TECHNICAL REPORT

ISO/TR 24971

First edition
2013-07-01

Medical devices — Guidance on the application of ISO 14971

Dispositifs médicaux — Directives relatives à l'ISO 14971

Reference number
ISO/TR 24971:2013(E)

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Published in Switzerland

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2. www.iso.org/directives

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ISO/TR 24971 was prepared jointly by Technical Committee ISO/TC 210, *Quality management and corresponding general aspects for medical devices*, and Technical Committee IEC/SC 62A, *Common aspects of electrical equipment used in medical practice*. The draft was circulated for voting to the national bodies of both ISO and IEC.

Introduction

Experience indicates that manufacturers have difficulty with practical implementation of some clauses of the risk management International Standard, ISO 14971:2007, *Medical devices — Application of risk management to medical devices*. This Technical Report provides guidance to assist in the development, implementation and maintenance of risk management for medical devices that aim to meet the requirements of ISO 14971. It provides guidance for specific aspects of ISO 14971 for a wide variety of medical devices. These medical devices include active, non-active, implantable, and non-implantable medical devices and *in vitro* diagnostic medical devices.

This Technical Report is not intended to be an overall guidance document on the implementation of ISO 14971 for organizations. It supplements the guidance contained in the informative annexes of ISO 14971 related to the following areas.

— Guidance on the role of international product safety and process standards in risk management

— Guidance on developing the policy for determining the criteria for risk acceptability

— Guidance on how the production and post-production feedback loop can work

— Guidance on the differentiation of information for safety as a risk control measure and disclosure of residual risk

— Guidance on the evaluation of overall residual risk

This Technical Report provides some approaches that an organization can use to implement and maintain some aspects of a risk management system that conforms to ISO 14971. Alternative approaches can be used if these satisfy the requirements of ISO 14971.

When judging the applicability of the guidance in this Technical Report, one should consider the nature of the medical device(s) to which it will apply, the risks associated with the use of these medical devices, and the applicable regulatory requirements.

Medical devices — Guidance on the application of ISO 14971

1 Scope

This Technical Report provides guidance in addressing specific areas of ISO 14971 when implementing risk management.

The guidance is intended to assist manufacturers and other users of the standard to:

— understand the role of international product safety and process standards in risk management;

— develop the policy for determining the criteria for risk acceptability;

— incorporate production and post-production feedback loop into risk management;

— differentiate between "information for safety" and "disclosure of residual risk"; and

— evaluate overall residual risk.

2 The role of international product safety and process standards in risk management

2.1 Overview

International product safety and process standards play a significant role in risk management as described by ISO 14971. In principle, these standards are developed using a type of risk management that can include identifying hazards and hazardous situations, estimating risks, evaluating risks, and specifying risk control measures. More information on a process for developing medical device standards using a type of risk management can be found in documents such as ISO/IEC Guide 51 and ISO/IEC Guide 63. International product safety and process standards are developed by experts in the field and represent the generally accepted state of the art (see D.4 of ISO 14971:2007).

These standards can have an important role in risk management. When performing risk management, the manufacturer first needs to consider the medical device being designed, its intended use and the hazards/hazardous situations related to it. Manufacturers can, if they choose, identify standard(s) that contain specific requirements that help manage the risks related to those hazards/hazardous situations.

For medical devices that satisfy the requirements and compliance criteria of these standards, the residual risks related to those hazards/hazardous situations can be considered acceptable unless there is objective evidence to the contrary. Some potential sources of objective evidence to the contrary can include reports of adverse events, product recalls and complaints. The requirements of International Standards, such as engineering or analytical processes, specific output limits, warning statements, or design specifications, can be considered risk control measures established by the standards writers that are intended to address the risks of specific hazardous situations that have been identified and evaluated as needing risk control.

In many cases, the standards writers have taken on and completed elements of risk management and provided manufacturers with answers in the form of design requirements and test methods for establishing conformity. When performing risk management activities, manufacturers can take advantage of the work of the standards writers and need not repeat the analyses leading to the requirements of the standard. International standards, therefore, provide valuable information on risk acceptability that has been validated during a worldwide evaluation process, including multiple rounds of review, comment, and voting.

