity of the API present.

In such scenarios, the most effective analytical tools are those equipped with comprehensive, well-curated reference databases capable of facilitating direct spectral or chromatographic matching. Among these, high-performance liquid chromatography coupled with mass spectrometry (HPLC-MS) and Raman spectroscopy stand out as the methods of choice, owing to their high discriminatory power and broad spectral coverage.

HPLC-UV, particularly when employing diode array detection (DAD) to capture full UV spectra, may yield some preliminary insights. However, UV absorption profiles are generally non-specific and offer limited discriminatory capacity. Consequently, HPLC-UV should be employed only in a confirmatory capacity, that is to corroborate the identity of a suspected API by direct comparison with a reference standard.

Mid-infrared spectroscopy benefits from commercial databases, but excipient interference often obscures API signals. It may still aid identification by revealing functional groups.

NIR spectroscopy is poorly suited for unknown API identification. Its broad, overlapping bands reflect both chemical and physical sample properties, hindering differentiation. While, in principle, comparison against a comprehensive database of FPPs could facilitate identification, no such commercially available NIR spectral library currently exists, further limiting the practical utility of NIR for untargeted API identification.

TLC can detect unknown APIs only if compared against a reference standard therefore requiring prior suspicion of the API. Thus, it serves confirmatory, not exploratory, purposes.

PADs are explicitly designed for targeted detection and are therefore unsuitable for untargeted screening.

6.2.5 Impurities testing

Analysis of impurities is critical to the quality of pharmaceutical products. Permitted levels vary by impurity type but are typically very low and often below the detection limit of most screening technologies.

Liquid chromatography with UV or MS detection remains the gold standard, offering the sensitivity and selectivity required for reliable identification and quantification of impurities.

TLC may detect some impurities, but the basic kit *(20, 33)* lacks quantitative capability, especially for low-level impurities. Advanced HPTLC may offer a viable alternative in select cases.

Raman, NIR, and MIR spectroscopies occasionally detect certain impurities but rarely with sufficient sensitivity or specificity for regulatory compliance. Structural similarity between compounds further limits their reliability.

PADs are not designed for impurity detection and cannot be used for this purpose.

6.2.6 Differentiation between brands with identical API composition

Identifying the brand of a FPP is important for detecting suspected falsified products by comparing samples with representative reference material. Screening tests are only indicative. Each screening technique provides specific information; when combined, these help to determine consistency between sample and reference products. However, confirmatory testing should be performed to unequivocally declare the falsified character of a sample. Further guidance is provided in a previous WHO document *(10)*.

Packaging analysis should be the first step in brand identity verification, being rapid, requiring no specialised equipment, and providing valuable information. Compare suspect packaging with authentic references for colours, fonts, printing quality, batch numbering, manufacturer details, and security features such as holograms and colour-shifting inks.

NIR spectroscopy in diffuse reflectance mode may effectively exclude medicines not belonging to specific brands by capturing physical and chemical information sensitive to formulation composition, particle size, density, and polymorphic forms. NIR transmission on intact solids may perform similarly or better, but transmission after dissolution cannot discriminate between brands as excipients are removed and physical information is lost.

Raman and MIR spectroscopy may exhibit spectral features from common excipients (lactose, microcrystalline cellulose, mannitol, titanium dioxide) aiding brand identification. However, strong API Raman signals (for example lumefantrine, paracetamol) may obscure excipient signals. MIR spectroscopy requires sample pulverisation, reducing physical information, and some APIs may dominate spectra.

HPLC and mass spectrometry create impurity fingerprints characteristic of manufacturing processes and raw material sources. Mass spectrometry provides additional markers such as isotope ratios. HPLC-MS can identify monosugars like lactose but not polymers (starch) or inorganic excipients.

TLC and paper analytical devices are unsuitable for brand confirmation as they detect only APIs, not complete formulation profiles. PADs may detect unexpected excipients like starch, revealing formulation changes. Whilst the TLC kit in this guidance *(20)* does not detect excipients, literature methods exist requiring targeted identification and method validation by qualified personnel.

6.2.7 Detection of manipulated expiry dates

It is important to distinguish between expiry date and medicine quality. The expiry date indicates the date until which a product is expected to remain within specifications when stored under defined storage conditions; the product should not be used thereafter.

A product does not necessarily undergo an analytically detectable change in physicochemical properties at the point of expiry. Therefore, screening technologies based on physicochemical properties analysis may not reliably detect manipulated or falsified expiry dates. Identifying such tampering requires visual packaging inspection and communication with manufacturers or regulatory authorities.

6.2.8 Detection of contamination with DEG/EG

The chapter of the International Pharmacopoeia dedicated to the testing of DEG/EG in liquid preparations for oral use describes a gas chromatography (GC-FID) as reference method to reach the 0.10% (w/w) level.

However, since GC-FID is not available in all national quality control laboratories, the chapter also describes an HPTLC procedure that can be implemented either as a semiquantitative limit test or as a fully quantitative test reaching the 0.10% (w/w) level, depending on the equipment used (such as automatic sample application and densitometric evaluation of chromatograms).

6.3 Practical, economic and environmental considerations

Practical considerations often determine whether screening technologies can be successfully implemented and sustained in specific operational environments. These factors encompass

operational requirements, resource needs, and usability characteristics that impact programme effectiveness. In addition to practical and economic considerations, environmental friendliness and operator safety are increasingly important in technology selection, particularly where waste management infrastructure is limited or operator safety training may be minimal.

