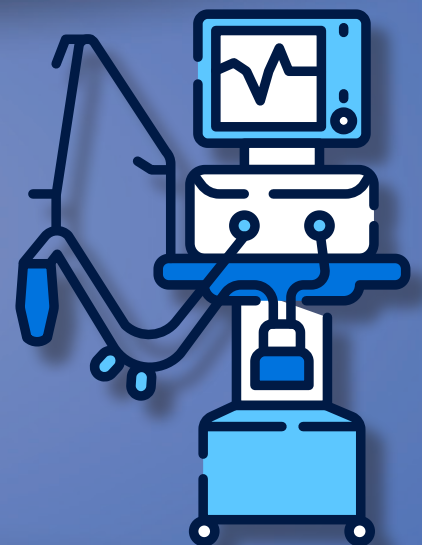
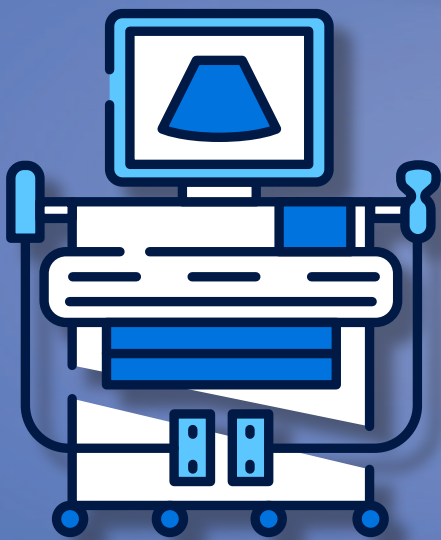


Guidance for post-market surveillance and market surveillance of medical devices, including in vitro diagnostics



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This guidance will be reviewed in 2025, unless substantive technological advancements are made that would require an earlier review. This guidance will be used as the basis for a series of training materials to be presented via the WHO Academy. Its impact on regulatory practice will be monitored through the WHO Global Benchmarking Tool for regulatory system strengthening once it has been rolled out for medical devices. Its impact on post-market surveillance obligations will be monitored through review of annual reports for WHO-recommended medical devices. This guidance will be made available in the six languages of the United Nations.

¹ English version (<https://apps.who.int/iris/bitstream/handle/10665/255576/9789241509213-eng.pdf?sequence=1>)

Version française (<https://apps.who.int/iris/bitstream/handle/10665/258534/9789242509212-fre.pdf?sequence=1>)

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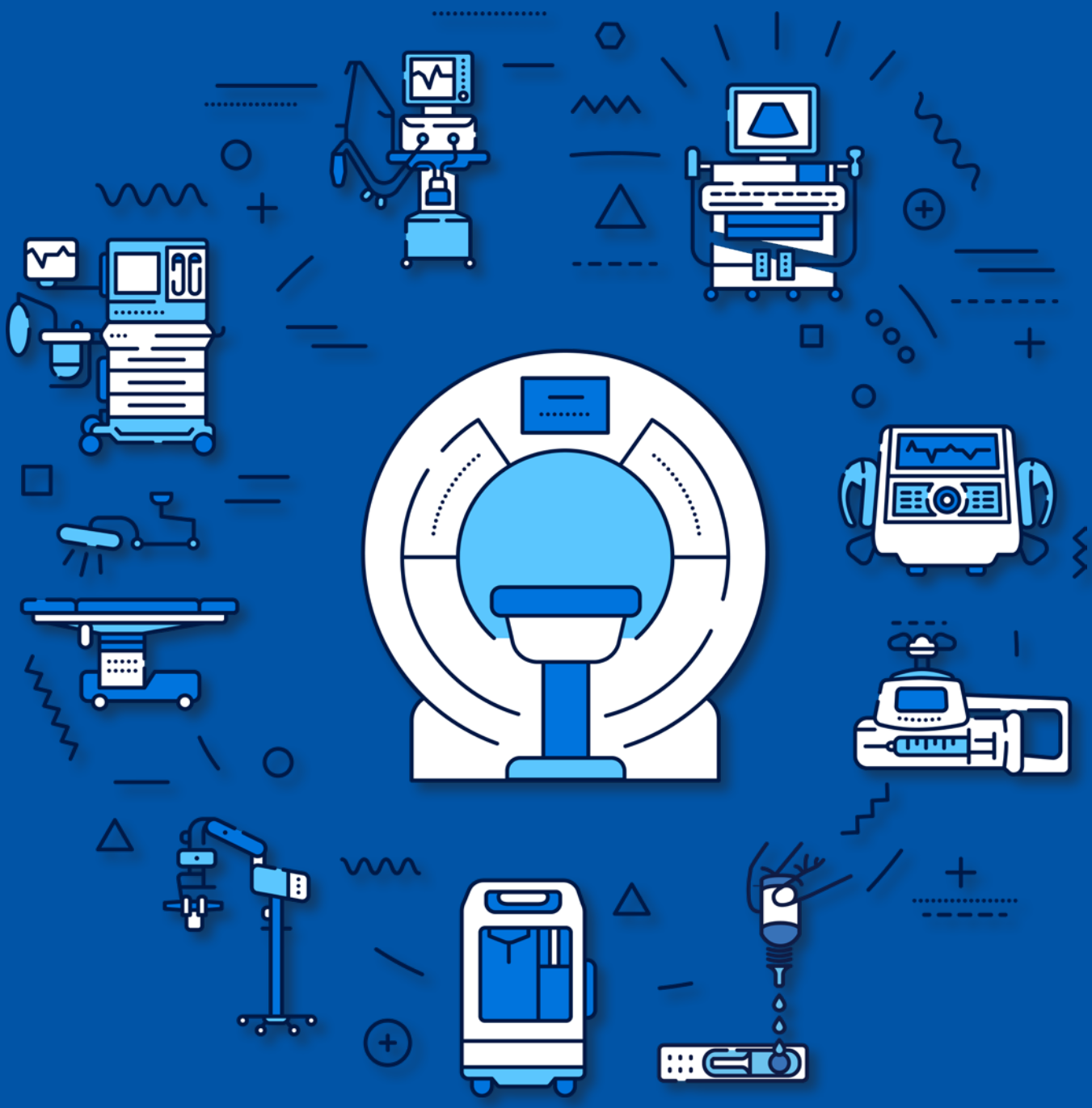
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Abbreviations

| | |
|---------------|--|
| CAPA | corrective and preventive action |
| CoA | certificate of analysis |
| EQAS | external quality assessment scheme |
| EU | European Union |
| EUL | Emergency Use Listing procedure (WHO) |
| FDA | Food and Drug Administration (USA) |
| FMEA | failure mode and effects analysis |
| FSCA | field safety corrective action |
| FSN | field safety notice |
| IA | immunoassay |
| IFU | instructions for use |
| IMDRF | International Medical Device Regulators Forum |
| ISO | International Organization for Standardization |
| IVDs | in vitro diagnostic medical devices |
| LoD | limit of detection |
| NAT | nucleic acid testing |
| NRA | national regulatory authority |
| PMCF | post-market clinical follow-up |
| PMPF | post-market performance follow-up |
| QC | quality control |
| QMS | quality management system |
| QR | quick read |
| RDT | rapid diagnostic test |
| UDI | unique device identification |
| UDI-DI | unique device identification device identifier |
| UDI-PI | unique device identification production identifier |
| WHO | World Health Organization |



Introduction

Post-market surveillance is a set of activities conducted by manufacturers, to collect and evaluate experience gained from medical devices that have been placed on the market, and to identify the need to take any action. Post-market surveillance is a crucial tool to ensure that medical devices continue to be safe and well performing, and to ensure actions are undertaken if the risk of continued use of the medical device outweighs the benefit. The evaluation of post-market surveillance experiences can also highlight opportunities to improve the medical device.

Medical devices and in vitro diagnostic medical devices (IVDs) will be collectively referred to as medical devices for the rest of this guidance or otherwise specified, if appropriate.

The WHO Global Model Regulatory Framework for Medical Devices, including in vitro diagnostic medical devices, like many other international regulatory frameworks, requires the implementation of post-market surveillance systems (1). It requires that receiving and evaluating feedback are the minimum requirements for post-market surveillance, but that this can be expanded to include other activities. The WHO Global Model Regulatory Framework for Medical Devices also includes the activities of the national regulatory authorities (NRAs) acting in response to reports of adverse events received, so-called vigilance. In different jurisdictions, the term "adverse event" might be interchanged with the word "incident". In this guidance, the term incident will be used to encompass a range of experiences that might be gathered on the use of a medical device. The definition of post-market surveillance in the WHO Global Model Regulatory Framework for Medical Devices focuses on the activities of NRAs. In the context of this document, such activities conducted by NRAs are called market surveillance. This document reserves use of the term post-market surveillance only for activities undertaken by the manufacturers.

Thus, the terms post-market surveillance, vigilance and market surveillance are closely linked. Experiences gathered on the use of medical devices by users are reported to manufacturers. Manufacturers report certain incidents to NRAs and keep them updated on the actions taken. The NRA will review the investigation undertaken by manufacturers and the further actions taken. This is connected to the market surveillance responsibilities of NRAs. Market surveillance comprises the total package of activities undertaken by NRAs to obtain an oversight of medical devices on the market in their territory and to ensure that the safety, quality and performance of medical devices on the market continues to be adequate.

Over the past years, several developments have had an impact on post-market surveillance systems. The WHO Global Model Regulatory Framework for Medical Devices, and new European Union (EU) regulations on medical devices and IVDs were published in 2017 (1, 2, 3). The EU regulations establish strong and relatively detailed requirements on post-market surveillance and on how post-market surveillance data are to be used (e.g. updates to the risk management file and to clinical evaluation). The United States Food and Drug Administration (FDA) has placed an increased emphasis on the possibilities for using data from experiences gained through the use of medical devices (4). An increasing number of regulators are considering the value of using real-world evidence for post-market surveillance, and other regulatory processes.

Recent horizontal International Organization for Standardization (ISO) standards for medical devices place increased emphasis on the importance of post-market surveillance. The ISO standard on quality management systems (QMS) for medical devices, used by most manufacturers, requires a post-market surveillance system to be in place (5). Furthermore, in the 2019 revision of the ISO standard on risk

management of medical devices requirements on post-market surveillance were also strengthened (6). The specific ISO guidance document on post-market surveillance for manufacturers of medical devices was recently published (7). Together, these documents provide a framework for conducting post-market surveillance and using post-market surveillance data to ensure the continued quality, safety and performance of medical devices.

Post-market surveillance, as described in this guidance, is essential for all medical devices in order to enable continuous improvement of medical devices. In **Part IV** of this guidance, specific requirements for manufacturers of WHO-recommended medical devices and IVDs are given, including reporting to WHO. Although the user/patient/client does not have an official responsibility in post-market surveillance, most of the information on the actual use of medical devices comes from their feedback. On the other hand, users/patients/clients will benefit if the medical devices on the market remain safe and well performing; therefore they should be encouraged to provide feedback to the manufacturer, and the manufacturer should facilitate such customer feedback.

Scope and intended audience

Scope

This document pertains to the objectives and processes for post-market surveillance for medical devices conducted by manufacturers with the assistance of their economic operators, as well as market surveillance conducted by regulators, and the role of other stakeholders in these processes. It describes the measures taken to ensure the ongoing compliance of medical devices with the requirements for safety, quality and performance after they are placed on the market.

All medical devices, including IVDs, are covered by this guidance, without prejudice to national or regional legislation.

Users and manufacturers should be aware that software as a medical device, including artificial intelligence, is subject to this guidance, where applicable.

Combination products will be subject to this guidance, if the principle intended use of the combination product is achieved by the medical device component of the combination product.

Audience

The intended audience of this guidance is:

- manufacturers of medical devices, and their economic operators in the medical device supply chain;
- health care providers and their patients/clients as users of medical devices;
- programme implementers, including procurement agencies and central medical stores; and
- NRAs.

Build on existing systems

The post-market surveillance procedures described in this document are intended to supplement, and not substitute, the internal procedures for post-market activities that are expected to be an integral part of the manufacturer's QMS.

Subject to the applicable provisions in force, national regulations can require manufacturers to perform post-market surveillance activities and submit relevant post-market information to NRAs. Specific reporting timelines and actions may differ between countries, and should be respected.

The market surveillance activities described in this guidance are also intended to supplement existing activities performed by NRAs. NRAs are encouraged to take a risk-based approach to expanding market surveillance activities for medical devices. The principles laid out in this document may be considered by NRAs when developing or amending existing national post-market surveillance and market surveillance obligations.

This guidance can also be used by procurement agencies and other entities that procure medical devices and wish to be assured of their continued quality, safety and performance.

Guidance for adaptation

This document intends to give an overview of the technical aspects of post-market surveillance and market surveillance for medical devices. NRAs are invited to adopt these guidelines in relation to the resources available, i.e. a phased implementation may be most appropriate.

Definitions

Abnormal use

Conscious, deliberate act or deliberate omission of an act that is counter to or violates normal use and is also beyond any further reasonable means of user interface-related risk control by the manufacturer. Examples of such acts are reckless use or sabotage or deliberate disregard of information for safety. Source: (8), some notes to entry deleted.

Note 1 to entry: An intended but erroneous action that is not abnormal use is considered a type of use error.

Note 2 to entry: Abnormal use does not relieve the manufacturer from considering non-user interface-related means of risk control.

Accessory to a medical device

Means an article intended specifically by its manufacturer to be used together with a particular medical device to enable or assist that device to be used in accordance with its intended use. Source: (9).

Accessory to an IVD

Means an article intended specifically by its manufacturer to be used together with a particular IVD medical device to enable or assist that device to be used in accordance with its intended use.

Note: Some jurisdictions include "accessories to a medical device" and "accessories to an IVD medical device" within their definitions of "medical device" or "IVD medical device", respectively. Other jurisdictions do not



adopt this approach but still subject an accessory to the regulatory controls (e.g. classification, conformity assessment, quality management system requirements etc.) that apply to medical devices or IVD medical devices. Source: (9).

Authorized representative

Any natural or legal person established within a country or jurisdiction who has received a written mandate from the manufacturer to act on their behalf for specified tasks with regard to their obligations under that country or jurisdiction's legislation. Source: (10).

Client/patient

Person undergoing testing with an IVD or person on whom a medical device is used.

Clinical evaluation

A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the device when used as intended by the manufacturer. Source: (11).

Combination products

Products which combine a medicinal product or substance and a medical device. Source: (3).

Competent authority

See NRA, this term is mainly used in the EU.

Component

One of the different parts of which a device is composed. Source: (12).

Conformity assessment

Determining whether the relevant requirements in technical regulations or standards are fulfilled. Source: (13).

Correction

Action to eliminate a detected nonconformity. Source: (14).

Note 1: A correction can be made in advance of, in conjunction with, or after a corrective action.

Note 2: A correction can be, for example, rework or regrade.

Corrective action

Action to eliminate the cause of a detected nonconformity or other undesirable situation. Source: (14).

Note 1: There can be more than one cause of nonconformity.

Note 2 to entry: Corrective action is taken to prevent recurrence, whereas preventive action is taken to prevent occurrence.

Note 3 to entry: There is a distinction between correction and corrective action.

Distributor

Any natural or legal person in the supply chain who, on their own behalf, furthers the availability of a medical device to the end user. Source: (10).

Note 1: More than one distributor may be involved in the supply chain of a medical device.

Note 2: Persons in the supply chain involved in activities such as storage and transport on behalf of the manufacturer, importer or distributor, are not distributors under this definition.

Economic operator

A manufacturer, an authorized representative, an importer, a distributor or the person combining different medical devices into one pack or sterilizing a system or procedure pack with the intent to place them on the market. Source: (3).

Note: definition amended to become self-explanatory.

Escalation

A situation in which something becomes greater or more serious. Source: (15).

External quality assessment scheme (EQAS)

A method/process that allows testing conducted by a laboratory, testing site or individual user to be compared with that of a source outside the laboratory – of a peer group of laboratories or a reference laboratory or testing sites. Also known as proficiency testing. Source: (16).

Field safety corrective action (FSCA)

An action taken by a manufacturer to reduce the risk of death or serious deterioration in the state of health associated with the use of a medical device. Such actions should be notified via a field safety notice (FSN). In assessing the need for FSCA, the manufacturer may use the methodology described in the international standard ISO 14971.

FSCAs may include:

- return of a medical device to the manufacturer or its representative;
- device modification;
- device exchange;
- device destruction;
- advice given by the manufacturer regarding the use of the device (e.g. where the device is no longer on the market or has been withdrawn but could still possibly be in use, e.g. implants).

Device modifications may include:

- Retrofit in accordance with the manufacturer's modification or design change.
- Permanent or temporary changes to the labelling or instructions for use (IFU).
- Software upgrades, including those carried out by remote access.
- Modification to the clinical management of patients to address a risk of serious injury or death related specifically to the characteristics of the device. For example, for implantable devices it is often clinically unjustifiable to explant the device.
- Corrective action taking the form of special patient follow-up, irrespective of whether any affected un-implanted devices remain available for return.
- For any diagnostic device (e.g. IVD, imaging equipment or devices), the retesting of affected patients, samples or the review of previous results.
- Advice on a change in the way the device is used (e.g. IVD manufacturer advises revised quality control procedure, use of third-party controls or more frequent calibration). Source: (17).

Field safety notice (FSN)

A communication sent out by a manufacturer or its representative to the device users in relation to an FSCA. Source: (17).

Note: An FSN can also be non-safety related, e.g. quality-related, customer product information.

Harm

Injury or damage to the health of people, or damage to property or the environment. Source: (6).

**Hazard**

Potential source of harm. Source: (6).

Hazardous situation

Circumstances in which people, property or the environment are exposed to one or more hazards. Source: (6).

