AFRICA MEDICAL DEVICES FORUM (AMDF) – TECHNICAL COMMITTEE UNDER THE AFRICAN MEDICINES REGULATORY HARMONIZATION (AMRH) INITIATIVE

STANDARD OPERATING PROCEDURE

for handling reports of substandard/falsified medical devices including in vitro diagnostics

version 0.5 - DRAFT

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Introduction

The African Medical Devices Forum (AMDF) is a technical committee under the African Medicines Regulatory Harmonization (AMRH) programme hosted by AUDA-NEPAD.

Though the support from the World Health Organization (WHO), AMDF established a COVID-19 task force comprised of four working groups. Working group 3 was devoted to establishment of a mechanism for notification of substandard/falsified medical devices including in vitro diagnostics (IVDs).

Purpose and scope

This SOP applies to the necessary steps for handling complaints/incidents related to substandard/falsified medical devices, including IVDs:

- reporting all complaints (by end-users to manufacturers or their economic operators)
- notifying certain incidents (by manufacturers or their economic operators to regulators)
- reviewing manufacturer investigation reports, and
- exchanging information between regulators.

This SOP applies to focal points for medical devices in national regulatory authorities and WHO technical staff responsible for handling substandard/falsified medical devices.

Definitions

Adverse event[1]	is any death or serious deterioration in state of health (also known as serious injury) that happens to the patient, end-user or other person that is either: ▪ Life threatening illness or injury. ▪ Permanent impairment of a body function or permanent damage to a body structure. ▪ A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.
Affected customer	in this context refers to person who is in possession of affected product, may be end-user or economic operator
Affected product	in this context refers to product that is the subject of a complaint and/or its investigation.
Complaint	any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.
Economic operator	manufacturer, agent, authorized representative, distributor of a medical device.
Falsified medical product[2]	medical products that deliberately/fraudulently misrepresent their identity, composition or source.
Field safety corrective action (FSCA)	is an action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device.
Field safety notice (FSN)	is how field safety corrective actions are notified.

[1] From Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices GHTF/SG2/N54R8:2006

Serious public health threat	any event type, which results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action.
Product problem	is any observation at the level of the medical device that alleges a deficiency, it may or may not be associated with an adverse event.
Substandard medical product[2]	also called "out of specification", these are authorized[3] medical products that fail to meet either their quality standards or specifications, or both.
Unregistered/unlicensed medical product[2]:	Medical products that have not received market authorization by the National or Regulatory Authority (NRA).

How end users report substandard/falsified devices

End-users must report any **adverse event** or **product problem** or **suspected falsified** product. End-users are those health care workers in hospitals, clinical laboratories, primary care and other health facilities, community-based services and non-governmental organizations or other implementing partners that support use of devices.

Supply chain actors must report **product problems** or **suspected falsified** products. These staff are in medical stores/warehouses, the facilities of relevant economic operators (agents, authorized representatives, distributers) and customs.

End users and supply chain actors must be look for adverse events and product problems, as per Table 1.

Table 1 – list of observations that are considered complaints

Adverse events may be: • Death of the patient, end-user or any other person • Serious deterioration in health of the patient, end-user or any other person • A false negative result • A series of false positive results • Non-reproducible results • High or low readings, too high or low test results	**Product problems** may be: • Packaging – damaged, defective, suspect tampered • Labelling– insufficient instructions for use, illegible prints? • 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

[2] From Appendix 3. WHO Member State Mechanism on Substandard/Spurious/Falsely Labelled/Falsified/Counterfeit (SSFFC) Medical Products. Working Definitions. A70/23

[3] Licensed or registered for sale and use in given country

1. **Fill out form**

End-users should report event or problem using the form and attach the instructions for use and any photos of the device and its labelling.

2. **Send the form**

End-users must send the filled form **immediately after they become aware of any incident** to:

- Legal manufacturer (check on instructions for use) and local authorized representative; and
- Their national regulatory authority and relevant national testing/laboratory programme; and
- WHO by email: rapidalert@who.int