The discussion below is based on the analysis of representative devices of each category considering preferably portable/low-cost devices to exhibit an objective technology scoring. Table 2 summarizes the performance of each screening device for practical, economic and environmental considerations. This score may change from the one displayed in Table 2 depending on the specific commercial device and the final application. The methodology used to compute the scores is detailed in *(29)*.

Table 2: Assessment of different analytical technologies based on practical, economic and environmental considerations.

●●●●● signifies the most desirable score for the respective criterion. The exact assessment of each technology depends on the specific experimental task, the specific device used, and the experimental protocol followed.

		Visual inspection and instrumental packaging analysis	Thin-layer chromatography	Raman spectroscopy	Near-infrared spectroscopy (reflection mode)	Near-infrared spectroscopy (transmission mode on sample solutions)	Mid-infrared spectroscopy	Paper-analytical devices	HPLC-UV	HPLC-MS
Practical and economical aspects	Time requirements for analysis	●●●●○	●◐○○○	●●●●●	●●●●●	●●●●○	●●●●●	●●●●○	○○○○○	○○○○○
	Cost of analysis	●●●●●	●●●◐○	●●○○○	●●●●●	●●●◐○	●●◐○○	●●●●●	◐○○○○	○○○○○
	Sample destruction	NA	○○○○○	●●●●◐	●●●●○	○○○○○	○○○○○	○○○○○	○○○○○	○○○○○
	Possibility to analyse different dosage forms	NA	●●●●◐	●●○○○	●●○○○	●●●●○	●○○○○	●●●○○	●●●●●	●●●●●
	Possibility to analyse different APIs	NA	●●●●●	●●●●●	●●●●●	●●◐○○	●●●●●	○○○○○	●●●●●	●●●●●
	Necessity to analyse a reference sample/substance	NA	○○○○○	●●●●●	●●●●●	●●●●●	●●●●●	●●●●●	○○○○○	○○○○○
	Portability	NA	●◐○○○	●●●●○	●●●●●	●●●●●	●●●●○	●●●●●	○○○○○	○○○○○
	Possibility for automatic interpretation of results	●○○○○	●●◐○○	●●●●◐	●●●◐○	●●●◐○	●●●●◐	●●●●●	○○○○○	○○○○○
	Calibration requirements	NA	●●◐○○	●●○○○	○○○○○	○○○○○	●●○○○	●●●●●	○○○○○	○○○○○
	Possibility for pre-calibration	NA	○○○○○	●●●●●	●●●●●	●●●●●	●●●●●	●●●●●	○○○○○	○○○○○
Environmental aspects	Use of chemicals	NA	○○○○○	●●●●●	●●●●●	●●○○○	●●●●●	●●●●◐	○○○○○	○○○○○
	Use of resources	NA	●●●◐○	●●●◐○	●●●◐○	●●◐○○	●●●◐○	●●●●○	◐○○○○	◐○○○○
	Safety of operator	NA	●●●◐○	●●●●○	●●●●●	●●●●◐	●●●●●	●●●●◐	●○○○○	●○○○○
	Waste generation	NA	○○○○○	●●●●●	●●●●●	●◐○○○	●●●●●	●●●◐○	○○○○○	○○○○○

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6.3.1 Time requirements for analysis.

Time requirements for analysis vary significantly between technologies and influence throughput capacity. One would expect a field-portable device to produce results as fast as possible. Among the technologies considered in this chapter, the fastest devices are the vibrational spectroscopy-based ones. They usually provide results in a few minutes (~2 min for a typical analysis). PADs and NIR spectroscopy in transmission mode for dissolved samples require more time (~10-15 min per sample). Longer analysis times are observed with TLC (~35 min per sample), and even more with HPLC which, in addition to the sample analysis time, requires a lengthy equipment preparation step before measuring each sample.

6.3.2 Cost of analysis

Cost of analysis includes both initial equipment investment and ongoing operational expenses.

Although handheld vibrational spectroscopy techniques can analyse samples at almost no cost per test, their high initial purchase price may constitute a barrier to acquisition. Therefore, the lowest overall cost of analysis is achieved with PADs and low-cost NIR miniature devices. TLC, NIR transmission mode, and MIR spectroscopy have an intermediate cost of analysis. The most expensive portable technology is Raman spectroscopy. This may change over time with the development of newer, less expensive devices.

Despite these differences among field-portable devices, their cost of analysis per sample remains significantly less expensive compared to HPLC-UV and HPLC-MS.

6.3.3 Sample destruction

Sample destruction occurs when measurements require a change of the sample's physical or chemical state, e.g. by crushing a tablet and extracting the API. Non-destructive methods are preferable as they preserve dosage units for further use. Non-invasive methods leave both dosage units and packaging undamaged. Destructive methods require collection of a sufficient number of dosage units for both screening analysis and confirmatory analysis, whereas non-destructive approaches permit the same dosage units to undergo both tests.

Many screening technologies (PADs, TLC, NIR spectroscopy in transmission mode, MIR spectroscopy) as well as HPLC require destruction of the sample through either dissolution or grinding. In contrast, NIR and Raman spectroscopy in reflection mode are non-destructive and potentially non-invasive. Indeed, both techniques allow analysis of samples through most thin translucent containers but may be limited by several factors (see 6.1.4.4).

6.3.4 Possibility to analyse different dosage forms

While tablets represent the most common dosage form and are typically straightforward to analyse, technologies differ in their ability to investigate capsules, liquids, powders, creams, and gels. This variation in dosage form compatibility affects the range of medicine types that can be effectively screened using a particular technology.

