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WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

PROPOSED FINAL DOCUMENT

Title: Adverse Event Reporting Guidance for the Medical Device
Manufacturer or its Authorized Representative

Author: Work Group 2

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1. Objectives

This document was developed by Work Group 2 of the AHWP to provide guidance and information to Regulatory Authorities (RA) and the Medical Device Industry (Industry) on Adverse Event (AE) Reporting.

2. Definitions

2.1 **Authorised Representative** means any natural or legal person¹ established within a country or jurisdiction who has received a written mandate from the manufacturer to act on his behalf for specified tasks with regard to the latter's obligations under that country or jurisdiction's legislation.

2.2 **Manufacturer (or legal manufacturer or known as 'product owner' in some countries)** means any natural or legal person¹ with responsibility for design and/or manufacturer of a medical device with the intention of making the medical device available for use, under his name; whether or not such a medical device is designed and/or manufactured by that person himself or on his behalf by another person(s).

3. Decision Process

Any event which meets the three basic reporting criteria listed in Sections 3.1 through 3.3 below is considered as an AE and should be reported to the relevant RA.

Reporting may be exempted if any one of the exclusion rules listed in Section 4 is applicable.

¹ The term 'person' includes legal entities such as a corporation, a partnership or an association.

- However those AEs involving particular issues of public health concern as determined by the relevant RA should be reported regardless of exemption criteria (see 3.1d).
- Similarly those AEs which are subject to an exemption become reported to the RA if a change in trend (usually an increase in frequency) or pattern is identified.

Specific rules apply to events involving use error can be found in Section 4.

3.1 An event has occurred

The manufacturer becomes aware of information regarding an event which has occurred with its device. This also includes situations where testing performed on the device, examination of the information supplied with the device or scientific information indicates some factor that could lead or has lead to an event.

Typical events are:

(a) A malfunction or deterioration in the characteristics or performance

A malfunction or deterioration should be understood as a failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.

The intended purpose means the use for which the device is intended according to the data supplied by the manufacturer on the labeling, in the instructions and/or in promotional materials.

(b) An inadequate design or manufacture

This would include cases where the design or manufacturing of a device is found deficient.

(c) An inaccuracy in the labeling, instructions for use and/or promotional materials

Inaccuracies include omissions and deficiencies. Omissions do not include the absence of information that should generally be known by the intended users.

(d) A significant public health concern

This can include an event that is significant and unexpected nature such as that it becomes alarming as a potential public health hazard, e.g. human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD). These concerns may be identified by either the RA or the manufacturer.

(e) Other information becoming available

This can include results of testing performed by the manufacturer on its products, or by the use prior to being used on the patient, or by other parties. This can also include information from the literature or other scientific documentation.

3.2 The manufacturer's device is associated with the event

In assessing the link between the device and the event, the manufacturer should take into account:

- The opinion, based on available information, from a healthcare professional;
- Information concerning previous, similar events;
- Other information held by the manufacturer

This judgment may be difficult when there are multiple devices and drugs involved. In complex situations, it should be assumed that the device was associated with the event.

3.3 The event led to one of the following outcomes

3.3.1 Death of a patient, user or other person

3.3.2 Serious injury of patient, user or other person

Serious injury (also known as serious deterioration in state of health) is either:

- Life threatening illness or injury
- Permanent impairment of 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.

The interpretation of the term '*serious*' is not easy, and should be made in consultation with a medical practitioner when appropriate.

The term '*permanent*' means irreversible impairment or damage to a body structure or function, excluding minor impairment or damage.

Medical intervention is not in itself a serious injury. It is the reason that motivated the medical intervention that should be used to assess the reportability of an event

3.3.3 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.

Some jurisdictions refer to these events as near incidents.

All events do not lead to a death or serious injury. The non-occurrence of such a result might have been due to circumstances or to the timely intervention of health care personnel.

The event is considered “adverse” if in the case of reoccurrence, it could lead to death or serious injury.

This applies also if the examination of the device or a deficiency in the information supplied with the device, or any information associated with the device, indicates some factor which could lead to an event involving death or serious injury.

Examples of Reportable AEs can be found in Appendix 1.

4. Exemption Rules

Whenever any one of the following exemption rules is met, the AE does NOT need to be reported to RA by the manufacturer.

4.1 Deficiency of a new device found by the user prior to its use

Regardless of the existence of provisions in the instruction for use provided by the manufacture, deficiencies of devices that would normally be detected by the user and where no serious injury has occurred, do not need to be reported.

