WHO DRAFT GUIDANCE ON TESTING OF “SUSPECT” FALSIFIED MEDICINES

(August 2017)

REVISED DRAFT FOR COMMENT

Should you have any comments on the attached revision, please send these to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int) with a copies to Mrs Xenia Finnerty (finnertyx@who.int) and bonnyw@who.int by 1 October 2017.

Our working documents will be sent out electronically only and will also be placed on the Medicines website for comment under “Current projects”. If you do not already receive our draft working documents please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list.

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1. INTRODUCTION

1.1 “Suspect” medicines

“Suspect” medicines can be divided into the following main categories of products:

(a) substandard (S) medicines

Also called “out of specification”, these are authorized medicines that fail to meet either their quality standards or their specifications, or both;

(b) unregistered/unlicensed medicines

Medicines that have not undergone evaluation and/or approval by the national regulatory authority (NRA) for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

These medicines may or may not have obtained the relevant authorization from the NRA of its geographical origin;

(c) falsified medicines

Medicines that deliberately/fraudulently misrepresent their identity, composition or source. Any consideration related to intellectual property rights does not fall within this definition.

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1 Based on WHA70.23 for “medical products”.

2 When the authorized manufacturer deliberately fails to meet these quality standards or specifications due to misrepresentation of identity, composition or source, then the product should be considered “falsified”.
Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized medicine or the manufacture of a medicine that is not an authorized product.

“Identity” shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized medicine.

“Composition” shall refer to any ingredient or component of the medicine in accordance with applicable specifications authorized/recognized by the NRA.

“Source” shall refer to the identification, including name and address, of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable.

Medicines should not be considered as falsified solely on the grounds that they are unauthorized for marketing in any given country.

This document deals specifically with products that are suspected to belong to the third category.

1.2 Responsibility of regulatory authorities

NRAs have a duty to establish rules and instruments that control the production, distribution and commercialization of medical products in order to ensure their quality through rigorous regulatory oversight, including postmarketing surveillance, in line with national legislation and regulations on pharmaceutical products. Rigorous regulatory oversight of medical products throughout their life cycle is necessary to recognize and remove unauthorized and/or falsified products and to protect the supply chain against infiltration of such products.

Falsified products originate from inside or outside the legal supply chain. It is important that NRAs secure the supply chain and raise awareness of health workers and patients of risks associated with medicines from illegal sources.
A legal definition of falsified medicines and specific legal provisions to penalize acts related to falsification of medicines will empower NRAs to take actions against this problem. In implementing and enforcing legal provisions on falsified medicines NRAs should collaborate with customs, police, legislature, industry experts, judiciary, prosecutors and enforcement agencies at the national and international level as appropriate.

1.3 The role of the World Health Organization

The World Health Organization (WHO), through its Expert Committee on Specifications for Pharmaceutical Preparations, sets technical standards on quality assurance of pharmaceutical products, including guidance on registration, good manufacturing practices (GMP), good distribution practices (GDP) and quality control (QC) testing of medicines and other topics that are relevant to the regulatory oversight of medicines.

The Committee provided a guideline on sampling and market surveillance (1). A survey conducted among regulatory authorities of WHO Member States (2) indicated the need for specific technical guidance on laboratory testing of suspected falsified products. The present document was developed in response to the survey findings.

The Member State mechanism on Substandard/spurious/falsely-labelled/falsified/counterfeit medical products, created in 2012, makes recommendations to support regulatory authorities to prevent, detect and respond to activities and behaviours that result in falsified medical products (3). This document is intended to complement the Member State Mechanism’s recommendations in accordance with resolution WHA67.20 on Regulatory system strengthening for medical products (4).

2. SCOPE

This document provides technical guidance on laboratory testing of samples of suspected falsified products detected on the markets of WHO Member States and related aspects of sampling and reporting.
3. GLOSSARY

authorized product. A product in compliance with national and regional regulations and legislation. National or regional regulatory authorities can, according to national or regional regulations and legislation, permit the marketing or distribution of medical products with or without registration/license.

chain of custody. A chronological and continuous record of the seizure and custody of the suspect product and the subsequent transfer of a sample of the suspect product to the laboratory as well as the handling of the sample within the laboratory. The chain has to remain intact.

falsified product. For the purposes of this document, a product that deliberately/fraudulently misrepresent its identity, composition or source, and which therefore requires testing beyond the routine quality control testing. Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized product or the manufacture of a product that is not an authorized product.

“Identity” shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized product. “Composition” shall refer to any ingredient or component of the product in accordance with applicable specifications authorized/recognized by NRA. “Source” shall refer to the identification, including name and address, of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable.

forensic. Related to analysis for law enforcement purposes.

marketing authorization (product license, registration certificate). A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free
distribution of a pharmaceutical product in the respective country after evaluation for safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf life and approved conditions of use.

**quality assurance.** A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

**quality control.** All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other pharmaceutical characteristics.

**screening technologies.** The qualitative and/or semi-quantitative technologies which could rapidly acquire the analytical information or data for preliminary identification of suspect medical products in the field.

**standard operating procedure.** An authorized written procedure giving instructions for performing standardized operations both general and specific.

**substandard product.** For the purposes of this document, a substandard product is an authorized product that fails to meet either its quality standards or its specifications, or both according to the requirements in the territory of use. These standards and specifications are normally reviewed, assessed and approved by the applicable national or regional medicines regulatory authority before the product is authorized for marketing.