Technologies requiring sample dissolution can usually be applied to a wide range of dosage forms (solids, liquids, or semi-solids). In contrast, technologies that analyse intact samples are typically more affected by changes in dosage form. In addition, infrared-based technologies are hindered by the presence of water in samples. Therefore, different databases and chemometric models must be developed for different dosage forms.

Reflection NIR and Raman measurements also experience difficulties analysing samples in hard capsules.

6.3.5 Possibility to analyse different APIs

Screening technologies vary in the number of APIs they can analyse. While broad coverage is ideal, each technology has limitations based on chemical properties, sensitivity, and the availability of reference materials.

Since most APIs exhibit Raman and/or IR-active bonds, vibrational spectroscopic techniques are highly versatile. However, spectroscopic techniques require reference spectra of the analysed APIs to be included in the database beforehand. Chromatographic methods may also be used to analyse a wide variety of APIs, but TLC and HPLC-UV require chemical reference standards. HPLC-MS is the most versatile technique, although APIs must be sufficiently volatile and ionizable under the instrument conditions. Transmission NIR spectroscopy on sample solutions may be limited by the solubility of the API in an appropriate solvent at detectable concentrations. PADs are the least versatile technology, as they are designed for specific APIs (covering only 20 APIs at the time of writing this guidance).

The analysis of several APIs in the same sample (that is fixed-dose combinations) may constitute a challenge for technologies apart from chromatographic techniques that separate the different components of the sample.

6.3.6 Necessity to analyse a reference

Reference requirements vary between technologies. TLC and HPLC require reference standards alongside test samples, creating logistical and financial challenges, particularly when screening diverse medicines or where reference materials are difficult to obtain.

Vibrational spectroscopy technologies require reference spectral databases containing previously recorded signatures for comparison. For Raman and MIR spectroscopies, laboratories can build databases using pure chemical standards, purchase comprehensive pre-built databases from manufacturers, or use third-party software platforms requiring recurring subscriptions. Commercial databases often contain thousands of reference spectra.

Currently, no commercial NIR spectral database of FPPs exists; each user must develop their own database, representing significant time and resource investment. This constitutes the main limitation to widespread NIR spectroscopy adoption. Additionally, NIR spectral databases cannot be easily deployed across devices from different manufacturers, further limiting broader use.

PADs do not require reference analysis.

6.3.7 Portability

Screening may be carried out directly at the site where medicines are encountered. Alternatively, samples can be collected and transported to a dedicated location for analysis. While in the latter scenario, benchtop devices with higher performances may be used, in the former scenario, portability of the device is essential.

Many field-portable devices are battery-powered and light enough to be carried by individual users if needed. Some other devices still require mains power and/or placement on a stable, vibration-free surface during measurement to ensure accurate data acquisition. Larger instruments may still be transportable with the aid of a vehicle.

Although some portable HPLC devices exist, most are benchtop systems requiring both mains power and laboratory settings. TLC *per se* is portable. However, the most well-known kit used in the frame of SF medicines analysis is rather classified as transportable *(20)*. MIR spectrophotometers exist as handheld devices and some NIR and Raman devices are classified as miniature. PADs, consisting of a small piece of paper, are also classified as miniature.

6.3.8 Possibility for automatic interpretation of results

Automatic reporting of an easy-to-understand result such as “pass” or “fail”, possibly with a confidence score, reduces operator skill requirements and improves result consistency. Some devices include built-in automatic reporting features, others allow such reporting after moderate method development (that is after building chemometric models), and again other technologies cannot provide automatic interpretation at present.

Most handheld MIR, NIR and Raman spectrophotometers have embedded computers and provide automatic spectral interpretation. Benchtop MIR, NIR and Raman instruments may require additional

software add-ons, potentially increasing cost. However, the spectral comparison algorithms (usually based on correlation computation) readily available in the devices may not be sufficient for more demanding tasks and will require the development of chemometric methods possibly outside the equipment software suite.

A mobile application is available for the automatic interpretation of PADs facilitating their analysis and removing between-operator variability *(25)*.

Ready-to-use software for reliable automatic interpretation of TLC results is not available at present.

6.3.9 Calibration and maintenance

Calibration and maintenance requirements directly affect operational sustainability, and local technical support availability significantly influences technology viability.

NIR reflection spectrophotometers, particularly handheld instruments, require minimal equipment maintenance but need regular updates of FPP spectral databases and chemometric models for reliable results. NIR transmission spectroscopy requires calibration and maintenance of chemometric models plus sample preparation consumables, relying on quantitative modelling rather than direct spectral matching.

Raman and MIR spectroscopy in reflection mode offer greater operational flexibility, usable with commercial pure reference spectral libraries requiring no calibration or maintenance for routine qualitative identification. However, advanced applications such as quantitative analysis or specific formulation detection require developed and maintained chemometric models.

PADs have no calibration or maintenance costs but are single-use devices requiring replacement after each use.

Thin-layer chromatography requires regular renewal of consumables (plates, solvents, reference standards) but minimal equipment maintenance.

HPLC requires the most substantial calibration and maintenance efforts. Beyond chemicals and consumables, several components need frequent replacement, including analytical columns, tubing, seals, and other hardware. Consumable needs create ongoing logistical and financial challenges, particularly in remote locations with unreliable supply chains.

6.3.10 Possibility for pre-calibration

Pre-calibration capabilities allow experienced personnel to perform initial device setup, enabling extended field use by operators with limited technical training. This characteristic is particularly valuable for spectroscopic technologies (Raman, NIR, and MIR) deployed in field applications and may

counterbalance the substantial efforts required for calibration and maintenance of spectral libraries and chemometric models.