2.2 Use of international product safety standards in risk management

An international product safety standard can establish requirements that, when implemented, result in acceptable risk for specific hazardous situations (e.g. safety limits). The manufacturer can apply these requirements in the following way when managing risk.

a) Where an international product safety standard specifies technical requirements addressing particular hazards or hazardous situations, together with specific acceptance criteria, compliance with those requirements is presumed to establish that the residual risks have been reduced to acceptable levels unless there is objective evidence to the contrary. For example, in IEC 60601-1, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*, leakage current must be controlled to achieve an acceptable level of risk. IEC 60601-1 provides leakage current limits that are considered to result in an acceptable level of risk when measured under the conditions stated in 8.7 of IEC 60601-1:2005. For this example, further risk management would not be necessary. The following steps need to be taken in this case.

   1) Implement 4.2 and 4.3 of ISO 14971:2007 to identify characteristics related to safety and identify hazards and hazardous situations associated with the device as completely as possible.

   2) Identify those hazards and hazardous situations relevant to the particular medical device that are exactly covered by the international product safety standard.

   3) For those identified hazards and hazardous situations exactly covered by the international product safety standard, the manufacturer may choose not to estimate (4.4 of ISO 14971:2007) or evaluate (Clause 5 of ISO 14971:2007) the risks so identified but rather rely on the requirements contained in the international standard to demonstrate the completion of risk estimation and risk evaluation.

   4) To the extent possible, the manufacturer should identify the design specifications that satisfy the requirements in the standard and serve as risk control measures (6.2 of ISO 14971:2007).

   NOTE For some international product safety standards, the possibility of identifying all the specific risk control measures is limited. One example is electromagnetic compatibility testing in IEC 60601–1-2, *Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance* — Collateral standard: *Electromagnetic compatibility — Requirements and tests*, for complex medical devices.

   5) Verification of the implementation of the risk control measures for these hazardous situations is obtained from the design documents. Verification of the effectiveness of the risk control measures is obtained from the tests and test results demonstrating that the device meets the relevant requirements of the international product safety standard.

   6) If the relevant requirements are met, the associated residual risk is considered acceptable.

b) Where an international product safety standard does not completely specify technical requirements and associated tests and test acceptance criteria, the situation is more complex. In some cases, the standard directs the manufacturer to perform specific tests related to known hazards or hazardous situations but does not provide specific test acceptance criteria (e.g. IEC 60601-2-16, *Medical electrical equipment — Part 2-16: Particular requirements for basic safety and essential performance of haemodialysis, haemodiafiltration and haemofiltration equipment*). In some other cases, the standard can simply direct the manufacturer to investigate specific hazards or hazardous situations in their risk analysis (e.g. 10.2 of IEC 60601-1:2005). The range of alternatives is too large to provide specific guidance on how to use such standards in the risk management process. Manufacturers are encouraged, however, to use the content of such standards in their risk management of the particular medical device.

c) For hazards or hazardous situations that are identified for the particular medical device but are not specifically addressed in any standard, the manufacturer needs to address those hazards or hazardous situations in the risk management process. The manufacturer is required to estimate and evaluate the risks and, if necessary, control these risks (see 4.4 and Clauses 5 and 6 of ISO 14971:2007).

See Figure 1 for a flowchart and an example outlining the use of international product safety standards.