Importer

Any natural or legal person in the supply chain who is the first in a supply chain to make a medical device, manufactured in another country or jurisdiction, available in the country or jurisdiction where it is to be marketed. Source: (10).

Incident

Malfunction or deterioration in the safety, quality or performance of a device made available on the market, any inadequacy in the information supplied by the manufacturer and undesirable side-effects. Source: (17).
Note: Depending on jurisdictions, the term adverse event (in its post-market meaning) and incident can typically be used interchangeably.

Instructions for use (IFU)

Information provided by the manufacturer to inform the device user of the medical device's intended purpose and proper use and of any precautions to be taken. Source: (18).

In vitro diagnostic medical device (IVD)

A medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.

Note 1: IVDs include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.

Note 2: In some jurisdictions, certain IVDs may be covered by other regulations. Source: (12).

Label

Written, printed or graphic information either appearing on the medical device itself, or on the packaging of each unit, or on the packaging of multiple devices. Source: (18).

Labelling

The label, IFU, and any other information that is related to identification, technical description, intended purpose and proper use of the medical device, but excluding shipping documents. Source: (18).

Lot

Defined amount of material that is uniform in its properties and has been produced in one process or series of processes. Source: (19).

Manufacturer

Any natural or legal person with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use, under their name; whether or not such a medical device is designed and/or manufactured by that person themselves or on their behalf by another person(s). Source: (10).

Market surveillance

The activities carried out and measures taken by competent authorities (regulatory authorities) to check and ensure that devices comply with the requirements set out in the relevant legislation and do not endanger health, safety or any other aspect of public interest protection. Source: (3).

Note: "union harmonization" deleted.

Medical device

Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury;
- investigation, replacement, modification, or support of the anatomy, or of a physiological process;
- supporting or sustaining life;
- control of conception;
- cleaning, disinfection or sterilization of medical devices;
- providing information by means of in vitro examination of specimens derived from the human body; and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means. Source: (12).

Note 1: Products which may be considered to be medical devices in some jurisdictions but not in others include:

- *disinfection substances;*
- *aids for persons with disabilities;*
- *devices incorporating animal and/or human tissues;*
- *devices for in vitro fertilization or assisted reproduction technologies.*

Note 2: For clarification purposes, in certain regulatory jurisdictions, devices for cosmetic/aesthetic purposes are also considered medical devices.

Note 3: For clarification purposes, in certain regulatory jurisdictions, the commerce of devices incorporating human tissues is not allowed.

(National) regulatory authority

A government body or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and that may take enforcement action to ensure that medical products marketed within its jurisdiction comply with legal requirements. Source: (20).

Nonconformity

Non-fulfilment of a requirement. Source: (13).

Post-market surveillance

Systematic process to collect and analyse experience gained from medical devices that have been placed on the market. Source: (5).

Note: For the purpose of this document, post-market surveillance includes the actions taken by the manufacturer based on the analysed data.

Preventive action

Action to eliminate the cause of a potential nonconformity or another undesirable situation. Source: (13).

Note 1: There can be more than one cause for nonconformity.

Note 2: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.

**Quality control (QC)**

Procedures that verify the attainment of the intended quality of results. Source: (21).

Registry (medical device)

Organized system with a primary aim to increase the knowledge on medical devices contributing to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional and health system). Source: (22).

Requirement

Need or expectation that is stated, generally implied or obligatory. Source: (13).

Risk

Combination of the probability of occurrence of harm and the severity of that harm. Source: (6).

Sample

One or more representative elements selected from a set to obtain information about that set. Source: (23).

Sample size

Number of sampling units in the sample. Source: (23).

Serious public health threat

Any event type or device deficiency which could result in imminent risk of death, serious deterioration in the state of health, serious injury, or serious illness of more than one patient, user or other person that requires prompt remedial action.

Signal detection

The process of determining patterns of association or unexpected occurrences that have the potential to impact patient management decisions and/or alter the known benefit-risk profile of a device. Source: (24).

Unanticipated

A condition leading to an event that was not considered in a risk analysis performed during the design and development phase of the device. Source: (17).

Unique device identification (UDI)

A series of numeric or alphanumeric characters created through a globally accepted device identification and coding standard. It allows the unambiguous identification of a specific medical device on the market. The UDI is comprised of the UDI-DI (device identifier) and UDI-PI (production identifier). Source: (24).

Note: The word "unique" does not imply serialization of individual production units.

Use error

User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. Source: (8), modified – Note 6 to entry deleted.

Note 1 to entry: Use error includes the inability of the user to complete a task.

Note 2 to entry: Use errors can result from a mismatch between the characteristics of the user, user interface, task, or use environment.

Note 3 to entry: Users might be aware or unaware that a use error has occurred.

Note 4 to entry: An unexpected physiological response of the patient is not by itself considered use error.

Note 5 to entry: A malfunction of a medical device that causes an unexpected result is not considered a use error.

User

The person, either professional or lay, who uses a medical device. The patient may be the user. Source: (19).

Basic principles of post-market surveillance

Post-market surveillance by medical device manufacturers

Pre-market evaluation of product quality, safety and performance is conducted by manufacturers of medical devices prior to entry on to the market. Decisions with regard to reducing risks and residual risk acceptability are made based on risk management principles. However, issues might arise after the medical device is placed on the market.

Manufacturers' responsibilities

Although medical devices are designed, developed, manufactured and distributed on the global market after thorough pre-market evaluation, residual risks regarding safety and performance will remain throughout the product's lifetime. This is due to a combination of factors, such as inherent product variability, factors affecting the medical device's use, environment, different user interaction, as well as, unforeseen medical device failure or misuse. Design and development activities for medical devices ensure the residual risks are acceptable with respect to anticipated benefits before the product is released on to the market. It remains important to continue to collect and evaluate information on the medical device during production and post-production to meet requirements for the monitoring of products and processes and to ensure the residual risks remain acceptable with respect to benefits. Appropriate processes allow for early detection of any undesirable effects. These processes can also reveal opportunities for improvement.

Post-market surveillance enables manufacturers to perform monitoring by collecting and analysing experiences from actual use of medical devices. Based on the outcome of this analysis, the need for further actions is decided, e.g. feedback into the risk management process, reporting incidents to NRAs, making a correction and/or FSCA which would be communicated to users through an FSN.

Post-market surveillance mechanisms

Post-market surveillance depends upon the information that can be/is to be collected. The manufacturer shall first establish the objectives of the post-market surveillance activities for each specific medical device or group of medical devices. Then, the manufacturer shall decide which sources are needed to fulfil these objectives. Based on this, the data shall be collected and analysed.

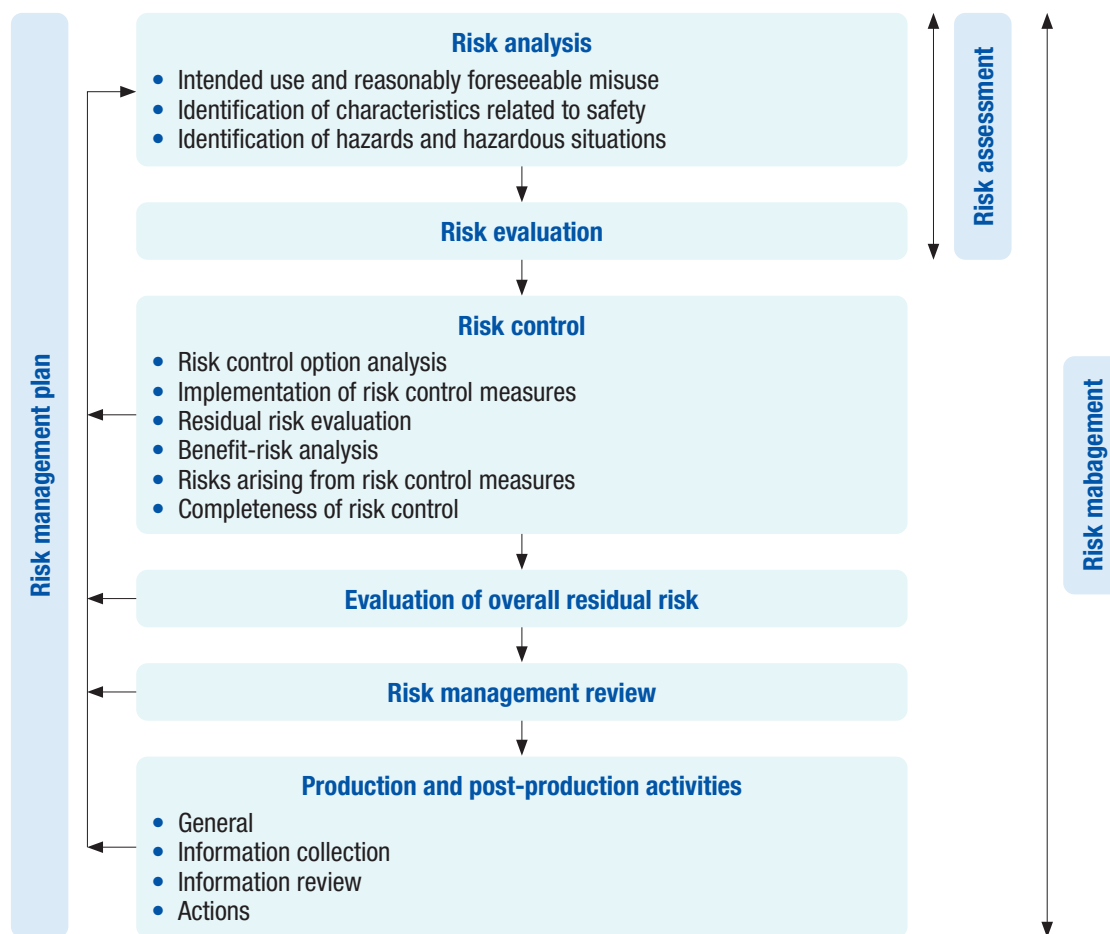
The most basic form of post-market surveillance, which shall always be performed, is reactive post-market surveillance. Reactive post-market surveillance is done through **collection and evaluation of feedback**. All feedback is evaluated to establish the severity of the incident and establish if it should be reported to the NRA. A root cause investigation might be launched, and further actions undertaken such as correction or corrective action.

Proactive post-market surveillance is the detection of issues through observing users during trainings, user support, scientific literature, conferences/trade shows and publicly accessible market surveillance information including FSNs, etc.

Post-market surveillance linked to risk management

Risk management of medical devices is a process that applies throughout all phases of the life cycle of a medical device. A risk management process should be implemented by all manufacturers of medical devices. The standard ISO 14971 on risk management for medical devices is recognized globally as the state-of-the-art process (6). Risk management should be a continuous and iterative process, during which the hazards associated with the medical device are identified. The associated risks are estimated and evaluated, these risks are controlled, and the effectiveness of the controls is monitored. Post-market surveillance has an important role in this process. It provides the essential link through which production and post-production information is gathered and analysed, so it can be fed back into the risk management process when needed. A schematic representation of the risk management process is provided in Fig. 1.

Fig. 1.
Risk management process for medical device manufacturers' feedback



Source: ISO 14971:2019 (6). Reproduced with the permission of ISO.

Risk management is a complex subject, because each stakeholder can place a different value on the acceptability of risks in relation to the anticipated benefits (6). The concepts of risk management are particularly important in relation to medical devices because of the variety of stakeholders.

It is generally accepted that the concept of risk has two key components:

- the probability of occurrence of harm; and
- the consequences of that harm, that is, how severe it might be.

How stakeholders manage risks

All stakeholders, including manufacturers and their economic operators, regulatory authorities, health care professionals, health care institutions and patients, need to understand that the use of a medical device involves an inherent degree of risk. The acceptability of a risk by a stakeholder is influenced by the stakeholder's perception of the risk and the benefit. It is important to realize this when deciding on the need for further actions, based on data gathered during the post-market surveillance process.

Stakeholders' roles and responsibilities

Post-market surveillance should be implemented by every manufacturer, at least in its most basic form, as a system to monitor, collect, evaluate and react to feedback. Other economic operators, such as importers, distributors and authorized representatives, play an important supportive role to ensure feedback from users reaches the manufacturer, including overcoming language barriers. National or regional legislation can require the manufacturer to perform more elaborate post-market surveillance, as simply reacting to feedback will only provide limited information on the experiences with the medical devices in actual use. Therefore, it then leaves information unused that could have been used to improve safety, quality and performance.

NRAs should raise awareness among users and clients/patients about the importance of providing feedback to manufacturers and their economic operators for post-market surveillance. Users and clients/patients will benefit from a medical device remaining safe and effective throughout its lifetime.

Users and clients/patients as well as implementers/procurers should be enabled to provide feedback to manufacturers and their economic operators.

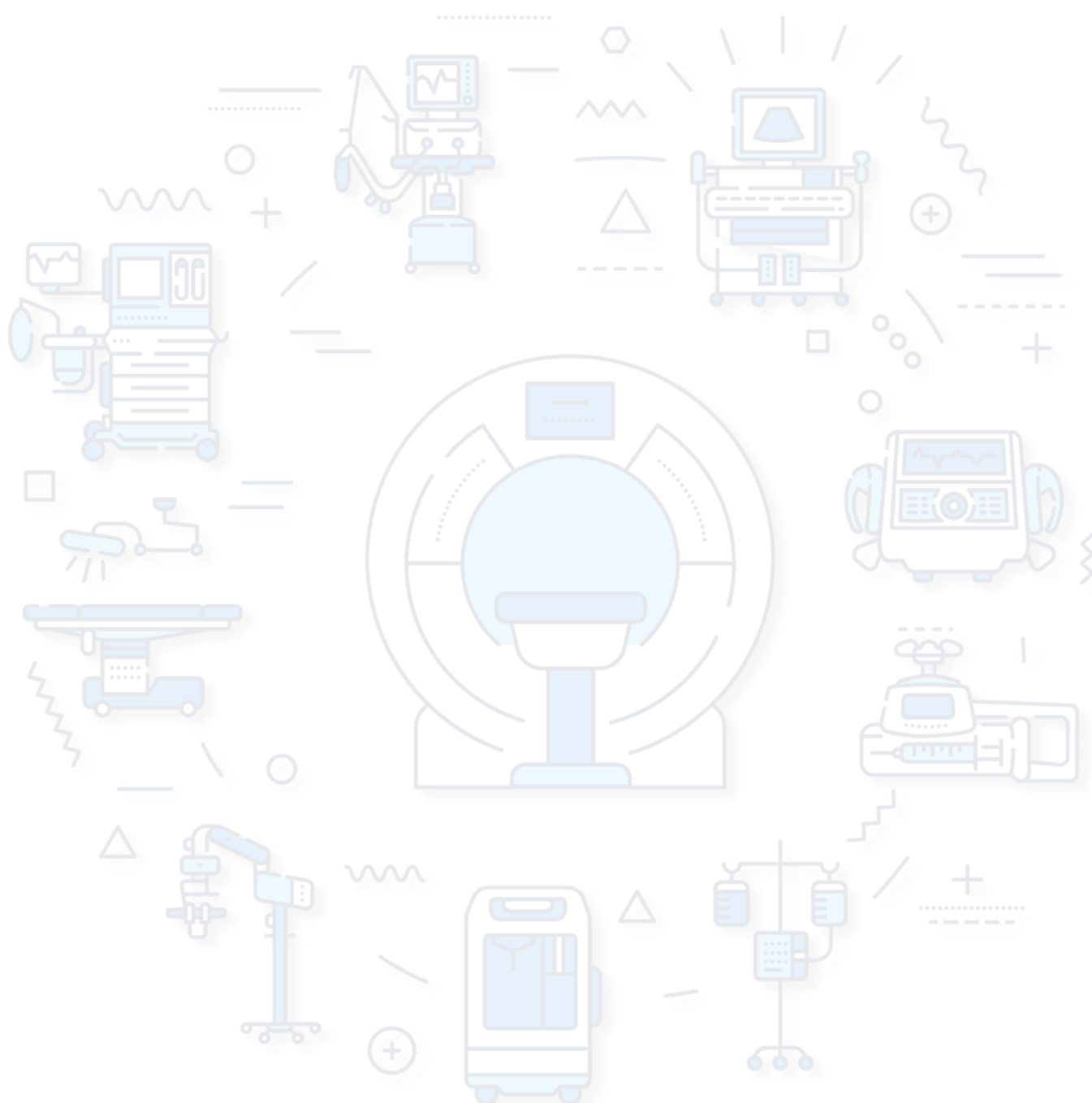
Table 1 gives an overview of the different stakeholders' roles in post-market surveillance and market surveillance of medical devices, as described in Parts I–IV of this document.

