

Annex 5

WHO guidance on testing of “suspect” falsified medicines

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1. Introduction

1.1 “Suspect” medicines

“Suspect” medicines can be divided into three main categories of products as follows:¹

(a) substandard medicines

Also called “out of specification”, these are authorized medicines that fail to meet either their quality standards or their specifications, or both.²

(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 their 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.

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.

This document deals specifically with products that are suspected to belong to the third category, i.e. “falsified” medical products.

1.2 Responsibility of regulatory authorities

NRAs should 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

¹ Based on World Health Assembly (WHA) A70/23 and WHA70(21) 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”.

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 medical products can originate from inside or outside the legal supply chain. It is important that NRAs secure the supply chain and raise awareness among 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 on other topics that are relevant to the regulatory oversight of medicines.

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

The Member State Mechanism on substandard and falsified 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 the sixty-seventh World Health Assembly resolution WHA67.20 on Regulatory system strengthening for medical products (4).

2. Scope

This document provides technical guidance on laboratory testing of samples of suspect deliberately falsified medical products detected on the markets of WHO Member States and related aspects of sampling and reporting. This guidance should be read in conjunction with the guidelines on sampling and market surveillance (2).

3. Glossary

The definitions given below apply specifically to the terms used in this document. They may have different meanings in other contexts.

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 and/or licence.

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.

falsified product. For the purposes of this document, a product that has been deliberately and/or fraudulently misrepresented as to 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 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.³

forensic. Related to analysis for law enforcement purposes.

marketing authorization (product licence, 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.

³ Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products. Report by the Director-General; 2017 (A70/23; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_23-en.pdf, accessed 27 February 2018).

medical product⁴ refers to medicines, vaccines and in vitro diagnostics (and in the future may include medical devices).

quality control. Embraces 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.

quality management. 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.

screening technologies. The qualitative and/or semiquantitative technologies that can rapidly acquire the information or analytical 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.

4. Detection of suspect 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 for removing them from the market.⁵

Suspect 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 or unexpected stock levels), discrepancy during verification and investigation of unexpected adverse events reported to have occurred with a specific product. It is important to evaluate any information on suspect falsified products reported by customs, medicines inspectorates and other authorities, procurement agencies, wholesalers and importers, pharmacies, health-care institutions, patients and other stakeholders.

⁴ Working Group of the Member State Mechanism (http://apps.who.int/gb/sf/pdf_files/A_SFFFC_WG2_2-en.pdf).

⁵ See also reference (3), Paragraph II.1. Quality monitoring and control.

4.2 Detection methods⁶

Falsified medical products may be identified by their packaging characteristics and/or by identity verification, physical and chemical testing. This may require confirmation, where appropriate, by the stated manufacturer, that the product was not manufactured by them (for example, written confirmation that packaging and other elements do not correspond to the genuine manufacturer's records).

When available, the packaging and patient information leaflets of suspect falsified medicines should always be examined visually and compared with samples or photographic images of genuine registered products if available.⁷ Product protection features may also be utilized to screen and/or authenticate suspect packaging components. Attention should be paid to any irregularities or inconsistencies, such as spelling mistakes, unusual batch numbers, unusual printing of batch number and shelf life, verification of serialization data when appropriate, unexpected or modified manufacturing or expiry dates, signs of repacking, for example, to circumvent inspection activities, or instructions in a language that does not match the area of their distribution. Microscopy and other analytical techniques (including but not limited to optical techniques) may be utilized for package examination. The purpose of these technologies is to rapidly provide evidence that the sample comes from a falsified product.

An extensive list of analytical techniques that can be used to screen the market for falsified products is provided in Appendix 1. More detailed descriptions of available technologies can be found in published literature and online guidance (5, 6, 7).

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

Some of the methods shown in Appendix 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 interfaces can provide strong support for the application of rapid screening technologies.

⁶ 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 comprising 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.

⁷ The manufacturer or marketing authorization holder should inform the relevant NRA of any changes to the artwork or packaging of its registered products. Details of analysis/observation of authentication features displayed on the product packaging, or embedded within the product itself, should also be included in the registration dossier. This will help the NRA to assess the authenticity of a given suspect product when conducting visual inspections.

4.3 Selection of analytical techniques

Appendix 1 provides an overview of the analytical techniques available at the time these guidelines were developed. The choice of analytical technology to be applied should be based on the information required. The regulatory authority should obtain advice about available analytical techniques including, for example, from the manufacturer and the analytical testing laboratory, before deciding which analytical technique to use, 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 licensing requirements, GMP or GDP;
- the availability of adequately trained local operators and cost of training;
- the expected cost of equipment, including its periodic calibration and qualification;
- recurring costs 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 suspect falsified products is typically performed by inspectors or enforcement officers (such as police or customs officers) or other competent personnel, for example, laboratory personnel. Suspect medical products can also be detected during the complaint process. Care should be taken to ensure that the sample taken or seized is representative of the suspect medical product. A sufficient number of dosage units should be taken to enable thorough analytical testing. Guidance and advice should be sought from a suitably qualified analytical testing laboratory (1). However, if the requisite amount is not available all units should be collected.