TLC and HPLC, by contrast, cannot be pre-calibrated in the same manner but require preparation of fresh reference standards for each analytical session. Quantitative HPLC analysis requires calibration curves, demanding more extensive user training and ongoing technical expertise throughout operation.

6.3.11 Training time

Training time needed to enable routine technology use by non-technical personnel varies significantly between technologies and affects implementation feasibility in settings with limited technical capacity. It may be defined as the time needed to undergo a basic training in the technology, enabling its routine use for a non-technical user *(20)*.

PADs require the least training time among screening technologies. Minimal training, even for users with no prior technical background, can be completed in less than one day.

Spectroscopic methods can be performed by non-technical users after 1-2 days of training for handheld pre-calibrated devices. Benchtop spectrophotometers typically require more extensive training of several days depending on the specific instrument and application. Advanced spectroscopy training (enabling users to create spectral libraries and develop chemometric models) requires substantially longer, specialized instruction spanning several weeks to months.

TLC and transmission NIR spectroscopy on sample solutions require intermediate training of approximately one week to enable non-technical users to execute pre-established methods reliably.

HPLC-UV and especially HPLC-MS require the most extensive training among screening devices, typically spanning several weeks to months depending on the complexity of methods and the user's prior analytical chemistry background.

6.3.12 Environmental impact and safety of operator

Reflection spectroscopic methods (NIR, MIR, and Raman) do not require chemicals and generate no waste, making them environmentally sustainable options. IR-based techniques (NIR and MIR) are inherently safe methods for operators. Raman spectroscopy employs powerful laser sources that may pose eye hazards if proper safety protocols are not followed; however, modern handheld Raman devices incorporate safety features that minimize these risks when used correctly. Spectroscopic methods consume minimal resources beyond electricity for instrument operation.

PADs have a relatively low environmental impact. The pre-loaded chemical reagents are present in very small amounts and generate non-toxic by-products, making them safe for operators to handle

without specialized protective equipment. However, PADs generate waste due to their single-use, disposable nature. While the materials are generally non-hazardous and can be disposed of as regular waste, the cumulative waste volume can become significant in high-throughput screening scenarios.

TLC, HPLC, and transmission NIR spectroscopy on sample solutions are "wet-chemistry" technologies requiring the use of chemicals (organic solvents, acids, bases, visualization reagents, etc.) that have a significant environmental impact. Among these techniques, HPLC requires the largest volumes of chemicals and generates the most waste, particularly organic solvent waste that requires proper disposal procedures. Due to the handling of potentially hazardous chemicals, these techniques pose greater safety risks to operators compared to other screening technologies. An appropriate laboratory infrastructure and personal protective equipment may be required to mitigate these hazards. TLC requires at least well-ventilated laboratory room, and fume hoods if spraying reagents are used for detection.

When in use, HPLC requires a stable mains power supply, which may complicate its implementation in laboratories with unreliable electricity infrastructure. In contrast, transmission NIR spectroscopy on sample solutions and TLC require only modest amounts of electricity—for UV light visualization or hot plate reactions—and can largely operate on battery power, making them more suitable for resource-limited settings.

7 Further screening technologies

This section briefly presents technologies which have not yet been used widely in the screening for SF medicines, and/or for which not yet sufficient evidence is available to allow a well-informed decision on their deployment for medicine quality testing. This section also includes technologies which are currently not commercially available.

7.1 X-ray fluorescence (XRF) spectroscopy

X-ray fluorescence spectroscopy employs X-rays to excite atoms within a sample, causing them to emit secondary (fluorescent) X-rays at element-specific energies. The analytical sensitivity increases with atomic number, making XRF particularly effective for detecting heavy elements and metals. XRF spectroscopy can therefore analyse the inorganic compound composition of pharmaceutical dosage forms and their coatings, which is often manufacturer-specific, enabling differentiation between authentic and falsified medicines *(34-37)*. The technology can also detect the presence of toxic heavy metals that may be present as contaminants *(38)*.

XRF spectroscopy requires minimal sample preparation and provides rapid, non-destructive analysis without the need for solvents or chemical reagents. The cost of XRF field-portable devices is comparable to that of portable Raman spectrometers. Training requirements for XRF operation are modest but must include comprehensive safety protocols due to ionizing radiation hazards. Effective use of XRF for pharmaceutical authentication requires access to a reference spectra database from authentic products for spectral comparison, which must be continuously updated with new formulations and manufacturers.

XRF spectroscopy has not been widely adopted for the detection of SF medicines, but the technology shows potential for broader implementation in medicine quality surveillance programmes.

7.2 Lateral flow immunoassays

Lateral flow immunoassays are widely used rapid diagnostic tests, exemplified by pregnancy tests and rapid COVID-19 antigen tests. These assays utilize monoclonal antibodies and are extensively employed for point-of-care diagnostic testing due to their low cost, operational simplicity, and minimal equipment requirements. In conventional diagnostic applications, target antigens are typically macromolecular structures. Small molecules such as most APIs require alternative assay designs, typically employing competitive format approaches *(39)*.

A few prototype lateral flow immunoassays have been developed for single APIs *(40, 41)*, or for simultaneous detection of different APIs *(42)*. These assays enable qualitative detection but have limited semiquantitative capability. The technology is limited by restricted analytical versatility—each assay typically targets only a narrow range of APIs—and poor quantitative performance. No lateral flow immunoassays specifically designed for detecting active pharmaceutical ingredients are currently marketed, apparently due to insufficient market demand. However, lateral flow immunoassays may offer significant advantages for detecting substandard and falsified vaccines *(43)*.