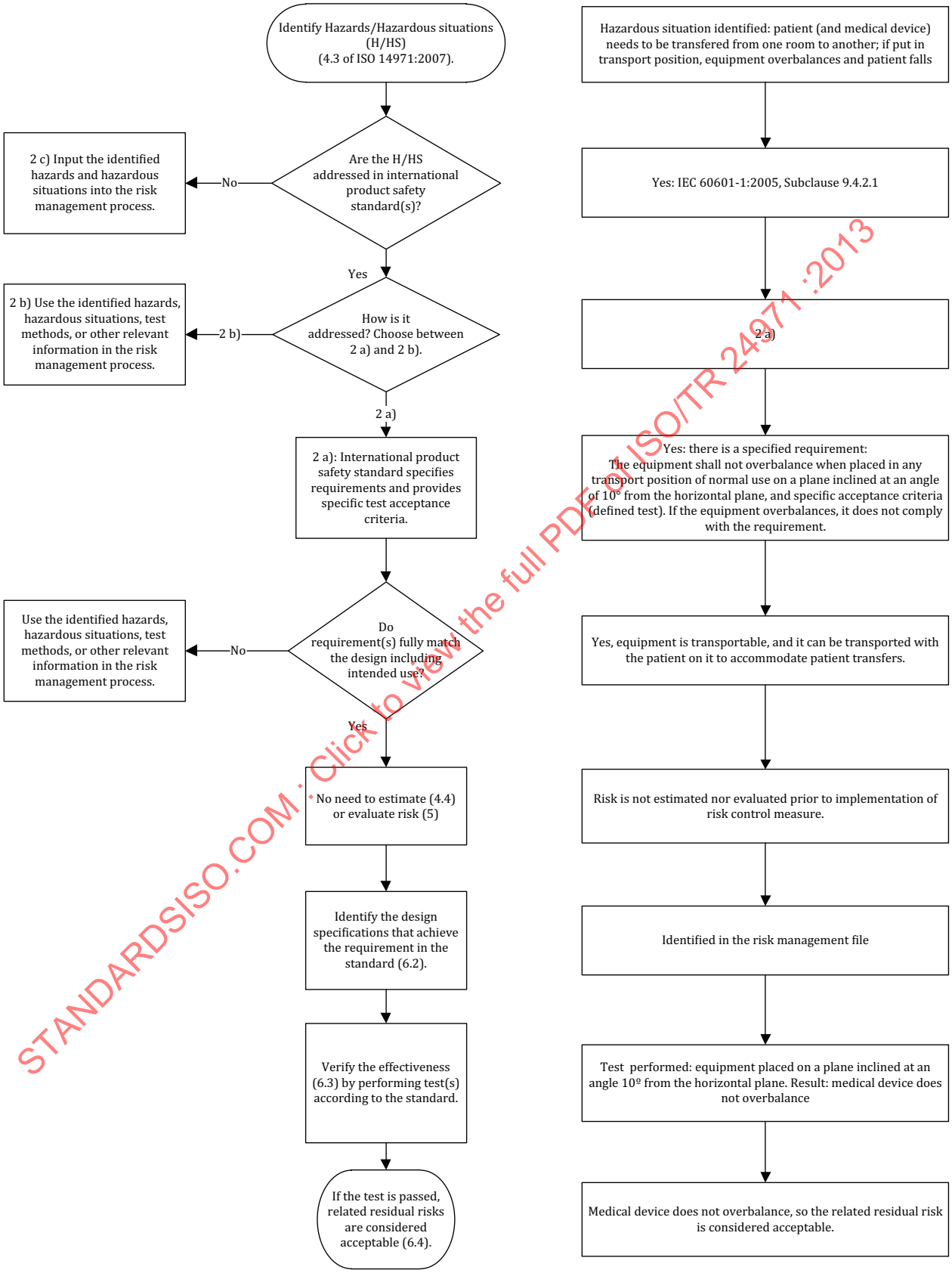

Figure 1 — Use of international product safety standards and example of such standard that specifies requirements and provides specific test acceptance criteria

2.3 International process standards and ISO 14971

International process standards, as shown in the examples below, can often be used in conjunction with ISO 14971. This is performed in one of two ways:

— The international process standard requires application of ISO 14971 as part of the implementation of the international process standard, e.g. IEC 62304 on software life cycle processes; or

— The international process standard is intended to be used in risk management, e.g. IEC 62366 on usability engineering and the ISO 10993 series on biological evaluation.

In either case, proper use of the international process standard requires attention to the interfaces between that standard and ISO 14971 in order to achieve acceptable levels of risk for the medical device. The two standards should work together such that inputs, outputs and their timing are optimized. Three examples are given below to demonstrate this ideal situation.

a) IEC 62304, *Medical device software — Software life cycle processes*

The relationship between IEC 62304 and ISO 14971 is well-described in the introduction to IEC 62304:

As a basic foundation it is assumed that MEDICAL DEVICE SOFTWARE is developed and maintained within a quality management system (see 4.1 of IEC 62304:2006) and a RISK MANAGEMENT process (see 4.2 of IEC 62304:2006). The RISK MANAGEMENT PROCESS is already very well addressed by the International Standard ISO 14971. Therefore IEC 62304 makes use of this advantage simply by a normative reference to ISO 14971. Some minor additional RISK MANAGEMENT requirements are needed for software, especially in the area of identification of contributing software factors related to HAZARDS. These requirements are summarized and captured in Clause 7 of IEC 62304:2006 as the software RISK MANAGEMENT PROCESS.

