Technical Guidance Series (TGS)

Risk management for manufacturers of in vitro diagnostic medical devices

TGS–07

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The World Health Organization (WHO) Prequalification Programme is coordinated through the Department of Essential Medicines and Health Products. The aim of WHO prequalification of in vitro diagnostic medical devices (IVDs) is to promote and facilitate access to safe, appropriate and affordable IVDs of good quality in an equitable manner. Focus is placed on IVDs for priority diseases and their suitability for use in resource-limited settings. The WHO Prequalification Programme undertakes a comprehensive assessment of individual IVDs through a standardized procedure aligned with international best regulatory practice. In addition, the WHO Prequalification Programme undertakes post-qualification activities for IVDs to ensure their ongoing compliance with prequalification requirements.

Products that are prequalified by WHO are eligible for procurement by United Nations agencies. The products are then commonly purchased for use in low- and middle-income countries.

IVDs prequalified by WHO are expected to be accurate, reliable and able to perform as intended for the lifetime of the IVD under conditions likely to be experienced by a typical user in resource-limited settings. The countries where WHO-prequalified IVDs are procured often have minimal regulatory requirements. In addition, the use of IVDs in these countries presents specific challenges. For instance, IVDs are often used by health care workers who lack extensive training in laboratory techniques, in harsh environmental conditions, without extensive pre- and post-test quality assurance (QA) capacity, and for patients with a disease profile different from those encountered in high-income countries. Therefore, the requirements of the WHO Prequalification Programme may be different from the requirements of high-income countries, and/or of the regulatory authority in the country of manufacture.

The Technical Guidance Series was developed following a consultation, held on 10–13 March 2015 in Geneva, Switzerland, which was attended by experts from national regulatory authorities, national reference laboratories and WHO prequalification dossier reviewers and inspectors. The guidance series is a result of the efforts of this and other international working groups.

This guidance is intended for manufacturers interested in WHO prequalification of their IVD. It applies in principle to all IVDs that are eligible for WHO prequalification for use in WHO Member States. It should be read in conjunction with relevant international and national standards and guidance.

The Technical Guidance Series guidance documents are freely available on the WHO website.
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1 Abbreviations and definitions

1.1 Abbreviations

CAPA corrective and preventive action
CLSI Clinical and Laboratory Standards Institute
FTA fault tree analysis
FMEA failure mode and effects analysis
FRACAS failure reporting and corrective action system
IFU Instructions for Use
GHTF Global Harmonization Task Force
IMDRF International Medical Device Regulators Forum
ISO International Organization for Standardization
IVD in vitro diagnostic or in vitro diagnostic device
KPI key performance indicators
QA quality assurance
QC quality control
QMS quality management system
R&D research and development
RPN risk prioritization number
RDT rapid diagnostic test
SQA supplier quality agreements
TMV test method validation

1.2 Definitions

The definitions below related to risk management of in vitro diagnostic devices (IVDs) are transcribed from ISO 14971:2007 Medical devices – application of risk management to medical devices (1) and are generally used in this guidance. When a source other than ISO 14971 is used, the source is indicated.

1.2.1 Definitions related to risk management
1 **Harm:** Physical injury or damage to the health of people, or damage to property or the environment

2 **Hazard:** Potential source of harm

3 **Hazardous situation:** Circumstance in which people, property, or the environment are exposed to one or more hazard(s)

4 **Residual risk:** Risk remaining after risk control measures have been taken

5 **Risk:** Combination of the probability of occurrence of harm and the severity of that harm. *(Note: The definition of risk in (2) is broader and more generally applicable than this, and is used by preference in this guide.)*

6 **Risk analysis:** Systematic use of available information to identify hazards and to estimate the risk

7 **Risk assessment:** Overall process comprising a risk analysis and a risk evaluation

8 **Risk control:** Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

9 **Risk estimation:** Process used to assign values to the probability of occurrence of harm and the severity of that harm

10 **Risk evaluation:** Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

11 **Risk management:** Systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

12 **Risk management plan:** For the particular IVD being considered, the manufacturer shall establish and document a risk management plan in accordance with the risk management process

13 **Severity:** Measure of the possible consequences of a hazard

14 **Safety:** Freedom from unacceptable risk

15 **1.2.2 General definitions**

16 **The following definitions are used throughout this guide.**

17 **Design input:** The physical and performance requirements of an IVD that are used as a basis for IVD design.

18 *Source: (3), definition (f).*
Evidence: Information that can be proved true based on facts obtained through observation, measurement, test or other means.

Source: Modified from (4), definition 3.8.1.

Instructions for Use (IFU): Information supplied by the manufacturer to enable the safe and proper use of an IVD.

Note: Includes the directions supplied by the manufacturer for the use, maintenance, troubleshooting and disposal of an IVD, as well as warnings and precautions.

Source: (5), definition 3.30.

In the United States, the acronym IFU occasionally stands for “indications for use”, and the acronym IU stands for “intended use” or “indications for use”. The ISO definition and requirements (5) for IFU cover the intended use and the precise method of use.

Intended use: Use for which a product, process or service is intended according to the specifications, instructions and information provided by the manufacturer.

Source: (1), definition 2.5.

Note 1: The clinical use for which the procedure was designed.

Note 2: The concept includes definition of the measurand, the target condition and the clinical use of the measurement procedure, which may include screening, diagnosis, prognosis, and/or monitoring of patients. (these notes are from the Clinical and Laboratory Standards Institute (CLSI) website http://htd.clsi.org.)

WHO note: The concept includes the physical, economic and resource limitations in the environments of intended use.

In vitro diagnostic (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: (5) and definition 3.27.

IVD reagent: Chemical, biological or immunological components, solutions or preparations intended by the manufacturer to be used as an IVD.

Source: (5), definition 3.28.

This guide uses the terms IVD and IVD reagent interchangeably.
Life cycle: All phases in the life of a medical device, from the initial conception to final decommissioning and disposal.

Source: (1), definition 2.7.

Measurand: Quantity intended to be measured

NOTE 1 The specification of a measurand in laboratory medicine requires knowledge of the kind of quantity (e.g., mass concentration), a description of the matrix carrying the quantity (e.g., blood plasma), and the chemical entities involved (e.g., the analyte).

NOTE 2 The measurand can be a biological activity

Source: (5), definition 3.39

Performance claim: Specification of a performance characteristic of an IVD as documented in the information supplied by the manufacturer.

Note 1: This can be based upon prospective performance studies, available performance data or studies published in the scientific literature.

Source: (5), definition 3.51.

“Information supplied by the manufacturer” includes but is not limited to: statements in the IFU, in the dossier supplied to WHO and/or other regulatory authorities, in advertising or on the Internet.

Referred to simply as “claim” or “claimed” in this document.

Process: Set of interrelated or interacting activities which transforms inputs into outputs

Note 1: Inputs to a process are generally outputs of other processes.

Note 2: Processes in an organization are generally planned and carried out under controlled conditions to add value.

Source: (4) definition 3.4.1.

Risk: Effect of uncertainty on objectives.

Note 1: An effect is a deviation from the expected — positive and/or negative.

Note 2: Objectives can have different aspects (such as financial, health and safety, and environmental goals) and can apply at different levels (such as strategic, organization-wide, project, product and process).

Note 3: Risk is often characterized by reference to potential events and consequences, or a combination of these.

Note 4: Risk is often expressed in terms of a combination of the consequences of an event (including changes in circumstances) and the associated likelihood of occurrence.

Note 5: Uncertainty is the state, even partial, of deficiency of information related to understanding or knowledge of an event, its consequence, or likelihood.

Source: (2) definition 1.1 and (4) definition 3.7.9
**State of the art:** What is currently and generally accepted as good practice. Various methods can be used to determine “state of the art” for a particular medical device.

Examples are:

- standards used for the same or similar devices,
- best practices as used in other devices of the same or similar type,
- results of accepted scientific research.