7.3 Nanosensors

Nanosensors employ nanoscale materials or phenomena to detect specific analytes, such as APIs in solution *(44)*. Due to features that arise at the nanoscale and are not present in bulk material, nanosensors can have benefits over sensors made from traditional materials, for example in their sensitivity and specificity. Detection usually relies on selective binding between the analyte and a recognition element. Many different types of nanosensors have been developed, but so far they have seen little use in the detection of SF medicines.

7.4 Microfluidic systems

A microfluidic system is a miniaturized device that processes very small volumes of fluids—typically in the microliter to nanoliter range. It may be used to perform laboratory functions such as chemical analysis, sample mixing, separation, and detection on a compact platform. Researchers at Boston University developed an automated portable microfluidic system *(27, 45-47)* which performs chemistry- or aptamer-based small molecule detection and allows analysis of API content as well as API release. However, it is currently limited to the detection of very few APIs, and the device is not commercially available.

7.5 Colorimetry

Since 1986, WHO has published several manuals *(48-50)* which describe colorimetric tests to identify pharmaceutical substances by producing a visible colour change when the drug reacts with a specific reagent, allowing qualitative and semiquantitative tests for the API content. Colorimetric tests have now been largely superseded by more powerful analytical technologies such as TLC and spectroscopic methods. The Global Pharma Health Fund (GPHF)-Minilab has discontinued the use of colour reactions and now only offers the kit for TLC analysis *(51)*. On the other hand, the paper-analytical devices described in section 6.1.3 represent a newly introduced type of colorimetric tests, using several colour reactions simultaneously.

7.6 Additional optical screening technologies

Reflectance. Several technologies measure diffuse and/or specular reflection of visible light of different wavelengths for investigating materials and surfaces. Examples include instruments that measure directional-hemispherical reflectance, glossmeters, or spectrophotometers measuring the reflectance spectrum of solid materials in the visible range. Some of these have been evaluated as screening devices for the detection of SF medicines *(52-54)*. However, most of the instruments used in these studies are not or no longer commercially available. The published evidence is currently too limited to support a recommendation regarding their deployment for medicine quality testing.

Multi-modal optical detection systems. The United States Food and Drug Administration has developed several generations of a “Counterfeit Detection Device” termed CDx (such as CD3 and CD3+), aimed primarily at the identification of falsified medicine. This handheld, relatively inexpensive tool is used to illuminate medicine samples (both packaging and dosage units) with light from multiple single wavelength light-emitting diodes (LEDs) *(55, 56)*. The image is visualized with charged-couple device (CCD) cameras, with various filters placed on the camera lenses. By comparison with an

authentic sample, falsified products are visually distinguishable. A problem observed in a field test *(57)* was that pharmaceutical manufacturers produced and marketed the same genuine medical product in differently styled packaging, making it difficult to use packaging analysis for the identification of falsified medicines. The CDx devices are not commercially available.

Another device, also not commercially available, was termed Counterfeit Drug Indicator (CoDI) *(58, 59)*. It is a battery-operated handheld device incorporating a 405-nm laser, a photoresistor, and digital voltmeter. The intensity of light either transmitted through the sample or generated by fluorescence is measured, with or without red or blue filters placed over the photoresistor. The measured values are used to distinguish authentic and falsified medicines. The device is not commercially available.

A spectroradiometer is a specialized spectrometer that measures the absolute amount of electromagnetic radiation at each wavelength. A study has been published on the use of such an instrument with a wavelength range of 350 - 1050 nm for the detection of falsified medicines *(60)*, but the employed instrument *(61)* is no longer commercially available.

7.7 Miscellaneous physical, chemical and microbiological screening technologies

Refractometry.

Measurement of the refractive index can be used as a non-specific method to estimate the concentration of an active pharmaceutical ingredient (API) in solution *(62)*. However, refractometry has not been mentioned among the important methods for SF medicine detection in recent years.

Density measurement. Density and specific gravity are important characteristics of pharmaceutical raw materials and formulations *(63)*. The density of liquid pharmaceutical raw materials, or of liquid formulations, may be measured with simple acoustic instruments, and this may allow the identification of falsified liquid oral formulations *(64)*. However, no detailed investigations have been published on this method.

Titration. Titration methods have been used for wet-chemical quantitative analysis for many decades but are not typical methods for screening analysis. An automatic titrator has been described for the rapid quantification of several APIs *(65)*, but the device is not commercially available.

Sterility testing. A field-portable device to detect microbial contamination in sterile liquid samples has been described *(19)*, but is no longer commercially available.

8 Laboratory-based analytical technologies

Sections 6 and 7 present screening technologies. These allow the rapid detection of SF medicines, are easy to use and affordable. In contrast, more advanced laboratory-based analytical technologies allow a more detailed investigation of suspect samples, including the identification of unknown components in the investigated medical product, and can be used for confirmatory analysis. The necessary equipment is usually expensive, and its operation and maintenance require highly skilled personnel and an appropriate support infrastructure. Therefore, an effective use of these technologies is only possible in well-equipped and well-staffed laboratories.

Beyond the three exemplary technologies listed below, many further ones exist for pharmaceutical analysis, as listed in Appendix 1 of a previous WHO guidance *(10)* and in scientific publications such as *(66, 67)*.

8.1 High-performance liquid chromatography

High-performance liquid chromatography with UV detection (HPLC-UV) is a standard technology in many compendial pharmaceutical analyses. While it may not be considered as an advanced technology, its operation does require regular professional maintenance and qualification, an appropriate laboratory infrastructure and access to reference standards, reagents and consumables, limiting its applicability in low-resource settings. HPLC-UV provides compound identification and quantitative information. The analysis duration varies from minutes to hours depending on the method complexity.