Whether software is a contributing factor to a HAZARD is determined during the HAZARD identification ACTIVITY of the RISK MANAGEMENT PROCESS. HAZARDS that could be indirectly caused by software (for example, by providing misleading information that could cause inappropriate treatment to be administered) need to be considered when determining whether software is a contributing factor. The decision to use software to control RISK is made during the RISK CONTROL ACTIVITY of the RISK MANAGEMENT PROCESS. The software RISK MANAGEMENT PROCESS required in this standard has to be embedded in the device RISK MANAGEMENT PROCESS according to ISO 14971.

IEC 62304 makes a normative reference to ISO 14971 and specifically requires:

— software development planning (5.1 of IEC 62304:2006) that is consistent with the risk management plan required by ISO 14971; and

— a software risk management process (Clause 7 of IEC 62304:2006) based upon ISO 14971.

b) IEC 62366, *Medical devices — Application of usability engineering to medical devices*

The flow diagram in Figure A.1 of IEC 62366:2007 demonstrates the relationship and interconnection of the two parallel and interconnecting processes. In addition to making a normative reference to ISO 14971, IEC 62366:2007 identifies three specific clauses where the usability engineering process can supplement and interact with risk management as described in ISO 14971:

— 5.3.1 of IEC 62366:2007 requires: “An identification of characteristics related to SAFETY (part of a RISK ANALYSIS) that focuses on USABILITY shall be performed according to ISO 14971:2007, 4.2.”

— 5.3.2 of IEC 62366:2007 requires: “The MANUFACTURER shall identify known or foreseeable HAZARDS (part of a RISK ANALYSIS) related to USABILITY according to ISO 14971:2007, 4.3.”

— 5.9 of IEC 62366:2007 on Usability Validation makes several references to activities that would be undertaken as part of risk management.

c) ISO 10993 (all parts), *Biological evaluation of medical devices*

The introduction to ISO 10993-1 states that ISO 10993-1 is intended to be a guidance document for the biological evaluation of medical devices within risk management, as part of the overall evaluation and development of each device.

Annex B of ISO 10993-1:2009 applies ISO 14971 to provide guidance on the risk management approach for identification of biological hazards associated with medical devices, estimation and evaluation of the risks, control of the risks, and monitoring the effectiveness of the risk control measures.

This approach combines the review and evaluation of existing data from all sources, with the selection and application of additional tests (where necessary), thus enabling a full evaluation to be made of the biological responses to each medical device, relevant to its safety in use.

ISO 10993-1:2009 aligns itself explicitly within risk management as described in ISO 14971.

The biological evaluation should be conducted in a manner similar to that used for other product risks, and should include:

— Risk analysis (What are the hazards and associated risks?)

— Risk evaluation (Are they acceptable?)

— Risk control (How will they be controlled?)

— Overall residual risk/benefit evaluation

Following the processes defined in ISO 14971, if the overall residual risk evaluation concludes from existing data that the identified risks are acceptable, no further risk control is needed. Otherwise, appropriate measures should be taken to further evaluate or mitigate the risks.

The output of this evaluation is a Biological Evaluation Report.

Application

— Conditions identified as hazards in ISO 10993-1 include:

  — Acute toxicity

  — Chronic toxicity

  — Irritation (skin, eye, mucosal surfaces)

  — Hypersensitivity

  — Genotoxicity

  — Carcinogenicity

— Do the proposed materials in the particular medical device cause such conditions?

  Methods that are used to determine if a material in the particular medical device can result in the conditions listed above include:

  — Chemical characterization and assessment

  — Literature review

  — Testing (*in vitro*/*in vivo*, non-clinical)

  — Field experience

— Are the exposure levels acceptable?

According to ISO 10993-1, expert assessors should determine if the available information/data are sufficient to determine if the overall residual risk associated with biological hazards is acceptable. This conclusion is documented in the Biological Evaluation Report, which becomes an element of the risk management file.

3 Developing the policy for determining the criteria for risk acceptability

According to 3.2 of ISO 14971:2007, top management is required to define and document the policy for determining the criteria for risk acceptability. This policy is intended to ensure that criteria:

a) are based upon applicable national or regional regulations;

b) are based upon relevant International Standards;

c) take into account available information such as the generally accepted state of the art and known stakeholder concerns.