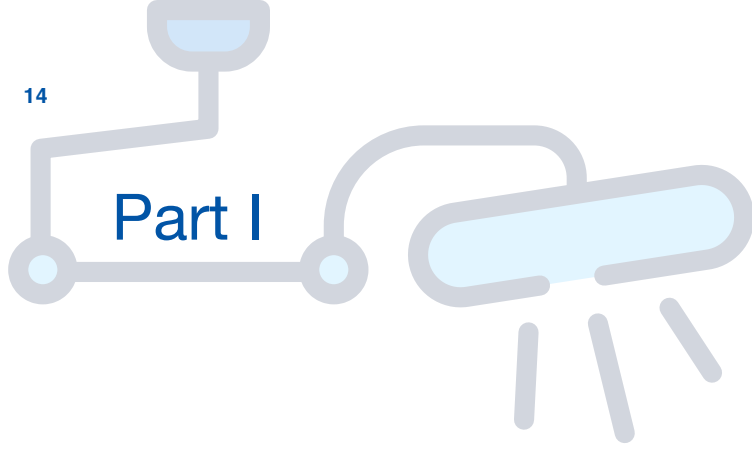
Table 1.
Stakeholders' roles in post-market surveillance and market surveillance of medical devices, with an emphasis on feedback

| Stakeholder | Activity | Details |
|--|--|---|
| I Users and clients/ patients (see Part I of this document) | Observe/detect issues | Users, and their clients/patients should be vigilant for issues with medical devices. |
| | Document feedback | Users should document the product codes/serial numbers/lot numbers and expiry dates of affected medical devices at the very least. |
| | Provide feedback | Users are encouraged to provide feedback to the manufacturer as soon as they become aware, and to inform their NRA at the same time, as applicable. |
| | Follow manufacturer's instructions | Users will be informed of important information on the use of the medical device via an FSN and should act as instructed in the FSN. |
| II Manufacturers and their economic operators (see Part II of this document) | Implement a system for post-market surveillance | An effective post-market surveillance system should include both active and passive collection of post-market information. Collecting and evaluating feedback are critical. |
| | Classify feedback and escalate if required | Manufacturers must establish a documented procedure for a feedback system and be able to quickly classify feedback. |
| | Establish if reporting to NRA is required | The manufacturer needs to establish if reporting to the NRA is required. Initial, follow-up and final investigation reports should contain all details of any investigation conducted. |
| | If required, undertake root cause analysis | The manufacturer should perform root cause analysis to establish the root cause for the issue, allowing adequate action to be initiated. Corrections and corrective/preventive actions may also be required to protect public safety. |
| | If required, make a correction | |
| III NRA (see Part III of this document) | If required, implement corrective and/or preventive actions | |
| | Ensure user feedback is forwarded to manufacturers | If NRAs receive feedback directly from users, they should forward user feedback to the manufacturer, with a copy to the local economic operator. The NRA may also conduct a risk assessment. |
| | Conduct risk assessment, as appropriate | |
| | Collect reports, review manufacturer investigation and other actions | NRAs should collect investigation reports (initial, follow-up, final), and review for evidence of documented procedures, timeliness and scientific rigour. |
| | Conduct or coordinate testing using a risk-based approach | NRAs may coordinate testing using a risk-based approach. |
| | Collect other market information | NRAs should strive to collect other forms of market intelligence. |
| | Take regulatory action, if needed, and ensure its implementation | NRAs may need to undertake their own regulatory action, if the manufacturer does not take adequate actions or not in a timely manner. The NRA may also undertake actions when they consider that the observed issues have wider implications. |
| Share information with other NRAs and/or WHO, if applicable | NRAs should share information with other NRAs. | |

Table 1. (continued)

| Stakeholder | Activity | Details |
|--|---|---|
| IV WHO (see Part IV of this document) | Provides support to manufacturers for post-market surveillance of WHO-recommended medical devices | For WHO prequalified medical devices, WHO reserves the right to conduct follow-up inspections to ensure that adequate actions are taken and corrective actions/preventive actions, if needed, have been implemented following post-market surveillance data analysis. |
| | Provides support to NRAs for market surveillance of WHO-recommended and other medical devices | WHO supports regulators through a variety of guidance and tools to strengthen their capacities. |
| | Provides support to users of medical devices to provide feedback | WHO supports users and patients/clients to report feedback using a variety of tools. |





Feedback from users and patients/clients

Overview of role of users

Feedback from users and patients/clients on the safety, quality and performance of medical devices is of crucial importance. Although users have no official responsibility for post-market surveillance, most of the information on the experience with the actual use of medical devices will come from users. Therefore, the role of users to provide feedback on the use of medical devices is essential for manufacturers' post-market surveillance obligations. As safe and effective medical devices are important for users, they should be encouraged to provide feedback and thereby take their role in the post-market surveillance process.

In this document, users, including lay users or lay caregivers, and patients/clients including self-testers, will be collectively referred to as users, unless otherwise specified.

Patients/clients are not typically regarded as users but are an important stakeholder in post-market surveillance. Certain problems might only be detected by the patient/client, particularly in health systems where information management is not integrated. Furthermore, as self-testing and self-care continues to grow, the need to engage patients/clients as users will increase.

Appropriate use of medical devices

Users should ensure they fully understand the intended purpose, handling and use of the medical device, according to manufacturer's IFU, to maintain its quality, safety and performance. The principles for the use of the medical device should be laid out in the manufacturer's IFU. The IFU is considered part of the medical device, as without it, the user is unable to use the medical device safely and correctly. The IFU describes how to correctly use and dispose of medical devices, as well as warnings, precautions and contra-indications. Every user must ensure proper storage of medical devices according to the manufacturer's IFU. This may include climate-control of the storage area, and to ensure that the storage areas are protected from sunlight, water, and excessive dust and dirt, as applicable.

Document feedback

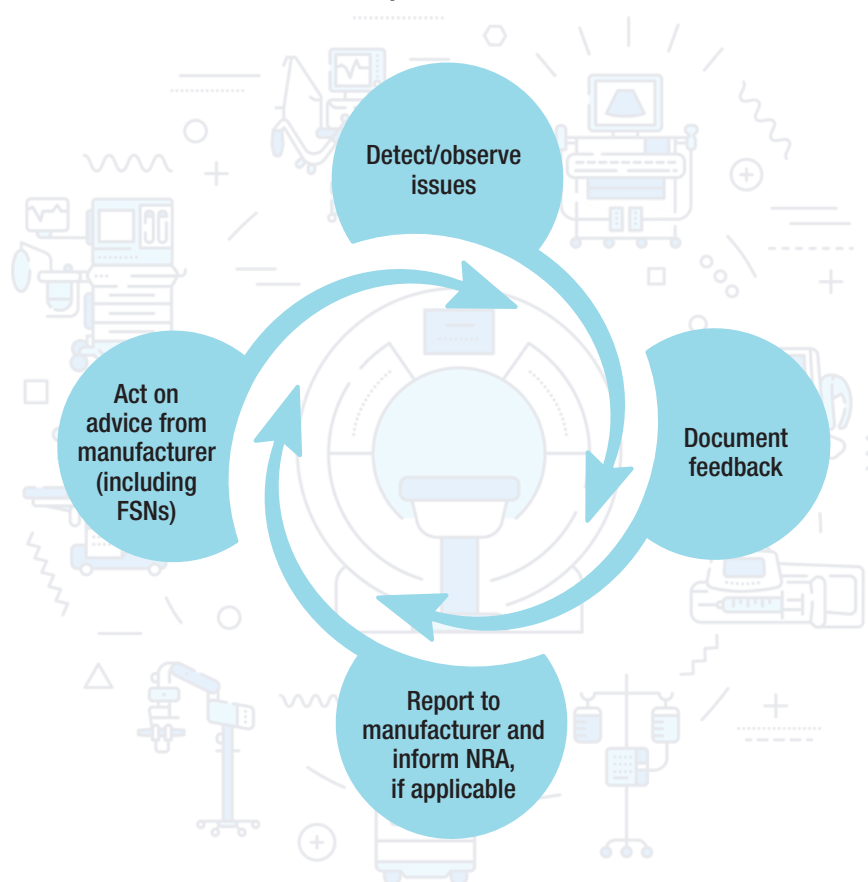
Users (in conjunction with appropriate technical expertise) should document their feedback in a broad sense, and as fully as possible. Users are not required to perform their own investigation unless described by their site's QMS. Moreover, they may assist the manufacturer's investigation.

Providing feedback

Users should provide feedback by reporting relevant information at their disposal to the manufacturer, see [Annex 1](#) for an example of a user feedback form. No information that could allow the patient to be personally identified should be reported. Feedback should be sent to the manufacturer's address as indicated in the contact details on the labelling or otherwise to the place where the medical device was bought/purchased, e.g. pharmacy, where staff will ensure the feedback is communicated to the manufacturer. Users may also inform the NRA directly, as applicable, in accordance with national regulations, see [Part III](#).

[Fig. 2](#) gives an overview of the steps involved in providing feedback to the manufacturer or their economic operator.

Fig. 2.
Actions of users in relation to manufacturers' post-market surveillance



1.1 Detect/observe

User feedback can be either positive or negative. Positive feedback may include, for example, experiences and suggestions for improvement. The user feedback form in **Annex 1** may be adapted for giving positive feedback.

Negative feedback can include incidents (see **Definitions**), use errors or abnormal use, etc.

How and what to detect

Upon delivery, users should, for example:

- Verify if the **correct product** was delivered and the presentation (configuration) of the product is what was ordered.
- Verify if **labelling matches** the labelling for the product on the manufacturer's website or NRA website, if possible.
- Ensure **manufacturer's contact details** are present.
- Check for any evidence of **tampering** of labels and/or packaging such as cracks, abrasion, erosion, breaks, seal integrity.
- Check for problems with **labelling (including IFU); and/or need for training**, including inadequate instructions to the user; unclear, missing, worn out, incorrect or inaccurate labels; if intended users are required to be adequately trained according to the labelling and IFU.
- Check for **manufacturing, packaging or shipping problems**, including defective components, defective medical devices, medical devices damaged prior to use, damage to the materials used to construct the cover or outer packaging (which can lead to compromised microbiological state, e.g. sterility of the medical device), missing listed components.
- Check for **storage conditions** (see label and/or IFU) and store medical device or IVD accordingly.

Users may request a certificate of analysis for the lot or serial number, if applicable, and use this as a reference for the physical inspection of the product name, product code, lot number, expiry date, etc. See **Annex 7** for an example of a certificate of analysis for IVDs.

During routine use of medical devices, users should be aware of product problems related to patient-device incompatibility, manufacturing, packaging or shipping, chemical composition, material integrity, mechanical or optical or electrical/electronic properties, calibration, output (such as false negative or false positive result for an IVD), temperature, computer software, connection, communication or transmission, infusion or flow, activation, positioning or separation, protective measures, compatibility, contamination/decontamination, environmental compatibility, installation-related, label, IFU or training, human-device interface, and use of device.

Incidents of a more serious nature, such as death or serious deterioration in health of the patient, user or other person, should always be considered part of feedback.

Registries

Registries are being increasingly used, especially for implantable medical devices, that can be used to collect data on clinical use and to assess use in the medical device's target population. Registries are generally maintained by health care facilities, health care authorities including regional databases, and relevant professional associations. Manufacturers might request access to certain data from a given registry at the discretion of the registry owner.

Signal detection may be conducted using data collected in registries whereby associations or unexpected occurrences can be detected that might impact patient management and/or change the established benefit-risk profile of a device.

1.2 Document

Users should document any feedback related to the use of medical devices at any facility or user site including product name and product code of the affected medical device, affected lot or serial numbers (and expiry dates), affected patients/clients (age, concomitant diseases, current treatments, etc.), procedure/treatment the device was used for and any measures taken, as applicable.

Feedback forms

Users should use a user feedback form, see **Annex 1** for an example.

Photographs of the affected medical device and labelling and/or injuries should be taken to illustrate the feedback, if possible. Please be mindful of ethical/privacy considerations when sharing information.

Retain samples

Users should appropriately store one or more of the affected medical devices as a retention sample for later inspection and testing, if possible. It is advised that the user contact the manufacturer or economic operator to ascertain the number of samples needed for later inspection and testing. With regard to software-driven medical devices, when possible and relevant, record the log files, or avoid resetting the medical device until the manufacturer has had the opportunity to check it.

Unique device identification

Documentation should describe in more detail the circumstances related to the feedback and will enable the manufacturer to conduct their investigation.

Implementation of International Medical Device Regulators Forum (IMDRF) guidance on unique device identification (UDI) systems for medical devices will aid documenting user feedback, and onward reporting to NRAs by manufacturers (24, 26). The UDI is a machine readable (such as a bar code) and a human interpretable code that is placed on the medical device which allows for the device and the production level data to be identified by all parties.

1.3 Report

Immediate feedback by users

All feedback, that reasonably suggests that the medical device has or may have caused or contributed to the death or serious deterioration in the health of a patient/client must be reported by the user to the manufacturer immediately (as soon as they become aware).

Contact details for the manufacturer are displayed on the label or in the IFU. If this information is not self-evident, users should go to the site where they obtained the medical device, e.g. health care facility, pharmacy, etc. Patients/clients should go back to the site where the medical device was used on them, e.g. health facility, laboratory. Users also may contact the relevant local economic operator (authorized representative, distributor, importer). Any other parties informed of user feedback should ensure this feedback is communicated to the manufacturer.

1.4 Act

Users can be called upon to act on the contents of FSNs including:

- Quarantine of devices at the request of manufacturer or NRA.
- Return of device or destruction of the device at the request of manufacturer.
- Device modification such as changes to the IFU or other labelling, software or hardware upgrades, clinical management (including retesting), etc.

Patients/clients should be made aware of FSNs usually via targeted mailings when users are known or by press release when not (e.g. over-the-counter medical device) – in any case they should contact their health care facility.

1.4.1 Specific user groups

Clinical laboratories

For clinical laboratories, feedback from users (laboratory technicians) will either be related to technical operation of the analysers or to the results obtained. If feedback relates to results obtained, these data should be made available to the manufacturer, allowing the manufacturer to perform an investigation into the issue. It is also important to provide details on the lot numbers of the consumables involved, and, preferably, some samples will be kept apart, to facilitate further investigation by the manufacturer.

Hospital/ health care facilities

Medical devices are mostly used in health care facilities, therefore, it is important for the manufacturer to obtain feedback from the users in these facilities. Preferably, the manufacturer or other economic operator involved will discuss providing feedback as part of the purchase order. The health care facilities should also consider how and which data they can make available to the manufacturer. The manufacturer on the other hand should be aware that health care professionals have limited time available and providing feedback other than incidents should be made as easy as possible.

Primary care facilities

In primary care facilities, staff time may be limited and providing feedback may not be the highest priority. Therefore, additional support and simple processes should be in place to support these sites. Manufacturers, or their economic operators, are encouraged to specifically support primary care facilities to report feedback.

Self-testing

Self-testing is usually performed by the individual on themselves, for example, blood glucose monitoring, HIV self-testing, etc. If observations are made during the performance of the assay, no expert will be available to assist the user. As such products are often purchased in pharmacies or supermarkets, it is unlikely that sufficient expertise is available there. Therefore, for feedback or advice, the labelling of the self-test shall contain the contact details of the manufacturer or the distributor.

Patients/clients

Many medical devices are purchased directly by users (e.g. thermometers, walking aids, HIV self-test kits) in a pharmacy, drugstore or supermarket. They can also be supplied for home use by a physician (e.g. crutches, wheelchair, blood glucose monitoring device). There is a growing trend to transfer the use of complex technology from health care facilities to the home environment (e.g. dialysis equipment and ventilation of patients). Patients/clients should either report feedback directly to the manufacturer or economic operator or contact the physician, pharmacy or site where they got the medical device to provide the feedback. Providing feedback through medical professionals is especially important if these professionals are involved in the treatment for which feedback is submitted. These professionals can then forward that information to the manufacturer. To ensure that patients/clients can provide feedback as easily as possible, the IFU or label of the medical device should include the relevant contact details.

1.4.2 Specific product groups

IVDs

For IVDs, sources of data on post-market surveillance include external quality assessment (EQA) schemes, also known as proficiency testing, and from external and internal quality control (QC).

Although the primary purpose of EQA is inter-laboratory comparison, these data can provide very useful information about the performance of IVDs, especially when many sites use the same product. Users who participate in EQA are encouraged to provide feedback to the manufacturer, if they report nonconforming results. EQA providers are encouraged to report to manufacturers, if they detect any observations from their analysis of EQA data.

Quality control is a process to detect whether performance requirements and quality objectives for an IVD have been met.

- For **internal quality control**, the manufacturer designs their product and may recommend QC procedures to be taken to verify that the IVD performs as intended.

- For **external quality control**, a user might use biological QC material of known reference results to test a sample of IVDs. It is critical to ensure that traceability of values assigned to such control materials is ensured through available reference measurement procedures or available reference materials of a higher order.

External QC materials are usually contrived biological specimens that are optimized for a given product and are developed independently of the IVD manufacturer. Ideally QC specimens should be tested in each test run or testing session. WHO recommends the following frequency of QC for monitoring quality by users:

- once weekly, preferably at the beginning of the week;
- for any new operator (including trained staff who have not conducted testing for some time);
- for each new lot of test kits;
- for each new shipment of test kits;
- when any environmental conditions (for example, temperature and humidity) fall outside the range recommended by the manufacturer.

Data from testing QC materials should be analysed and results outside a pre-determined acceptance range should be identified and investigated. For IVDs returning qualitative results such as rapid diagnostic tests (RDTs) or qualitative nucleic acid testing (NAT) technologies, other instructions may be given. Any implementation of QC for quality monitoring should consider using a risk-based approach.

A network of sentinel sites may be capacitated to conduct user quality monitoring in order to proactively detect trends in performance of IVDs in settings where typical users are unable to routinely run QC materials. These sites would test QC materials, and collect data to be forwarded to the relevant manufacturer. These data may also be fed into the risk management framework of the NRA and help to determine specific products that might require prioritization for market surveillance, see **Part III**.

Implants

For implants, feedback will usually be submitted by the physician in attendance, as events will be discussed between the patient and the physician. This will also allow the exchange of relevant medical information, taking into consideration legal requirements on data protection.

Software as a medical device

Software can either be embedded in a medical device or be stand-alone software. For software, the same principles apply as for other medical devices. Especially for stand-alone software, the contact details will most likely be included in the software and even a way to contact the developer can be included in the software. When providing feedback, it is important to include the software version and it is encouraged to include screenshots of the event on which feedback is given.