**unauthorized product.** A product that is not in compliance with national and regional regulations and legislation, being unknown to the authorities, and which therefore requires testing beyond the routine quality control testing.
4. DETECTION OF SUSPECTED FALSIFIED PRODUCTS

4.1 Entry points for detection

Regulatory authorities are responsible, in collaboration with relevant national and international stakeholders, for establishing mechanisms to detect falsified products circulating in their territories and to remove them from the market.³

Suspected falsified products can be detected using a range of approaches, including routine inspections performed by national or regional authorities and enforcement agencies, targeted risk-based surveys (1), investigation of complaints, follow-up of reports on any suspicious observations in the supply chain (for example, inconsistent documentation, unexpected stock levels) and investigation of unexpected adverse events reported to have occurred with a specific product. It is important to evaluate any information on suspected falsified products which may come from customs authorities, procurement agencies, pharmacies, health-care institutions or patients.

4.2 Detection methods⁴

Falsified products may be identified by their fake packaging and/or by physical and chemical testing.

³ See also reference (3), Paragraph II.1. Quality monitoring and control.

⁴ Further guidance on screening technologies is provided by the Working Group of the WHO Member State Mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products (3) through its prioritized activities 2014–2015, specifically Activity C, aiming to establish and convene a working group comprised of Member States experts to assess and report on: (a) existing “track and trace” technologies in use by Member States; and (b) existing field detection devices in use or available to Member States.
The packaging and patient information leaflets of suspect falsified medicines should always be examined visually and compared with samples or images of genuine products if available. Attention should be paid to any irregularities or inconsistencies, such as spelling mistakes, unusual batch numbers, unexpected or modified manufacturing or expiry dates, signs of repacking, for example, to circumvent inspection activities, or instructions in a language that do not match the area of their distribution. Microscopy and other analytical techniques (including but not limited to optical techniques) may be utilized for the package examination. The purpose of these technologies is to rapidly provide evidence that the sample is a falsified product.

A list of analytical techniques for testing of products that can be used to screen the market for falsified products is provided in Annex 1. More detailed descriptions of available technologies are found in published literature and online guidance (5,6).

The result of a screening test is only indicative (preliminary or presumptive adverse analytical result) and other analytical techniques must be applied to unequivocally confirm that a falsified product has been detected.

Some of the methods shown in Annex 1 rely on a comparison with suitable reference materials or data available in a library or a reference database. Sharing of reference values and screening results through access-controlled information technology (IT) interfaces can be a strong support for the application of rapid screening technologies.

### 4.3 Selection of analytical techniques

Annex 1 provides an overview of available analytical techniques at the time of developing these guidelines. The choice of analytical technology to be applied should be based on the information required, the regulatory authority should obtain updated information about available analytical techniques before making decisions on the use of analytical techniques mentioned, taking into account:
• the expected benefits of each technology (scientifically based), given its applicability and performance characteristics;
• opportunities for efficient use within existing postmarketing surveillance activities such as inspections for compliance with licencing requirements, GMP or GDP;
• the availability of adequately trained local operators and cost of training;
• the expected cost of equipment, including periodic calibration and qualification;
• ongoing cost and availability of consumables, reference materials/libraries and maintenance;
• any other factors that may influence the use of analytical techniques in the national context.

5. SAMPLING AND DOCUMENTATION

5.1 Sampling

Sampling of suspected falsified products is typically performed by inspectors or enforcement officers (such as police or customs officers) upon detection of a suspicious product. Suspected products can also be detected during the complaint process. Care should be taken to ensure that the sample taken/seized is representative of the suspect product. A sufficient number of dosage units should be taken to enable analytical testing. Guidance in this regard is found in reference (1), and advice should be sought from a suitably qualified analytical testing laboratory.

5.2 Documentation of information on suspected falsified medicines

An information collection form which is to be completed by the inspector or enforcement officer should be comprehensive and include:

– the point of detection;
– the quantity of suspect product found;
– a visual description of its packaging;
– the dosage units;
any signs of irregularities;
the supply history of the product; and
a description of the circumstances leading to its detection (e.g. adverse effects and any other relevant information).

This document should accompany the sample from the time it is taken up until it is delivered to the testing laboratory. An example of an information collection form that may be used is presented in Annex 2.

5.3 Chain of custody considerations

From the time of collection or seizure of the suspected falsified product until its ultimate destiny a rigorous chain of custody should be maintained to ensure that the integrity of the sample and its accompanying documentation has been preserved. Secure packing, labelling, appropriate transport and storage conditions of the sample must be implemented. In addition, adequate security arrangements must be in place to prevent any theft, tampering, substitution or unauthorized disclosure of information.

The chain of custody of a sample consists of two parts. The first starts at the location where the suspected falsified product was seized or purchased by the inspector, or when a suspected falsified product has been detected by a manufacturer and includes all stages of the process to deliver the sample to the analytical testing laboratory. The second part refers to the laboratory where all transfers of the sample must be recorded so that the analytical report generated by the laboratory can be unequivocally linked to the source of the sample.

The inspectors or enforcement officers should document details of the suspected falsified product including (but not limited to):

See also reference (3), Paragraph IV.1.1. 30.
• location of detection (name or title and address);
• location of detection in the supply chain (manufacturer, wholesaler, pharmacy, hospital, patient);
• pharmaceutical product type, pharmaceutical dosage form (tablet, capsule, injection, etc.);
• quantity and/or volume;
• date and time of seizure/purchase;
• names and signatures of the inspector/enforcement officer and the owner of the suspected falsified medicine at the location;
• description of packaging;
• location to which the sample is sent;
• other relevant information (international nonproprietary name (INN), brand name, batch number, shelf life, dosage/strength).