NOTE Other relevant information can also be included.

The policy could cover the entire range of a manufacturer's medical devices or it can take different forms depending on whether the medical devices are similar to each other, or whether the differences between groups of medical devices are significant.

When developing or maintaining the policy the following should be taken into consideration:

— The applicable regulatory requirements in the regions where the medical device is to be marketed.

— The relevant International Standards for the particular medical device or an intended use of the medical device that can help identify principles for setting the criteria for risk acceptability (see 2.2).

— Information on the state of the art can be obtained from review of the literature and other information on similar medical devices the manufacturer has marketed, as well as those from competing companies.

— The validated and comprehensive concerns from the main stakeholders. Some potential sources of information on the patient and clinician perspective can include news media, social media, patient forums, as well as input from internal departments with expert knowledge of stakeholder concerns such as the clinical department.

The manufacturer should provide guidelines for developing the actual criteria for risk acceptability to be used in the risk management plan for the particular medical device being considered (see 3.4 of ISO 14971:2007).

The review of the suitability of the risk management process at planned intervals, as required by 3.2 of ISO 14971:2007, can demonstrate the appropriateness of previously used criteria for risk acceptability or lead to changes in the policy. Such changes can also lead to reviewing the appropriateness of previous risk acceptability decisions.

4 Production and post-production feedback loop

4.1 Overview

Typically, the initial risk assessment is based on experience with similar medical devices or applications on the market, or on assumptions when new medical devices are released to the market. Information received after market entry is valuable for confirming or correcting assumptions and estimates (both overestimates and underestimates), or identifying omissions made during the risk analysis and risk control phases. Clause 9 of ISO 14971:2007 requires that a feedback loop is established in the

manufacturer's organization to collect and evaluate such information for potential relevance to medical device safety (see Figure 2). The feedback loop should consist of the following steps:

— Observation and transmission

— Assessment

— Action

For the feedback loop to be effective, it is necessary that the responsibility for maintaining the risk management file is defined.

4.2 Observation and transmission

An observation provides information on, or experience with, a medical device that should be compared against the current risk management file. The observation can come from a number of different sources each of which can have a bearing on the safety of the medical device. For example:

— Information from manufacturing or research and development (R&D) activities within or contracted by the manufacturer;

— Information from installation, servicing and/or training personnel within or contracted by the manufacturer;

— Information from the use/users of the medical device (e.g. customer complaints, user surveys);

— Information from experience with competitor's medical devices through incident reports (for example, from databases provided by local regulatory agencies to collect and generate an overview of device experience);

— Clinical information (e.g. post-market clinical trials on the manufacturer's own medical devices or other published clinical literature on competitors' and similar medical devices);

— Information on new or amended standards and regulations;

— For combination products with a drug constituent part, consider also drug related information.

For information to be relevant to a manufacturer's medical device it need not be directly related to their own or a competitor's product. Information relating to similar medical devices with similar intended use or similar principles of operation can yield useful post-market information on the relevance of the risks of the manufacturer's medical device.

When designing a means of acquiring or detecting post-market information, manufacturers should be careful not to introduce bias into the process. The means of acquiring or asking for feedback should be neutral with regard to achieving negative or positive feedback. Furthermore, feedback should include events that have occurred (including corrective action) as well as events that could occur (including preventive action).

For any post-market information to be useful it has to be communicated to the persons or department within the organization that have the responsibility and authority to compare against the current risk management file and enact change where necessary.