State of the art does not necessarily mean the most technologically advanced solution.

*Source: (1) paragraph D.4.*

**Top management:** Person or group of people who direct(s) and control(s) a manufacturer at the highest level

*Source: (1) definition 2.26.*

## 2 Introduction

### 2.1 Standards, guidance and WHO prequalification assessment

Risk management is essential to the competent manufacture of a safe in vitro diagnostic medical device (IVD). Evidence of appropriate risk management within a quality management system must be provided in dossiers supplied to the World Health Organization (WHO) for prequalification assessment (6), including through formal dossier review and information from the dossier request during manufacturing site inspection (7).

If no dossier is submitted for formal dossier review, as in the case of the abridged WHO prequalification assessment, evidence of a risk management process will be reviewed during inspection of the manufacturing site and at the stage one inspection, if applicable.

This guidance is intended as an aid for manufacturers of IVDs in compiling a product dossier for submission to WHO and in preparation for the site inspection aspect of the WHO prequalification assessment. The guidance does not cover instrumentation, analysers nor software, except in a general way. It must be read in conjunction with the internationally accepted regulations, requirements and guidance documents.

The principal international standard for risk management of IVDs is ISO 14971:2007 *Medical devices – Application of risk management to medical devices (1)*, together with the harmonized European version, EN ISO 14971.
ISO 31000 (8) and its supporting standard, ISO 31010:2009 Risk management – Risk management techniques (9) and guide, ISO Guide 73:2009 Risk management – Vocabulary (2) are generic standards providing the framework for managing (analysing, evaluating, controlling and monitoring) all types of risk including, but not specifically for, those relevant to IVD design, manufacture and use. They are powerful adjuncts to ISO 14971 (1) when considering the complete life cycle of an IVD, including commercial, financial and manufacturing aspects. In addition, they provide essential information on the development and application of any aspect of risk management.

Other internationally recognized guidance on the techniques and tools for risk management is available from the CLSI (10, 25) and GHTF (12). The CLSI guide (11) is concerned, like ISO 14971 (1), with safety at the point of use, whereas CLSI EP23-A (10) covers many aspects of safety in clinical laboratories. The guidance from GHTF [12] is also primarily concerned with safety in use and considers all stages of the product life cycle from that viewpoint.

### 2.2 Key concepts

Four characteristics of successful risk management underlie the methods and practices:

- Risk management is specific for a process (e.g. development of a product, use of a product, design of labelling, installation of equipment, managing a change of use to a product, evaluation of a production procedure) and not generic. Although lists of factors to consider with respect to use of an IVD are available (13, 14), these factors need to be evaluated and appropriately extended depending on the intended use, the measurand, the environment of use and the specific features of the IVD involved.

- Risk management is a whole life cycle activity and is not retrospective. It begins with the conception of the IVD and ends only when the IVD is withdrawn from the market. Lessons learnt can be applied to subsequent IVDs. This means that risk management of an IVD is not a one-time process: it is iterative. The risk management documentation must be revisited and revised, within change control, as knowledge and circumstances alter, including as post-market information becomes available.
Note: For an IVD that was developed and marketed prior to the enforcement of risk management regulatory requirements, the development of a product specific risk management file might have to be retrospective. Updates and revisions, however, should be made in “real time”.

- Risk management is an important activity helping to produce market-leading, technically innovative products and in driving cost reduction.
- Risk management is a company-wide activity and is not restricted to a specific department.

2.3 Cautions

- Different groups of similarly qualified people assessing the same system, process or problem with the same risk management methods will produce different lists of hazards and will assign different priorities (section 4.1.3) to those that they find in common (15).
- The different tools used in risk management (section 4) produce different lists and priorities of hazards for the same subject (16).
- The validity of the weightings (criticality and risk prioritization number, section 4.1.2) calculated in FMEA is disputable (17, 18): because “the concept of multiplying ordinal scales to prioritize failures is mathematically flawed” (18).
- Risk management can be time-consuming (and hence expensive) and without top management support is unlikely to be useful, despite being a regulatory requirement and one that is valuable in practice.
- Risk management documentation must reflect the input from all departments (including the quality department) involved in the IVD development, manufacture and user environment of the organization.

Despite the cautions listed above, risk management, however practised, is a necessary, important and useful tool in the production of safe and innovative IVD. It is important to have the outcomes in mind, to think constructively, and not to become obsessed with the assessment processes and marginal quantitation. With appropriate training within the organization and skilled facilitation of risk management, groups of suitably experienced
people can pool their knowledge. They can then reason in a constructive, structured manner about ways to eliminate potential harm, solve current problems, produce novel solutions and optimize manufacturing and financial factors.

2.3.1 Issues observed during WHO prequalification assessment

Some deficiencies, only a few examples of which are outlined in Box 1, will result in noncompliance with the requirements of ISO 13485:2016 (13). Of greater concern is that these deficiencies indicate the possibility of unsuspected problems with the IVD resulting from poor risk management of the development and verification processes.

Box 1 Examples of issues identified during WHO prequalification assessment

- FMEA are submitted in the form of a tick-list related to the Essential Principles (13) with little analysis of the particular measurand, IVD format or use of the IVD.
- Risk analysis content is poorly written; sometimes it is not even possible to discern the IVD format or measurand in question.
- The risk management documentation has not been updated properly during the product life cycle; for example risk assessment for IVDs that have been marketed in high-resource settings has not been changed before entering into commerce in more challenging environments.
- Insufficient consideration has been given to the skills required of users and the reproducibility of the results obtained with the IVD in their hands, their physical environment and potentially interfering substances that may be present.

2.4 Risk management in a regulated environment

Risk management has long been an expectation in IVD design, manufacture and commercialization. ISO 13485:2016 requires “a risk based approach to the control of the appropriate processes needed for the quality management system”, clause 4.1.2 b. Compliance with ISO 13485:2016 and ISO 14971: 2007 satisfies the basic regulatory requirement for risk management of most authorities. However, the standards might not reflect the state of the art nor all of the scientific and business aspects of the IVD life
cycle. As noted previously, the IVD regulatory requirements are predominantly safety related but the organization will also want to manage business, manufacturing and environmental risks.

The primary responsibility for the preparation of the risk management plans for any IVD development project or subproject in its early phases is generally controlled by research and development department. As the project progresses, the department of manufacturing, and then customer services, normally take the lead roles. The QA department is usually responsible for ensuring that risk management is documented in the QMS of an IVD manufacturer. This includes preparing the policies (in association with, and with the approval of, top management), procedures (in association and agreement with multiple departments) and documenting allocated responsibilities. The QA department is involved with all risk management activities throughout the organization but not necessarily in a leading role.

3 Risk management process

The required risk management process from an IVD safety viewpoint is set out in ISO 14971 (1), and as a flow diagram in Annex B of that document. This information is summarized here in Figure 1. The general descriptions will be expanded with examples of risk management at various stages of the life cycle in later sections of this guide.
Risk management is a process that involves feedback as knowledge of the topic being managed increases, as is shown in the process flow diagram.

The process summarized in Figure 1 is concerned primarily with safety of an IVD, but this general process of risk management is applicable to any aspect, for example, financial, commercial, regulatory or manufacturing. Reference can be made to the ISO 31000 series (2, 8, 9) for substantial guidance on these processes. Further information is available in the WHO Prequalification mock dossiers (20–22).

### 3.1 Responsibilities

#### 3.1.1 Top management

1. Responsibility for establishing the criteria for acceptability of residual risk: this is a key responsibility that cannot be delegated, although developing the criteria should
be a team effort. The documented criteria with their justifications and verification must be recorded in the files associated with the IVD – the design control files or the risk management files. The risk management report for an IVD must be approved and signed by top management, in particular the statement of acceptability of the overall residual risk.