5.2 Documentation of information on suspect falsified medical products

An information collection form, which is to be completed by the inspector or enforcement officer, should be comprehensive and include, but not be limited to:

- the point of detection in the supply chain (manufacturer, wholesaler, pharmacy, hospital or patient);
- the quantity of suspect product found;
- a visual description of its packaging;
- product name as marketed (if any);
- name of active substance (if known);
- the dosage units;
- the batch number;
- photographs;
- any signs of irregularities;
- the supply history of the product including the name, address of parties involved, date of transfer, etc.;
- a description of the circumstances leading to its detection (for example, adverse effects and any other relevant information).

This document should accompany the sample from the time it is taken until it is delivered to the testing laboratory. An example of an information collection form is presented in Appendix 2.

5.3 Chain of custody considerations⁸

From the time of collection or seizure of the suspect falsified medical product until its ultimate fate is decided, a rigorous chain of custody should be maintained to ensure that the integrity of the sample and its accompanying documentation is preserved. Secure packing, labelling, appropriate transport and storage conditions for the sample must be provided and documented. 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 suspect falsified medical product was seized or purchased by the inspector, or when a suspect falsified medical product has been detected by a manufacturer or any other stakeholder and includes all stages of the process of delivering the sample to the analytical testing laboratory. The second part relates 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.

⁸ See also reference (3), Paragraph IV.1.1.30.

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

- location of detection (name or title and address);
- at what point in the supply chain detection occurred (manufacturer, wholesaler, pharmacy, hospital, patient, etc.);
- pharmaceutical product type, pharmaceutical dosage form (tablet, capsule, injection, etc.);
- quantity and/or volume;
- date and time of seizure or purchase;
- names and signatures of the inspector or enforcement officer and the owner of the suspect falsified medicine at the location;
- the amount collected;
- 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, etc.).

The inspector or enforcement officer is responsible for securing the sample appropriately and arranging transport to the testing laboratory. Whenever possible, samples that cannot be transported immediately are to be stored according to the storage conditions defined by the manufacturer, in a secure place. Otherwise, whenever possible, samples are to be stored in a secure, cool environment.

The inspector or enforcement officer should include a copy of the appropriate documentation (see section 5.2) in each transport bag or container holding 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 or enforcement officer or handed over to a qualified and approved courier for transportation.

If an approved courier company is used to transport the samples, this should be documented in the chain of custody of the samples and the inspector or enforcement officer should record the waybill and tracking numbers of the shipment. The recipient of the sample should be informed of the expected delivery date and the storage and transportation conditions.

Within the laboratory, samples are considered to be in custody when they are:

- in the physical possession of authorized staff;
- visible to 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 logbooks, worksheets, photographs and analytical reports where the custody of the samples during analysis and storage is recorded with the signature of the staff member concerned 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. At each stage, the authorized staff involved must sign and date the entry for the action performed (for details see WHO *Guidance on good data and record management practices* (8)).

It is essential to ensure traceability throughout the process – from the seizure or purchase of the suspect falsified medical product to the conclusion of the investigation.

6. Regulatory actions upon detection of suspect falsified medical products

6.1 Risk assessment

When a suspect falsified medical product has been found, the relevant NRA is to be informed (for details see section 8). The NRA should then perform a risk assessment to determine what further action is required to protect public health.⁹ This assessment should be done in communication and collaboration with the marketing authorization, licence or registration holder, and if applicable with the manufacturer of the genuine product, and an analytical testing laboratory with experience in testing suspect falsified medical products. WHO and other regulatory authorities should also be informed as appropriate.

Further action may 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 send the 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 concerned, the NRA should identify a competent and suitably equipped laboratory in its 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

⁹ See reference (3), Section III. Assessment of alerts, reports and notifications received.

provide information or methods (including reference substances and a sample of the genuine product), which may be used for the testing of suspect samples and/or may be requested to analyse the samples.

Upon receipt of a suspect falsified medical product, the regulatory authority, enforcement agencies and other relevant stakeholders 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 include specific unexpected active ingredients or groups of active ingredients, specific impurities and any substances that are consistent with reported adverse effects.)
- What additional parameters should be tested to assess the health impact of the ingredients? (Examples include content, dissolution or disintegration properties and sterility.)
- Is there a forensic relationship between different falsified products? If yes, in what aspects?
- Are there any market authorization specifications and methods of analysis available for the suspect samples? *Note:* Check if there is a product monograph in *The International Pharmacopoeia*, or any national or regional pharmacopoeia.

What are the expected excipients (if any) in the suspect samples?

Note: 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 when communicating information about suspect or confirmed falsified medical 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 who might be affected by falsified medical products should be advised to consult their health professional. Health professionals and procurement agencies, wholesalers and importers 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 of the products should be described as the “*Stated* manufacturer”, making it clear that the falsified medical product may not have originated from the stated 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 a suspect falsified medical product must be handled as confidential. Where necessary, material transfer agreements or confidentiality agreements are to be invoked.