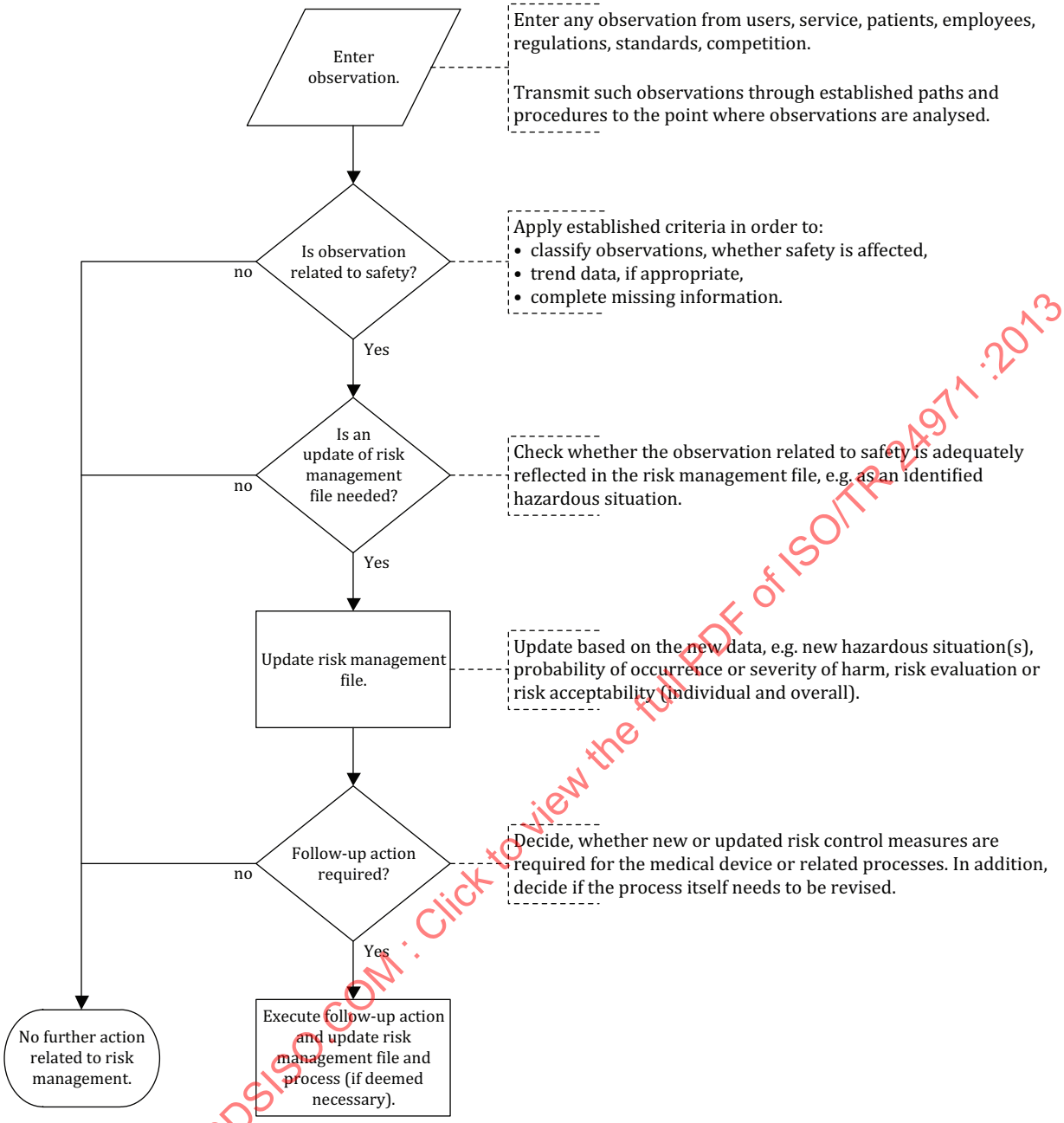

Figure 2 — Production and Post-Production Feedback Loop

The means of transmission of this information will depend on the source of the information. Some information will be pulled (initiated by the manufacturer) and some information will be pushed (initiated by sources like the customer, authorities, or patient). In either case, the organization should ensure that efficient communication channels are planned and established to allow for timely and accurate receipt of information. The rate at which the manufacturer pulls information from the various sources (including users) depends on the maturity of the medical device, its technology and the specific market.

Various departments within the manufacturer's organization can receive and handle different kinds of information, for example:

— customer complaints or adverse event reports

— service and installation reports

— new or revised regulations, standards or guidance

— production non-conformance reports

It is important that all relevant information from these groups is reviewed and distributed to that part of the manufacturer's organization with the responsibility and authority for the risk assessment (see 4.3).

Where the probability of events (e.g. component failures) is a relevant factor contributing to the evaluation of risk, statistical trending of such events should be considered.

4.3 Assessment

Any revision to the risk assessment based on new observations should be subject to the same level of control and review as the initial risk assessment. This would include any subsequent identification of risk control measures, if required. Such controls should include review and approval by individuals in the same functions or departments as those who signed off originally. Any new safety-related observations are to be assessed using the current criteria for risk acceptability.