Examples of non reportable AEs

- User performs an inflation test prior to inserting the balloon catheter in the patient as required in the instructions for use accompanying the device. Malfunction on inflation is identified. Another balloon is used. Patient is not injured.
- Sterile single use device packaging is labeled with the caution “do not use if package is opened or damaged”. Open package seals are discovered prior to use, device is not used.
- Intravenous administration set tip protector has fallen off the set during distribution resulting in a non-sterile fluid pathway. The intravenous administration set was not used.

4.2 Adverse event caused by patient conditions

When the manufacturer has information that the root cause of the AE is due to patient condition, the event does not need to be reported. These conditions could be preexisting or occurring during device use.

To justify no report, the manufacturer should have information available to conclude that the device performed as intended and did not cause or contributed to death or serious injury. A person qualified to make a medical

judgment would accept the same conclusion.

Examples of non reportable AEs

- Orthopedic surgeon implants a hip joint and warns against sport-related use. Patient chooses to go water skiing and subsequently requires premature revision due to not following directions
- Early revision of an orthopedic implant due to loosening caused by the patient developing osteoporosis.
- A patient died after dialysis treatment. The patient had end-stage-renal disease and died of renal failure.

4.3 Service life of the medical device

When the only cause for the AE was that the device exceeded its service life as specified by the manufacturer and the failure mode is not unusual, the AE does not need to be reported.

The service life must be specified by the device manufacturer and included in the master record [technical file] or, where appropriate, the instructions for use (IFU). Service life is defined as: the time or usage that a device is intended to remain functional after it is manufactured, placed into use, and maintained as specified. Reporting assessment shall be based on the information in the master record or in IFU.

Reporting of AEs related to the reuse of devices labeled for single use (or labeled “for single use only”) is handled under Section 5: Use Error.

Examples of non reportable AEs

- Loss of sensing after a pacemaker has reached end of life. Elective replacement indicator has shown up in due time according to device specification. Surgical explanation of pacemaker required.
- A drill bit was used beyond end of specific life. It fractured during invasive operation. Operation time was prolonged due to the difficulty to retrieve the broken parts.

4.4 Protection against a fault functioned correctly

AEs which did not lead to serious injury or death, because a design feature protected against a fault becoming a hazard (in accordance with relevant standards or documented design inputs), do not need to be reported.

Examples of non reportable AEs

- An infusion pump stops, due to a malfunction, but gives an appropriate alarm (e.g. in compliance with relevant standards) and there was no injury to the patient.
- Microprocessor-controlled radiant warmers malfunction and provide an audible appropriate alarm (e.g. in compliance with relevant standards) and there was no injury to the patient.
- During radiation treatment, the automatic exposure control is engaged. Treatment stops. Although patient receives less than optimal does, patient is not exposed to excess radiation.

4.5 Remote likelihood of occurrence of death or serious injury

AEs which could lead, but have not yet led, to death or serious injury, but have a remote likelihood of causing death or serious injury, and which have been established and documented as acceptable after risk assessment do not need to be reported.

If an AE resulting in death or serious injury occurs, the AE is reportable and a reassessment of the risk is necessary. If reassessment determines risk remains remote, previous reports of near incidents of the same type do not need to be reported retrospectively. Decisions not to report subsequent failures of the same type must be documented. Note that change in trend of these non-serious outcomes must be reported as specified in Section 3.

Examples of non reportable AEs

- Manufacturer of pacemaker released on the market identified a software bug and determined that the likelihood of occurrence of a serious injury with a particular setting is remote. No patients experienced adverse health effects.
- Manufacturer of blood donor sets obtains repeated complaints of minor leaks of blood from these sets. No patient injury from blood loss or infections of staff has been reported. Chance of infection or blood loss has been reevaluated by manufacturer and deemed remote.

4.6 Expected and foreseeable side effects

Side effects which are clearly identified in the manufacturer's labeling or are clinically well known as being foreseeable and having a certain functional or numerical predictability when the device was used as intended need not be reported.

Some of these events are well known in the medical, scientific, or technology field; others may have been clearly identified during clinical investigation and labeled by the manufacturer.

Documentation, including risk assessment, for the particular side effect should be available in the device master record prior to the occurrence of AEs: manufacturer cannot conclude in the face of events that they are foreseeable unless there is prior supporting information.

Examples of non reportable AEs

- A patient receives a second-degree burn during the use in an emergency of an external defibrillator. Risk assessment documents that such a burn has been accepted in view of potential patient benefit and is warned in the instructions for use. The frequency of burns is occurring within range specified in the device master record.
- A patient has an undesirable tissue reaction (e.g. nickel allergy) previously known and documented in the device master record.
- Patient who has a mechanical heart valve developed endocarditis ten years after implantation and then died.
- Placement of central line catheter results in anxiety reaction and shortness of breath. Both reactions are known and labeled side effects.