The inspector/enforcement officer is responsible for securing the sample appropriately and arranging transport to the testing laboratory. Samples which cannot be transported immediately are to be refrigerated or frozen to minimize sample degradation due to factors like time delays and high temperature. Whenever possible, samples are to be stored in a secure, cool environment, with warm conditions avoided.

The inspector/enforcement officer includes a copy of the appropriate documentation (see section 5.2) in each transport bag/container, containing the samples, to ensure that the laboratory can verify the contents upon delivery.

Samples may be taken directly to the analytical testing laboratory by the inspector/enforcement officer or handed over to an approved courier for transportation.

If an approved courier company is used to transport the samples, it should be documented in the chain of custody of the samples and the inspector/enforcement officer should record the waybill number of the shipment.
Within the laboratory, samples are considered to be in custody when:

- in the physical possession of authorized staff;
- within the view of authorized staff after being in his/her physical possession;
- stored in a secure location.

The laboratory chain of custody should be reflected in all the documentation generated by the laboratory, which may include log books, work sheets, photographs, analytical reports, etc., where the custody of the samples during analysis and storage is recorded with the signature of the staff member and the date and time of the action(s). The laboratory chain of custody shall be a continuous record of authorized staff with custody of the samples at all stages of the process from receipt to disposal of the samples. At each stage, the authorized staff involved must sign and date for the action performed.

It is essential to ensure traceability throughout the process – from the seizure/purchase of the suspected falsified product to the conclusion of the investigation.

6. REGULATORY ACTIONS UPON DETECTION OF SUSPECTED FALSIFIED SAMPLES

6.1 Risk assessment

When a suspected falsified product has been found the relevant NRA is to be informed. The NRA should then perform a risk assessment of the issue to determine what further action is required to protect public health. This assessment should be done in communication and collaboration with the marketing authorization/license/registration holder, and if applicable with the manufacturer of the genuine product, and an analytical testing laboratory with experience in

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6 See reference (3), Section III. Assessment of alerts, reports and notifications received.
testing suspected falsified products. WHO and other regulatory authorities should also be informed as appropriate.

In most cases, further action will include confirmatory laboratory testing of the suspect samples.

6.2 Questions to be answered by analytical testing

If laboratory analysis is to be conducted, NRAs should refer samples to a laboratory with adequate capacity to perform the testing as described in this document. If no such laboratory is available in the country NRAs should identify a competent and suitably equipped laboratory in their region or elsewhere that can advise on designing a testing plan and/or perform some or all of the testing. The manufacturer of the genuine product may also be requested to provide information or methods (including reference substances and a sample of the genuine product) that may be used for the testing of suspect samples.

The regulatory authority, enforcement agencies and other relevant stakeholders on receipt of a suspected falsified product need to clarify the purpose and aims of testing. Some examples of questions that laboratories may be requested to answer (with the assistance of the regulatory authority, enforcement agencies and other relevant stakeholders) are listed below.

- Does the sampled product fall under the national legislation for pharmaceutical products?
- Does the sample meet specifications defined as part of the stated product’s marketing authorization?
- What specific substances should the testing be designed to detect? (Examples: specific unexpected active ingredients or groups of active ingredients, specific impurities, any substances that are consistent with reported adverse effects.)
- What additional parameters should be tested to assess the health impact of the ingredients? (Examples: content, dissolution or disintegration properties, sterility.)
- Is there a forensic relationship between different falsified products? If yes, on what aspects?
- Are there any market authorization specifications and methods of analysis available for the suspect samples? N.B. Check if there is a product monograph in The International Pharmacopoeia, or any national or regional pharmacopoeia.
- What are the expected excipients (if present) in the suspect samples? N.B. As it is often not possible to answer that question, the testing should be arranged in such a way that there is no (negative) interference of the excipients in the identification and quantification of the substance that is expected to be contained in the sample.

6.3 Communication

Care should be taken by the NRA to convey clear and appropriate messages in communicating information about suspected or confirmed falsified products to the stakeholders. Dissemination of information should be well planned, to reach all relevant stakeholders while ensuring confidentiality as appropriate. NRAs should keep a record of the date, recipients and content of information disseminated. WHO and other regulatory authorities should also be informed as appropriate.

Patients should normally be advised not to stop taking their medication without consulting their health professional. Health professionals and procurement agencies should be instructed on the action(s) to be taken to enable a continued supply and treatment while ensuring patient safety. In all communications the manufacturer whose name is printed on the packaging products should be described as the “Stated manufacturer”, making it clear that the falsified medicine may not have originated from that manufacturer. Miscommunication can amount to falsely accusing the legitimate manufacturer of falsifying a product, which would be grounds for legal action by that manufacturer.

7. CONFIRMATORY ANALYTICAL TESTING

NRAs should refer samples to a laboratory with adequate capacity to perform the testing as described in this document. The manufacturer of the genuine product may also be requested to provide information or methods (including reference substances and a sample of the genuine
product) that may be used for the testing of suspect samples or may provide technical support.

Any information and/or materials provided by the marketing authorization holder to a
government laboratory in support of an investigation of suspect product must be handled as
confidential. As necessary, material transfer agreements/confidentiality agreements may be used.

7.1 Laboratory capacity

Best practices for quality control (QC) laboratories and the minimum requirements for
equipment are described in WHO guidance (6), which focuses on QC laboratories using
compendial or manufacturers’ methods, as described in dossiers submitted for marketing
authorization, to ensure compliance with the requirements of compendial monographs or
manufacturer’s specifications. However, these methods are designed to detect problems that may
arise during the approved manufacturing process and subsequent storage and distribution and
may not necessarily be adequate to detect all possible issues that could arise with medicines that
have been deliberately falsified. Methods used to authenticate suspected products must be
suitable for their intended use.