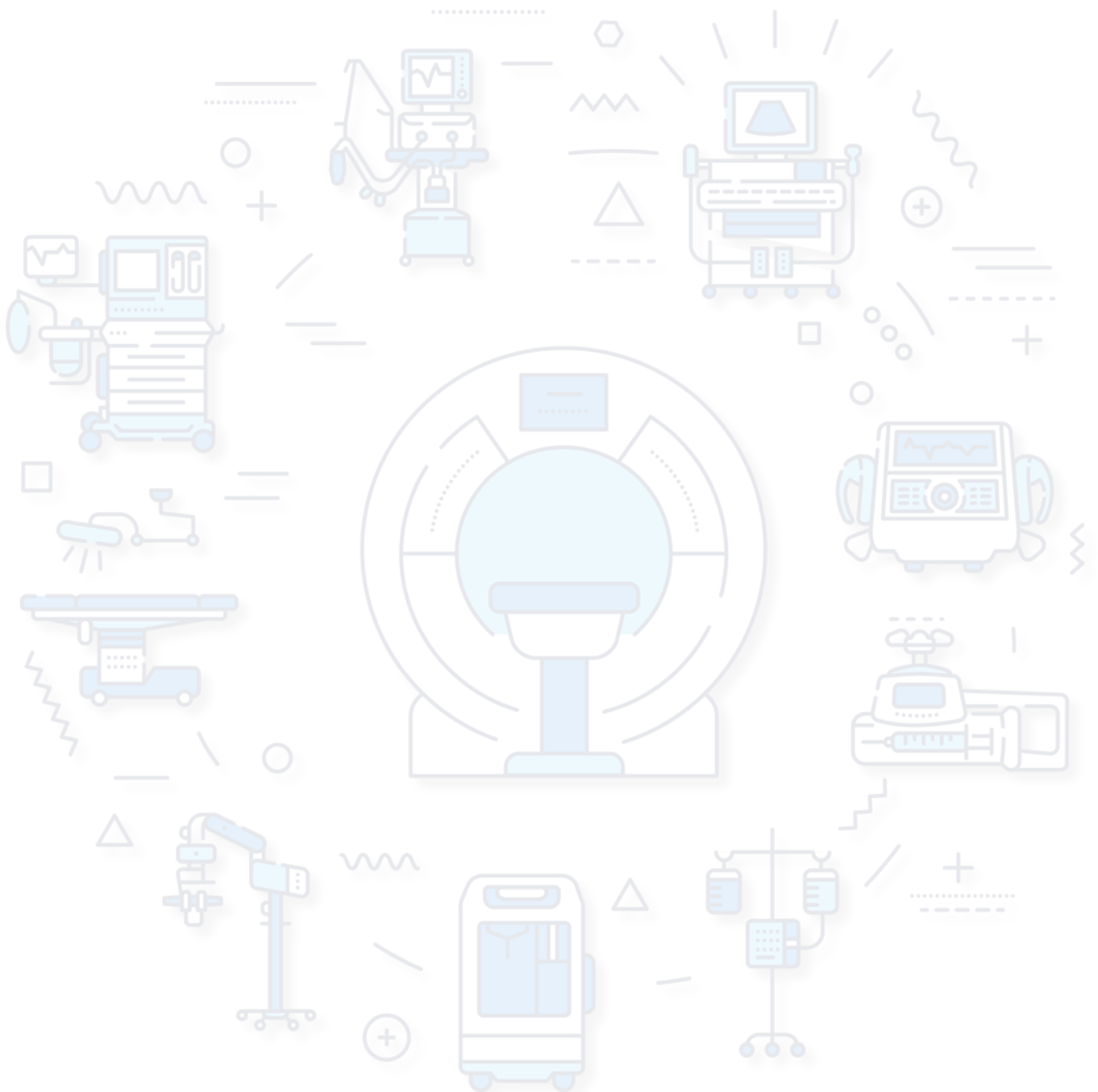
When software is embedded in a medical device, the approach for providing feedback does not differ from feedback on the medical device itself.

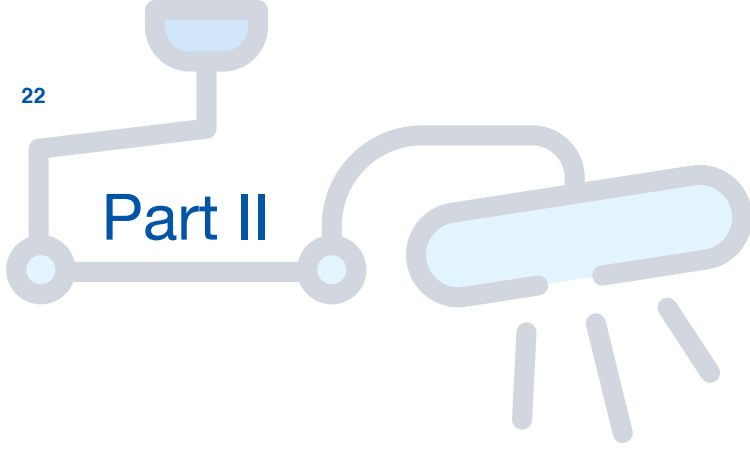
Artificial intelligence

As artificial intelligence is a particular type of software, the same principles apply as for software.

In-house developed

In-house developed medical devices, including IVDs, may be subject to national legislation. Note there may be different regulations for those in-house developed medical devices that are only used within that institution vs those that are then distributed to other users. Also, for in-house developed medical devices, the health care facility should make it possible for users to provide feedback and the health care facility shall have a system in place to evaluate the feedback.





Post-market surveillance by manufacturers

Overview of responsibilities of manufacturers

This section describes manufacturers' post-market surveillance obligations and focuses on the evaluation of feedback. Other economic operators (authorized representatives, distributors, importers) may be required to act on behalf of the manufacturer. Therefore, an agreement should be in place between manufacturers and their respective economic operators to receive feedback from users and to forward this feedback to the manufacturer in a timely manner. This may include translation of feedback into the language used by the manufacturer. Depending on the jurisdiction, economic operators may also be required to submit reports to the NRA. By including these economic operators, more feedback might be collected, thereby providing the manufacturer with more information on the safety, quality and performance of the medical devices during actual use. Economic operators may conduct investigation on feedback, at the request of and/or in agreement with manufacturer.

Basics of post-market surveillance

The manufacturer (and their economic operators, as applicable) shall have a post-market surveillance plan in place, which, at minimum, includes the following steps (7):

1. Scope of the post-market surveillance plan: the manufacturer shall indicate for which specific medical device, medical device type or family the plan is applicable.
2. Objective of the post-market surveillance plan: the manufacturer shall indicate what is to be achieved by the post-market surveillance for that device.
3. Responsibilities: the manufacturer shall indicate responsibilities for all stages of the post-market surveillance process.
4. Data collection: the data collection method shall be described.
5. Data analysis: the method for data analysis shall be described.

6. Using data analysis in risk management and other processes: a system shall be in place to input the data obtained from post-market surveillance into other processes, such as risk management, improvement, clinical evaluation.
7. Consider, decide upon and implement required actions: based on the data analyses and further analysis in the appropriate processes, mainly risk management, required actions must be considered, and the most appropriate action must be decided and implemented, if needed.

As a plan will cover a specific medical device, medical device type or family, a number of plans can be required to cover the manufacturer's portfolio.

Scope of the post-market surveillance plan

The manufacturer shall indicate for which products the post-market surveillance plan is applicable, as for different medical devices, different approaches might be needed (7). This can be due not only to differences in medical devices and risks associated with them, but also to differences in time spent on the market and experiences gained.

Objectives of the post-market surveillance plan

The manufacturer shall indicate what the objectives are for post-market surveillance. At a minimum, for every post-market surveillance plan, the manufacturer shall include the following objectives (7):

- Has any new hazard or hazardous situation been identified for the medical device or similar medical devices or has the risk acceptability changed?
- Has any misuse of the medical device occurred?
- Are there any unforeseen side-effects for the medical device or similar medical devices?
- Is there a medical device malfunction that impacts the benefit-risk analysis?

The above-mentioned questions relate mainly to the observation of incidents that users will report to the manufacturer.

Other objectives can be addressed as part of post-market surveillance. These objectives will provide the manufacturer with more information on the performance of the medical device(s). Examples of other objectives are:

- Do users experience any usability issues?
- Are recurring malfunctions due to service/maintenance deficiencies?
- How does treatment affect the quality of life of the patient?
- Can user/patient training reduce the likelihood of malfunction?
- Are there any improvements that can be made to the medical device?
- Has state-of-the-art changed since design and development of the medical device?
- Are indications or contra-indications appropriate to ensure safety and effectiveness for the intended use of the medical device?

Responsibilities

Responsibilities and capabilities for post-market surveillance activities shall be defined by the manufacturer. The manufacturer shall ensure the availability of resources for post-market surveillance activities. Preferably, a team of people with the necessary independence and competence should be involved in post-market surveillance, covering all expertise required.

Data collection

As stated earlier, reactive post-market surveillance, based on collecting feedback, should always be in place. The manufacturer shall choose the appropriate data sources to allow the fulfilment the objectives of the post-market surveillance plan. For example, to ensure that the medical device remains state-of the-art, actively collecting data on similar medical devices and procedures from literature, congresses and trade shows is required. The data sources selected should provide reliable data, which need to be verified.

After the appropriate data sources have been selected, methods to collect the data need to be in place, including the time span for which the data need to be collected. When establishing the data collection method, it is necessary to ensure the data collected can be examined in a meaningful way.

Data analysis

To be able to obtain useful information from the data collected through post-market surveillance, the data need to be analysed. Data analysis should be considered when setting up the data collection. The data analysis can vary from simple qualitative analysis to advanced statistical analysis. Qualitative analysis will often be required as an initial step for the analysis of an incident. The data obtained from the qualitative analysis of incidents can also be used for quantitative analysis. A frequently used method for quantitative analysis is trend analysis. Trend analysis can only be performed if enough data for a sufficiently long period are available.

Using data in risk management and other processes

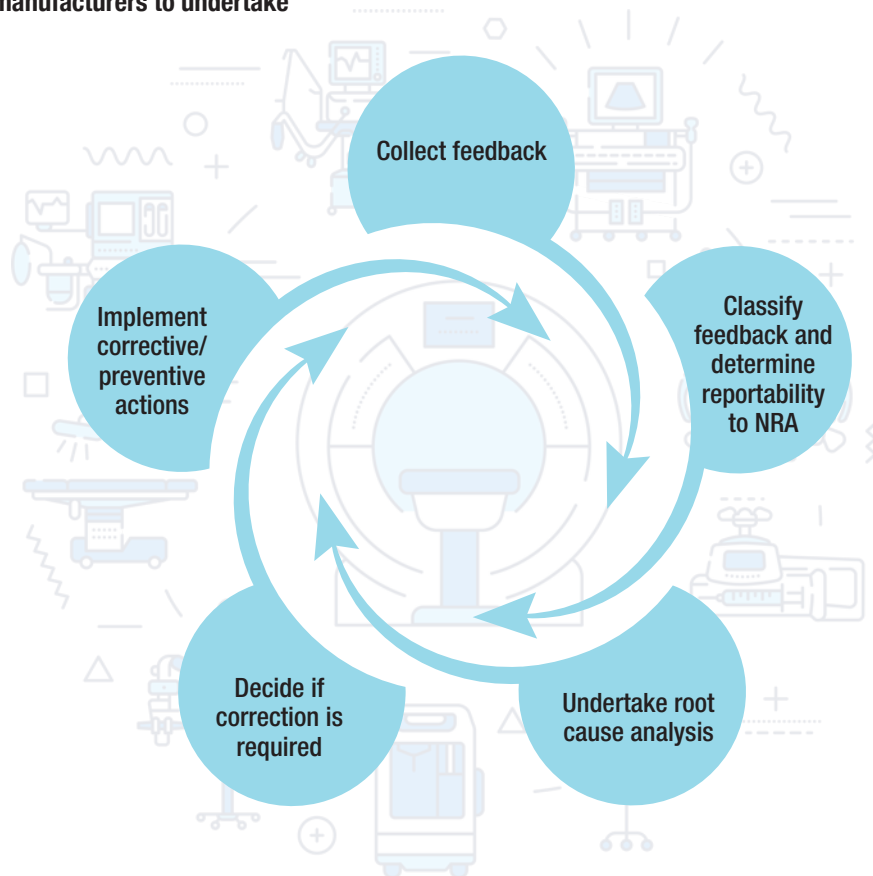
The data collected and analysed shall be used in other processes, such as risk management, quality improvement and clinical evaluation. In this document, the focus will be on the use of post-market surveillance data in risk management. By using the post-market surveillance data in other processes, conclusions can be drawn on the changes in risk, the need to make changes to a medical device or to obtain more clinical data.

Manufacturers should be familiar with standards such as ISO 13485 on quality management systems, ISO 14971 on risk management and ISO/TR 20416 on post-market surveillance, that outline the manufacturer's requirements for compliance with post-market surveillance aspects (5, 6, 7). WHO prequalification guidance on risk management for manufacturers of IVDs is another beneficial resource (25).

Considering and implementing required actions

Based on the outcome of further analysis of post-market surveillance data in other processes, actions might be required to correct problems or defects related to a medical device (correction), to remove cause of nonconformity to avoid recurrence (corrective action) or to prevent occurrence of additional issues (preventive action). The manufacturer shall consider the options to remedy the unwanted situation and decide on the appropriate action and implement that action. See **Fig. 3** for details on actions taken by manufacturers.

Fig. 3.
Actions for manufacturers to undertake



Unique device identification

Implementation of IMDRF's UDI systems for medical devices is intended to "facilitate unambiguous identification of the medical device through distribution and use by providing a single global identifier that can be used to link and integrate existing government, clinical, hospital, and industry databases" (24, 26). Unique device identification will allow manufacturers and their economic operators, as well as NRAs to more rapidly identify medical devices implicated by user feedback. The UDI may be added to manufacturer reports, and to registries. The UDI device identifier (UDI-DI) and UDI production identifier (UDI-PI) allow for traceability of the medical device throughout distribution and use (24, 26).

2.1 Collect feedback

Emphasis on feedback

Receiving and acting upon user or other feedback is the most basic form of post-market surveillance that must always be performed by the manufacturer, irrespective of their resources.

The manufacturer shall make it possible for users and patients/clients to provide feedback as easily as possible. This means that the methods to submit feedback shall be readily available and provide as few barriers as possible to users and patients/clients to provide the feedback. The contact details of the manufacturer should be included on the labelling in a way that is evident to the user and patients/clients. By making it easier for users and patients/clients to provide feedback, more feedback will be received, allowing the manufacturer to obtain more information on the experiences gained through actual use of the device.

Other methods of collecting user feedback may be considered. Use of smartphone applications, quick read (QR) codes, and web forms that directly send feedback to a database have been successfully used by some NRAs. Manufacturers should also consider alternative methods that leverage such technology for eliciting user feedback. Emerging solutions such as blockchain which is decentralized (data is not stored by any one entity), transparent (uses self-sovereign identity so the reporter's identity is secured by cryptography) and immutable (data cannot be tampered with, all transactions are recorded) may be explored.

The manufacturer shall document all feedback collected. Feedback should be analysed as soon as possible and escalated, where appropriate.

Feedback may be:

- **Administrative/contractual** in nature related to any aspect of the procurement contract not fulfilled, for example, agreed delivery time not adhered to, agreed guaranteed shelf life upon delivery not adhered to, incorrect product and/or quantity delivered etc.
- **Technical** in nature affecting the safety, quality or performance of a medical device.

Initially, the manufacturer shall distinguish between administrative feedback and technical feedback. Administrative feedback is not typically linked to safety, quality or performance issues. However, the investigation of administrative feedback might reveal potential issues with quality, safety and/or performance of the product, and should be considered as technical in nature. As such, timely periodic investigation and analysis of administrative feedback is strongly encouraged.

Other sources of post-market information

Information about the product may become available in sources of post-market information other than user feedback, for example, through literature and other scientific documentation, from within the production site and/or quality management system such as through management review, high rates of nonconforming product, risk assessment, and the relevant standards (5, 6).

Manufacturers should, if possible, employ other proactive sources for post-market surveillance. Such sources can be aimed at obtaining other information from users and patients/clients by using enquiries, which also allows more positive feedback to be solicited. From scientific literature, the manufacturer can obtain information on safety, quality and performance of its product/s as well as similar medical devices and about the state of the art.

The manufacturer shall choose the appropriate sources in line with the objectives of the post-market surveillance plan. A non-exhaustive overview of possible data sources includes (7):

- incidents reported to the organization;
- maintenance (including preventive maintenance/corrective maintenance and repair);
- installation;
- returned medical devices;
- explants;
- medical device registries;
- post-market clinical follow-up (PMCF) studies, and post-market performance follow-up (PMPF) if IVD;
- controlled market release phase;
- user training;
- advisory notices;
- scientific literature;
- market surveillance activities by regulatory authorities and their related publications and recommendations;
- publicly accessible databases from regulatory authorities on incidents and FSNs;
- conferences, tradeshow, etc.;
- regulatory requirements, standards, guidance and best practices;
- social media;
- public media;
- medical device distribution and medical device tracking;
- finished products, product quality information; and
- internal audits and external inspections.

For equipment requiring regular servicing, service reports can provide insights into performance of the equipment, including information on wear of parts taken from parts that need replacing and other observations.

User training is an opportunity to observe users, understand their thought processes and challenges, and estimate the distribution of user skills. Feedback from user training can also provide insights into new risks due to unforeseen user interaction with the medical device and possibilities for improvement.

Each data source may require a specific method of collecting the data and the method for analysis of each data source might be different. For example, obtaining data from scientific literature will require expert judgement, whereas extracting information from maintenance records requires administrative work.

When more data are collected, a quantitative analysis can be performed. Appropriate data sources should be selected to maximize the quality of the data to be analysed.

2.2 Classify feedback and determine reportability to NRA

All feedback should be initially evaluated to determine if immediate action is required to protect public health and safety.