2. Review of the suitability and progression of the risk management process at planned intervals. This would normally be included in policies regarding routine reviews of the QMS and design progression (19). Organizing the review is commonly an activity prepared for top management under the control of the management representative (19).

3. Appropriate resources and suitably qualified personnel for risk management must be provided throughout the product life cycle. Sufficient numbers of competent personnel must be trained in risk management and have sufficient time and the physical resources needed to perform the tasks required of a risk management team. Without top management’s total support, risk management may be poorly performed, as the activities require significant resources (23).

3.1.2 Departments

It is important that all departments within the company are involved in all risk management planning and subsequent activities, except certain aspects that only affect a few departments. These exceptions would need to be documented in the overall quality policies and the justification for excluding some departments would be noted in the risk assessment. For example, a safety risk assessment of the chemicals for a manufacturing process might not require the involvement of the marketing and financial departments.

Everyone involved in the development and implementation of the risk management process must understand the objectives – i.e. they must have an understanding of the risk management plan, the available risk management tools and the methods of assigning the level of risk. High-level technical knowledge of each process being evaluated is not necessary for every individual on the team; however, there must be at least one person with such knowledge involved.
Specific training for risk management has proven invaluable in ensuring sufficiently knowledgeable individuals who can conduct the meetings, collect and present the information arising in a systematic way and write effective reports. They should also be able to apply, in a consistent manner, the organization’s methods for assignment of degree of probability, severity and detectability to the hazards that have been identified.

The extent of training needed will vary between those who prepare company policies and plans (high-level), those who lead risk management meetings, and those who attend risk management meetings to provide insight into specific processes. To meet the requirements of ISO 13485:2016 (19) on risk management, formal training is essential organization-wide and many training companies already exist to provide this, either in person or via the Internet.

Evidence of successful training in the principles and application of risk management must be readily available for assessment during an audit. This would include training records, interviews with relevant staff members and observation of the effectiveness of implementation of risk management within the organization.

**Example: Job description requirements for a senior risk manager**

*The risk manager will need to be able to:*

- Develop and maintain a strategic risk management policy, framework, annual plan and budget for risk management activities that will help achieve the objectives of the organization and meet stakeholder expectations.
- Manage communication about risk management activities throughout the organization including timely reporting to top management.
- Collate and analyse the results of risk assessments and contribute to managing the actions required.
- Ensure risk management activities meet current regulatory requirements, both in the country of manufacture and countries of distribution, including audit readiness.
- Manage risk management training requirements within the organization, attract and retain suitably qualified personnel.
- Maintain current knowledge of risk as applied to the IVDs of the organization or similar IVDs both nationally and internationally.
• Promote a proactive and performance-based risk aware culture within the organization.

3.2 Policies and planning

ISO 14971 (1) requires documentation showing that risk management activities are planned in detail. This standard lists activities that must be covered by a risk management policy and plan and Annex F gives a comprehensive guide to planning. Detailed guidance for preparing quality plans is available in ISO 10005:2005 (24), ISO 31000 (8) and ISO 31010 (9). Together these documents cover all aspects of policies and plans for risk management. CLSI QMS02 (11) provides guidance on the contents of - and the relationship between - policies, plans and procedures and is helpful in the preparation of clear documentation that allows good traceability.

There will usually be an overall plan for risk management of an IVD covering all phases of its life cycle and more specific plans for the management of the risks for each phase. Risk management policies must always contain definitions of the occasions in the life cycle of a product when risk management activities will take place. At a minimum these will be:

• when an IVD or one of its related processes is being designed, after the design inputs have been obtained.

• before and after design verification and validation studies and prior to launch of a new or modified product.

• before using an existing IVD in a different way, for example with new specimen types, new environments of use (such as when an IVD that has been used in a high-resource setting is to be used in a low resource setting, or one that has been used in major clinical laboratories is to be used at primary level testing sites), or new intended users (such as extending from professional use to self-testing).

• before and after any change to the manufacturing processes, whether as an improvement of any kind or in response to problems.

• before and after any field safety corrective actions – whether following complaints from users or for other reasons.
at regular, frequent, defined intervals during the commercial life of a product to ensure that no information has been overlooked.

The risk management policy must include methods for assigning degrees of severity to effects of potential failure modes and also to the categories of probability and detectability (see 4.1.2).

3.3 Training for risk management

Risk management is central to the development and maintenance of a quality system and at all stages of the life cycle of an IVD as outlined in ISO 13485 (19). Hence, a comprehensive knowledge of the philosophy and tools of risk identification and analysis must be available within an organization commercializing an IVD.

Responsibilities listed within a risk management policy would include preparing the risk management plans, organizing the meetings, preparing the reports, updating the risk analyses, preparing any change control documentation and ensuring timely completion of tasks identified as a result of the analyses. Responsibilities would also include post-commercialization activities such as searching sources (for example, the Internet and reviewed literature) for information that may affect the IVD risk management, integrating feedback (for example from customers and the manufacturing process) and checking continuing compliance with regulatory requirements.

3.4 Risk management file

The results of risk management activities must be collected in a risk management file, which can be managed in various ways. For example, the information could be held with the design control documentation, which might be an electronic system (possibly a database or custom software). However, the file format must allow ready access to all interconnected aspects of the risk management of each process, and to the relationship of that process to other processes, within the overall risk management plan for the IVD.

The risk management file will provide traceability. It will include such information as the risk analyses on the hazards identified and a record of the risk assessment and evaluation. It will also include information on risk controls (including verification of adequacy) and summarize the acceptability of residual risk in a risk management report. Top
management must sign the documentation of the acceptability of any overall residual risk.

The file contents might not be held in a single place. However, references to and locations of associated documentation must be included. A link to meeting minutes and to top management reviews and approvals must also be included. This documentation must be retrievable without delay for review by auditors.

Example: Table of contents of a risk management file. (The risk management file might not physically contain all items listed in the table of contents, but must include links or instructions on how to locate the information quickly.) Contents will be replicated for each of the risk evaluations at key points in the life cycle of the product, e.g. for design input, design verification, design validation, IFU validation, post-market surveillance.

Table of contents

- Description of the IVD including intended use; safety data sheet
- Description of risk management scope, timeline and tools to be used
- Design and development risk management documentation
- Risk management plan
- Hazard identification, analysis and evaluation (biological, physical and environmental)
- Residual risk acceptance or risk mitigation (criteria and outcome)
- Verification and validation of risk control measures
- Production risk documentation: risk assessment of each production process
- Post-production data analysis report (for example using data from manufacturing, customer feedback etc.)
- List of participants in risk management teams; minutes of meetings including attendees, action items etc.
- Risk management summary report including risk–benefit statement
- Sign-off by stakeholders and top management
3.4.1 Demonstrating regulatory compliance

“The manufacturer shall establish, document, and maintain throughout the life cycle an ongoing process for identifying hazards associated with a medical device, estimating and evaluating associated risks, controlling these risks and monitoring the effectiveness of controls and shall include:

– Risk analysis
– Risk evaluation
– Risk Control
– Production and post-production information” (1).

As previously mentioned, the basis for requirements can be found in ISO 13485 (19) and ISO 14971 (1). These standards offer the broad outline of the principles and practices that are required. In addition, the annexes provided, particularly in ISO 14971 (1), together with many other resources such as those in the reference list, are very useful to suitably trained and qualified personnel.

Within this context, the intent of the standards is used by WHO to assure compliance with internationally recognized best practice in the manufacture of IVDs and to meet the needs of WHO and its stakeholders. WHO’s technical guidance (including this guidance document), together with published procedures and mock dossiers available on the WHO website (http://www.who.int/diagnostics_laboratory/evaluations/en/) are intended to assist manufacturers in their understanding of this approach.