Laboratories, normally national medicine testing laboratories, that test suspected falsified
medicines should preferably be ISO 17025 accredited by a recognized accreditation body
(affiliated, e.g. to the International Laboratory Accreditation Cooperation, etc.) to perform the
appropriate analytical procedures that are listed in their scope of accreditation and/or be a WHO-
prequalified laboratory with the capability to test falsified products with an appropriate array of
analytical techniques and sufficient expertise. Furthermore, they should be able to perform,
interpret and document the testing according to rigorous procedures to ensure that the results can
withstand legal scrutiny.

Beyond the requirements of good practices, described in general WHO guidance (6) and ISO
17025, some additional skills and capacity as outlined below are required for testing of suspected
falsified medicines.
Expertise

- **Critical thinking.** Laboratory staff should have the ability to critically appraise all that is known about each case of a suspected falsified product and not just accept pre-existing standard testing procedures. This skill can be strengthened through discussions with peers on specific cases and by learning from senior experts in the field.

- **Experience.** Laboratories should have access to staff with experience in designing and implementing science-based, tailor-made falsified testing plans. Where this is not the case they should cooperate with other institutions and/or refer the testing request to an institution where the required experience is available.

- **Knowledge.** Laboratory staff should have up-to-date scientific expertise enabling them to fully understand the scientific methods used in testing falsified products, to apply them correctly and to interpret the results adequately.

Equipment

Laboratories should take care that technical equipment for testing of suspected falsified products for which they have adequate knowledge and experience is periodically qualified and maintained in good condition. Investments should be planned so as to enable the basic functioning of the laboratory for all its intended purposes and to maximize the benefits of any additional specialized equipment purchased. The cost of the equipment should be considered together with that of accessory products such as consumables, reagents, standards, databases and libraries, as well as the costs of and access to installation, maintenance and training. Sharing of equipment in regional cooperation approaches can be considered to minimize the costs while maximizing the benefits.

Laboratories also need a secure and adequate storage place for the samples, when not being tested, to ensure the chain of custody.

7.2 **Standard operating procedure**
Laboratories should develop, implement and maintain a standard operating procedure (SOP) for testing of suspected falsified products. Such an SOP cannot define each step in the testing, since this will be determined on a case-by-case basis. Rather, it should ensure that the laboratory follows good practice and internal quality management systems in planning, implementing and documenting its actions with regard to each request for testing.

WHO guidelines for sampling of pharmaceutical products and related materials (7) and *Good practices for pharmaceutical quality control laboratories* (6) should be followed, as applicable.

Measures should be taken to minimize bias. Sampling should be separate from testing. Staff performing each analysis of the testing plan should be blinded to the results of the other analyses as far as possible.

The laboratory should ensure full traceability of samples and results as described in relevant WHO guidelines (*I*, *6*, *7*), and should follow rigorous procedures to preserve the integrity of samples and documentation, with a chain of custody that will stand up to scrutiny in legal action. An example of an SOP for testing of suspected falsified products is provided in Annex 3.

### 7.3 Testing plan and test procedures

All the available information about the samples should be provided to the laboratory in the form of a request for analysis that would clearly indicate what is expected from experimental testing. The inspector/enforcement officer who has collected the sample should inform the laboratory as completely as possible and necessary for an efficient running of the testing.

A suitable analytical testing programme should be prepared to detect the suspected substances. An initial study should then be undertaken, having in mind the number of sampling units available, to determine the substances to expect in the sample and parameters to be tested and to design a science-based testing plan identifying the most efficient combination of methods to provide the required answers.
A wide range of methods may be considered for inclusion in the testing plan, including simple visual checks, the technologies listed in Annex 1 and other forensic analyses which may assist in determining likely sources of suspected falsified medicines. Each technique should be reappraised to determine its most appropriate use in order to achieve the best possible performance in the given context.

More detail on combining technologies to identify falsified products can be found in literature (e.g. 5). Various examples of flowcharts describing how one can proceed with testing are reproduced in Annex 4 for illustrative purposes with kind permission of the authors, the European network of official quality control laboratories.

7.4 Interpretation and reporting of results

General good practices in interpreting laboratory testing results are described in WHO guidance (7). Specific points to document for testing of falsified products include:

- reasons for selecting the particular methods used in the testing plan;
- measures taken to avoid bias in analysis and reporting;
- traceability of the measurements, with links to all physical material and to the original sample on which the test was done;
- limitations of the selected methods as used in the testing plan, together with an estimate of the measurement of uncertainty of a quantitative result, if performed, and the conclusions.

8. REPORTING AND REGULATORY ACTION OF CONFIRMED FALSIFIED PRODUCTS

A legal framework for reporting of falsified products should be in place at national level.

The confirmed testing results should be reported to the regulatory authority of the country where the falsified product was found. It is the responsibility of the NRA, under the given
circumstances, to decide how the findings should be translated into appropriate action, in accordance with national legislation and in cooperation with enforcement agencies and other stakeholders. The affected manufacturer should be kept informed of the results of testing. Other regulatory authorities should be informed as appropriate. A report should be submitted to the WHO Global Surveillance and Monitoring system for Substandard and Falsified Medical Products (8).

9. ARCHIVING OF SAMPLES AND REPORTS

The laboratory should store the samples adequately and archive related documentation in separate secure locations for future reference as required by legislation, documenting that the integrity of samples and results has been preserved.