7.1 Laboratory capacity

Best practices for QC laboratories and the minimum requirements for equipment are described in WHO guidance (6). That guidance 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 appropriate to detect all possible issues that could arise with medical products that have been deliberately falsified. Methods used to authenticate suspect medical products must be suitable for their intended use.

Laboratories, normally national medicines testing laboratories, that test suspect falsified medical products should preferably be ISO/IEC 17025 accredited by a recognized accreditation body (affiliated, for example, to the International Laboratory Accreditation Cooperation, etc.) to perform the appropriate analytical procedures that are listed in their scope of accreditation. Alternatively, a WHO-prequalified laboratory with the capability to test suspect falsified medical products, an appropriate array of analytical techniques and

sufficient expertise, may be chosen. Furthermore, the laboratories 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/IEC 17025, some additional skills and capacity, as outlined below, are required for the analytical testing of suspect falsified medical products.

7.1.1 Expertise

- **Critical thinking.** Laboratory staff should have the ability to critically appraise all that is known about each case of a suspect falsified product and not simply rely on 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 testing plans for suspect falsified medical products. 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 medical products, to apply them correctly and to interpret the results adequately.

7.1.2 Equipment

Laboratories should ensure that technical equipment for testing of suspect falsified medical products about which they have adequate knowledge and experience is appropriately 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 accordance with regional cooperation agreements can be considered to minimize the costs while maximizing the benefits.

Laboratories also need secure and adequate storage facilities for the suspect falsified 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 suspect falsified medical 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 on 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 (1, 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 case of legal action.

An example of an SOP for testing of suspect falsified products is provided in Appendix 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 clearly indicates what is expected from experimental testing. The inspector or enforcement officer who collected the sample should inform the laboratory as comprehensively as possible and necessary for efficient running of the testing.

A suitable analytical testing programme should be prepared to detect the suspect substances. An initial study should then be undertaken, keeping 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, which includes simple visual checks as well as the technologies listed in Appendix 1, and other forensic analyses that may assist in determining likely sources of suspect falsified medical products. Each technique should be appraised 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 medical products can be found in the literature (e.g. (5)). Various examples of flowcharts describing how to proceed with testing are reproduced in Appendix 4 for

illustrative purposes (with the kind permission of the authors, the European Network of Official Medicines Control Laboratories).

7.4 Interpretation and reporting of results

General good practices in interpreting laboratory testing results are described in WHO guidance (6). Specific points to document for testing of suspect falsified medical 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 on confirmed falsified medical products

A legal framework for reporting of falsified products should be in place at national level (9).

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.¹⁰ The marketing authorization holder 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 (10).

9. Archiving of samples and reports

The testing laboratory should store the samples appropriately and archive the related documentation in separate secure locations for future reference as required by legislation, documenting that the integrity of samples and results have been preserved.¹¹

¹⁰ <http://www.who.int/medicines/regulation/ssffc/surveillance/en/>.

¹¹ See also reference (3), Paragraph IV.1.1. 30.

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Appendix 1

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

The list in Table 1 provides examples of analytical techniques that may be considered. These include compendial methods as well as specific advanced techniques. Each technique should be appraised 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 1
Illustrative examples of commonly available techniques

Main use	Technique	Full name	Remark
Identification	ATR/FTIR spectroscopy	Attenuated total reflectance/Fourier transform infrared spectroscopy	–
Identification	Melting point	–	–
Identification	XRPD	X-ray powder diffractometry	–
Identity	RI	Refractive index	–
Identification assay	Spectrophotometry (colorimetry)	–	–
Identification assay impurities	TLC	Thin-layer chromatography	–
Assay identification impurities	GC/FID	Gas chromatography with flame ionization detection	–

Table 1 *continued*

Main use	Technique	Full name	Remark
Forensics identification assay impurities	GC/MS	Gas chromatography with mass spectrometric detection	–
Assay identification impurities	LC/UV	Liquid chromatography with ultraviolet detection	–
Residual solvents impurities	HS-GC/FID	Headspace gas chromatography with flame ionization detection	–
Forensics residual solvents impurities	HS-GC/MS	Headspace gas chromatography with mass spectrometric detection	–
Inorganic impurities	ICP/OES	Inductively coupled plasma with optical emission spectroscopy	–
Inorganic impurities	ICP/MS	Inductively coupled plasma with mass spectrometric detection	–
Elemental and chemical analysis	XRF	X-ray fluorescence	–
Finished pharmaceutical product testing	Dissolution testing	–	Indication on bioavailability of the active pharmaceutical ingredient (API)
Finished pharmaceutical product testing	Disintegration testing	–	Indication of bioavailability of API
Specific testing	Sterility	–	–
Specific testing	BET	Bacterial endotoxins test	–