Throughout this document there are examples of frequently encountered occurrences of failure to comply with requirements set out in the two main standards used by WHO ISO 14971 (1) and ISO 13485 (19). These examples come from dossiers submitted to, and on-site inspections performed on behalf of, the WHO Prequalification Programme and are given here to assist manufacturers in avoiding similar deficiencies and nonconformities.

Examples: The main examples of inadequate risk management resulting in nonconformities include:
• Resourcing (and approval of outcomes) of risk management activities by top management is underestimated and hence insufficient to meet compliance expectations.

• The qualifications of personnel performing risk management activities are inadequate.

• Risk management activities are superficial in nature, generic, and do not consider all of the layers of complexity required in risk management as outlined in the standards.

• Risk management is not applied to all aspects of the product life cycle as it must be according to ISO 13485:2016 and according to best practice. It is rare to find risk management applied to manufacturing and business processes as would be expected to ensure product quality and continuity of supply.

• The risk management documentation submitted with the dossier is incomplete.

• Documentation, in terms of a risk management file, is scattered and not easily accessible: it is not retrievable within a reasonable time frame (within one hour) at on-site inspections.

• Traceability of risk management activities throughout the whole life cycle of the IVD is inadequate.

• Review and updating of the risk management assessment at timely intervals is not performed.

• The “worst-case” environment of the end user is not considered.

Comment 1: As with all submissions to WHO, accuracy of information and data (truthfulness) is considered to be an essential requirement.

Comment 2: Evidence of effectively implemented risk management across all aspects of the life cycle of an IVD presented to WHO for prequalification builds significant trust in the manufacturer’s ability to provide a high quality IVD.

4 Tools and methods

ISO 31010 (9) has a comprehensive list of risk assessment and problem-solving tools, their applicability and their strengths and weaknesses. Both ISO 31010 (9) and CLSI EP18-A2 (25) provide excellent guidance.
The techniques most commonly used in the IVD industry are:

- failure mode and effects analysis (FMEA)
- fault tree analysis (FTA)
- failure reporting and corrective action system (FRACAS)

When using these tools, it must be remembered that:

- FMEA deals with single failure modes
- FTA can lead to discovery of some effects caused by two or more failure modes occurring simultaneously
- FRACAS can be used to feed information into the other two tools about existing failure modes with known causes and effects

This interdependency explains why the tools are most effective when used together. In addition, usage, descriptions and techniques for the “seven basic tools” for problem solving (including those of risk management) can be found in most manuals about quality processes including that of the American Society for Quality (26).

4.1 FMEA

FMEA will be described in detail as it is the most commonly used basis for hazard discovery and quantification during the processes of IVD design, manufacture and use. However FMEA is not always the most appropriate basis for risk management. The techniques described in ISO 31010 (9) are of more general applicability because they are concerned with risk defined as “effect of uncertainty on objectives” (2 and 4), not simply with potential harm as in ISO 14971 (1). For example, management of the risks in preparation of the IFU is probably not efficiently based on an FMEA: the potential harms arising from the IVD and its use should have been assessed during the various design and development evaluations. Development of the IFU, especially in an established IVD manufacturing organization, is more likely to relate to provision of correct and complete information in a user accessible fashion and regulatory compliance than in identifying, quantifying and minimizing the effect of hazards as defined in (1). Similarly some aspects of performance evaluation and supplier management are best risk assessed using techniques from (9) other than FMEA (but probably not those involved with defining
criteria for incoming goods inspections) because the related hazards should have been evaluated during design and development of the IVD. Whatever the techniques of risk management, their use and outcome must be recorded for compliance with (19).

### 4.1.1 The start-up work

The following sections are written predominantly from an ISO 14971-compliant safety stance (1). However, the principles and comments are applicable to risk assessment for most processes in the IVD life cycle including R&D, manufacturing and post-market surveillance. These sections also apply to most business-related activities when read with reference to guidance in ISO 31010.

The first step in preparing an FMEA is to obtain a complete description of the process—the scope—with as much detail as practicable. Often a flowchart of the process can be prepared from the scope, giving a detailed overview of the activities in the process in the sequence in which they take place, as this makes the subsequent analysis easier to document.

A template for the FMEA should have been developed from the policy and planning for risk management in the QMS of the organization. Conventionally this is prepared as an electronic spreadsheet with a worksheet with headings as in Figure 2 (25).

<table>
<thead>
<tr>
<th>Item in scope: characteristic</th>
<th>Existing situation</th>
<th>After action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item in scope: characteristic</td>
<td>Failure mode</td>
<td>Effect of failure mode</td>
</tr>
<tr>
<td>Item in scope: characteristic</td>
<td>Potential cause of failure mode</td>
<td>Controls</td>
</tr>
<tr>
<td>Item in scope: characteristic</td>
<td>Detectability</td>
<td>Criticality</td>
</tr>
<tr>
<td>Item in scope: characteristic</td>
<td>Action to be taken</td>
<td>Action taken</td>
</tr>
<tr>
<td>Item in scope: characteristic</td>
<td>Occurrence</td>
<td>Criticality</td>
</tr>
</tbody>
</table>

**Figure 2 Example of an FMEA template**

There are examples of spreadsheets in the WHO HIV self-test sample dossier (20), and the two nucleic acid testing sample dossiers (21, 22). The spreadsheet must have a start-up
worksheet with details of QMS factors such as version control, participants in the various
meetings, signatures and dates. The organization’s risk grid (see section 4.1.4) is also
usually added to the spreadsheet.

Comment: There are many other ways of capturing hazard data. However, the FMEA
format seems to be the most frequently used and is easy to read and understand.

It is generally the task of the risk management leader to assemble the scope
documentation, draw up the flowchart of the process and from that to prepare the
spreadsheet using the template. The risk management leader then completes as much as
possible of the start-up information and also the first column (“Item in scope:
characteristics”) of the main worksheet.

With this preparation completed, a team of people from across the organization who
have diverse knowledge of the topic should be assembled to develop the risk assessment.
The team should include representatives from various levels of seniority and all should
have basic training in risk management and FMEA processes. They should be well
informed about the agenda of the meeting, having reviewed the scope document and the
flowsheet and considered independently the specific risk management needed.

A useful aid to simplify and hasten progress is to project the worksheet onto a screen and
complete it electronically as the meeting progresses. After the meeting the leader can
add to the worksheet from his or her notes, agree about follow-up work with other staff
and if necessary use it to report to senior management.

Risk management is iterative and spreadsheets will be reworked several times during the
lifetime of a process, whether that process is commercialization of an IVD or risk
management of a factory process. Controls will be added, new failure modes discovered,
changes in probabilities and detectability calculated, new characteristics added (for
eexample submission of an IVD to a new regulatory authority or addition of a new
intended use). Use of a spreadsheet helps in managing this activity, as extra rows and
worksheets can be added, all within a document change control system.
4.1.2 The FMEA process

The assessment group starts work by creating lists of ways that each item in the scope could fail (or become noncompliant or nonconforming). These are the failure modes and must be as comprehensive as possible. Hazards in normal use not caused by a failure mode of the IVD (although perhaps caused by a failure mode of the design), such as contamination of the user with specimen, must also be considered during the design and use FMEA processes.

For each failure mode the group must next generate a list of all the effects of that type of failure on the output of the process concerned. When compiling this list every aspect that might be affected should be taken into consideration, for example, manufacturability, safety of the user or the patient, continuity of supply, cost and so forth. These listings are

Figure 3 The FMEA process

- Prepare for the meeting
  - Input documents
    - Flow sheets
    - Worksheets
  - Circulate to attendees
- Identify failure modes
  - For each item in the scope and in logical order
- Identify the effects of the failure mode
- Determine severity
- Identify the potential causes of each failure mode
  - Use problem solving tools
  - Possibly several potential causes for each failure mode
  - Ensure the real (root) cause is identified
- Determine probability of occurrence of HARM from each cause
- Calculate criticality and risk priority number
- Risk evaluation and control measures
- Re-evaluate FMEA with new controls
  - New hazards?
  - Severity cannot be changed
the effects of the failure modes. The following sections give guidance on this for each major point in the life cycle of an IVD.