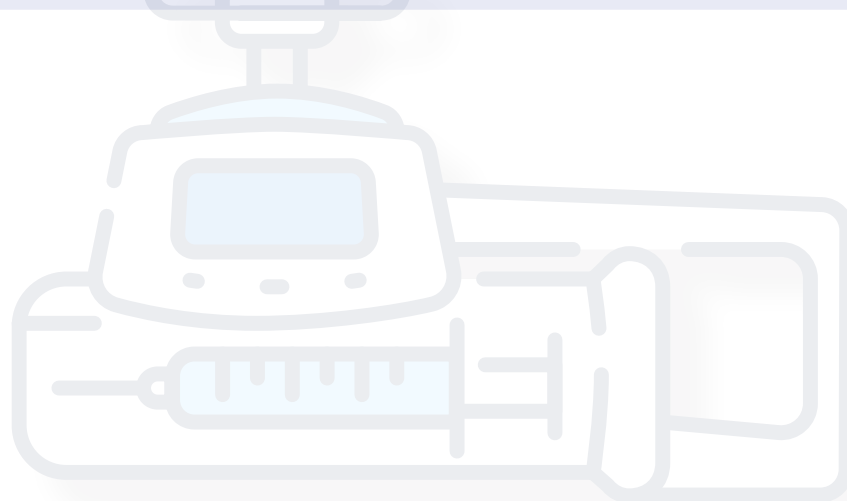
Categories of medical device product problems are listed in **Table 2**. These are adapted from IMDRF guidance (27, 28).

Table 2.
Categories of medical device product problems

| No. | Problem category | Description |
|-----|---|---|
| A01 | Patient-device incompatibility problem | Problem related to the interaction between the patient and the device. |
| A02 | Manufacturing, packaging or shipping problems | Problem associated with any deviations from the documented specifications of the device that relate to nonconformity during manufacture to the design of an item or to specified manufacturing, packaging or shipping processes (out of box problem). |
| A03 | Chemical problem | Problem associated with any deviation from the documented specifications of the device that relate to any chemical characterization, i.e. element, compound or mixture. |
| A04 | Material integrity problem | Problem associated with any deviations from the documented specifications of the device that relate to the limited durability of all material used to construct device. |
| A05 | Mechanical problem | Problem associated with mechanical actions or defects, including moving parts or subassemblies, etc. |
| A06 | Optical problem | Problem associated with transmission of visible light affecting the quality of the image transmitted or otherwise affecting the intended application of the visible light path. |
| A07 | Electrical/electronic property problem | Problem associated with a failure of the electrical circuitry of the device. |
| A08 | Calibration problem | Problem associated with the operation of the device, related to its accuracy, and associated with the calibration of the device. |
| A09 | Output problem | Problem associated with any deviation from the documented specifications of the device that relate to the end result, data, or test results provided by the device. |
| A10 | Temperature problem | Problem associated with the device producing unintended temperatures. |
| A11 | Computer software problem | Problem associated with written programs, codes and/or software system that affects device performance or communication with another device. |
| A12 | Connection problem | Problem associated with linking of the device and/or the functional units set up to provide means for a transfer of liquid, gas, electricity or data. |
| A13 | Communication or transmission problem | Problem associated with the device sending or receiving signals or data. This includes transmission among internal components of the device to which the device is intended to communicate. |
| A14 | Infusion or flow problem | Problem associated with the device failing to deliver or draw liquids or gases as intended (e.g. delivering drugs at incorrect rate, problems with drawing fluid from a system). This includes vacuum collection devices. |

Table 2. (continued)

| No. | Problem category | Description |
|-----|--|---|
| A15 | Activation, positioning or separation problem | Problem associated with any deviations from the documented specifications of the device that relate to the sequence of events for activation, positioning or separation of device. Note: deployment is synonymous with activation. |
| A16 | Protective measure problem | Problem associated with any deviations from the documented specifications of the device that relate to the implemented and inherited design features specific to devices used for reducing risks to patient or caregiver or maintaining risks within specified levels. |
| A17 | Compatibility problem | Problem associated with compatibility between device, patients or substances (medication, body fluid, etc.). |
| A18 | Contamination/decontamination problem | Problem associated with the presence of any unexpected foreign substance found in the device, on its surface or in the package of materials, which may affect performance or intended use of the device, or problems that compromise effective decontamination of the device. |
| A19 | Environmental compatibility problem | Problem associated with the surrounding conditions in which the device is being used such as temperature, noise, lighting, ventilation or other external factors such as power supply. |
| A20 | Installation-related problem | Problem associated with unsatisfactory installation, configuration and/or setup of a specific device. |
| A21 | Label, IFU or training problems | Problem associated with device markings/labelling, IFU, training and maintenance documentation or guidelines. |
| A22 | Human-device interface problem | Problem associated with an act or omission of an act that has a different result than that intended by the manufacturer or expected by the operator. |
| A23 | Use of device problem | Problem associated with failure to process, service or operate the device according to the manufacturer's recommendations or recognized best practices. |
| A24 | Adverse event without identified device or use problem | An adverse event (e.g. patient harm) appears to have occurred, but there does not appear to have been a problem with the device or the way it was used. |
| A25 | No apparent adverse event | A report has been received but the description provided does not appear to relate to an adverse event. This code allows a report to be recorded for administration purposes, even if it doesn't meet the requirements for adverse event reporting. |
| A26 | Insufficient information | An adverse event appears to have occurred but there is not yet enough information available to classify the device problem. |
| A27 | Appropriate term/code not available | The device problem is not adequately described by any other term. Note: this code must not be used unless there is no other feasible code. The preferred term should be documented when submitting an adverse event report. This information will be used to determine if a new term should be added to the code table. |



What should be reported

Unless otherwise required by national legislation, the manufacturer (or their economic operator) should send an investigation report to the NRA, in the following circumstances:

- Discovery of a serious public health threat (see **Definitions**).
- When use of a medical device led to:
 - death of a user, patient/client or other person;
 - serious deterioration in health of a user, patient/client or other person.
- No death or serious deterioration in health of a user, patient/client or other person occurred but might have.

This may include indirect harm, such as misdiagnosis, delayed diagnosis, delayed treatment, inappropriate treatment, absence of treatment or transfusion of inappropriate materials.

An investigation reporting form can be found in **Annex 2**. National or regional forms that contain similar information may also be used.

| What to report | Time to report to NRA |
|--|--|
| Serious public health threat | Immediately but no later than 48 hours |
| Death, serious deterioration in state of health of patient, user or other person occurred | As soon as possible but no later than 10 calendar days |
| Death, serious deterioration in state of health of patient, user or other person might have occurred | As soon as possible but no later than 30 calendar days |

National regulations might specify other timelines which should be observed.

Further investigation of the incident will be required. This might require the manufacturer to obtain additional information from the person providing the feedback.

A system shall be in place for such incidents to be monitored for the frequency of occurrence or change in the type/severity of the outcome following such an incident. This is known as trending and should happen periodically, e.g. on a monthly basis. Based on this analysis, it might be necessary to undertake further actions such as changes to manufacturing, update of the IFU, etc.

In addition to the above immediate reporting of incidents, all feedback should be reported to the NRA as part of a periodic summary of post-market surveillance reports, if required by national legislation.

Use error

A **use error** (see **Definitions**) might include slips, lapses, mistakes and reasonably foreseeable misuse. Examples include:

- inserting a test strip backward into a glucose monitor;
- not engaging the handbrake on a wheelchair when using public transportation.

Issues occurring despite adequate IFU and proper design according to the manufacturer's analysis could be potential use errors. The error may be due to the medical device being poorly designed, or it may have been used in a situation that promoted incorrect usage (foreseeable misuse). By reporting such near misses, it helps the manufacturer to reduce the chance of other users making the same use error with similar or worse consequences.

Abnormal use error

An **abnormal use error** (see **Definitions**) is contrary to the instructions provided by the manufacturer. Examples include:

- use of a medical device despite obvious packaging breach;
- failure to follow manufacturer's instructions for clean care, i.e. use of antiseptic;
- continued use of a medical device after the manufacturer's stated expiry date;
- a use error when the user is inadequately trained.¹

Ideally, there should be no barrier to reporting use errors or abnormal use errors within the health care facility (safe reporting). This will provide the manufacturer with insights into problems that occur during routine use.

Manufacturers might also receive feedback internally through their quality management system. This does not typically need to be reported to the NRA, unless an FSCA is implemented as a result, if required by national legislation.

2.3 Undertake root cause analysis

The manufacturer should undertake an investigation to determine if the feedback can be independently verified and if the root cause(s) can be established. All reasonable efforts should be made by the manufacturer to determine if there is a causative link between the medical device and the incident.

"Root cause analysis helps identify what, how and why something happened, thus preventing recurrence.

- Root causes are underlying, are reasonably identifiable, can be controlled by management [review] and allow for generation of recommendations.
- The process involves data collection, cause charting, root cause identification and recommendation generation and implementation" (29).

As stated above, a systematic approach should be used to determine the root cause(s) of an incident by establishing a methodology for determining the causes, then determining all probable causes and likelihoods for each cause (i.e. the probability that the cause contributed to the incident); and the evidence for reported causes and likelihoods.

A variety of methods exists for root cause analysis. Manufacturers may also use failure mode and effects analysis (FMEA). At the very least, the following set of information is to be obtained:

- device involved (medical device, accessory or part)
- intended use of the device

¹ This list does not purport to be definitive and each case should be handled individually.

- the event
- effect of the event
- cause of event
- current control
- recommended action.

A fishbone diagram approach is useful as a guide to rule in or rule out the following causes: material, methods, mother nature, measurement, person and machine (30).

2.4 Decide if a correction is required

The manufacturer must consider if a correction is required, whereby a correction (see **Definitions**) refers to any:

- Repair, modification, adjustment, relabelling, destruction or inspection (including patient monitoring) of a product without its physical removal to some other location (31).

The manufacturer might also consider other corrections:

- additional surveillance of the device in use
- retraining
- explanation
- additional clinical review of patients/clients
- retesting, if IVD.

The manufacturer may decide the nonconformity has little associated risk or is unlikely to recur. In such cases the manufacturer may decide only to carry out a correction.

The manufacturer might also decide that an FSCA is required. Such urgent information is notified to those responsible for the device or affected by the problem through an FSN. The manufacturer might decide that no action is required.

2.4.1 Field safety corrective action (FSCA)

What can trigger FSCA

An FSCA is triggered by information about the occurrence of one or more incidents with already distributed medical devices that poses an unacceptable increase in risk when that device is used. Such incidents may include malfunctions or deterioration in the safety, quality or performance of a medical device made available on the market, any inadequacy in the information supplied by the manufacturer and undesirable side-effects.

Assessing the need for FSCA

In assessing the need for FSCA, the manufacturer is advised to use the risk management principles and activities prescribed within their QMS (8).

Thus, risk assessment is a key element for the manufacturer to determine the need for an FSCA see **Fig. 1**. Personnel with appropriate expertise and competency must be consulted to determine the potential harm and the risk appropriately.

Possible actions

FSCA may include:

- return of a type of device to the manufacturer or its representative (also known as recall, in some jurisdictions);
- device modification;
- device exchange;
- device destruction;¹
- advice given by the manufacturer regarding the use of the device.

Device modifications can include:

- retrofitting in accordance with the manufacturer's modification or design change;
- permanent or temporary changes to the labelling or IFU;
- software upgrades including those carried out by remote access; and,
- modification to the clinical management of patients to address the risk of death or serious injury or death specifically to the characteristics of the device.

An FSCA is communicated through an FSN.

Reporting FSCA

The manufacturer should report any FSCA to the relevant NRAs where the medical device is supplied, if required by national legislation. It is advised to use internationally recognized reporting terminology for classification and coding of incidents (27). FSCA reports should mention the scope of updates made as a result of risk management activities.

An FSCA report should be submitted to NRAs of all the countries affected through an FSCA report, if required by national legislation. This should include information on the effectiveness of the action per country involved (e.g. percentage of devices that underwent the FSCA).

If the FSCA includes return of affected stock to the manufacturer or an update of the IFU or a modification/update of existing medical devices on- or offsite, records of completed actions should be fully reconciled against distribution records in order to maintain control of the progress of the FSCA (8).

¹ The NRA should ensure a record of disposal of affected product and inform the manufacturer so that they may reconcile product distributed and product destroyed.

The FSCA final report should contain the following information:

- A final assessment of the root cause of the problem and proposed corrective action to reduce the chance of recurrence, e.g. redesign, update in the field, improved IFU etc. and the progress of the implementation of such actions.
- The outcome of the reconciliation of the FSCA.

National regulations might require other items to be included.

2.4.2 Field safety notice (FSN)

Purpose of FSN

Field safety notices are an important means of communicating FSCA and safety information to users. They may also be used to provide updated information about how a medical device should be used (8).

Distribution of FSN

Manufacturers should inform affected users of any FSCA via an FSN, and inform the relevant NRAs. Affected users will usually receive the FSN via their procurement agents or through economic operators, who must inform all users within their region of supply. To be able to reach out to the affected users, the manufacturer and the other economic operators need to keep records to allow traceability of the medical devices to the users.

The manufacturer should ensure that the FSN is distributed to all affected users and must keep track of confirmation of receipt of the FSN. A full, detailed distribution list with contact name and (e-mail) address for each intended recipient must be kept and must be made available to WHO on request for WHO-recommended medical devices.

Content and format

The manufacturer should use a standardized format for an FSN, see [Annex 4](#) for an example. The FSN should be written on company letterhead and in English or a language accepted in the country concerned. It may be translated into required local languages by in-country economic operators.

The FSN should include the following items, see (14):

- A clear title such as “Urgent Field Safety Notice” on the notice itself, and the subject line, if sent by e-mail.
- The intended audience: clear statement about the intended recipient of the notice.
- Concise description of product, product code, lot number(s).
- A factual statement explaining the reasons for the FSCA, including a description of the problem.
- A clear description of the hazards associated with the specific failure of the device and, where appropriate, the likelihood of occurrence, being mindful of the intended audience.

- The recommended action(s) to be taken by the recipient of the FSN including any action(s) recommended for people that have previously used or been treated by the affected device, including recalls.
- Where appropriate, include timeframes by which the action(s) should be taken by the manufacturer and user.
- Designated contact point for the recipient of the FSN to obtain further information.

The FSN should not include any:

- Comments and descriptions that downplay the level of risk.
- Information that is intended to promote a manufacturer or their product's market visibility for the purposes of sales and marketing.

Prior consultation with NRA

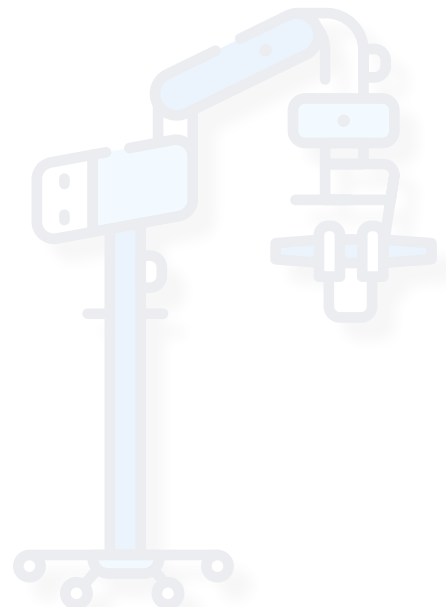
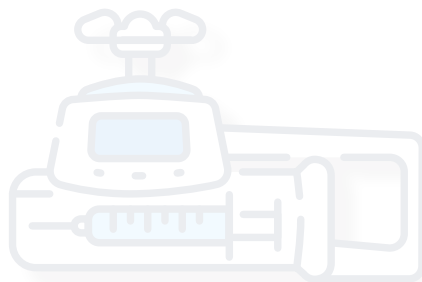
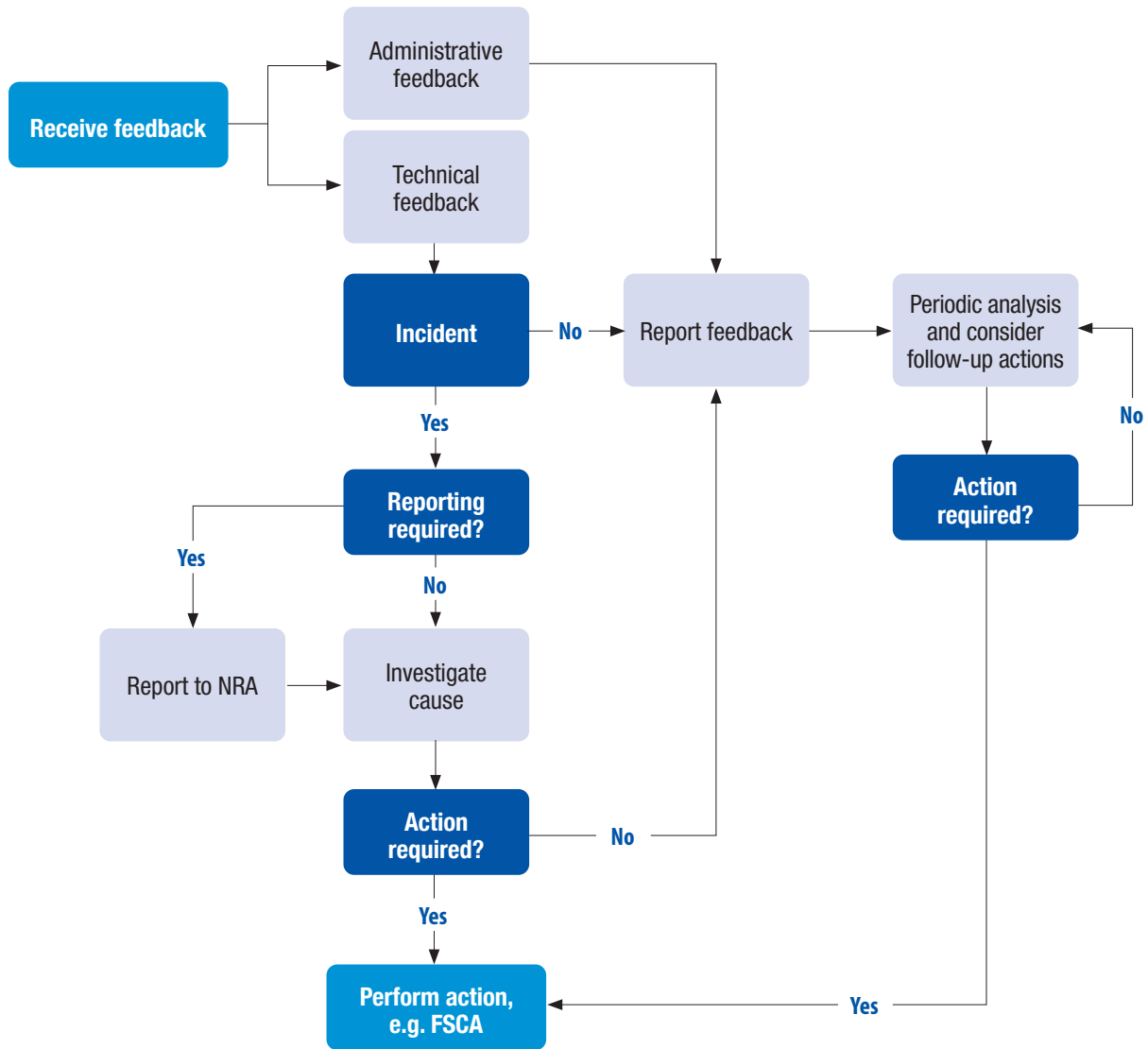
Manufacturers should provide a draft of the FSN to the NRA allowing a minimum of 48 hours for review unless the nature of the FSCA dictates a shorter timescale due to safety risks, e.g. for serious public health threat, in which case the NRA may accept that prior review may not be possible.