10. REFERENCES


Report by the Director-General


8. WHO project for the surveillance and monitoring of SSFFC medical products. WHO Drug Information 2013;27(2): 97-100. Available at:

ANNEX 1

Examples of analytical techniques that may be used for package identification, screening and testing of suspected falsified products

The list shown below contains examples of analytical techniques that may be considered. These include compendial methods as well as specific advanced techniques. Each technique should be reappraised to determine its most appropriate use in order to achieve the best possible performance in the given context. Laboratories may decide to outsource some of the analyses necessitating specific advanced techniques to other suitably qualified laboratories.

Note: The list should not be considered to be complete or exhaustive. It is intended to provide illustrative examples of commonly available technologies. Moreover, not all techniques are required for a laboratory that undertakes such testing.

<table>
<thead>
<tr>
<th>Main use</th>
<th>Technique</th>
<th>Full name</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>ATR/FTIS</td>
<td>Attenuated total reflectance/Fourier transform infrared spectroscopy</td>
<td></td>
</tr>
<tr>
<td>Identification</td>
<td>Melting point</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Identification</td>
<td>XRPD</td>
<td>X-ray powder diffractometry</td>
<td>-</td>
</tr>
<tr>
<td>Identity</td>
<td>RI</td>
<td>Refractive index</td>
<td>–</td>
</tr>
<tr>
<td>Identification</td>
<td>Spectrophotometry (colorimetry)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Identification</td>
<td>TLC</td>
<td>Thin-layer chromatography</td>
<td>–</td>
</tr>
</tbody>
</table>

The list should not be considered to be complete or exhaustive. It is intended to provide illustrative examples of commonly available technologies. Moreover, not all techniques are required for a laboratory that undertakes such testing.
<table>
<thead>
<tr>
<th>Assay identification impurities</th>
<th>GC/FID</th>
<th>Gas chromatography with flame ionization detection</th>
<th>–</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forensics identification assay impurities</td>
<td>GC/MS</td>
<td>Gas chromatography with mass spectrometric detection</td>
<td>–</td>
</tr>
<tr>
<td>Assay identification impurities</td>
<td>LC/UV</td>
<td>Liquid chromatography with UV-detection</td>
<td>–</td>
</tr>
<tr>
<td>Residual solvents impurities</td>
<td>HS-GC/FID</td>
<td>Headspace gas chromatography with flame ionization detection</td>
<td>–</td>
</tr>
<tr>
<td>Forensics residual solvents impurities</td>
<td>HS-GC/MS</td>
<td>Headspace gas chromatography with mass spectrometric detection</td>
<td>–</td>
</tr>
<tr>
<td>Inorganic impurities</td>
<td>ICP/OES</td>
<td>Inductively coupled plasma with optical emission spectroscopy</td>
<td>–</td>
</tr>
<tr>
<td>Inorganic impurities</td>
<td>ICP/MS</td>
<td>Inductively coupled plasma with mass spectrometric detection</td>
<td>–</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------</td>
<td>-------------------------------------------------------------</td>
<td>----</td>
</tr>
<tr>
<td>Elemental and chemical analysis</td>
<td>XRF</td>
<td>X-Ray fluorescence</td>
<td>–</td>
</tr>
<tr>
<td>Finished pharmaceutical product testing</td>
<td>Dissolution testing</td>
<td>–</td>
<td>Bioavailability of API and quality of finished pharmaceutical preparations (FPP)</td>
</tr>
<tr>
<td>Finished pharmaceutical product testing</td>
<td>Disintegration testing</td>
<td>–</td>
<td>FPP and indication on bioavailability of active pharmaceutical ingredient (API)</td>
</tr>
<tr>
<td>Specific testing</td>
<td>Sterility</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Specific testing</td>
<td>BET</td>
<td>Bacterial endotoxins test</td>
<td>–</td>
</tr>
<tr>
<td>Specific testing</td>
<td>Osmolarity and osmolality</td>
<td>–</td>
<td>Characterization of injections and infusions</td>
</tr>
<tr>
<td>Finished pharmaceutical</td>
<td>Light microscopy</td>
<td>–</td>
<td>Particle characterization</td>
</tr>
<tr>
<td>product testing</td>
<td>forensics</td>
<td>Identification</td>
<td>Raman spectroscopy</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
<td>----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Forensics</td>
<td>Photo scan/overlay</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Forensic</td>
<td>FTIR/Raman imaging spectroscopy</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Forensics</td>
<td>TEM</td>
<td>Transmission electron microscopy</td>
<td>–</td>
</tr>
<tr>
<td>Forensics</td>
<td>SEM-EDX</td>
<td>Scanning electron microscopy with energy dispersive X-Ray spectroscopy</td>
<td>–</td>
</tr>
<tr>
<td>Forensics identification impurities</td>
<td>LC-HRMS</td>
<td>Liquid chromatography – with high resolution mass spectrometric detection</td>
<td>Characterization of unknowns down to trace levels</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------</td>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Forensics identification assay impurities</td>
<td>LC/MS</td>
<td>Liquid chromatography – with mass spectrometric detection</td>
<td>Qualitative analysis of volatiles and semi-volatiles in solid samples (direct analysis/without sample preparation)</td>
</tr>
<tr>
<td>Forensics impurities</td>
<td>TDS-GC/MS</td>
<td>Thermodesorption gas chromatography with mass spectrometric detection</td>
<td></td>
</tr>
<tr>
<td>Forensics</td>
<td>LC/ELSD</td>
<td>Liquid chromatography with evaporative light scattering detection</td>
<td>–</td>
</tr>
<tr>
<td>Forensics identification assay impurities</td>
<td>NMR, qNMR</td>
<td>Nuclear magnetic resonance, quantitative nuclear magnetic resonance</td>
<td>Characterization of unknown compounds and mixtures – qualitative and quantitatively</td>
</tr>
</tbody>
</table>
ANNEX 2