The next action, determining the severity of all the possible harms of each of the effects, presents difficulties. It is common practice to give each harm a score between 1 and 5 or between 1 and 10 (higher being more serious) but different groups will nearly always assign different degrees of severity to the same harm for the same process, sometimes markedly different (15, 17). One approach is to take the best opinions available from the members of the assessment group and calculate the median of the values. Another possibility is to obtain a consensus value through group discussion. (See reference (17) for apparently more rigorous methods but which still face the same difficulty.)

Some failure modes might have more than one effect. In that case it is possible that only the most serious effect needs to be considered further. However, in view of the difficulty of assigning severity, this could present problems. This is particularly likely if the range of severity values assigned to an effect is wide but the value finally chosen is low (relative to other effects from the same failure mode). However, failure modes with effects on a critical outcome of the process (for example safety, continuity of supply, user perceptions or cost in a manufacturing environment) are usually given high scores.

All the potential causes of each failure mode must next be listed (generally using routine problem solving tools, for example Ishikawa (fishbone) diagrams) and bearing in mind that there might be more than one potential cause for each failure mode. The potential causes are given an estimated probability of occurrence using the current state of the process and its existing controls if any. As with severity, the probability of occurrence can be debatable. It might be possible to obtain probabilities from similar processes, failures and causes, but it is more likely that a consensus view will be necessary. A procedure for estimating qualitative frequencies and probabilities from available data is presented in CLSI QMS11 (27, Appendix D) and a thorough approach is described in (28). This probability is known as $P_1$ (see Annex E of ISO 14971), it is the probability of the occurrence of the hazard. Risk, however, is defined in relationship to harm, and the existence of a hazard or hazardous situation does not always lead to harm – usually a second effect or event must occur to bring about the harm. The probability of this second
effect is known as P2. Thus the probability of harm being caused by the hazard is composed of the combined probability of the hazard and the second event, P1*P2, which is lower than the probability of either event alone. This overall probability of causing harm is given the score (from 1–5 or 1–10, higher being more probable) to be used in the occurrence column of the spreadsheet and in the various risk calculations. As discussed above assigning such probabilities and scores is subjective!

Examples:

1.) Consider an effect being a false-positive result, a harm of this is a misdiagnosed and maltreated patient. A recombinant protein might occasionally have an impurity, depending on the efficacy of its manufacture, that could be incorporated into an assay. The probability of the presence of the impurity is P1, the probability of the hazard. An individual tested in the assay might have antibodies that react with the impurity (the probability of this second event is P2) giving rise to a false-positive reaction, probability P1*P2, which is the probability of occurrence of the harm. In the presence of either the impurity or the individual with the antibody, but not both, no harm will occur. This is frequently the case in HIV and HCV testing, when the recombinant proteins purified from E. coli cultures are not subjected to stringent evaluation prior to use and some individuals have strong anti-E. coli reactivity.

2.) Consider an effect being a technician becoming infected as a result of using the IVD. A potential cause being exposure to patient body fluid because of a poorly designed sample entry port. The hazard is that the user might touch the specimen, the hazardous situation arises if this happens (probability P1), and with probability P2 the patient has an infection (not necessarily that being tested) that affects the technician. The probability of harm is then P1*P2 – coincidence of both hazard and second event.

3.) Two events are not always directly involved. Consider an IVD which has been subject to maltreatment during transport so that it no longer detects reactive specimens (the probability is P1, the hazard). If the IVD has a control line which becomes visible when an assay is performed but which only monitors flow, not function, and the presence of the line is said in the IFU to validate the assay: harm (wrong diagnosis and its consequences) will be caused with probability P1.
In IVD manufacturing organizations, *detectability (probability of detection)* of the failure mode is occasionally taken into consideration during an FMEA. As with severity and probability, opinions on detectability can differ; indeed whether detectability should be included in risk management at all is subject to debate (29). If the failure can be detected (for example by the user, or by the operator during manufacturing) the effect should not occur, but the process of detection itself should form part of the risk evaluation of the control mechanism. For example, could a visually impaired user notice that a control line was unusually weak? The probability of detection is given a score of 1–5 or 1–10. A score of 1 is assigned if the failure will always be detected (100%) and a score of 5 or 10 when there is no possibility of detection. Whichever methods of assigning severity, probability and detectability are used, it is important to validate them as thoroughly as possible and to re-evaluate the FMEA as knowledge increases.

Finally, the *risk priority number* (RPN: severity × occurrence × detectability) and the criticality (severity × occurrence) might be calculated for each effect of the failure modes (see Box 2).

### Box 2 Explanatory notes on probability × severity × detectability

- Probability (occurrence) is related to likelihood, occurrence or frequency of the HARM arising. A probability estimate can be quantitative (using data and statistics) or qualitative (based on experience and considered opinion). Each hazard and hazardous situation will give rise to a risk estimate.
- Severity measures the possible consequence of a hazard.
- Detectability (probability of detection) of the hazard or hazardous situation *before* it leads to harm and so reduces the likelihood of harm and reduces the estimated risk.

#### 4.1.3 Risk evaluation

Once the FMEA has been completed, the risks can be placed in order of criticality or priority (possibly with aid of Pareto diagrams) and also measured against the company risk grid. The risks that are unacceptable can be dealt with by introducing appropriate controls (see section 5 and later in this section) and subsequently reviewed by further
FMEA for newly introduced hazards. Decisions can then be made about how to proceed with risks that are unacceptable. Every measurement or action by QC or QA should be the outcome of, and traceable to and a risk evaluation.

For IVDs that are to be CE-marked under the EU directive on *In vitro diagnostic medical devices (30)*, risk must be reduced “as far as possible” through safe design and construction. This is usually interpreted as meaning that the cost of ameliorating a risk cannot be used as a factor in deciding acceptability. While CE marking is not a prerequisite for acceptance to the WHO Prequalification Programme, if an IVD is CE-marked, the dossier would be expected to prove compliance with this aspect. ISO 14791 (1) is more lenient in that risk must “as low as reasonably practicable”.

### 4.1.4 Risk grid

The most common form of risk evaluation is against a risk grid similar to that shown in Table 1, which uses a grading scheme with scores of 1–5. The risk grid is usually incorporated as a worksheet on the FMEA spreadsheet together with a table of actions similar to those shown in Table 2, which must be taken subsequent to the FMEA. The detailed action is added to the “action to be taken column” either after discussion at the FMEA meeting or by the risk management leader in consultation with technical staff.

<table>
<thead>
<tr>
<th>Probability of occurrence</th>
<th>Severity of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 Critical</td>
</tr>
<tr>
<td>5 Frequent</td>
<td>High</td>
</tr>
<tr>
<td>4 Probable</td>
<td>High</td>
</tr>
<tr>
<td>3 Occasional</td>
<td>High</td>
</tr>
<tr>
<td>2 Rare</td>
<td>High</td>
</tr>
<tr>
<td>1 Improbable</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Table 1 Risk Grid

---

4.1.4 Risk grid

The most common form of risk evaluation is against a risk grid similar to that shown in Table 1, which uses a grading scheme with scores of 1–5. The risk grid is usually incorporated as a worksheet on the FMEA spreadsheet together with a table of actions similar to those shown in Table 2, which must be taken subsequent to the FMEA. The detailed action is added to the “action to be taken column” either after discussion at the FMEA meeting or by the risk management leader in consultation with technical staff.