If the NRA does not conduct any prior review of the FSN, they would be informed of the FSCA via an FSN at the same time as affected users.

2.5 Implement corrective/preventive actions

The difference between a correction and corrective action is that a correction is an action undertaken by the manufacturer to eliminate detected nonconformity – most typically this would be a device destruction or modification to labelling. Whereas a corrective action is to eliminate the cause of detected nonconformity or undesirable situation – such as increased quality control stringency, manufacturing process modification, etc. These are both reactive in nature. A correction may be made in conjunction with a corrective action.

Fig. 4.
Schematic representation of how manufacturers handle feedback



CAPA

Based on the results of root cause analysis for one or more observations, corrective action and preventive action (CAPA) should be considered.

Corrective action (see **Definitions**) should be handled depending on whether a nonconforming medical device is involved or if action is taken to prevent recurrence of a nonconforming medical device (32).

Preventive action (see **Definitions**) is a proactive process undertaken by the manufacturer to identify opportunities for improvement of the medical device in advance, before a problem is identified (32).

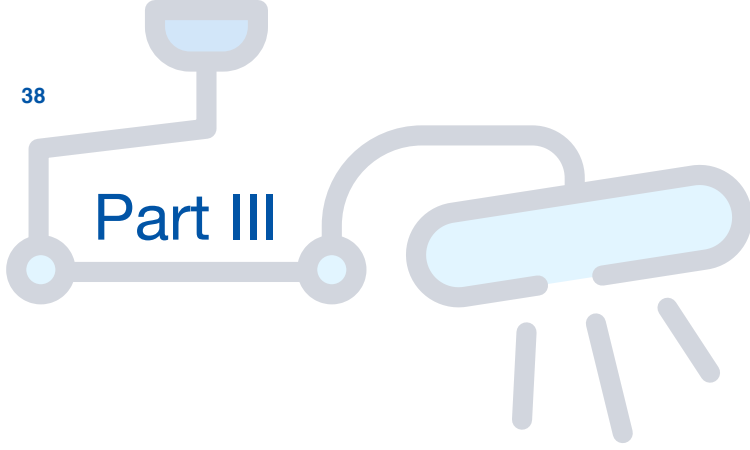
Preventive action is taken when a potential nonconformity is identified as the result of QMS activities, and other relevant sources of information. Examples of sources for identification of preventive action include (but are not limited to):

- reviews of contracts (with key suppliers), purchasing, processes, design
- supplier surveillance
- management review of quality management system
- user training programmes, job aids
- benchmarking.

Often CAPA are improvements made to the manufacturing process or the design of the medical device, or to the QMS to eliminate causes of nonconformities to prevent their reoccurrence (5). Any process for CAPA should use the outcome of the systematic investigation of reported incidents. To ensure that CAPA are effective, the systematic investigation of the incidents is pivotal in identifying the CAPA to be undertaken. The degree of action taken should be dependent upon and related to the risk, size and nature of the problem and its effect(s) on product safety, quality and performance.

All types of reports related to feedback should be kept on file by the manufacturer. These documents include: the initial, follow-up and final manufacturer investigation reports; root cause analysis reports; CAPA plans; FSCA reports, FSNs; and periodic summary reports.





Market surveillance by NRAs

Overview of responsibilities of NRAs

Market surveillance is a set of activities conducted by NRAs to ensure that medical devices used in their market continue to meet safety, quality and performance requirements.

Health authorities, including the NRA, should raise awareness among users and clients/patients about the importance of providing feedback. NRAs should develop a system to receive feedback directly from users and their patients/clients, and to forward it on to the manufacturer. NRAs may conduct a **risk assessment** when forwarding feedback to ensure that a registered/authorized medical device is the subject of the feedback. Medical devices that are not registered/authorized would be considered non-compliant and regulatory action may be undertaken.

Falsified medical devices

The NRA should take steps to determine if the concerned medical device is an original one or if it was manipulated or falsified. For-cause testing, described below, might assist the NRA's risk assessment of unregistered medical devices.

Plan market surveillance

In view of the resources required, a plan for market surveillance should be developed with resource requirements; human and financial. The market surveillance plan might include which medical devices will be prioritized using a risk-based approach for closer surveillance. It should also describe roles and responsibilities, include elements of monitoring and evaluation, timelines for the various activities and a budget.

The NRA should review investigation reports received from manufacturers that will contain a description of any actions taken in relation to a reported incident, including a root cause analysis and analysis of impact on similar products that they manufacture.

The NRA may establish a mechanism for the testing of medical devices to ensure that they continue to meet their quality, safety and performance requirements. Such testing should be conducted at a laboratory designated by the NRA.

It is acknowledged that testing capacity to cover all device types may not be possible or even required, and that any testing activities should be guided by a risk-based approach.

Take regulatory actions

The NRA should take regulatory actions, as appropriate, to address any issues identified through investigation reports, or through their own market surveillance activities. This includes overseeing any FSCA undertaken by the manufacturer. The ultimate objective is to ensure their citizens are protected.

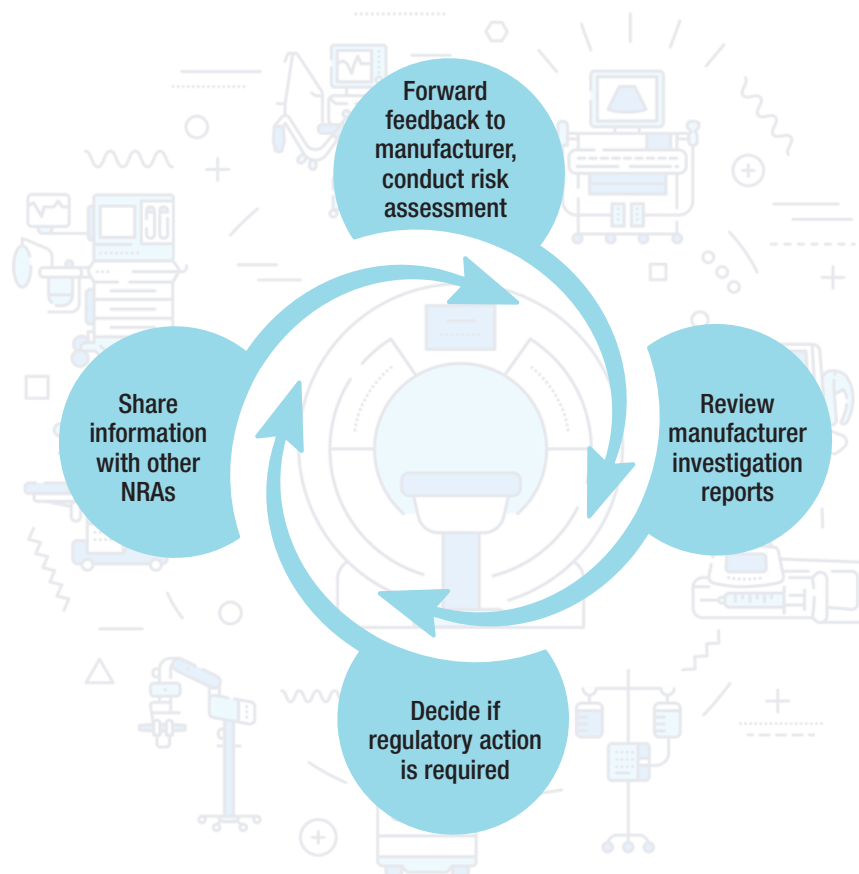
The NRA should appoint a unit responsible for market surveillance activities related to medical devices, including market surveillance information exchange with other NRAs (confidentiality agreements may need to be signed).

In certain countries, the NRA may not be capacitated or be mandated by legislation to guide market surveillance activities. In such cases, the NRA should be advised to appoint a contact person, in the absence of legislation within their institution. Certain arrangements can be made within the NRA to facilitate market surveillance for medical devices such as ensuring users report feedback, and to receive and act on FSNs to minimize risk to public safety.

Phased implementation

The implementation of market surveillance measures will depend on the maturity and capacity of the NRA to review investigation reports and notify manufacturers of their evaluation. Testing activities might be implemented later after procedures for reviewing investigation reporting are well established. **Fig. 5** describes the various actions that could be undertaken by the NRA.

Fig. 5.
Potential actions of regulators to oversee manufacturer investigation of feedback





3.1 Forward feedback and conduct risk assessment

Forward feedback

The NRA may receive feedback directly from users and their clients/patients as described in **Part I**. NRAs should forward such feedback on to the manufacturer immediately.

Risk assessment

Depending on the nature of the feedback, the NRA may also conduct a risk assessment, to ensure public safety is immediately protected, which may include the following steps:

1. Check if this product is registered, or otherwise authorized for importation.
2. Check the local economic operator has permission to import the product.
3. Contact the health facility where the issue/observation occurred with a request for clarification of any details as required (recommend minimum three attempts to contact).
4. Determine if quarantine of affected product is warranted; consider a risk-based approach whereby the absence of a device and a defective device are considered against a functioning device (is something better than nothing, or vice versa).
5. Inform manufacturer and the local representative, as soon as the NRA becomes aware. This step may be in parallel or closely timed with step 3.
6. Continue dialogue with manufacturer to ensure timelines for their response(s) are followed.

These steps will also facilitate detection of suspected falsified medical devices.

3.2 Review manufacturer investigation reports

Manufacturers of medical devices are obliged to report to the NRA (or otherwise nationally designated focal point).

Any serious public health threat should be reported immediately to the relevant NRAs and no later than 48 hours of becoming aware.

Incidents of death or serious deterioration in health of a patient, user or other individual that occurred should be reported as soon as possible to the relevant NRAs and no later than 10 calendar days of becoming aware.

Incidents of death or serious deterioration in health of a patient, user or other individual that might have occurred should be reported as soon as possible to the relevant NRAs and no later than 30 calendar days of becoming aware.

A template for manufacturer investigation reports can be found in **Annex 2**.

Review reports

The NRA would expect to receive a series of investigation reports from the manufacturer containing a summary of the steps taken by the manufacturer to investigate the incident and initiate corrections and implement corrective actions.

1. The manufacturer should submit an initial manufacturer investigation report to the NRA according to the timelines stated above, without prejudice to local or regional legislation.
2. The NRA should review the report for scientific rigour, evidence of documented procedures, timeliness and rationality.
3. Follow-up manufacturer investigation reports should be submitted when interim updates are required but should follow **no later than 15 calendar days after** the initial investigation report is sent or after the previous follow-up report, unless otherwise specified.
4. The manufacturer should submit a final investigation report to the NRA, preferably **within 15 calendar days** of the initial investigation report or the last follow-up investigation report.

The NRA reserves the right to make any reasonable request for clarification of the investigation undertaken and possibly the conclusions drawn.

Certain aspects of the manufacturer's report that might require clarification such as greater clarity on protocols used, and other methodologies.

Where appropriate, the manufacturer may initiate an FSCA which is notified to affected users through an FSN. The NRA should maintain a repository of FSNs and make these publicly available on their website. At the completion of the FSCA, the manufacturer should submit an FSCA report to the NRA.

The NRA should also review and determine their acceptability, at their discretion:

- suggested corrective/preventive actions
- suggested actions for users
- risk management file updates.

NRA follow-up

If the NRA determines that the investigation as detailed in the report is unacceptable, they should send these findings in writing to the manufacturer. It is suggested to present findings in tabular format with headings such as topic, clarification(s), action(s) by manufacturer, or similar. Any review of documentation should focus on evidence of implementation of any written procedures, and any data integrity concerns. If any issue(s) cannot be accepted and/or resolved through desk review of documentation, the inspectorate may be requested to go onsite to review actual records of investigations.

The NRA may decide to take regulatory action until they have objective evidence that products placed on their market do not present any safety issues.

The NRA must be informed of any FSCA as soon as the manufacturer initiates it, usually by sending the draft FSN for review, see [Annex 4](#) for an example FSN format. If the NRA does not conduct a prior review of the draft FSN, they will receive the FSN at the same time as affected users. This also applies to FSCA that were initiated based on user feedback generated in other jurisdictions.

3.3 Oversee testing

It is critical to establish a plan for testing as a market surveillance activity which uses a risk-based approach. In particular, the better the user feedback system and the more compliant the QMS of the manufacturer, the less the need for testing activities.

Elements of the plan for testing as market surveillance include which medical devices are to be collected based on risk assessment, where to collect, how to collect, who will collect, number of samples to be collected, and where to test (laboratories, depending on capacity). If a country does not have the capacity to test all types of medical devices, they may rely on results generated by certified testing laboratories in other jurisdictions.

Testing conducted by or for the NRA is not intended to replace the manufacturer's QC activities undertaken throughout the manufacturing process, and lot testing at final release of the product.

Quarantine and store

The NRA may arrange for an appropriate number of samples of medical devices to be quarantined and stored according to the manufacturer's storage instructions, until testing takes place.

The following types of testing may be requested by the NRA:

- Reactive testing, with due cause when a public health threat presents.
- Proactive testing, without specific cause, to determine ongoing compliance with regulatory requirements based on risk management principles.

Reactive testing

For-cause (reactive) testing may be conducted by the NRA when user feedback does not accord with the manufacturer's investigation findings, on a case-by-case basis. It may also be applied to unregistered products that may have been widely used. It may help to determine if the device in the hands of the user still meets the manufacturer's claims for safety, quality and performance as stated in the IFU. Reactive testing provides additional information to assist the NRA in any decision to take regulatory action of its own.

The testing laboratory (in conjunction with the user) should be able to undertake an investigation of perceived issues to eliminate all other possible causes that are not device-related (i.e. user-related, etc.).

Proactive testing

For any device that has undergone evaluation of clinical evidence to support safety, quality and performance, any proactive testing should only be considered using a risk-based approach.

Implementing such testing may not be justified if user feedback systems are operational – as one would expect that users should detect a majority of problems related to use of the product.

Limitations

This approach to testing will not necessarily be able to detect quality issues if the lot has not been homogeneously produced. Pre-distribution testing cannot detect stability issues that might lead to degradation of the device during shelf life, including all components and accessories.

Sampling

Samples should be taken by appropriately trained and qualified NRA personnel (or otherwise delegated agency). During sampling, the collector should record the storage conditions for the sample at the time of collection. Samples should be transported to the testing laboratory in such a way that the integrity of the medical device is not adversely affected and that the appropriate storage conditions, as specified by the manufacturer, are maintained. If applicable, temperature log monitors should be included within the transportation packing for the samples. The sampler should collect an adequate number of samples according to the sampling protocol.

A risk-based approach, that utilizes a suitable methodology, should be considered to minimize waste of resources and to leverage on the previous regulatory assessment decision.

For testing, each lot should be sampled initially. After a certain period of acceptable results (12 months or 10 lots, whichever comes first), the sampling frame may change from systematic sampling and testing of each lot, to random sampling of lots delivered to countries. The random sampling frame should be selected (every fifth lot). If any issue is observed with random pre-distribution testing, the NRA may elect to recommence systematic testing of each lot. The decision about the sampling frame is therefore made using a risk-based approach.

Testing laboratory

A testing laboratory should be identified to perform testing and should:

- Be mandated by national authorities to perform testing for market surveillance of medical devices, and therefore have enough resources to conduct lot testing.
- Strive to adhere to internationally recognized quality standards, e.g. ISO 17025.
- Participate in EQA and act on results, as required.



Testing staff

Staff performing the lot testing should be qualified and competent to undertake the task and to demonstrate that they can perform the test procedure correctly.

The **technical supervisor** should:

- Ensure that technicians are blinded to the reference test results for the lot testing panel.
- Supervise the performance of the testing.
- Collate the readings from technicians and sign off the data collection sheets at the end of each testing day.
- Transcribe or verify that correct transcription of final results of lot testing into the testing report to be provided to the NRA has occurred.

The **technicians** should:

- Perform the procedure according to the manufacturer's IFU.
- Record any readings on the data collection sheet.
- Store all data collection sheets in a folder.

The supervisor and technicians should not proceed with testing until they are confident regarding every aspect of the testing procedure.

Quality assurance measures must always be in place and be adhered to.

What to test?

In this guidance, testing is generally comprised of the following elements, depending on the device:

- physical examination
- functional testing
- chemical and microbiological testing.