Table 1 *continued*

Main use	Technique	Full name	Remark
Specific testing	Osmolarity and osmolality	–	Characterization of injections and infusions
Finished pharmaceutical product testing forensics	Light microscopy	–	Particle characterization (size distribution, size, particulate impurities)
Identification	Raman spectroscopy	–	Characterization of material
Forensics	Photo scan/overlay	–	Documentation, comparison (e.g. packaging, leaflets)
Forensic	FTIR/Raman imaging spectroscopy	–	Characterization of material composition (distribution, particulate impurities)
Forensics	TEM	Transmission electron microscopy	Characterization of material morphology (tablet, particles)
Forensics	SEM-EDX	Scanning electron microscopy with energy dispersive X-ray spectroscopy	Characterization of material (surface, distribution in mixtures, particulate impurities)
Forensics; identification of impurities	LC-HRMS	Liquid chromatography with high resolution mass spectrometric detection	Characterization of unknowns down to trace levels
Forensics; identification assay impurities	LC/MS	Liquid chromatography with mass spectrometric detection	–

Table 1 *continued*

Main use	Technique	Full name	Remark
Forensics; impurities	TDS-GC/MS	Thermodesorption gas chromatography with mass spectrometric detection	Qualitative analysis of volatiles and semi-volatiles in solid samples (direct analysis/ without sample preparation)
Forensics	LC/ELSD	Liquid chromatography with evaporative light scattering detection	–
Forensics; identification assay impurities	NMR, qNMR	Nuclear magnetic resonance, quantitative nuclear magnetic resonance	Characterization of unknown compounds and mixtures – qualitative and quantitative

Appendix 2

Example of an information collection form

RECEIPT OF SUSPECT FALSIFIED PRODUCT		
Date on which the suspect product was received:		
Suspect product received by:		
Signature of the inspector/ enforcement officer and that of the owner of the product collected or seized		
Suspect product:		
Supply history of the product		
Source of the suspect product:		
Contact details of source of suspect product:	Name and surname:	
	Physical address:	
	Email:	
	Telephone number(s):	
	Other:	

INFORMATION ON SUSPECT FALSIFIED PRODUCT

1. Suspect product name(s):	
2. Type of product (select the most appropriate box):	
Innovator product	<input type="checkbox"/> Generic product <input type="checkbox"/>
Vaccine	<input type="checkbox"/> Blood product <input type="checkbox"/>
Other biological product	
Diagnostic	<input type="checkbox"/> Herbal medicine <input type="checkbox"/>
Traditional medicine	<input type="checkbox"/> Other, please specify <input type="checkbox"/>
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):	

Table continued

INFORMATION ON SUSPECT FALSIFIED PRODUCT		
6. Does the packaging contain any holographic security features or short message service (SMS) verifiable coding?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Provide description (if applicable):		
7. Is there a patient information leaflet available with the product?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
8. Batch number/lot number (if available):		
9. Date of manufacture (if available):		
10. Expiry date (if available):		
11. Does this product fall under the national legislation for pharmaceutical products?		
	Yes <input type="checkbox"/>	No <input type="checkbox"/>
12. Market authorization holder (if applicable):		
13. Manufacturer(s) details as given on the suspect product packaging:		
14. Quantity of suspect product received:		

Table continued

INFORMATION ON SUSPECT FALSIFIED PRODUCT	
15. Does the suspect product meet specifications defined as part of the stated product's marketing authorization?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Provide full data content by scanning the code (if applicable):	
Additional information:	
16. Any other information applicable:	

TESTING REQUIREMENTS

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

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If "Yes" provide a summary of results

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

3. What tests or parameters should be considered to assess the product?

4. Is this sample physically and/or chemically similar to other samples (either specified or in general)?

5. Are the market authorization specifications available?	Yes	No
	<input type="checkbox"/>	<input type="checkbox"/>
6. Are official testing methods available?	Yes	No
	<input type="checkbox"/>	<input type="checkbox"/>

Description of methods available:

7. Any specific testing requests:

IMPACT ON PUBLIC HEALTH				
Have any adverse reactions been reported?	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
If "Yes" provide more information:				
Estimated number of patients adversely affected?				
Estimated number of patients at risk?				
Any other related information:				

Appendix 3

Example of the content of a standard operating procedure for testing suspect falsified tablets

1. Purpose

The standard operating procedure (SOP) describes the workflow and the required test procedures for the testing of suspect falsified tablets.

2. Scope

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

3. Sample receipt, documentation and storage

a. Sample receipt

Upon receipt of a shipment of suspect falsified tablets for analysis, the receiving laboratory should:

- record the
 - name and signature of the person delivering the sample or courier company waybill;
 - date and time of receipt of the sample in the laboratory with signature of the staff member;
 - presence of accompanying documentation in the shipment;
- check integrity (e.g. damage, 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 that contains the suspect falsified tablets as received as photographic image(s);

- document package insert or patient information leaflet as photographic image(s);
- check contents using shipping documents and previously received information from sending party;
- document each sample: secondary packaging and primary packaging (e.g. blister) including labels as photographic image(s);
- archive all documents and photographic images in the appropriate project files as per the corresponding SOP xxx.xxx.xxx;
- store samples under appropriate storage conditions according to SOP xxx.xxx.xxx until testing, record storage location;
- prior to testing let samples equilibrate to ambient temperature.

c. Checklists and records of observations

- All the above observations should be recorded on a checklist and signed and dated upon completion by the staff member responsible for these duties.
- The time and date of storage should be verified and recorded, with the signature of the person responsible.
- The time and date of sample removal from storage for equilibration to room temperature should be recorded, with the signature of the person responsible

d. Remarks

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

e. Observations

Any observations such as damaged packaging, missing or additional samples should be documented and communicated to the sending party in order to decide how to proceed.