3. **Secure samples**

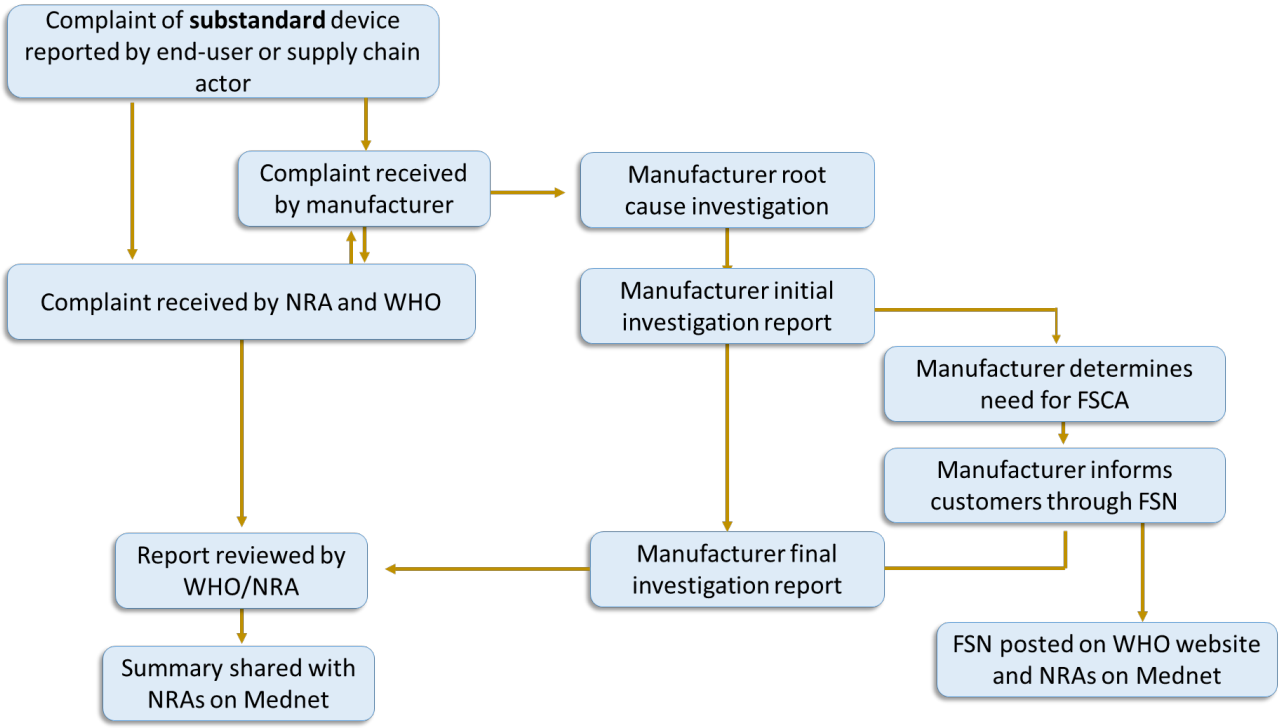
End-users/supply chain actors should take samples of the affected devices and labelling, and if possible:

- Send samples of affected product and patient specimen back to the manufacturer for their investigation; and
- Send some samples of affected product to national regulatory authority for records.

This may be impractical if the device is large or is implanted/on-body.

The procedure for reporting/investigating/acting on substandard devices is summarized in figure 1.

Figure 1- End to end procedure for handling reports of substandard medical devices including IVDs



How manufacturers report substandard/falsified devices

1. **Record all incidents**

The manufacturer must enter all complaints from end-users or **economic operators** (agent, distributor, authorized representative) as incidents into their customer feedback database.

2. **Report certain incidents**

Manufacturers must report certain categories of incidents to:

- All national regulatory authorities where affected product was distributed, and
- WHO by email: rapidalert@who.int

Incidents that represent a serious public health threat should be **reported by manufacturers to NRAs immediately and not later than 2 calendar days**.

Other serious incidents including death or serious deterioration in health occurred or may have occurred for the patient, end-user or other individual should be **reported by manufacturers to NRAs within 5 calendar days.**

3. **Investigate incidents**

For suspected **substandard** products; the manufacturer must undertake the following pathway of investigation (and corrective action, if required) and report to the regulator and WHO:

1. Root cause analysis (how/why did this happen)
2. Analysis regarding related areas (is this same issue impacting/occurring elsewhere)
3. Correction (fix now) with completion dates
4. Corrective action, if applicable (to prevent recurrence) with planned completion dates.

It is suggested to use International Medical Device Regulators Forum (IMDRF) terminologies for categorized Adverse Event Reporting (AER): terms, terminology structure and codes (IMDRF/AE WG(PDI)/N43).

For suspected **falsified** products; the manufacturer must provide a reply to the regulator/WHO for the following five questions:

1. Do you manufacture this product? If yes, does the product and packaging look genuine? photographs and samples will be provided if available)
2. Are the manufacturing/lot/expiry dates authentic and do they correspond to your manufacturing records? If yes, where, and when was it distributed?
3. Have you had falsified, or substandard versions of this lot reported previously? If yes when and where?
4. Have you received any complaints (including adverse events and product problems) related to this product or to this lot? If so, from whom, where, and when?
5. Is there any other information we should be aware of?