Example of an information collection form

<table>
<thead>
<tr>
<th>RECEIPT OF SUSPECT FALSIFIED PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date on which the suspect product was received:</td>
</tr>
<tr>
<td>Suspect product received by:</td>
</tr>
<tr>
<td>Signature of the inspector/enforcement officer and that of the owner of the product collected/seized</td>
</tr>
<tr>
<td>Suspect product issued by:</td>
</tr>
<tr>
<td>Source of the suspect product:</td>
</tr>
<tr>
<td>Contact details of source of suspect product: Name and surname:</td>
</tr>
<tr>
<td>Physical address:</td>
</tr>
<tr>
<td>Email:</td>
</tr>
<tr>
<td>Telephone number(s):</td>
</tr>
<tr>
<td>Other:</td>
</tr>
</tbody>
</table>
### SUSPECT FALSIFIED PRODUCT INFORMATION

1. **Suspect product name(s):**

2. **Type of product (select the most appropriate box):**

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovator product</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Vaccine</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other biological product</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Traditional medicine</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Generic product</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Blood product</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Herbal medicine</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other, please specify</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

   **Additional comments (if applicable):**

3. **API(s) present in the product and declared strengths:**

4. **Description of the dosage form:**

5. **Description of product packaging (primary and secondary):**
### 6. Does the packaging contain any holographic security features or SMS verifiable coding?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

Provide description (if applicable):

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### SUSPECT FALSIFIED PRODUCT INFORMATION (CONTINUED)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### 7. Is there a patient information leaflet available with the product?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### 8. Batch number/Lot number (if available):

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### 9. Manufacturing date (if available):

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### 10. Expiry date (if available):

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### 11. Does this product fall under the national legislation for pharmaceutical products?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### 12. Market authorization holder (if applicable):

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### 13. Manufacturer(s) details:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### 14. Quantity of suspect product received:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

### 15. Does the suspect product meet specifications defined as part of the stated product’s

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>marketing authorization?</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>--</td>
</tr>
<tr>
<td>16. Is the sample likely to have been falsified, rather than poorly manufactured or degraded?</td>
<td>Falsified ☐</td>
</tr>
<tr>
<td>Additional information:</td>
<td></td>
</tr>
<tr>
<td>16. Any other information applicable:</td>
<td></td>
</tr>
</tbody>
</table>
## TESTING REQUIREMENTS

**1. Has the product been subjected to any preliminary testing?**

| Yes | ☐ | No | ☐ |

If “Yes” provide a summary of results

**2. What specific substances should the testing be designed to detect?**


**3. What parameters should be tested to assess the health impact?**


**4. What are the forensic relationships between different fakes?**


**5. Are the market authorization specifications available?**

| Yes | ☐ | No | ☐ |

**6. Are official testing methods available?**

| Yes | ☐ | No | ☐ |
**IMPACT ON PUBLIC HEALTH**

1. Have any adverse reactions been reported?  
   - Yes [□]  
   - No [□]  

If “Yes” provide more information:

2. Estimated number of patients adversely affected?  

3. Estimated number of patients at risk?  

4. Any other related information:
ANNEX 3

Example of a content of a standard operating procedure for testing of suspected falsified tablets

1. Purpose

The actual standard operating procedure (SOP) describes the workflow and the required test procedures necessary to carry out a testing of suspected falsified tablets.

2. Scope

The actual SOP is only valid for the good laboratory practices/good manufacturing practices test facility of YYYY.

3. Sample receipt, documentation and storage

a. Sample receipt

When receiving a shipment of suspected falsified tablets for analysis the receiving laboratory shall:

- record
  - name and signature of the person delivering the sample or courier company waybill,
o date and time of receipt of the sample in the laboratory with
signature of the staff member,
o presence of accompanying documentation in the shipment;
- check integrity (e.g. damages, broken sealing) of shipment
  packaging;
- check completeness of shipment against shipping documents;
- read out and check data logger (e.g. temperature control) – if
  applicable;
- check and sign shipment documentation – if applicable;
- archive all documents in the corresponding project files as per the
  corresponding SOP xxx.xxx.xxx.

b. Sample documentation

After sample receipt and unpacking:

- document packaging which contains the suspected falsified tablets as
  received by photographic image(s);
- document package insert/patient information leaflet by photographic
  image(s);
- check contents using shipping documents and previously received
  information by sending party;
- document each sample: secondary packaging and primary packaging
  (e.g. blister) including labels by photographic image(s);
- archive all documents and photographic images in the corresponding
  project files as per the corresponding SOP xxx.xxx.xxx;
- store samples according to storage conditions according to SOP
  xxx.xxx.xxx until testing, record storage location;
- prior to testing let samples equilibrate to ambient temperature.
c. All the above observations should be recorded on a checklist and signed and dated on completion by the responsible staff member. There should be a checklist which should be signed and dated by the staff member responsible for these duties. The time, date of storage (identified) by whom (with signature) should be recorded. Who removed sample from storage for equilibration to room temperature and when – signature required.

d. Remarks

- When using photographic images for documentation purposes check image quality (e.g. readability of text elements, colour correctness) before proceeding further.
- Ideally sample documentation includes dimensions (e.g. primary and secondary packaging, thickness and diameter of tablets).
- Sending party should be informed on sample receipt – if applicable.

e. Observations

Any observations like damages of packaging, missing or additional samples shall be documented and communicated to the sending party in order to decide how to proceed further.