HPLC can also be used with other types of detectors beyond UV detectors, and it can be coupled with mass spectrometric detection (HPLC-MS, see 8.2) offering highly specific information on the analyte through molecular mass and fragmentation patterns.

8.2 Mass spectrometry

Mass spectrometry is a powerful analytical technology that measures the mass-to-charge ratio of ionized molecules and molecular fragments. Mass spectrometers can be equipped with different ionization sources and mass analysers, adapted to specific analytical purposes.

In pharmaceutical analysis, mass spectrometry is often coupled with separation techniques such as liquid chromatography (LC-MS) or gas chromatography (GC-MS). This allows highly specific detection of APIs and excipients in pharmaceutical preparations, as well as the identification of unknown components and contaminants. MS-based techniques thereby provide high sensitivity and specificity and allow both qualitative and quantitative analysis of medicine samples.

Mass spectrometers are mostly benchtop instruments which require stable power supply, controlled laboratory environment, high-purity solvents and gases, and operators with specialized training in both chromatography and mass spectrometry. Portable spectrometers have been investigated for the rapid detection of SF medicines *(27, 68)*, but are expensive and have not seen widespread use in low-resource settings.

8.3 X-ray powder diffraction (XRPD).

X-ray powder diffraction is a crystallographic technique that measures the diffraction of an X-ray beam by crystalline structures. Mathematical analysis of the resulting diffraction pattern provides detailed information about the chemical structures and crystalline phases present in the sample. Commercial databases containing extensive diffraction data for APIs and excipients are available.

XRPD enables rapid, non-destructive analysis of multi-component mixtures with minimal sample preparation requirements. The technique offers high specificity for identifying crystalline APIs and excipients and is uniquely capable of distinguishing different polymorphic forms of the same compound *(69, 70)*. However, XRPD does not provide direct quantification of API content and therefore cannot reliably detect substandard medicines containing incorrect amounts of active ingredients, except for gross deviations.

XRPD devices suitable for pharmaceutical analysis range in cost from tens of thousands to hundreds of thousands of US dollars. The technique requires highly trained operators. Therefore, XRPD may primarily be used for confirmatory analysis of suspect medicine samples in well-equipped laboratories, rather than as a primary screening technology. XRPD has not been widely used in the detection of substandard and falsified medicines but shows potential for broader implementation in future.

9 Procurement of field-portable screening devices

9.1 General procurement considerations and qualification of commercial suppliers

The procurement of screening and detection technologies for substandard and falsified medicines must follow transparent, competitive, and documented procedures that are proportionate to the value and complexity of the purchase. These procedures should ensure best value for money, promote fair competition among qualified suppliers, and create an auditable trail that can withstand internal and external scrutiny. The United Nations Procurement Manual *(71)* and the WHO Guidance for

Procurement of in vitro Diagnostics and Related Laboratory Items and Equipment *(72)* provide guidance for such procedures.

In accordance with WHO rules and regulations, the present guidance does not describe individual branded devices, their manufacturers and their prices. Information on individual devices, including manufacturer names and contacts, price ranges, as well as technical and scientific data, can be found in the DAFODIL dashboard *(7)*, an interactive website on portable technologies for medicine quality screening established by the Medicine Quality Research Group of the University of Oxford. The current guidance should therefore be read in conjunction with the DAFODIL dashboard or similar sources of information.

9.2 Procurement considerations for specific screening technologies

9.2.1 Thin-layer chromatography

For medicine quality screening in LMICs, the materials and reagents for TLC are most commonly purchased in the form of a commercially available kit *(20)* which is also listed on the DAFODIL website *(7)*. The supplier offers international shipment, also of consumables for replenishment. The kit includes a manual with protocols for TLC analysis of 126 APIs, for testing disintegration and weight uniformity, and for visual inspection *(51)*.

However, the laboratory glassware, materials and consumables for TLC analysis (such as TLC plates, solvents, references, and staining reagents) can also be purchased from laboratory suppliers. Usually, TLC plates of 5 x 10 cm size coated with silica gel 60F254 are used. "60" denotes the average pore size of 60 Å, and "F254" denotes the presence of a fluorescence indicator which allows visualization of spots of UV-absorbing compounds under $UV_{254\ nm}$. Aluminium- or plastic-backed plates of larger sizes (for example 20 x 10 cm) can be cut to the desired sizes using scissors. Inexpensive battery-operated UV lamps may be used for detection, and an inexpensive commercial flat iron can replace a laboratory hot plate. International shipment of organic solvents is expensive, and attempts may be made to procure them locally.

References can be purchased from the supplier of the above-mentioned kit *(33)*. But also locally available medicines of good quality (for example medicines which have been investigated in the national medicine quality control laboratory) can be used as references; this may improve availability and save costs.

9.2.2 Colorimetric paper analytical devices (PADs)

The PADs described in section 6.1.3 are a relatively recent development by researchers at the University of Notre Dame, Indiana, USA. The technology has not yet been fully commercialized, and

international orders must be placed through that university *(73)*. Only a single type of paper cards is required for the analysis of all the APIs currently covered by this technology. The PADs can be ordered in packs of 10 or 20 cards. For initial training and certification of the analysers, a Training and Certification Pack including 14 PADs and 14 blinded samples can be ordered. The manufacturer states that PADs sealed in their original packaging are stable for at least 12 months if stored in a refrigerator, and stable for at least 4 months under tropical conditions. Once the zip-top bag is opened, the PADs should be stored in the bag and used within 2 weeks.