4.7 Adverse events described in an advisory notice

AEs that occur after the manufacturer has issued an advisory notice need not to be reported individually if they are specified in the notice. Advisory notices include removals from the market, corrective actions, and product recalls. The manufacturer should provide a summary report, the content and frequency of which should be agreed with the relevant RA.

Examples of non reportable AEs

- Manufacturer issued an advisory notice and recall of coronary stent that migrated due to inadequate inflation of an attached balloon mechanism. Subsequent examples of stent migration were summarized in quarterly reports concerning the recall action and individual AEs did not have to be reported.

4.8 Reporting exemptions granted by Regulatory Authorities

Common and well-documented events may be exempted by RA from reporting or changed to periodic reporting upon requested by the manufacturer.

5. Use Error

The reportability of AEs involving use error is not globally harmonized. Reportability is subject to requirements of the relevant RA.

The term '*use error*' covers unintentional and intentional misuse.

Some jurisdictions may require reporting of AEs involving use error even though the events did not occur in their own jurisdiction.

RAs generally prefer to receive use error reports, especially those involving death or serious injury.

The reprocessing and re-use of device labeled by the manufacturer of single use ("single use only") is a common practice. However, since this is clearly outside the intended use of the device as stated by the manufacturer, reports of AEs potentially associated with reuse should be treated as reports of use error.

Similarly, AEs due to the use of any device for clinical situations not intended by the manufacturer (also called "off label" use) should be treated similar to use error.

6. References

- 6.1 Framework for AHWP Safety Alert Dissemination System (SADS) (AHWP/WG2/SADS/001)
- 6.2 Safety Alert Dissemination System: Safety Alert Dissemination Criteria, Procedures and Form (AHWP/WG2/SADS/002)
- 6.3 Definitions of the Terms Manufacturer, Authorised Representative, Distributor and Importer (GHTEF/SG1/N055:2009)
- 6.4 Medical Device Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices (GHTEF/SG2/N54R8:2006)

Appendix 1 - Examples of Reportable Adverse Events

- Loss of sensing after a pacemaker has reached end of life. Elective replacement indicator did not show up in due time, although it should have according to device specification.
- On an X-ray vascular system during patient examination, the C arm had uncontrolled motion. The patient was hit by the image intensifier and his nose was broken. The system was installed, maintained, and used according to manufacturer's instructions.
- It was reported that a monitor suspension system fell from the ceiling when the bolts holding the swivel joint broke off. Nobody was injured in the surgical theater at that time but a report is necessary (near incident). The system was installed, maintained, and used according to manufacturer's instructions.
- Sterile single use device packaging is labeled with the caution '*do not use if package is opened or damaged*'. The label is placed by incorrect design on inner packaging. Outer package is removed but device is not used during procedure. Device is stored with inner packaging only which does not offer a sufficient sterile barrier.
- A batch of out-of-specification blood glucose test strips is released by manufacturer. Patient uses strips according to instructions, but readings provide incorrect values leading to incorrect insulin dosage, resulting in hypoglycemic shock and hospitalization.
- Premature revision of an orthopedic implant due to loosening. No cause yet determined.
- An infusion pump stops, due to a malfunction, but fails to give an alarm. Patient receives under-infusion of needed fluids and requires extra days in hospital to correct.
- Manufacturer of a pacemaker released on the market identified a software bug. Initial risk assessment determined risk of serious injury as remote. Subsequent failure results in new risk assessment by manufacturer and the determination that the likelihood of occurrence of a serious injury is not

remote.

- Patients undergoing endometrial ablation of the uterus suffered burns to adjacent organs. Burns of adjacent organs due to thin uterine walls were an unanticipated side effect of ablation.
- Manufacturer does not change ablation device label and fails to warn of this side effect which may be produced when the device is working within specification.
- Healthcare professional reported that during implant of a heart valve, the sewing cuff is discovered to be defective. The valve was abandoned and a new valve was implanted and pumping time during surgery was extended.
- During the use of an external defibrillator on a patient, the defibrillator failed to deliver the programmed level of energy due to malfunction. Patient died.
- An intravenous set separates, the comatose patient's blood leaks onto the floor, the patient bleeds to death.
- Unprotected ECG cable plugged into the main electricity supply – patient died.
- Fatigue testing performed on a commercialized heart valve bioprosthesis demonstrates premature failure, which resulted in risk to public health.
- After delivery of an orthopedic implant, errors were discovered in heat treatment records leading to non-conforming material properties, which resulted in risk to public health.
- Testing of retained samples identified inadequate manufacturing process, which may lead to detachment of tip electrode of a pacemaker lead, which resulted in risk to public health.
- Manufacturer provides insufficient details on cleaning methods for reusable surgical instruments used in brain surgery, despite obvious risk of transmission of CJD.