4. Sampling and samples

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

5. Overall aspect

Inspect known product protection features (i.e. holograms, colour-shift inks, etc.)

a. Packaging

- Use Subset 1 (see section 4).
- Visually inspect the secondary and primary packaging, use authentic comparators whenever possible.
- Report observations of the external appearance of the packaging materials (including labels and printing) such as visible damage, holes, discoloration and stains, spelling mistakes and unusual typography.
- Document observations as photographic images and archive them together with corresponding notes in the project files as per the SOP xxx.xxx.xxx.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

b. Samples

- Use Subset 2 (see section 4).
- Visually inspect the tablets.
- Report observations of the external appearance of the tablets, such as visible fissures, holes, inclusions, discoloration or stains, presence or absence of score lines, and presence or absence of film or sugar coating.
- Document observations as photographic images and archive them together with corresponding notes in the project files as per the SOP xxx.xxx.xxx.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

6. Analytical testing

a. Packaging testing

- Use Subset 1 (see section 4).
- Record Fourier transform infrared spectroscopy (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.
- A reporting form should be signed and dated on completion by the staff member responsible.

b. Solid medicine (tablet) testing

i. Active pharmaceutical ingredient (API)

- Use Subset 2 (see section 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 sample using the reference standard and 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 its intended use should be proven by means of validation reports and should be a stability indicative method.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

ii. 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 from 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.

iii. Additional tests

If tests as described in sections i. and ii. do not deliver unambiguous results additional screening tests can be performed on Subset 2. These screening tests can include:

- elemental analysis screening using inductively coupled plasma with optical emission spectroscopy (ICP-OES) or ICP/mass spectrometry (MS) as per SOP xxx.xxx.xxx;
- screening for volatiles and semi-volatiles using thermodesorption gas chromatography (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 high pressure liquid chromatography mass spectrometry (HPLC)/MS as per SOP xxx.xxx.xxx.

7. Dissolution and disintegration testing

- Use Subset 2.
- 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

GC/MS	gas chromatography/mass spectrometry
HPLC/MS	high-pressure liquid chromatography/mass spectrometry
ICP/OES	inductively coupled plasma/optical emission spectrometry
ICP/MS	inductively coupled plasma/optical mass spectrometry
SOP	standard operating procedure

Appendix 4

Examples of flowcharts for testing of suspect 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.

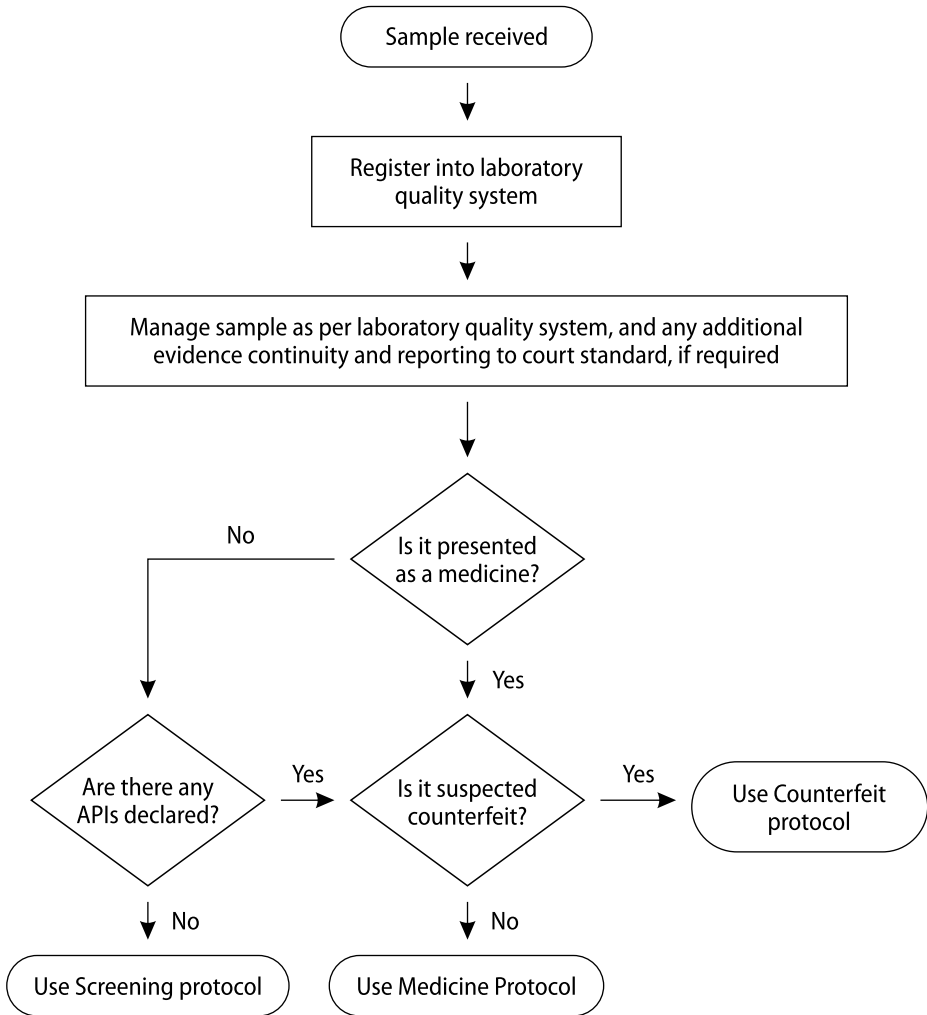
This document has been prepared to include example high-level process flows/decision trees to assist OMCLs and promote a harmonised approach across the Network. It is recognised that OMCLs will have existing processes in place and this document does not supersede existing systems. This document is intended 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