9.2.3 Vibrational spectroscopy

As discussed above, vibrational spectrophotometers require very few consumables or specific furniture. Standards required for calibration and qualification of the equipment are either furnished with the equipment, available from the equipment's manufacturer or from organizations like pharmacopoeias or the National Institute of Standards and Technology (NIST).

Considering the discussion in section 6, the user should pay attention to the following elements:

Common considerations:

- **Portability requirement:**
    - **Laboratory use:** Benchtop systems typically provide superior spectral performance, stability, and can operate on mains power for continuous operation.
    - **Field deployment:** Field-portable devices require careful evaluation of battery life, device weight, and ruggedness specifications (IP ratings for dust/water protection)
- **Spectral libraries/analysis capabilities:**
    - Availability of a preloaded database of pharmaceuticals (check the inclusion of APIs relevant for your application).
    - Possibility to build custom libraries.
    - Spectral comparison algorithms and/or possibility to develop and use own chemometric models
    - Targeted vs. untargeted analysis algorithms
- **Environmental and operational considerations:**
    - Temperature and humidity specifications for routine use.
    - Availability of local technical support, training, and spare parts.
    - Other additional considerations involve the availability of a training programme, warranty terms, spare parts availability and policies on software upgrades.
- **Regulatory and compliance aspects (if required):**

  - Software data integrity considerations
  - IQ/OQ/PQ documentation and services
  - Availability of qualification accessories/software options compliant with pharmacopoeia chapters
- **Sampling accessories:**
  - Availability of sampling probes (for solids, for liquids, …)
  - Measurement mode (usually reflection or transmission)

Specific considerations:

Raman spectroscopy:

When selecting a Raman spectrometer, regulatory staff should be aware that these devices (at the exception of some benchtop devices) have fixed technical specifications with limited or no possibilities for future upgrades or modifications. This makes the initial selection process critical for ensuring the device meets the laboratory's specific needs. It is therefore crucial for the user to correctly identify the final application and select the most appropriate device.

- Laser wavelength: 785 nm or 830 nm for general use, 1064 nm for fluorescence mitigation.
- Laser safety class: Class 1 laser systems preferred to maximize operator safety
- Wavenumber range: ensure that the selected device covers at least the 400 – 2000 cm^{-1} for identification purposes.
- Resolution requirements: ≤15 cm^{-1} resolution as specified in European Pharmacopoeia (2.2.48) for identification purposes (measured between 1000-1100 cm^{-1}).
- Analysis through packaging:
  - Working distance should be a few millimetres.
  - Availability of accessories to improve the depth penetration of the laser.
  - If analyses are intended to be performed through opaque containers, consider specialized technology such as SORS.

NIR spectroscopy:

- If the spectral range is smaller than 800 – 2500 nm (or 12500 – 4000 cm^{-1}), ensure that it is compatible with the expected application
- The spectral resolution may be modified for most Fourier transform instruments. It may however be fixed for field-portable devices. A typical spectral resolution of 10-15 nm is generally sufficient depending on the considered spectral range and application.
- If it is not possible to replace the light source, its lifetime is to be considered

MIR spectroscopy:

- For qualitative analysis, a spectral resolution of ≤ 4 cm^{-1} is generally adequate; higher resolution may be necessary for complex mixtures.
- Select crystal material (diamond, ZnSe, or Ge) based on sample type and chemical resistance.
- Benchtop MIR-ATR instruments require stable environmental conditions and mains power.

The DAFODIL dashboard *(7)* can be used to assist in selecting field-portable devices based on the criteria mentioned above.

10 Sampling, testing, and regulatory response for suspect SF medicines

Guidance on these topics is provided in the *WHO guidance on testing of "suspect" falsified medicines (10)*, which includes flow charts for testing and a model standard operating procedure. Additional WHO guidelines address procedures for sampling *(74, 75)*, for documentation *(76)*, and confirmatory testing *(11, 12, 75)*, including a model analysis request form *(11)*. Recently, comprehensive WHO guidance on *Good regulatory practices for market surveillance and control of medical products* was published *(13)*. It includes guidance on the use of screening technologies and should be read in conjunction with the present guidance.

Sampling: The size of any sample should be sufficient to carry out all anticipated test procedures, including all repetitions and including the retention samples. If the quantity of material available is not sufficient for the intended analyses and for the retention samples, the inspector must record that the sampled material is the available sample and the evaluation of the results must take account of the limitations deriving from the insufficient sample size. Samples should be stored in accordance with storage instructions for the respective medicine; closures and labels should be of such a kind that unauthorized opening can be detected.

National Action Plans. Rules for sampling, documentation, confirmatory testing, reporting, and regulatory action upon detection of suspect substandard and falsified (SF) medicines should be included in a national action plan (NAP) for prevention, detection, and response strategies. Guidance for developing such NAPs is provided in previous WHO documents *(13, 77)*.

Role of screening technologies in regulatory action. Screening technologies cannot replace confirmatory testing against official specifications and therefore cannot be used for licensing,

marketing authorization, or legal proceedings. Any litigation against suppliers or manufacturers of SF medicines must await confirmatory analysis results. However, a risk-based approach should guide decisions to quarantine medicines when severe quality deficiencies are suspected. As outlined in the recent WHO guideline on *Good Regulatory Practices for Market Surveillance and Control of Medical Products (13)*, confirmation by screening technologies that a product lacks the active ingredient or that API amounts are well below labelled amounts is sufficient to trigger regulatory action, such as quarantining the suspect medicines, particularly when confirmatory quality testing is not readily accessible. Quarantine should also be considered for medicines for which screening analysis indicates the presence of toxic contaminants such as diethylene glycol (DEG) or ethylene glycol (EG).