How NRAs investigate substandard/ falsified devices

1. **Record details from all manufacturer investigation reports**

The regulator will receive reports from manufacturers and should capture the following information for each incident and assign a reference number:

- Product name and product code
- Lot number(s) and expiry date(s)
- Type of incident (e.g. substandard, falsified)
- Date incident report received from end user
- Date investigation report received from manufacturer
- Root cause identified
- Correction (action taken to eliminate a detected nonconformity, e.g. a recall)
- Corrective action (action is taken to eliminate the cause of a detected nonconformity, e.g. change in procedure for incoming goods quality control)
- Manufacturer reference number
- Date incident closed.

NRAs may also receive complaints directly from end-users and supply chain actors – these should be forwarded to the manufacturer for their action.

WHO will enter relevant incidents they receive into their global database.

2. Review manufacturer investigation reports for substandard devices

The regulator and WHO will review the initial, follow-up and final investigation reports submitted by the manufacturer to establish whether the investigation conducted by the manufacturer is scientifically valid, timely and appropriate.

A reasonable manufacturer investigation would include:

- **Retained** samples of affected lot
  - Testing using the final QC lot release panel;
  - Physically inspecting retained samples from affected lots;
- **Returned** samples of lots from the incident
  - Testing using the final QC lot release panel;
  - Physically inspecting returned samples from the incident;
- Reviewing stability of product (all components) against claimed shelf life, in-use stability, shipping stability;
- Determining the need for a specific investigative panel (and acceptance criteria) for additional testing;
- Updating the risk management file.

Common shortcomings of manufacturer investigations:

- Root cause analysis procedure is not documented or is not followed;
- Resting is not blinded;
- Suggested corrective/preventive actions are unacceptable;
  - Suggested actions for end-users are unacceptable;
  - Risk management file not updated post-FSCA.

NRA/WHO must provide a summary of their review outcomes to the manufacturer including any request for clarification or additional investigation.

3. Investigate suspect falsified devices

The NRA might start inquiries or investigations by:

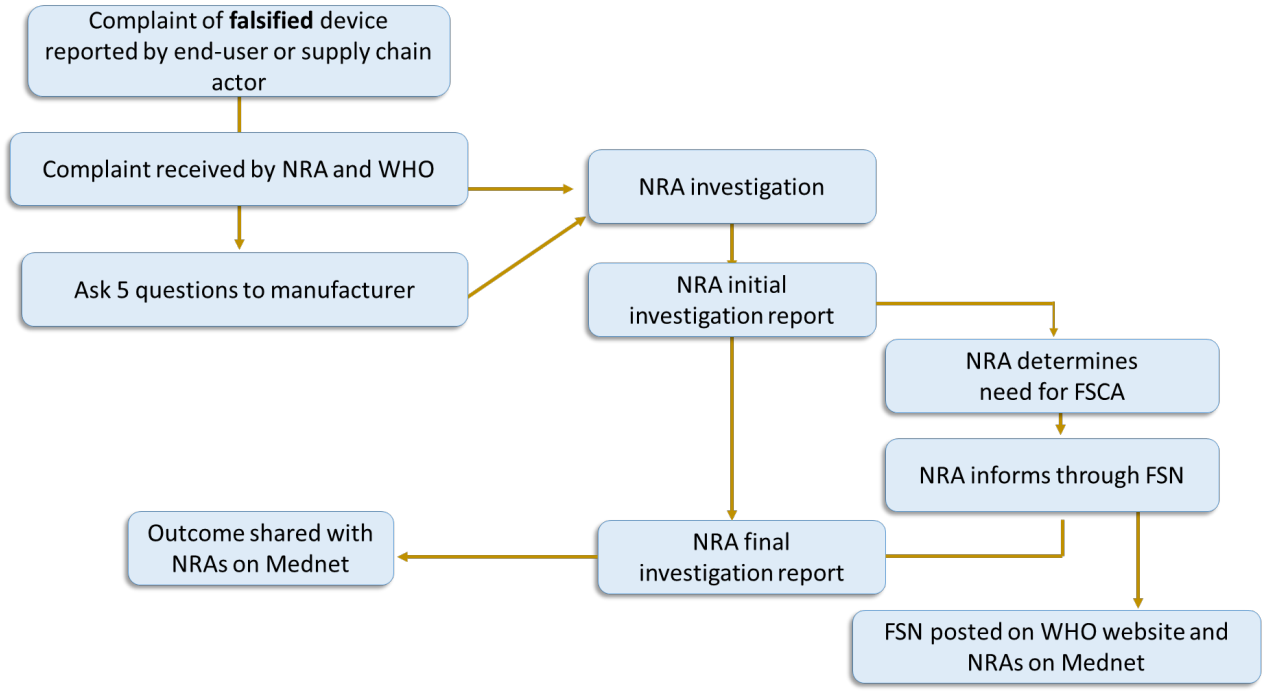
1. Establishing the facts
   a. Reliability of the source: What is their motivation for supplying information, is source easily contactable, are their contact details accurate, have they reported before?
   b. Credibility of information: Has similar information been received from different sources, any sources that can corroborate the information, any obvious inaccuracies?
   c. Questions for manufacturers: Review response from manufacturer for the 5 questions.
2. Identifying and assessing risks
   a. Where is the product available (sectors: public or private; supply chain level: laboratories, communities, etc.)?
   b. What quantities were discovered (number of devices))
   c. What number of patients would be affected?
   d. Is there evidence that the product is in recent/current circulation, is it widely circulated?
   e. Is the product in strong demand, or in short supply?
3. Immediate public health protection
   a. Quarantine or seize any suspected product (remove the defective/harmful devices from supply)
   b. Ensure product is securely stored and in compliance with manufacturer's storage instructions.
   c. Consider alternative supplier or product to fulfil the same intended use.
4. For-cause laboratory analysis
   a. If capacity exists, physical inspection, and possibly testing of sampled test kits, may be conducted.
5. Managing the incident