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<tbody>
<tr>
<td></td>
<td>5 Critical</td>
</tr>
<tr>
<td>5 Frequent</td>
<td>High</td>
</tr>
<tr>
<td>4 Probable</td>
<td>High</td>
</tr>
<tr>
<td>3 Occasional</td>
<td>High</td>
</tr>
<tr>
<td>2 Rare</td>
<td>High</td>
</tr>
<tr>
<td>1 Improbable</td>
<td>Medium</td>
</tr>
</tbody>
</table>
Table 2 Actions to be taken following the FMEA

<table>
<thead>
<tr>
<th>Outcome zone</th>
<th>Risk assessed</th>
<th>Action to be taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Harm A</td>
<td>Process must be redesigned, or, if that is not possible, a mode of control must be added. This must be agreed by top management.</td>
</tr>
<tr>
<td>Medium</td>
<td>Harm B</td>
<td>Process to be redesigned or a control added. This may need agreement by top management.</td>
</tr>
<tr>
<td>Low</td>
<td>Harm C</td>
<td>Control to be added.</td>
</tr>
</tbody>
</table>

How the grades for severity and probability are assigned and what action should be taken must be defined in the QMS policies and might vary from process to process. There is no regulatory standard and very little guidance on quantifying any of the factors, nor for determining the acceptability of overall risk for an IVD.

For safety aspects, ISO 14971:2007 (1) suggests that severity could be classified qualitatively using three grades as shown in Table 3 (1).

Table 3 Qualitative classification of severity using three grades

<table>
<thead>
<tr>
<th>Term</th>
<th>Description of the harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant</td>
<td>Death or loss of function or structure</td>
</tr>
<tr>
<td>Moderate</td>
<td>Reversible or minor injury</td>
</tr>
<tr>
<td>Negligible</td>
<td>Will not cause injury or will injure slightly</td>
</tr>
</tbody>
</table>

But more usually severity is classified in at least five grades as shown in Table 4.

Table 4 Qualitative classification of severity using five grades

<table>
<thead>
<tr>
<th>Severity</th>
<th>Description of the harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Critical</td>
<td>Life-threatening, loss of limb, threat to community</td>
</tr>
<tr>
<td>4 Major</td>
<td>Severe lasting effects, requiring medical action</td>
</tr>
<tr>
<td>3 Moderate</td>
<td>Short-term effects, requiring medical action</td>
</tr>
<tr>
<td>2 Minor</td>
<td>No lasting effects</td>
</tr>
<tr>
<td>1 Minimal</td>
<td>Slight or no effects to users or patients</td>
</tr>
</tbody>
</table>

For an IVD these harms might be caused by:

- Misdiagnosis.
- physical, chemical or microbiological failure mode of the device itself.
- a hazard present in the use of the IVD with no failure mode.
use of the device in an unintended fashion ("off-label use").

Annex D of ISO 14971 (1) provides guidance on estimation of risk.

No regulatory standards have been established for probability and detectability of risk for IVD. The usually accepted levels for probability are listed in Table 5.

### Table 5 Commonly used probability levels for risk assessment of IVDs

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Frequent</td>
<td>1:100</td>
</tr>
<tr>
<td>4</td>
<td>Probable</td>
<td>1:1 000</td>
</tr>
<tr>
<td>3</td>
<td>Occasional</td>
<td>1:10 000</td>
</tr>
<tr>
<td>2</td>
<td>Rare</td>
<td>1:100 000</td>
</tr>
<tr>
<td>1</td>
<td>Improbable</td>
<td>1:1 000 000</td>
</tr>
</tbody>
</table>

Whatever characteristics are selected for severity, occurrence of harm and detectability of the hazardous situation, the QMS must include a policy on how to choose and justify them, together with the justification of acceptability of overall residual risk (ISO 13485 (13)). Given the variability in outcome of assessing risk quantitatively (see the comments above and references in section 2.3) the policy must encourage the exercise of caution and be carefully and comprehensively written. Use of a qualitative risk grid and action table as described above avoids the need to calculate RPN or criticality scores and this in turn avoids much debate about calculating “exact” values and their interpretation.

### 5 Risk control options

Once risks have been quantified using the tools described in previous sections they must be controlled. ISO 14971 (1) prescribes the options for risk control and the order in which they must be applied:

- Safety by design comes first and foremost and is usually interpreted as meaning “inherently safe design and construction” (30). For this reason, risk management must start from the inception of an IVD (or any process) so that the design can be planned safely and controls do not need to be built in later on to overcome design flaws that should have been avoided. Experience shows that risk management at the design input stage can also lead to much greater user satisfaction, as ideas for novel and functional features often arise during the risk management meetings.
Protective measures in the IVD itself or in the manufacturing process are features that prevent a failure mode in the first place. They are not features such as run controls (31) that warn users that a failure has already occurred.

Example: A shield over the specimen addition port of a rapid diagnostic test to prevent contact with potentially infectious material.

Information for safety. Well-written and validated IFU provide control of risk, but this is the least effective method of control. It is not the same as a warning, which alerts users to the existence of risk but neither prevents nor ameliorates it.

Run controls might be viewed as providing information for safety but they are weak controls in that, if activated, indicate the failure of that test run.

Control measures must be evaluated to ensure they do not present new hazards. They must be verified and validated in the user environments.

Example: Many run controls for rapid diagnostic tests indicate successful flow of reagents only and do not confirm that the test would have detected a positive specimen. Such a run control might not indicate thermal inactivation of the IVD, and so give a false sense of security to a user. Limitations must be clearly stated.

6 Risk management – selected activities

6.1 Quality management system

As noted in section 2.4 ISO 13486:2016, unlike earlier versions of the standard, specifically states that the QMS must be developed using risk management principles. Quality management and risk management of all processes of the organization must be linked and have feedback interchange mechanisms between them. All steps in the risk management process must be performed in accordance with the organization’s quality manual. For example, document control will apply to risk management activities and include document identification, version control, traceability, review intervals, identification of responsible personnel, links to competence and training records of personnel, records of meetings and links to management review, among others. The risk management documentation – the risk management file – is managed within the
manufacturer’s QMS and is an essential component of the risk management documentation linking and feeding back to the quality manual

Input leading to changes in the quality manual and the QMS from risk management of activities within the system might include for example:

- potential lack of staff competence determined during particular risk management activities and any training needs documented.
- Overall risk to the organization from customer feedback mechanisms such as the CAPA system; problems found when using particular transportation suppliers or modes; lack of clarity in IFU and subsequent unintended uses; reviews of literature related to the manufacturer’s products, analytes, assay methods or failure to notify regulators and WHO about critical change to a product.
- Information from a manufacturing risk assessment to assess the need for a general change in documentation (e.g. styles, use of language, font size in policies, procedures) within the QMS that might be needed to minimize risk from lack of readability by non-technical personnel, sometimes through the use of photographs, diagrams or translation into the language in use on the manufacturing floor.
- Overall risk to the organization caused by poor suppliers found from particular failings in the supplier audit methods noticed during supply-risk analyses

6.2 Risk management and design control

Risk management is an integral part of design control. The two processes have the same goal from a manufacturer’s viewpoint: to produce a safe, efficacious, regulatory-compliant product with wide customer appeal, good profitability and continuity of supply.