Physical examination

All samples should be physically examined, and any observations recorded, for example:

- **Packaging:** including defective components, defective medical devices, medical devices damaged prior to use, damage to the materials used to construct the cover or outer packaging of the medical device, compromised decontamination of the device, one or more of the listed components is missing.
- **Label, IFU or training problems:** including inadequate instructions to the user and their patients/clients; unclear, missing, worn out, incorrect or inaccurate labels.
- **Material integrity problem:** including broken, cracked, degraded, deformed, disintegrated, split/cut/torn, scratched materials/components.

NRAs should apply international standards in force for the respective category of medical devices.

The testing laboratory should present the results in the report to be sent to the requesting NRA.

Annex 6 details how to conduct lot testing for IVDs. Other types of medical devices may be subjected to testing in accordance with internationally recognized standards.

3.4 Issue certificate of analysis for IVDs

A model certificate of analysis (CoA) is used by manufacturers of IVDs to report the results of the final quality control for lot release, and state that the lot complied with the specifications stated in the IFU for the IVD. It may also be used by quality control laboratories that act on behalf of NRAs to conduct market surveillance.

The items included are based on Technical Guidance Series for WHO Prequalification – Diagnostic Assessment: *Panels for quality assurance and quality control of in vitro diagnostic medical devices* (33); WHO guidance on post-market surveillance of in vitro diagnostics (34); and *WHO guidance for procurement of in vitro diagnostics and related laboratory items and equipment* (35). In addition, requirements of the ISO standard for general requirements for the competence of testing and calibration laboratories (36) have been considered.

If any specific legal requirements exist in the country of issue or importation they should be respected when issuing the certificate. A model of such certificate is shown in **Annex 7**.

3.5 Collect other post-market information

Sentinel sites

If sentinel surveillance sites are established, these sites can collect information on safety, quality and performance of medical devices.

Signal detection

Signal detection is the process for identification of patterns of incidents associated with a particular medical device that warrant further investigation. When internationally recognized coding is used, it allows for incidents to be differentiated and renders the data ready for signal detection (27). For example, a medical device problem can be analysed in terms of the cause investigation conclusion.

Post-market evaluation

If national registries, mainly for implanted or other high-risk medical devices, are kept, this can provide useful information to detect signals.

Post-market evaluation conducted by NRAs or other designated authority (in the context of IVDs).

For all the above, the NRA may pass the information to manufacturers for them to act upon, including informing their relevant economic operators.



3.6 Decide if additional regulatory action is required

Depending on the risk/benefit posed by an incident reported in the post-market phase and/or potential for future harm, NRAs should consider the following possibilities:¹

- No action.
- Perform additional surveillance of the medical device concerned in use.
- Issue a safety alert giving advice to users.
- Require the manufacturer to make appropriate changes in the design, manufacturing process or information/labelling supplied with the medical device.
- Mandate (enforce and monitor) an FSCA (e.g. a medical device return/disposal or withdrawal from the market).
- Send the data acquired to the manufacturer and store them in a database to help identify trends that require action.

NRAs should prioritize regulatory action using the following questions:

1. How much product was supplied?
2. Where product is located?
3. Remaining shelf life for product?
4. Percentage of product remaining (if reagents, accessories, consumables)?
5. Is the manufacturer providing timely updates on progress of recall?
6. Is there an alternative product for users?

The NRA may request users to quarantine the product while the decision to undertake an FSCA is made by the manufacturer.

Economic operators may assist the manufacturer to conduct the FSCA. Therefore, any agreement for key suppliers should note that the economic operator should help with FSCA. Centralized warehouses and other governmental storage facilities might also have a role as they would have distribution records that are useful to locate affected users.

Timelines should be set for FSCAs to be completed.

3.7 Share information

Certain information should be made publicly available, including a searchable list of products that meet regulatory requirements (or are otherwise approved for importation). NRAs may consider making a searchable list of products that have been withdrawn/terminated/cancelled from the market publicly available, especially if they might present a serious risk to public health.

All FSNs for registered products should be maintained in a repository by the NRA, if possible as a searchable list online. NRAs might offer an email subscription service whereby users can receive alerts on current FSNs.

¹ This list does not purport to be definitive and each case should be handled individually.

IMDRF publishes a table that provides links to medical device safety information as published by IMDRF National Competent Authority Report (NCAR) Exchange Members (<http://www.imdrf.org/safety/safety.asp>).

Annex 5 provides an information exchange reporting form that may be used by NRAs for sharing post-market data gathered through market surveillance.

NRAs may consider to exchange information, if they possess any information that indicates the consequences of using a medical device:

- have led or are highly likely to lead to serious public health threat;
- may affect other jurisdictions.

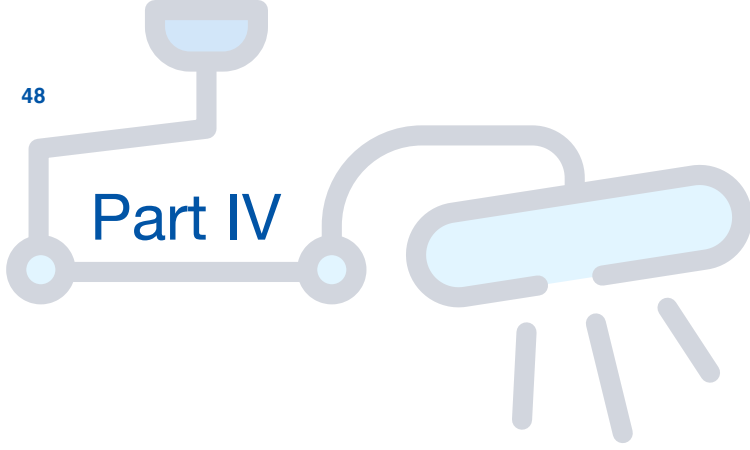
This process can be used to exchange early information on significant concerns or potential trends that individual NRAs have observed, but that have not yet resulted in FSCA.

The reporting forms should be completed and supportive documentation attached. It remains at the NRA's discretion to fill in fields in the form, as appropriate. This is built on IMDRF guidance for exchange of information between NRAs (17).

NRAs might request confidentiality agreements for such sharing of information, but the objective of the exchange is to ensure that information can be acted upon by the NRA.

NRAs reserve the right to directly contact the manufacturer for additional information such as investigation reports, FSCA reports or FSNs.





Specific requirements for medical devices recommended by WHO

Overview of WHO role

WHO lists or makes eligible for procurement medical devices based on the following criteria:

- WHO prequalification (PQ)¹
- WHO emergency use listing (EUL)²
- Recommendation by the technical unit based on risk assessment.

Beneficiaries

The findings of WHO prequalification³ and WHO EUL are used to provide independent technical information on safety, quality and performance of IVDs and other medical devices, principally to other United Nations agencies but also to WHO Member States and other interested organizations.

Reviewing investigations

WHO receives feedback and forwards to the manufacturer. Manufacturers are expected to report to WHO using a manufacturer investigation reporting form, see **Annex 2** for example. Upon receipt of initial, follow-up or final reports, WHO reviews investigations conducted by the manufacturers for any WHO-recommended medical devices.

Manufacturers of WHO-listed medical devices agree to certain terms of the prequalification overview document or EUL procedure as a condition of listing by WHO.⁴

¹ <https://extranet.who.int/pqweb/vitro-diagnostics/vitro-diagnostics>

² <https://extranet.who.int/pqweb/vitro-diagnostics/coronavirus-disease-covid-19-pandemic-%E2%80%94-emergency-use-listing-procedure-eul-open>, <https://extranet.who.int/pqweb/vitro-diagnostics/zika-virus-disease>, <https://extranet.who.int/pqweb/vitro-diagnostics/ebola-virus-disease>

³ Prequalification does not imply any approval by WHO of the product and manufacturing site(s). Moreover, prequalification does not constitute any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety, quality, or performance.

⁴ <https://extranet.who.int/pqweb/in-vitro-diagnostics>

For medical devices that are not listed but are otherwise made eligible for procurement, the following conditions apply:

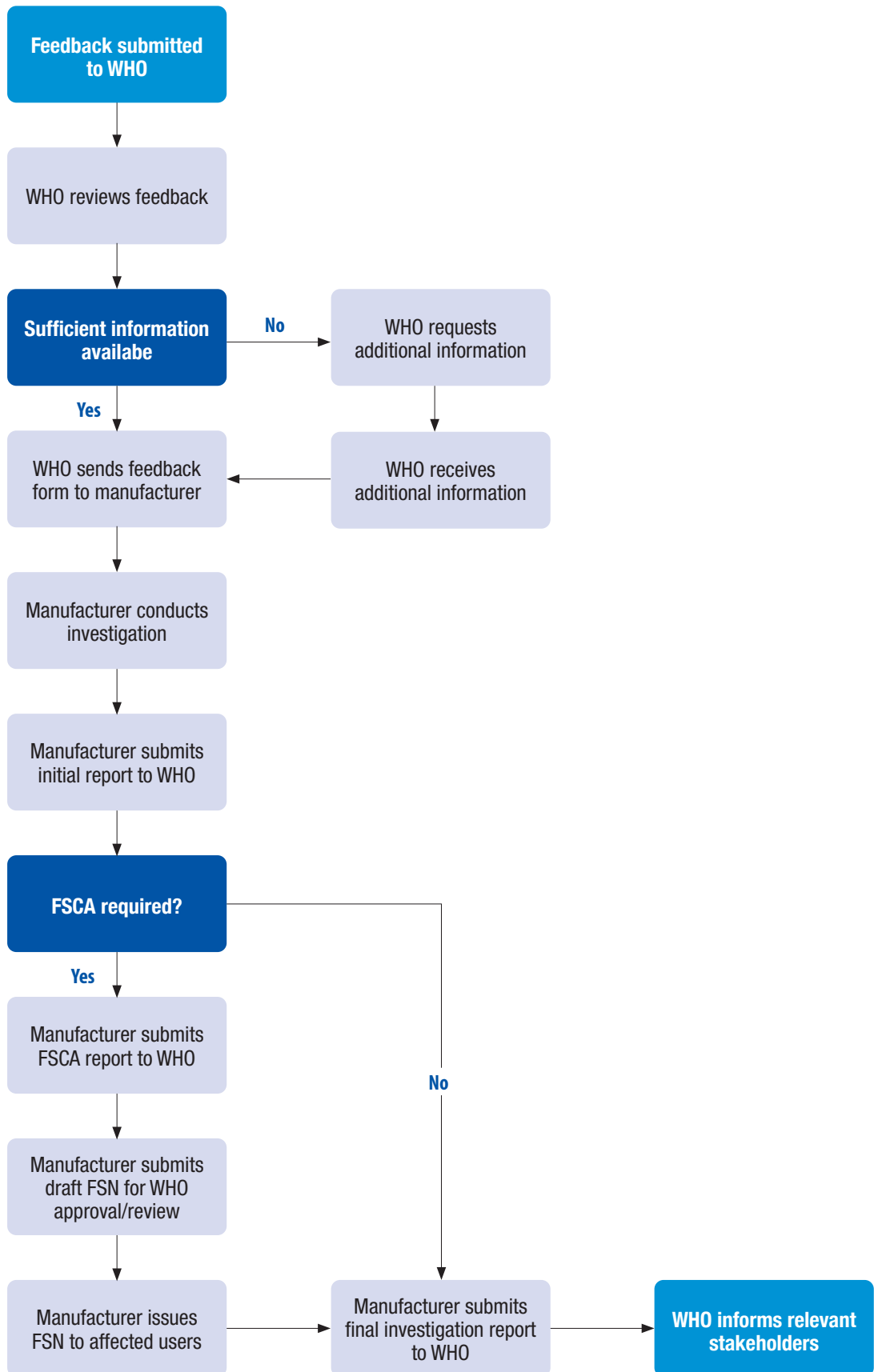
- Actively encourage users and their patients/clients to report any feedback related to use of a medical device to manufacturers so that action can be taken, if needed.
- Notify WHO of any problems relating to the product that have affected (or could have affected) the performance of the medical device, safety of the client, users or any person associated with the product.
 - Any incident should be reported to WHO in accordance with timelines.
 - Serious public health threat: immediately but no later than 48 hours.
 - Death, serious deterioration in state of health of patient, user or other person *occurred*: immediately but no later than 10 calendar days of the manufacturer becoming aware.
 - Death, serious deterioration in state of health of patient, user or other person *might have occurred*: immediately but no later than 30 calendar days.
- WHO will request that the manufacturer provide further information relating to the incident, including details of the root cause analysis, any analysis of impact on similar products, any corrections made, and any correction action proposed.
- Notify WHO of all events that require FSCA such as withdrawal of medical devices from sale or distribution, physical return of a medical device to the manufacturer, medical device exchange, destruction of the medical device, medical device modification/s or additional advice provision to customers to ensure that the medical device continues to function as intended.
- Submit information concerning all incidents for WHO-recommended medical devices, including any FSCA, carried out in the previous calendar year as part of the mandatory annual summary reporting.
- Note: These actions do not replace the responsibilities of the manufacturer to report to NRAs, see [Part II](#).

The outcomes of certain investigations are notified through post-market information exchange to other NRAs and procurers/implementing partners such as nongovernmental organizations as per [Annex 5](#). WHO may act with regard to WHO-recommended medical devices, as appropriate, including:

- Post-market surveillance information exchange with NRAs.
- Publishing safety notices on the WHO website.¹
- Performance of additional surveillance of the medical device concerned.
- Removal of the product from the list of WHO-recommended products (WHO prequalified IVDs, WHO EUL IVDs, etc.), if needed.
- Inspection of manufacturing site to ensure that CAPA as a result of any incidents have been implemented.

¹ <https://www.who.int/health-topics/substandard-and-falsified-medical-products>

Fig. 6.
Flow chart for handling user feedback for WHO-recommended medical devices



WHO information notices

Where WHO believes that the FSN does not fully meet the requirements as described in this document, explain the risk and how it will be removed/reduced, it reserves the right to issue information notices for users in certain circumstances for WHO-recommended medical devices:

- If the manufacturer has not undertaken an appropriate FSCA within an appropriate timeframe.
- If the manufacturer has not disseminated an appropriate FSN.
- To give information to users about how to interpret the contents of an FSN.

WHO information notices may include any recommendations to programmes and implementing partners for alternative testing arrangements and to procurers for past, ongoing or future purchase orders of affected or potentially affected products.



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The following reference documents have been used in preparing this document. Notwithstanding the reference to any specific clause, readers are encouraged to use the latest version of documents.

Medical device post-market surveillance

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Annexes

Annex 1: User feedback form

Send feedback to: manufacturer and their local economic operator and as soon as you become aware.

Types of feedback:

- **Death or serious deterioration in health** of the patient/client, user or any other person *occurred*.
- **Death or serious deterioration in health** of the patient/client, user or any other person *might have occurred*.
- **Positive feedback** may include suggested improvements, positive experiences, etc.

List of medical device product problems that should be considered for feedback

- Patient-device incompatibility
- Manufacturing, packaging or shipping
- Chemical
- Material integrity
- Mechanical
- Optical
- Electrical/electronic property
- Calibration
- Output, e.g. false negative or false positive result for an IVD
- Temperature
- Computer software
- Connection
- Communication or transmission
- Infusion or flow
- Activation, positioning or separation
- Protective measure
- Compatibility
- Contamination/decontamination
- Environmental compatibility
- Installation-related
- Label, instructions for use or training
- Human-device interface
- Use of device
- Adverse event without identified device or use

Note: this is not an exhaustive list of potential user feedback.



1 Contact details of the reporting user (organization/person)

| | |
|--|--|
| Name of organization: | Street name and no.: |
| City and postcode: | Country: |
| Name of contact person (for organization): | Mobile telephone of contact person (for organization): |
| Position of contact person (for organization): | E-mail of contact person (for organization): |
| Report date: | Reporter's report identifier: |

2 Product details

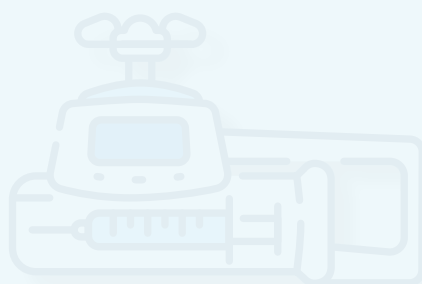
| | |
|--|---|
| Product name/commercial name/brand name: | Product code/catalogue number(s): |
| Serial number(s): | Model number(s): |
| Lot number/batch number(s): | Expiry date(s): |
| Instructions for use version number: | Software version number: |
| Associated devices/accessories (lot numbers/expiry dates): | UDI-DI/UDI-PI: |
| Manufacturer name: | Authorized representative name: |
| Manufacturer contact details (e-mail): | Authorized representative contact details (e-mail): |

Please attach a copy of the instructions for use and photographs of the device and its labelling.

3 Event details

| | |
|---|--|
| Describe the clinical/analytical procedure during which the observation was made (note: in the case of IVD, state specimen type used): | |
| Event description (e.g. in the event of negative feedback, explain what went wrong with the medical device, and what was the health impact [death, life-threatening, indirect harm such as misdiagnosis or delayed diagnosis/treatment], and in the event of positive feedback, explain suggestions for improvement or positive experiences): | |
| Date of observation/event was made: | % of devices involved: |
| Number of devices involved: | Number of patients involved: |
| Operator/user at the time of the observation/event (please choose): <input type="checkbox"/> Health care professional <input type="checkbox"/> Patient/lay user <input type="checkbox"/> Other (specify): | Has more than one user had the observation with the product? <input type="checkbox"/> Yes <input type="checkbox"/> No |
| Comments: | |
| Date of report: | Signature: |

Disclaimer: The act of reporting an observation is not an admission of manufacturer, user or patient liability for the event or its consequences.