a. Establish an incident team
b. Keep records of all meetings and decisions made.
c. Consider a recall, if the manufacturer has not already moved to do so.
d. Consider issuing an alert.

Report the incident to the WHO Global Surveillance and Monitoring Systems for Substandard and Falsified Medical Products: rapidalert@who.int

The procedure for reporting/investigating/acting on falsified devices is summarized in figure 2.

Figure 2- End to end procedure for handling reports of falsified medical devices including IVDs



How to conduct a field safety corrective action

1. **Determine if field safety corrective action is required**

The manufacturer may decide to initiate **field safety corrective action** (FSCA). This is an action taken by the manufacturer to **reduce a risk of death or serious deterioration in the state of health** associated with the use of a device that is already placed on the market.

FSCA may include:

- Return of a device to the manufacturer or its representative (recall);
- Device modification;
- Device exchange;
- Device destruction (recall);
- 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).

Device modifications can include:

- Retrofitting in accordance with the manufacturer's modification or design change;
- Permanent or temporary changes to the labeling or instructions for use;
- Software upgrades including those carried out by remote access;

- 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. For example, the manufacturer may advise to:
    - Retest affected patients or specimens or review previous results.
    - Change the way the device is used e.g. use a revised quality control procedure, use third party quality controls, or do more frequent calibration.

The NRA and WHO must be notified of any FSCA.

Regulators may decide to conduct their own FSCA, at their own discretion if they believe that public health is threatened.

Furthermore, WHO may decide to issue their own WHO Information Notice for Users, if the manufacturer has not taken reasonable action to reduce individual and public health risks.

2. **Notify customers/public of field safety corrective action**

Field safety corrective actions are notified to affected customers via a **field safety notice**. It must be sent by email with confirmation of receipt.

Regulators may post FSN on their website. WHO will post all FSN here and on AMDF Mednet.

A final manufacturer investigation report and FSCA report that describes the effectiveness of the FSCA must be submitted to the NRA and WHO in a timely manner.

What information will be exchanged with other regulators?

WHO will post the following information on their website and send to focal points via MedNet.

- Field safety notice from manufacturers – for substandard devices
- WHO Medical Product Alert – for falsified devices
- WHO Information Notice for Users – which gives information to end-users on how to interpret FSNs.

Between regulators, only events that have led or are highly likely to lead to unanticipated serious public health threat and fulfill the following criteria should be exchanged, such as:

- Death of a patient, end-user or other person
- Serious injury of a patient, end-user or other person
- No death or serious injury occurred but the event might lead to death or serious injury of a patient, user or other person if the event recurs.

Single incidents need not be exchanged unless those incidents have a clear implication for public health.

Certain trends that are noticed by the regulator may be exchanged where the frequency is significantly higher than the manufacturers technical file or when the trend has led or is highly likely to lead to a serious public health threat.

References

Global Harmonization Task Force. *Medical Devices Post Market Surveillance: Content of Field Safety Notices* (GHTF/SG2/N57R8:2006) http://www.imdrf.org/docs/ghtf/final/sg2/technical-docs/ghtf-sg2-n57r8-2006-guidance-field-safety-060627.pdf

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World Health Organization. *WHO post-market surveillance of in vitro diagnostics*. 2015. ISBN 978 92 4 150921 http://www.who.int/diagnostics_laboratory/postmarket/150819_pms_guidance_final_version.pdf