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.

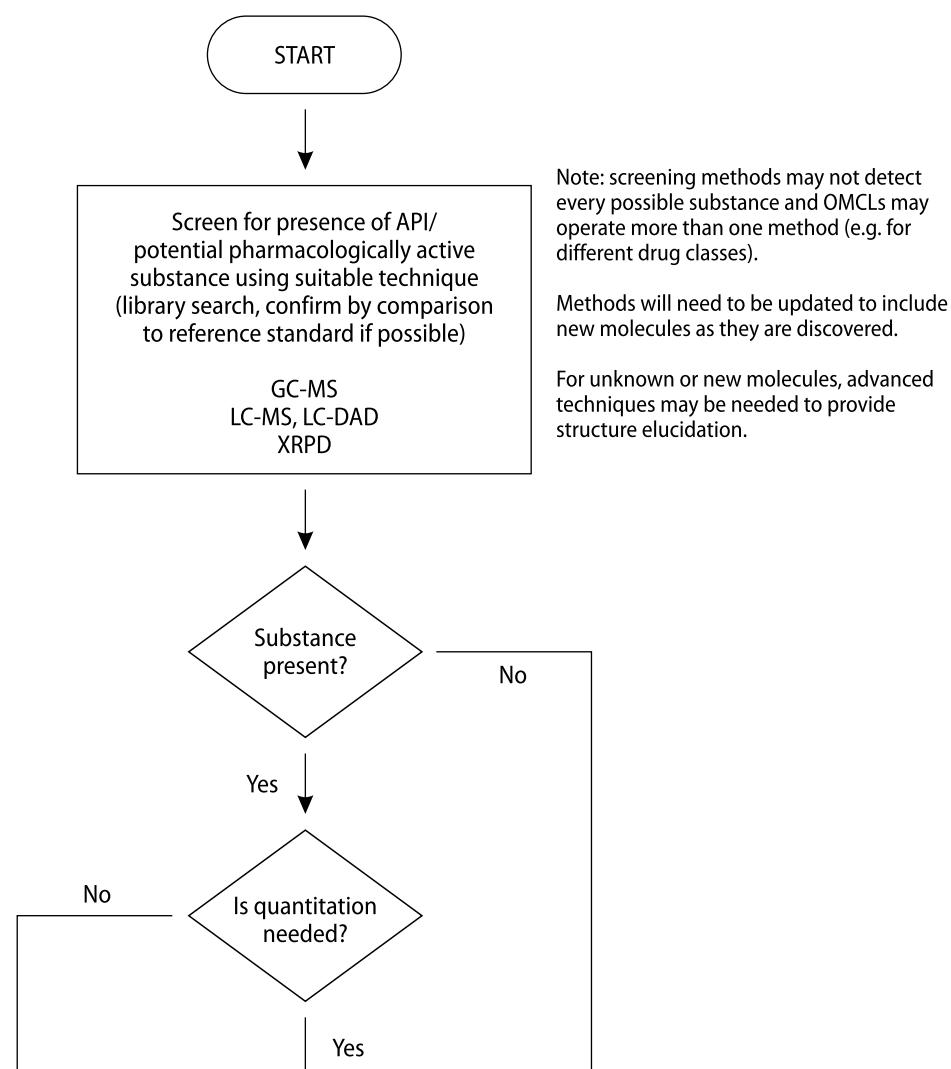
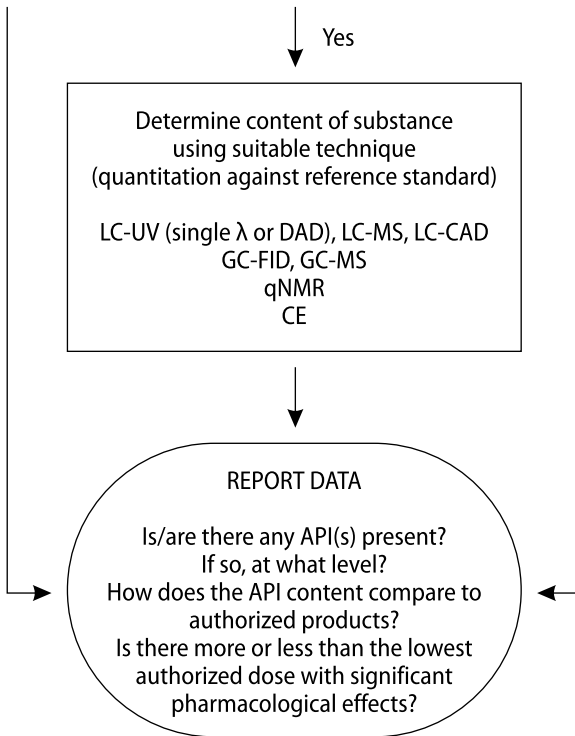