Annex 2: Manufacturer investigation reporting form

- Incidents that represent a serious public health threat should be reported to the relevant NRAs **immediately and not later than 48 hours**.
- Other incidents, including death or serious deterioration in health, which *occurred* for the patient, end-user or other individual should be reported to the relevant NRAs within **10 calendar days**.
- Other incidents, including death or serious deterioration in health, which *might have occurred* for the patient, end user or other individual should be reported to the relevant NRAs **within 30 calendar days**.

Send to: relevant national regulatory authorities and, if applicable, to the World Health Organization (e-mail: rapidalert@who.int).

1 Report details

| | |
|--|--|
| Name of recipient organization (name of NRA/WHO): | |
| Street name and no.: | City and postcode: |
| Country: | Telephone: |
| Name and position of recipient contact person: | E-mail of contact person: |
| Identifier assigned by the manufacturer: | Identifier assigned by NRA: |
| Type of report: <input type="checkbox"/> Initial report <input type="checkbox"/> Follow-up report <input type="checkbox"/> Combined initial and final report <input type="checkbox"/> Final report | State any other NRAs who were also sent this report: |



2 Reporting manufacturer details

| | |
|---------------------------------|--------------------|
| Name of reporting manufacturer: | |
| Street name and no.: | City and postcode: |
| Country: | Telephone: |
| Name of contact: | E-mail of contact: |

3 Product details

| |
|---|
| Product name: |
| Product code/catalogue number(s): |
| Lot number/batch number/serial number(s): |
| Expiry date(s): |
| Associated devices/accessories (lot numbers/expiry dates): |
| Instructions for use version number: |
| Software version number: |
| UDI-DI/UDI-PI: |
| Falsification status check: <input type="checkbox"/> Genuine <input type="checkbox"/> Manipulated (by user or by supply chain actor?) <input type="checkbox"/> Falsified |

Please attach a copy of the instructions for use.



4 Event details

| | |
|---|--|
| Where observation/event happened: | |
| Date(s) observation/event happened: | |
| Date feedback reported to manufacturer (and/or economic operator) by user: | |
| Event/problem description narrative (explain what went wrong with the product, and a description of the health effects [if applicable], i.e. clinical signs, symptoms, conditions as well as the overall health impact [death, life-threatening, indirect harm]), and the health/medical condition for which the device was being used: | |
| IMDRF Medical Device Problem Code(s) (Annex A): | |
| IMDRF Medical Device Component(s) (Annex G): | |
| User at the time of the event/problem (please choose): <input type="checkbox"/> Health care professional/lay provider <input type="checkbox"/> Patient/client <input type="checkbox"/> Other (specify): | Has more than one user experienced the problem with the product? <input type="checkbox"/> Yes <input type="checkbox"/> No |
| Number of devices involved: | Number of patients involved: |
| IMDRF Clinical Sign Codes (Annex E); | IMDRF Health Impact Codes (Annex F): |

5 Manufacturer's preliminary comments (initial/follow-up reports)

| |
|---|
| Manufacturer's preliminary analysis of event: |
| IMDRF Type of Investigation (Annex B): |
| IMDRF Investigation Findings (Annex C): |
| Initial correction implemented by manufacturer: |
| Expected date of next report: |

⑥ Results of the final investigation (final report)

| |
|---|
| Manufacturer's analysis of event: |
| IMDRF Type of Investigation (Annex B): |
| IMDRF Investigation Findings (Annex C): |
| IMDRF Investigation Conclusion (Annex D): |
| Any additional corrections implemented by manufacturer: |
| Corrective action/preventive action implemented by manufacturer: |
| Field safety corrective action by manufacturer: |
| Date field safety notice issued: |
| Field safety notice identifier: |
| Time schedule for implementation of the identified actions: |
| Final comments from the manufacturer: |
| Further investigations, including analysis of other impacted areas: |
| Is the manufacturer aware of similar events with this device with a similar root cause? <input type="checkbox"/> Yes <input type="checkbox"/> No |
| If yes, state in which countries: |
| If yes, number of similar incidents: |
| State which countries this report has been disseminated to: |

7 Signature

| |
|------------|
| Name: |
| Signature: |
| Date: |

Disclaimer: The act of reporting an observation is not an admission of manufacturer, user or patient liability for the event or its consequences. Reporting of incidents, and serious public health threats in itself, represent a conclusion by the manufacturer that the content of this report is complete or confirmed, that the device(s) listed failed in any manner. It is also not a conclusion that the device caused or contributed to the incident.



Annex 3: Field safety corrective action report

Send to: relevant national regulatory authorities and, if applicable, to the World Health Organization (e-mail: rapidalert@who.int).

1 Report details

| | |
|--|---------------------------|
| Date of this report: | |
| Type of report: <input type="checkbox"/> Initial report <input type="checkbox"/> Follow-up report <input type="checkbox"/> Final report | |
| FSCA reference number assigned by NRA: | |
| Name of recipient organization: | |
| Name of contact person: | E-mail of contact person: |
| Street and no.: | City and postcode: |
| Country: | Telephone: |

2 Reporter details

| | |
|--|--------------------------|
| Name of reporting manufacturer: | |
| Street name and no.: | City and postcode: |
| Country: | Telephone: |
| Name of contact person: | Email of contact person: |
| Identifier assigned by the manufacturer: | |



3 Product details

| |
|--|
| Product name: |
| Product code/catalogue number(s): |
| Lot number/batch number/serial number(s): |
| Expiry date(s): |
| Associated devices/accessories (lot numbers/expiry dates): |
| Instructions for use version number: |
| Software version number: |
| UDI-DI/UDI-PI: |

Please attach a copy of the instructions for use.

4 FSCA description

| | |
|---|---|
| Background information and reason for the FSCA: | |
| Description and justification of action (corrective/preventive): | |
| Date feedback reported by manufacturer: | |
| Advice on actions to be taken by distributor and the user: | |
| Field safety notice attached: <input type="checkbox"/> Yes <input type="checkbox"/> No | Status of FSN: <input type="checkbox"/> Draft <input type="checkbox"/> Final |
| Time schedule for implementation of different actions: | |
| List of countries this FSCA has been distributed to: | |

5 Additional remarks

| |
|--|
| |
|--|

6 Signature

| |
|------------|
| Signature: |
| Name: |
| Date: |





Annex 4: Field safety notice (example)

Urgent field safety notice

Product name: [insert name of the affected product]

FSCA-identifier: [insert]

Type of action: [e.g. return of device to supplier, device modification (including instructions for use), device exchange, device destruction, retrofit of device by purchaser or manufacturer's modification or design change, advice given by manufacturer regarding use of the device and/or follow-up of patients, users, or others].

Date: dd/mm/yyyy

Attention: [insert intended audience]

Details on affected device: [specific details to easily identify the affected device, e.g. product name, product code(s)/serial number(s), lot number(s), UDI-DI, UDI-PI]

Description of the problem: [a factual statement explaining the reasons for the FSCA, including description of the problem and a clear description of the potential hazard associated with the continued use of the medical device and the associated risk to the patient, user or other person]

Advice on action to be taken by the user: [include, as appropriate]

- Identifying and quarantining the device;
- Method of recovery, disposal or modification of device, including instructions for use and labelling;
- Recommended patient follow-up;
- Timelines;
- Confirmation form to be sent back to the manufacturer.

The above recommended action(s) are to be taken by all recipients of this FSN, including action(s) recommended for people that have previously used or been treated by affected devices.

Transmission of this field safety notice: [as appropriate]

This notice needs to be passed on all those who need to be aware within your organization or to any organization where the potentially affected product has been transferred. Please be aware of this notice and resulting action for an appropriate period to ensure effectiveness of the corrective action.

Contact person for further information: [Insert name, organization, address, contact details]

The undersigned confirms that this notice has been notified to the appropriate national regulatory authorities.

Signature:

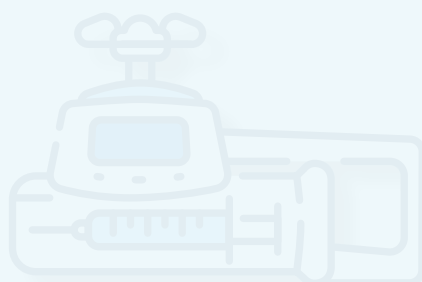
Annex 5: Post-market information exchange reporting form for NRAs

1 Report details

| |
|---|
| NRA report number: |
| Purpose of exchange: <input type="checkbox"/> Share information <input type="checkbox"/> Serious public health threat <input type="checkbox"/> Observations from national trend analysis <input type="checkbox"/> Request information <input type="checkbox"/> Summary of query findings |
| Confidentiality: <input type="checkbox"/> Yes <input type="checkbox"/> No |

2 Initiating NRA

| | |
|-------------------------|---------------------------|
| Name of NRA: | |
| Name of contact person: | E-mail of contact person: |
| Street and no.: | City and postcode: |
| Country: | Telephone: |



3 Product details

| | |
|--|---------------------------|
| Product name: | |
| Product code/catalogue number(s): | |
| Lot number/batch number/serial number(s): | |
| Expiry date(s): | |
| Associated devices/accessories (lot numbers/expiry dates): | |
| Instructions for use version number: | |
| Software version number: | |
| UDI-DI/UDI-PI: | |
| Manufacturer name: | |
| Street and no.: | City and postcode: |
| Country: | Telephone: |
| Name of contact person: | E-mail of contact person: |

Please attach a copy of the instructions for use.



4 Background information

| |
|---|
| Background information and reason for this report: |
| Is the investigation of the report completed? <input type="checkbox"/> Yes <input type="checkbox"/> No |
| Attachments [insert FSN, FSCA reports etc.]: <input type="checkbox"/> Yes <input type="checkbox"/> No |

5 Additional remarks

| |
|--|
| |
|--|

6 Details of responding NRA

| | |
|-------------------------|---------------------------|
| Name of NRA: | |
| Name of contact person: | E-mail of contact person: |
| Street and no.: | City and postcode: |
| Country: | Telephone: |

7 Signature

| |
|------------|
| Name: |
| Signature: |
| Date: |

Annex 6: Lot testing for IVDs

Rationale

The manufacturer has an obligation to conduct QC activities throughout production and at release. However, variations in the characteristics of each lot may occur due to differences in lots of key components used, different personnel involved in production processes, and a range of other variables. Therefore, testing might be considered as part of a risk-based approach to the NRA's market surveillance activities. In this regard, the NRA has a mandate to conduct testing of IVDs in their market place. They may sub-contract this function to an appropriate entity.

Lot testing, under the auspices of the NRA, may occur pre-distribution to users or post-distribution to users using a risk-based approach. The objective of such testing is to evaluate inter-lot variability (lot-to-lot consistency) against a baseline (reference) lot using a standardized methodology.

This annex does not refer to lot release testing conducted by the manufacturer.

What is meant by “lot”?

For an IVD, lot sizes vary, depending on how the manufacturing site configures operations. The following definition of lot is used, “*A defined amount of material that is uniform in its properties and has been produced in one process or series of processes. The material can be either starting material, intermediate material or finished product*” (19). In the context of these guidelines, lot testing is focused on a commercially available test kit which is provided with a unique lot number and where the single components are matched to this kit.

Sampling

Refer to **Part III** for guidance on the sampling frame, characteristics of the reference testing laboratory and testing staff.

Quality assurance measures must always be in place and be adhered to.

What to test?

In this guidance, testing is generally comprised of the following elements:

- physical examination
- functional testing.

Physical examination

All samples should be physically examined, and any observations recorded.

Packaging, including defective components, defective devices, devices damaged prior to use, damage to the materials used to construct the cover or outer packaging of the device, compromised decontamination of the device, one or more of the listed

components is missing.

- Label, instructions for use or training problems, including inadequate instructions to the user and their patients/clients; unclear, missing, worn out, incorrect or inaccurate labels.
- Material integrity problem, including broken, cracked, degraded, deformed, disintegrated, split/cut/torn, scratched materials/components.

Functional testing

Samples may undergo functional testing, and any observations recorded. The following list of possible functional testing is not exhaustive:

- sampling: device doesn't collect/transfer specimen;
- liquid: leak, splash;
- mechanical: misalignment, jam;
- electrical: unable to charge, power loss or fluctuation;
- data: capture, display, or storage affecting product functionality;
- software: network, program, algorithm, or security affecting product functionality;
- environmental: noise, temperature, humidity/moisture, fungal/bacterial growth, or dust affecting product functionality;
- failure to calibrate;
- increased rate of invalid or unreturnable test results;
- obviously incorrect, inadequate or imprecise result or readings;
- unable to obtain reading.

For testing IVDs, a set of clinically derived reference specimens are constructed into a panel. The testing should be conducted on a standardized panel.

Any post-distribution lot testing should be carried out using the same standardized panel as the pre-distribution lot testing.

A criteria for pass/fail (or a range of tolerable error) should be defined, based on the reference results for the standardized panel.

Reporting results

The reference testing laboratory should present results in the report as defined in **Annex 7**, which would be sent to the requesting NRA.

Specific elements for physical inspection and functional testing that may be used for different assay formats

| | Physical inspection | Panel functional testing |
|---|--|---|
| Rapid diagnostic tests (RDTs) | <ul style="list-style-type: none"> • secondary packaging • primary packaging • desiccant • buffer vials • specimen transfer devices • lancets • alcohol swabs, etc. | <ul style="list-style-type: none"> • 3 replicates of 5 positive serum/plasma specimens; near to the cut-off claimed by the manufacturer • 3 replicates of 5 negative serum/plasma specimens • 3 replicates of 5 positive whole blood specimens; near to the cut-off claimed by the manufacturer • 3 replicates of 5 negative whole blood specimens |
| Immunoassays (IAs) | <ul style="list-style-type: none"> • secondary packaging • primary packaging • reagent vials, etc. | <ul style="list-style-type: none"> • 3 replicates of 5 positive serum/plasma specimens; near to the cut-off claimed by the manufacturer • 3 replicates of 5 negative serum/plasma specimens |
| Nucleic acid testing (NAT) assays (quantitative) | <ul style="list-style-type: none"> • secondary packaging • primary packaging • reagent vials, etc. | <p>For IVDs used in a laboratory (conventional platform):¹</p> <ul style="list-style-type: none"> • 25 replicates at LoD claimed by manufacturer • 25 replicates at 2x LoD claimed by manufacturer • 25 replicates of 1000 copies/mL; • 5 replicates of 10 000 copies/mL • 4 replicates of negative (normal human plasma) <p>For IVDs used at point of care: same as above.</p> |
| Nucleic acid testing (NAT) assays (qualitative) | <ul style="list-style-type: none"> • secondary packaging • primary packaging • reagent vials, etc. | <p>For IVDs used in a laboratory (conventional platform):</p> <ul style="list-style-type: none"> • 24 replicates at 4x LoD claimed by manufacturer • 24 replicates at 2x LoD claimed by manufacturer • 24 replicates at LoD claimed by manufacturer • 24 replicates at 0.5x LoD claimed by manufacturer • 24 replicates at 0.25x LoD claimed by manufacturer • 5 replicates of negatives <p>Plus: minimum of 3 replicates for the most common subtypes/genotypes² at 2x LoD claimed by manufacturer</p> <p>For IVDs used at point of care: same as above</p> |

¹ For example, for a conventional NAT assay with an LoD of 45 copies/mL, the following concentrations would be used: 10 000 copies/mL (5 replicates), 1000 copies/mL (25 replicates), 100 copies/mL (25 replicates), 50 copies/mL (25 replicates), and negative dilutions (4 replicates).

² For HIV-1 A, B, C, D, CRF02_AG and HIV-2 Group A.

Annex 7: Model certificate of analysis for IVDs

1 Laboratory issuing certificate of analysis

| | |
|---|-----------|
| Organization name: | |
| Responsible person (Surname, Given name): | Position: |
| Street, Postcode, City, Country: | |

2 Reference for this certificate of analysis

| |
|---------------------------|
| Identification number: |
| Date issued (dd/mm/yyyy): |

3 Requestor of certificate of analysis

| |
|----------------------------------|
| Organization name: |
| Surname, Given name: |
| Street, postcode, City, Country: |

4 Sample details

| |
|-------------------------------------|
| Registration number for this sample |
| Date sampled/received (dd/mm/yyyy): |
| Quantity sampled/received: |

5 Product details

| |
|---|
| Name of product: |
| Unique device identification (UDI-DI + UDI-PI): |
| Regulatory version: |
| Product code: |
| Lot number: |
| Date of manufacture (dd/mm/yyyy): |
| Date of expiry date (dd/mm/yyyy): |
| Packaging configuration (number of tests): |
| Contents of sample: |

6 Results of physical inspection

| Date of inspection (dd/mm/yyyy): | | |
|----------------------------------|-----------------------------|-----------|
| Element inspected | Result | Accepted |
| | x defective/x not defective | Pass/fail |
| | x defective/x not defective | Pass/fail |
| | x defective/x not defective | Pass/fail |
| | x defective/x not defective | Pass/fail |
| | x defective/x not defective | Pass/fail |

Expand as needed.

Attach photographs of all inspected samples of reagents/kits.

7 Results of panel functional testing

| Date of inspection (dd/mm/yyyy): | | | |
|----------------------------------|---------------------|-------------------|-----------|
| Panel identification number | Result | Reference results | Accepted |
| | x detected/x tested | | Pass/fail |
| | x detected/x tested | | Pass/fail |
| | x detected/x tested | | Pass/fail |
| | x detected/x tested | | Pass/fail |
| | x detected/x tested | | Pass/fail |

Expand as needed.

Attach photographs of all testing results, if subjectively read assay format.

8 Additional comments (including any invalid or unreturnable results)**9 Conclusion on compliance of the sample with the specifications**

| |
|----------------------------------|
| Compliance statement: |
| Surname, Given name: |
| Street, Postcode, City, Country: |
| Date issued (dd/mm/yyyy): |
| Signature: |



CONTACT

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https://www.who.int/health-topics/substandard-and-falsified-medical-products#tab=tab_1