New observations related to safety should be compared with the established risk management file to test the validity of any assumptions made. Several questions are suggested below:

a) Is the intended use still valid?

b) Is there an increasing trend of off-label use?

c) Are there occurrences of misuse which were not foreseen in the original risk management process?

d) Is there evidence of new hazards or hazardous situations not originally identified in the hazard identification process?

e) Are the severity and probability estimations for a particular risk still valid?

f) Is there any evidence that the criteria for risk acceptability should be adjusted?

g) Is the effectiveness of risk control measures proven adequate?

h) Does the risk/benefit analysis accurately represent the actual market experience?

If data suggest correction or adjustment of the current risk management file, the residual risks need to be evaluated based on the new data. In addition, the overall residual risk of the device should be reviewed.

4.4 Action

In a case where the residual risk based on new data is judged unacceptable and the risk/benefit analysis shows the benefit does not outweigh the risk, further risk control is required in two areas:

a) The medical devices currently installed and used in the market need to be corrected.

b) The design of the medical devices manufactured from that point in time or related processes need to be revised and implemented.

For medical devices currently installed and used in the market, the risk control measures can be different from those applied to devices in current production.

For medical devices currently installed and used in the market, immediate information (e.g. a customer letter) can be provided to users before risk control measures are developed and verified for effectiveness. Where modification or replacement of medical devices is necessary, the speed of action contributes to the effectiveness of the risk reduction.

NOTE This immediate information is known as an Advisory Notice in ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes* and as a Field Safety Notice in the European MEDDEV 2.12-1, *Guidelines on a Medical Devices Vigilance System*.

The result of assessing post-production information can serve as input to a review of the suitability of the risk management process at planned intervals to ensure continuing effectiveness of the risk management process (see of 3.2 in ISO 14971:2007).

5 Differentiation of information for safety and disclosure of residual risk

5.1 Difference between "information for safety" and "disclosure of residual risk"

The difference between "information for safety" and "disclosure of residual risk" is explained in Annex J of ISO 14971:2007. However, experience of manufacturers has shown that there is confusion between these two concepts. This guidance document is intended to clarify these differences.

Information for safety is considered to be a risk control measure. It is instructive, and ISO 14971 requires it to be verified for effectiveness. It can be provided in the form of warnings or (pre)cautions.

Residual risk is defined in ISO 14971:2007 as the risk remaining after all risk control measures (which can include information for safety) have been taken.

ISO 14971 requires that all information for safety be traceable in the risk management file. The decision of the manufacturer regarding disclosure of residual risk can be recorded in the risk management file.

5.2 Information for safety

Although information for safety is regarded as a risk control measure in 6.2 c) of ISO 14971:2007, it is the least preferred option after inherent safety by design and protective measures. This means that information for safety should be used after the manufacturer has determined that further risk reduction by making the medical device inherently safe and taking protective measures is not practicable. The text for information for safety can be prescribed by local regulations. The verification of the effectiveness of the information for safety can be performed by the usability engineering process (IEC 62366).

Information for safety needs to give the user clear instructions of what actions to take or to avoid, in order to avoid a hazardous situation or harm from occurring. This is usually provided in the form of warnings or (pre)cautions (see J.2 of ISO 14971:2007).

Information for safety can be given in the form of a warning label attached to medical devices or as a warning statement in the instructions for use. Some examples are given below.

— Warning: Do not step on surface.

— Warning: Do not remove cover, risk of electric shock.

— Warning: Use with caution. Serum samples containing more than 60 mg/dl haemoglobin will interfere with the test principle, thereby limiting the diagnostic result.

5.3 Disclosure of residual risk

Disclosure of residual risk is descriptive and can provide background on the residual risks involved in using the medical device. The aim is to disclose in the accompanying documents information to enable the user, and potentially the patient, to make an informed decision that weighs the residual risks against the benefits of using the medical device (see J.3 of ISO 14971:2007).

The manufacturer should consider means and media to disclose the residual risk. This information can be significant in the process of clinical decision making. Within the framework of the intended use, the operator or the user can decide in which clinical settings the medical device can be used to achieve a certain benefit for the patient. The disclosure of the residual risk can also be useful for the operator, the user or the hospital organization to prepare the patient for possible side effects or hazards that can occur during or after the use of the medical device. Note that operator, user and patient can be the same person, for example for medical devices used in the home healthcare environment.