Figure continued



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.

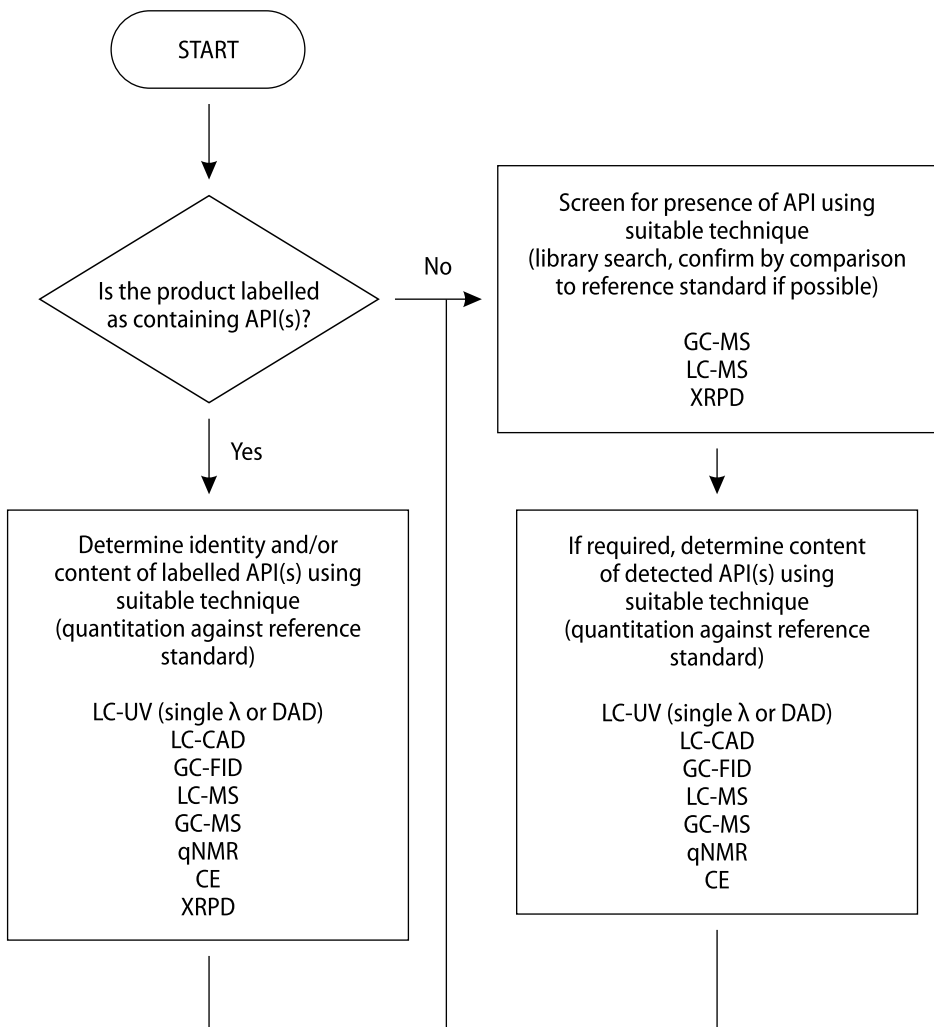
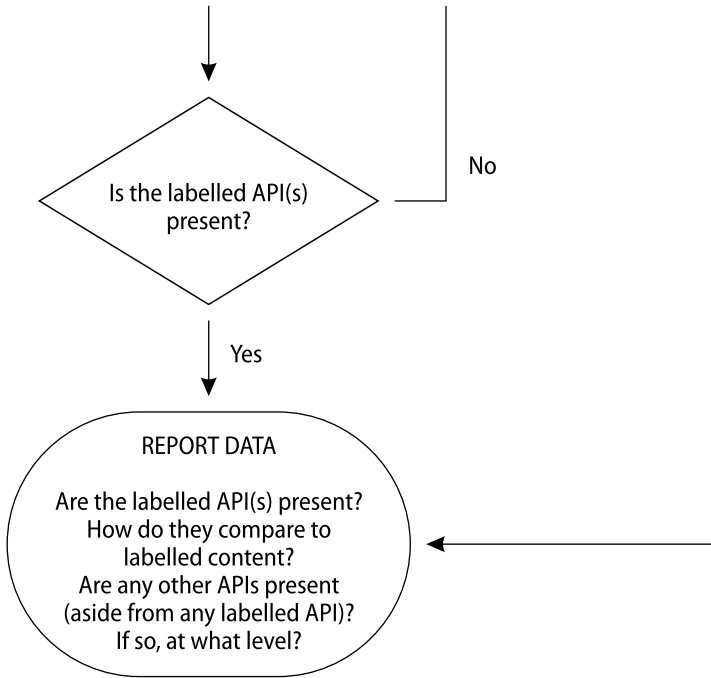
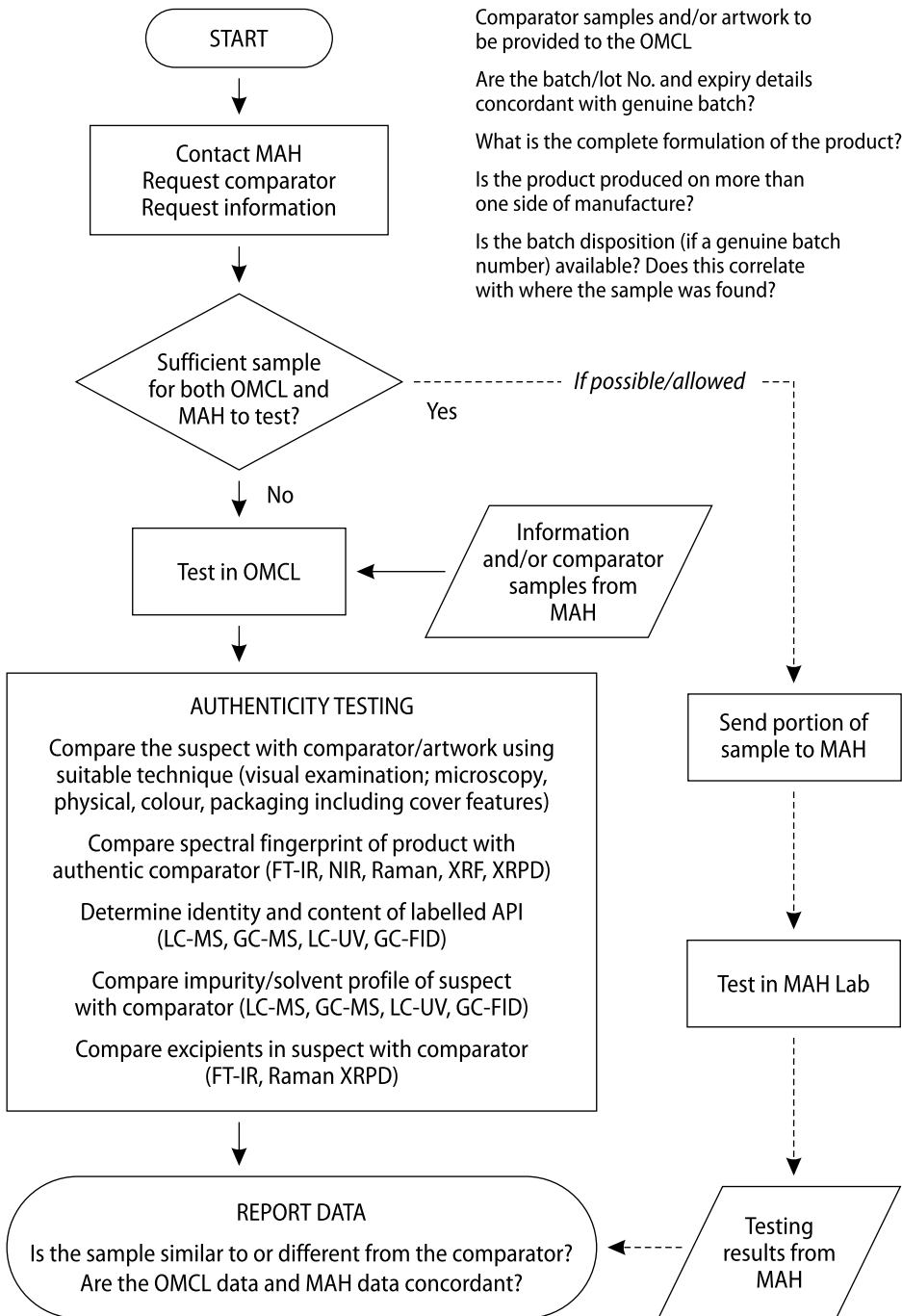


Figure continued



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 of the genuine product. This may either be directly or through the competent authority, inspectorate or enforcement group. Genuine comparator batches (ideally three 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.



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