A typical design and development flowchart with integral risk management is shown in Figure 4. This is a suggested process flow only but is typical of current practices. A risk management process is associated with each critical stage of the life cycle of the product, within the overall plan (see section 3.2). The risk management performed as the product is withdrawn from commerce (mainly user satisfaction and business oriented but also
summarizing the life cycle of the IVD) is not shown in Figure 4, but the design information obtained from this activity should be used in the development of any future IVD.
Design inputs
  User requirements
  Regulatory requirements
  Manufacturing requirements and capabilities
  Management expectations

"Customer" requirements document
  Design will be validated against this
  Design change control begins when this document is approved

Product specifications
  Numeric design requirements for R&D
  Product will be verified against this

R&D phase 1
  (under design change control)
  Format and instrumentation developed
  Processes developed and qualified. Manufacturing documentation started
  Guard bands for all process parameters defined and validated
  QA and QC parameters and materials defined, sourced and documented
  Calibrators and internal controls developed and metrologically traceable
  Beginning of stability work for in-process intermediates and final device
  IFU initiated

R&D phase 2
  Transitioning to factory
  Change control begins
  Instruments and material suppliers finalised and audited
  Instrumental PQ, OQ in the factory
  Pilot batches made, tested against putative QC
  Interfering substances evaluated, efficacy of microbiocides proven
  Process documentation finalised and approved
  All aspects of device and specimen stability using devices made to approved specifications
  IFU finalised and approved
  QA and QC specifications finalised and approved

R&D phase 3
  Design verification using material made in the factory to approved documentation
  (R&D evaluation of all aspects of product specification document
  e.g. performance, repeatability, reproducibility, lot to lot variability, all aspects of stability)

R&D phase 4
  Design validation using material made in the factory at scale to approved documentation
  (User evaluation of all aspects of product specification document and customer requirements document
  e.g. performance, repeatability, reproducibility, lot to lot variability, functionality of IFU, training manuals, software)
  Normally done in three user-labs with three independent lots of reagent

Manufacture
  CE marking declarations and inspections
  Full scale manufacture under change control
  On-market surveillance
  Review of scientific literature for independent clinical evaluations

Pre-commercial launch risk analyses
  Production of Declaration of acceptable residual overall risk

Pre-verification and validation risk analyses
  Final IFU risk analysis

User, patient, manufacturing risk analyses started, re-evaluated regularly

Design and development plan written
  including risk management plan

Design risk analysis

Continuous on-market monitoring and risk re-assessment

Figure 4 Design control and risk management
6.2.1 Design risk assessment

This is the first stage of risk management for the whole life cycle of the IVD. It begins as soon as the concept of the product is finalized, after the customer inputs and requirements have been obtained. “Customer” in this context is any entity that the potential product will be affected by or will affect. Customers will be both outside the organization, for example patients, users, distributors, purchasers and regulators and within the organization, for example finance department, patents managers, QA, manufacturing, R&D, sales, marketing and customer support. Design input from all of these sources will define the intended use and lead, in turn, to defining the design requirements of the proposed IVD.

Once the design requirements are available, the basic features of the proposed IVD will become apparent and the design risk management planning can begin. Normally the outline of the plan will be described in the QMS and policies, but the details will need to be defined. These include determining responsibilities overall and identifying the participants in the initial risk assessment meetings. Design risk management planning will consider everything that is known about the potential product, in line with and taking into account the Essential Principles (13, 14). This will be focused specifically on the proposed IVD and its uses and is not a generic assessment.

The initial design risk management meeting should address as a minimum the factors listed in Table 6.

Table 6 Factors related to the specific IVD to be considered in initial design risk management

<table>
<thead>
<tr>
<th>Factor</th>
<th>Example characteristics to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen</td>
<td>Method of obtaining specimen from patient, type, storage, transport, likely interfering substances and cross-reacting materials in that specimen type</td>
</tr>
<tr>
<td>Patient</td>
<td>Environment, age, sex, likely concurrent and similar illnesses, potential pharmaceutical treatments, vaccinations, potential drugs and other social factors</td>
</tr>
<tr>
<td>User</td>
<td>Environment (especially temperature, humidity, altitude, microbial flora), training, skill level, social factors (intolerance of some constituents)</td>
</tr>
</tbody>
</table>
### Factor Example characteristics to consider

**IVD**
- Known failure modes with a similar IVD using the same format (for example prozone effect, lack of or poor specimen/reagent flow, reversal of specimen/reagent flow, insufficient specimen addition, cross-contamination, failure to link result to patient, contamination with enzymes)

**Measurand**
- Known failure modes with all formats of IVD for the measurand (for example cross-reaction with other substances, vaccination status of patient, drug treatment interference, confusion with disease that has similar symptoms, specific problems in certain populations or age groups)

Many of these factors will interact with other factors. For example, the patient’s environment is likely to affect the possible concurrent illnesses and possible treatments unrelated to, but potentially affecting, the proposed IVD. This assessment requires considerable knowledge of the disease, technicalities of the measurand, the device formats available and state of the art for the proposal. The initial design risk management meetings must also take into account the internal requirements of the organization such as business and commercial factors, manufacturing factors including training and equipment and regulatory issues.

The control factors coming from the design risk assessment should lead to features of the design of the IVD, to requirements for many of its performance features, to supplier considerations and to in-built controls. Many risks should be removed by appropriate design of the format of the device, choice of reagents and method of addition of reagents. This process might lead to at least some features that will give the product commercial and possibly societal advantages and provide more than a “me too” device that would be perceived by potential purchasers as competing simply on cost.

As the design is developed, new ideas will be generated, new problems will arise and the risk assessment and controls will need to be re-evaluated. Once the main design risk management process, usually an FMEA supported by an FTA, has been completed just after design initiation, subsequent amendments are simple to document. Review of the design risk management together with the progress of the whole project at the regular design control review meetings (19) is usually sufficient.
As the various phases of the design progress, risk assessment will become necessary for manufacturing processes, the IFU, verification and validation work and pre-launch matters (see Figure 4 and subsequent sections in this guide). All of these assessments should be specified in the QMS policies and will provide information especially related to safety and QA matters and to the main design risk management process, although they are to some extent independent of it.

Any changes to the design, manufacturing process or IFU at any stage and for any reason (for example because input requirements cannot be met, supplier change, regulation change, CAPA, a new intended use, a new population of patients or users of the IVD, or a new environment of use) must trigger input to the design risk management files and a new assessment, even if only to report and justify that there is “no change” in risks.

### 6.3 Verification and validation

Design verification, in accordance with the manufacturer’s QMS, will confirm that the design output meets the design input requirements. Results of the design verification will usually be documented in, for example, a design history file. Verification occurs at multiple stages and includes testing, inspection and analysis of results. Verification will include hazards associated with handling and use, environmental effects, packaging integrity tests, biocompatibility testing of materials to be used, bio-burden testing and comparison with existing similar designs.

Design validation confirms that products conform to user needs and are suitable for their intended use. Design validation must include risk analysis. Consideration must be given to the robustness of the process. That is, expected variations of components, materials, manufacturing processes and the user and user’s environment must be taken into account. Validation must use routine production units tested under actual or simulated conditions.

Process validation confirms that a process produces a result or product that consistently meets requirements (and hence that the product consistently meets the correct specifications).
Comment: The absence of “re-validation” (ongoing verification) programmes for equipment and processes and inadequate qualifications of personnel performing such tasks have resulted in nonconformities being recorded during WHO PQ inspections.

6.4 Analytical and clinical performance studies (design validation)

The risk management methodology and tools already described apply to performance studies.

Existing WHO guidance and mock dossiers support a risk management approach to analytical performance studies to confirm intrinsic performance capabilities relative to design specifications and to clinical performance studies to confirm that the expected performance of the IVD is achieved in its intended use by intended users (19).

The WHO publication Principles of performance studies (Technical Guidance Series 3) refers to risk management in the context of analytical and performance studies throughout (33). In addition, the sample dossiers (20, 21, 22) have information that can be used when preparing for risk management of the processes.

The risk management plan, assessment, evaluation and control actions related to the studies must be documented and executed.

Note: “Clinical performance studies should ensure that the rights, safety, and well-being of subjects participating in a clinical performance study must be protected ... That is, each clinical performance study should generate new data, the benefits to health must outweigh risks to study participants and any risks must be minimized, and confidentiality must be respected” (33 Study rationale 4.6.1).

Furthermore, “The risk assessment conducted as part of product development should also include a component that accounts for any hazards posed (to user and/or patient) by the product during the course of the clinical study” (33 Study method 4.6.3).