Standard operating procedures (SOP) for handling non-compliant results. Procedures for screening analysis results which are "non-compliant" should be part of the regulatory authority's QMS. These SOPs should be tailored to available confirmatory testing capacity. When confirmatory analysis capacity is limited, SOPs may recommend the following sequential steps:

i. Repeat the screening test with other dosage units from the same sample.
ii. If possible, repeat the screening analysis by a different operator.
iii. Re-test the sample using a second, orthogonal screening technology (for example thin-layer chromatography following initial testing with a spectroscopic technology).
iv. Conduct confirmatory testing using compendial methods (or equivalent methods) as soon as possible.

Further guidance is provided in the WHO Good Practices for Pharmaceutical Quality Control Laboratories *(12)*.

Reporting and communication protocols. The SOPs should specify after which of the above steps the suspect sample should be reported to the regulatory authority, to the manufacturer or marketing authorization holder, and to the WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products *(2)*. The SOPs should also indicate at which step quarantine should be considered. As described in previous WHO guidance *(10)*, all communications should refer to the manufacturer whose name appears on the packaging as the "stated manufacturer", making clear that the falsified medical product may not have originated from that manufacturer. Further guidance is provided in Appendix 9 of the WHO guideline on market surveillance and control *(13)*, which comprises WHO tools for collection, handling, and assessment of incidents, including an Aide-Mémoire on Substandard and Falsified Medical Products Incident Management and questions to consider when assessing risk.

11 Need for future research

While developing this guidance document, numerous evidence gaps and underexplored areas were identified. The following sections outline these gaps to strengthen the research foundation and direct future investigations.

11.1 Study methodology and reporting

Protocols for conducting and documenting screening technology evaluations lack adequate standardization. The resulting heterogeneity in evaluation methods and reporting formats impedes objective technology comparisons. Suggestions for standardization exist *(78)*, and the STARD Guidelines for Reporting Diagnostic Accuracy Studies provide additional guidance *(79)*.

Current research literature shows the need for:

- **Comprehensive API testing.** Studies should evaluate 20-50 active pharmaceutical ingredients (APIs) from the WHO Model List of Essential Medicines *(80)*. A systematic review found that the current median number of APIs tested per device was only two *(81)*.
- **Standardized API testing panels.** The seven essential antibiotics and antimalarials tested by Zambrzycki et al. *(27)*—artemether-lumefantrine, artesunate, azithromycin, amoxicillin-clavulanic acid, dihydroartemisinin-piperaquine, ofloxacin, and sulfamethoxazole-trimethoprim—could serve as a starting point.
- **Harmonized evaluation protocols.** These should assess field-portable devices against the tasks listed in Table 1 and evaluate their environmental, economic, and user safety profiles as outlined in Table 2.
- **Complete documentation.** Results should include the qualitative and quantitative composition of all investigated samples and the corresponding analytical results obtained with screening technologies.
- **Testing across dosage forms.** Evaluations should cover tablets, capsules, semi-solids, syrups, and injectable preparations.
- **Fixed-dose combination products.** These should be included in evaluations.
- **Quantitative assessment.** This should follow international guidelines *(9)*.
- **Limits of detection.** These should be determined for each technology.
- **Independent evaluation.** Researchers or institutions not involved in technology development or marketing should conduct assessments.

- **Real-world field testing.** Performance should be demonstrated under actual operational and environmental conditions.
- **Economic analyses.** Cost-effectiveness and return on investment should be evaluated.
- **Training requirements.** The extent and nature of necessary training should be assessed.
- **Maintenance protocols.** Requirements for maintenance, qualification, and calibration should be documented.
- **Technology combinations.** The performance of two or more screening technologies used together should be evaluated.
- **System integration.** How screening technologies can be integrated into market surveillance systems should be assessed.

11.2 Specific vibrational spectroscopy research requirements

- **Comprehensive reference spectral libraries.** Strategies are needed for creating extensive libraries of finished pharmaceutical products and raw materials, including international partnerships and collaborations with pharmaceutical manufacturers.
- **Cross-device spectral data transferability.** Methods to improve the transferability of spectral data across different devices should be developed.
- **User-friendly chemometric software.** Software should enable straightforward qualitative and quantitative vibrational spectroscopy applications without requiring extensive technical expertise.
- **Analysis through packaging.** The possibilities and limitations of analyzing dosage forms through sealed blister packaging and opaque containers should be determined.

11.3 Innovation requirements for screening technologies

Beyond currently available screening technologies, innovation is necessary in the following areas:

- **Low-dose formulations.** Qualitative and quantitative analysis methods for low-dose pharmaceutical formulations should be developed.
- **Dissolution testing.** Methods for dissolution testing of solid oral dosage forms are needed.
- **Chiral differentiation.** Technologies capable of differentiating between chiral enantiomer forms of APIs should be developed.
- **Impurity detection.** Testing methods for impurities and contaminants are required.
- **Sterility testing.** Rapid sterility testing methods should be developed.

- **Safety and sustainability profiles.** The environmental, economic, and user safety profiles of screening technologies should be improved.
- **Biologicals and vaccines.** Screening methods for biologicals (including monoclonal antibodies) and vaccines are needed.
- **Accelerated development pathways.** Mechanisms to expedite development and market introduction of novel screening technologies should be established, potentially using target product profiles.

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