4. Sampling and samples

- Split each sample set into 2 to 3 subsets.
- Keep Subset 1 for packaging inspection and documentation and Subset 2 for analytical testing as described in the following chapters.
- Keep Subset 3 as retained sample for any further investigation.

5. Overall aspect

a. Packaging

- Consider Subset 1 (see Chapter 4).
- Visually assess the aspect of the secondary and primary packaging.
- Report observations of the external aspect of the packaging materials (including labels and printing) like visible damages, holes, discoloration or stains.
- Document observations by photographic images and archive them together with corresponding notes in the project files as per the SOP xxx.xxx.xxx.
- Report results.

There should be a reporting form to be signed and dated on completion by the staff member responsible.

b. Samples

- Consider Subset 2 (see Chapter 4).
- Visually assess the aspect of the tablets.
- Report observations of the external aspect of the tablets like visible fissures, holes, inclusions, discoloration or stains, presence/absence of score lines, presence/absence of film/sugar coating.
- Document observations by photographic images and archive them together with corresponding notes in the project files as per the SOP xxx.xxx.xxx.
• Report results.

There should be a reporting form to be signed and dated on completion by the staff member responsible.

6. Analytical testing

a. Packaging testing

• Use Subset 1 (see Chapter 4).
• Record FTIR or Raman spectra according to the SOP xxx.xxx.xxx in order to confirm or elucidate the identity of the primary packaging.
• Report results.

There should be a reporting form to be signed and dated on completion by the staff member responsible.

b. Solid medicine (tablet) testing

1. Excipients

• Use Subset 2 (see Chapter 4).
• Record FTIR or Raman spectra of a reference sample (i.e. certified medicine reference sample) according to the SOP xxx.xxx.xxx.
• Record FTIR or Raman spectra according to the SOP xxx.xxx.xxx of the tablet, which was homogenized by mechanical grinding and compare against a reference sample in order to confirm presence and relative concentration of expected excipients.
If differences to the data of the reference sample are observed perform in-depth analysis of experimental data (e.g. presence of unexpected substances or lack of expected substances).

- Report results

There should be a reporting form to be signed and dated on completion by the staff member responsible.

### ii. API

- Use Subset 2 (see Chapter 4).
- Homogenize at least one of the tablets of Subset 2 by mechanical grinding and use the homogenized material for the next steps.
- Confirm identity and concentration of the expected API in the suspect and reference sample using the corresponding compendial method. Alternatively, an in-house method can be used as long as the suspect tablet is tested against a suitable reference sample. The suitability of the in-house method for intended use should be proven by means of validation reports and should be a stability indicative method.

- Report results.

There should be a reporting form to be signed and dated on completion by the staff member responsible.

### iii. Additional tests

If tests as described in sections 6.2.1 and 6.2.2 do not deliver unambiguous results additional screening tests can be performed on Subset 1 or Subset 3 after agreement with the sending party. These screening tests can include:

- elemental analysis screening via ICP-OES or ICP/MS as per SOP xxx.xxx.xxx;
• screening for volatiles and semi-volatiles via TDS-GC/MS as per SOP xxx.xxx.xxx;
• screening for volatiles and semi-volatiles via GC/MS as per SOP xxx.xxx.xxx;
• screening for non-volatile, polar compounds via HPLC/MS as per SOP xxx.xxx.xxx.

7. Dissolution testing

• Use Subset 1.
• Perform dissolution testing in comparison to suitable reference sample.
• Report results.

There should be a reporting form to be signed and dated on completion by the staff member responsible.

8. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC/MS</td>
<td>gas chromatography mass spectrometry</td>
</tr>
<tr>
<td>HPLC/MS</td>
<td>high pressure liquid chromatography mass spectrometry</td>
</tr>
<tr>
<td>ICP/OES</td>
<td>inductively coupled plasma optical emission spectrometry</td>
</tr>
<tr>
<td>ICP/MS</td>
<td>inductively coupled plasma optical mass spectrometry</td>
</tr>
<tr>
<td>SOP</td>
<td>standard operating procedure</td>
</tr>
</tbody>
</table>
ANNEX 4

Examples of flowcharts for testing of suspected falsified medicines

Explanatory note to the Appendix

This Appendix includes the examples from an “Aide-Memoire for the Testing of Suspected Illegal and Counterfeit Medicines” prepared by the European Official Medicines Control Laboratory (OMCL) Network (Reference: PA/PH/OMCL (06) 81 R6, Strasbourg, July 2016) which has been reproduced with the kind permission from the Network members. Terminology may therefore differ from WHO style.

“The original version of this document was produced in response to many presentations given at a number of Annual General Meetings of the OMCL Network (GEON).

The paper provides some practical and theoretical advice to OMCLs on the development of protocols for the confirmation or determination of counterfeit medicinal products and was adopted by the Network in 2007.

Subsequently, the testing of potentially illegal and counterfeit medicines throughout the Network has expanded and many laboratories now have established processes and expertise.

At the GEON annual meeting in June 2015, it was agreed that the “aide-memoire” document should be revised and updated to provide an overview of the overall approaches that should be taken for OMCLs analysing suspected illegal/counterfeit medicines.
This document has been prepared to include example high level process flows/decision trees to assist OMCLs and promote a harmonised approach across the Network. It is recognised that OMCLs will have existing processes in place and this document does not supersede existing systems. This document is intended as an “aide memoire” only and OMCLs are not expected to be audited for compliance with the document.

The techniques listed in this document are examples only and should not be seen as exclusive or even preferred techniques. OMCLs should choose and use appropriate equipment to meet their testing needs.

The individual OMCLs’ choice of specific analytical techniques and detailed testing SOPs are outside the scope of this document and should be decided locally in accordance with local legislation or policies (for example, some OMCLs may routinely quantify APIs found but others may not – either approach is acceptable), equipment availability and staff expertise/preferences.

The final decision on what techniques to use and equipment to purchase and exactly what testing to apply is left to individual OMCLs.”
Example 1. Decision tree to determine testing requirements

- Sample Received
- Register into laboratory quality system
- Manage sample as per laboratory quality system, and any additional evidence continuity and reporting to court standard, if required
- Is it presented as a medicine?
  - Yes: Use Counterfeit protocol
  - No: Are there any APIs declared?
    - Yes: Is it a suspected counterfeit?
      - Yes: Use Counterfeit protocol
      - No: Use Screening protocol
    - No: Use Medicine Protocol

Note:
Where no APIs are declared, often the name or marketing of the item can indicate what APIs may be present (for example, products may be marketed as weight loss or sexual potency enhancers, or have suggestive pictures/branding that implies the product’s intended effect).
Also internet searches using the product or producer name of the item can often provide information on APIs, use and/or indication. Further details of the protocols that may be applied are given in the following sections.

**Example 2. Screening protocol (testing for “medicines in disguise”)**

Samples may be presented as a food supplement, health tonic, “nutraceutical” or naturally derived or herbal product. Usually there will be either no mention of API(s) in the product or even a more positive statement such as “100 % natural extracts” or similar. Alternatively samples may be presented in foreign language variants, or even unlabelled.

In these circumstances the priority of the testing is to establish whether there are any APIs/potential pharmacologically active substances present and, if there is, at what level if required.
Screen for presence of API/
Potential pharmacologically active substance
using suitable technique
(library search, confirm by comparison to reference standard if possible)

GC-MS
LC-MS, LC-DAD
XRPD

Substance present?
Yes
No

Is quantitation needed?
Yes
No

Determine content of substance using suitable technique
(quantitation against reference standard)

LC-UV (single λ or DAD), LC-MS, LC-CAD
GC-FID, GC-MS
qNMR
CE

REPORT DATA
Is/are there any API(s) present?
If so, at what level?
How does the API content compare to authorised products?
Is there more or less than the lowest authorised dose with significant pharmacological effects?

Note: screening methods may not detect every possible substance and OMCLs may operate more than one method (e.g. for different drug classes).

Methods will need to be updated to include new molecules as they are discovered.

For unknown or new molecules, advanced techniques may be needed to provide structure elucidation.
Example 3. Medicine protocol (testing of “unapproved products”)

Samples may be legal, licensed medicines in other countries, but not necessarily in the country where they have been found, or they may be legal medicines sold outside of the correct, legal supply chain. They might also contain drug substances that are not licensed or legally authorized for sale or treatment. Usually the API(s) in the product will be listed on the label and the product will be packaged and presented as a medicine. In some cases, the samples may be presented in foreign language variants, so the API(s) present may be unclear.

The priority of the testing is to establish that the labelled API is present, and (if required) at what level.
START

Is the product labelled as containing API(s)?

Yes

Determine identity and/or content of labelled API(s) using suitable technique (quantitation against reference standard)

- LC-UV (single λ or DAD)
- LC-CAD
- GC-FID
- LC-MS
- GC-MS
- qNMR
- CE
- XRPD

No

Screen for presence of API using suitable technique (library search, confirm by comparison to reference standard if possible)

- GC-MS
- LC-MS
- XRPD

If required, determine content of detected API(s) using suitable technique (quantitation against reference standard)

- LC-UV (single λ or DAD)
- LC-CAD
- GC-FID
- LC-MS
- GC-MS
- qNMR
- CE

Is the labelled API(s) present?

No

REPORT DATA

Are the labelled API(s) present?

Yes

How do they compare to labelled content?

Are any other APIs present (aside from any labelled API)?

If so, at what level?

No
Example 4. Counterfeit protocol

For samples that are presented as licensed medicines but are suspected of being falsified, or counterfeit, it is essential that the OMCL is able to make contact with the market authorization holder (MAH) of the genuine product. This may either be directly or through the competent authority, inspectorate or enforcement group. Genuine comparator batches (ideally 3 batches including the suspicious lot) should be obtained. If the product is manufactured at a variety of production sites, samples should be obtained from each. It is not usually possible for a laboratory to determine conclusively that a sample of product is counterfeit based on testing alone. The priority of the testing can only be to say whether the suspect sample is consistent with the genuine product or not.
Authentication Testing

Start

Contact MAH
Request comparator
Request information

Sufficient sample for both OMCL and MAH to test?

Yes

Authenticity Testing

Compare the suspect with comparator/artwork using suitable technique
(visual examination; microscopy, physical, colour, packaging including covert features)

Compare spectral fingerprint of product with authentic comparator
(FT-IR, NIR, Raman, XRF, XRPD)

Determine identity and content of labelled API
(LC-MS, GC-MS, LC-UV, GC-FID)

Compare impurity/solvent profile of suspect with comparator
(LC-MS, GC-MS, LC-UV, GC-FID)

Compare excipients in suspect with comparator
(FT-IR, Raman, XRPD)

No

Test in OMCL

Send portion of sample to MAH

Test in MAH Lab

Report data

Is the suspect sample similar to or different from the comparator?
Is the OMCL data and MAH data concordant?

Note: when a suspect sample is found not to contain labelled API, the OMCL may wish to apply the screening protocol to determine what, if anything is present.