As an example, assessment would need to include the following:

- a well-defined study protocol (to include risk assessment and plans, assess data collection, amendments and changes protocol).
- monitoring of study (monitoring plan that considers complexity of study design, clinical complexity of study population, geography of study location, experience of investigators, relative safety of the product and data collection methods).
- recruitment risk (selection of sites and patients, adequacy of medical records, informed consent risk).
- risk of deviation from the protocol (rules for cessation of study).
- data collection risk (quality of data and staff turnover).

### 6.5 Change controls

Changes made to, for example, any design, manufacturing processes or intended use of the product must be implemented and documented in line with the manufacturer’s QMS change control requirements. The QMS will have procedures for the identification, documentation, validation (or where appropriate verification), review and approval of changes before implementation. The reason for and justification of the change and any retraining required must also be documented.

Many changes will be related to the product design and so the risk management will likely be based on hazard evaluation using FMEA as the main tool, closely linked to the overall design risk management. Other changes, for example to labelling, would be expected to be linked to risk management documentation already established for both the design and the process concerned for that IVD. Risk evaluation of change must be initiated before any changes are made so that the planning for the change will take into consideration any risk to be minimized and ensure that appropriate verification or validation of the process and IVD is performed in a timely fashion. Any changes must be assessed and documented in relation not only to the product or process that is changed but also taking into account the possible repercussions across subsystems and the system as a whole because modification of one aspect of a process might well introduce hazards elsewhere.

The following paragraphs exemplify some of the change processes which are frequently found to be poorly managed during inspections by WHO PQ. The changes are often not managed in compliance with (19) and any risk evaluation is not documented. Aspects of particular concern are absence of the following: traceability, justification for change, verification and validation of the change and notification to the user of the change.
6.5.1 Equipment change

Criticality of the equipment or process will affect the level of risk management of change control. High-risk equipment or processes will require a higher level of qualification, change control, maintenance and monitoring.

In addition, the category of equipment change will affect the risk management activities.

- If it is an “identical” replacement, then assessment may be limited to demonstrating that the equipment is identical as defined in the manufacturer’s procedures, and documenting the process within the change control procedures, recording specifications and operating parameters to demonstrate they are identical. An abridged functional qualification may suffice.
- If the equipment has the same dimensions, uses the same methodology and has the same performance characteristics, then the activities described for identical replacement plus additional performance testing may suffice.
- A “true” change (neither of the above) would require a full risk management approach covering the whole life cycle of the equipment and the products concerned.

6.5.2 Change of supplier of a critical component of an IVD

Example: A recombinant protein is purchased from a new supplier.

- The processes and the intermediate products must be re-validated to ensure the new protein meets all of the requirements.
- The design must be re-validated as the change will potentially affect assay stability, sensitivity and specificity (ideally validation by users although this depends on the risk evaluation).
- The change must be notified to regulatory bodies as it is the change of a critical component.

6.5.3 Change of intended use

Example: Risk management of change of the types of anticoagulants for plasma used in the IVD: a change in the IFU is required.

- The design must be re-validated, at least partly, because:
– the change will affect the intention in the IFU.
– the stability of the new plasma type must be documented.
– performance claims must be maintained.

• The change may need to be notified, certainly if plasma types are restricted and perhaps if increased.

6.6 The IFU and other labelling

Risk management for some processes such as the design, safety in use and development of most of the manufacturing and QA procedures for an IVD can be based efficiently on an FMEA and associated tools for quality management and improvement. However, as noted previously (section 4) ISO 31010 (9) provides a comprehensive list of techniques which might be better than FMEA for managing risks for processes for which the basic hazards should be well understood and documented from the design and manufacturing assessments.

6.6.1 IFU

As the IFU is the main communication between user and manufacturer it is regarded with particular importance by WHO PQ. The contents of the IFU and their validation must be evidence based. The following must be read in conjunction with TGS 5 “Designing Instructions for use for in vitro diagnostic medical devices” (34) which presents WHO expectations for IFU, and is consistent with international regulation (5 and 35). For established manufacturing companies the use of checklists and properly facilitated brainstorming as described in (9) should be sufficient to control the risks to be managed during the IFU development process, perhaps with organization of the output using FMEA like spreadsheets but with different column headings. The main residual risks related to using, storing and disposing the IVD, its specimens and accessories should be available from the design and manufacturing groups, the risks from not satisfying the regulatory requirements laid out in the ISO 18113 (5) series from the company’s regulatory group and risks related to the supply and physics of the IFU from the logistics managers. Each of these departments plus the customer support group should be present at the IFU risk management meetings of which records must be maintained (19). A specific risk, relevant for WHO, is that the users’ language might not be included in the instructions for
use or the level of language might be not be appropriate for the level of training of the intended user. As a consequence, diagrammatic aids for use are provided frequently but this needs considerably thought to ensure they are appropriate for all intended users in all environments. The culture of the users must be evaluated in each intended setting to ensure the information is appropriate and accurate. Whatever “simple” user aids are made available it is critical that the risk management process ensures that the intended method and the depicted method are identical, changed in tandem as necessary, and validated relative to the clinical evaluation of the product.

Although the risks will be product dependent and risk management must make specific reference to the IVD concerned there are recognized, repeated deficiencies (and non-compliances with (5)) found in the IFU presented to WHO PQ. These deficiencies might be found from the IFU itself, in comparison of the claims in the IFU with the data in dossiers, or during on-site inspections. The following table, which can help with the risk management process by contributing to checklists, brings together the principle issues found (many of which should have been dealt with and made acceptable during IVD development). Reading through the table it will be apparent that risk management for the IFU needs to evaluate that all statements and numerical data required from (5, 3 and 35) are present and that there is evidence in the design history file for each. In addition it will be apparent that consideration must be given to users who might have different educational, language and technical skills from those with equivalent roles familiar to the manufacturer.

<table>
<thead>
<tr>
<th>Vulnerability</th>
<th>Description</th>
<th>Detail</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>disposal</td>
<td>method inappropriate or not defined</td>
<td>IVD, specimens, accessories</td>
</tr>
<tr>
<td></td>
<td>warnings</td>
<td>none or inadequate</td>
<td>harmful chemicals, biocides, thiomersal, azide</td>
</tr>
<tr>
<td></td>
<td>control specimens</td>
<td>inactivation of positive specimens not proven</td>
<td>SOP invalid, equipment inadequate</td>
</tr>
<tr>
<td>Intent</td>
<td>intended use not defined</td>
<td>no statement of purpose</td>
<td>diagnostic, screening, quantitation, prognostic</td>
</tr>
<tr>
<td>Vulnerability</td>
<td>Description</td>
<td>Detail</td>
<td>Examples</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>population to be tested</td>
<td></td>
<td>no restricting statement of what has been validated – or no exclusions for populations not tested not validated in claimed medical setting</td>
<td>paediatric, elderly, treated point of care; clinics, laboratories for screening, diagnosis</td>
</tr>
<tr>
<td>intended users</td>
<td></td>
<td>not stated or no supporting data</td>
<td>evaluated only by expert local laboratories or only by manufacturer</td>
</tr>
<tr>
<td>limitations</td>
<td></td>
<td>known limitations of method, reagents, patient type: some or all not stated</td>
<td>IgM not detected, strains of target organism not detected (malaria, cholera, HIV), treated patients</td>
</tr>
<tr>
<td>specimen types</td>
<td></td>
<td>plasma types not specified or not validated no statement of what has been validated – or no exclusion of types not tested</td>
<td></td>
</tr>
<tr>
<td>performance</td>
<td></td>
<td>not evaluated on appropriate populations</td>
<td>specificity not tested appropriately</td>
</tr>
<tr>
<td>precision</td>
<td></td>
<td>not evaluated by intended users</td>
<td>only by expert users or in manufacturers own facility and staff</td>
</tr>
<tr>
<td>stability</td>
<td></td>
<td>not proven rigorously partial or no stability data for specimens</td>
<td>based on QC panel not on the critical specimens</td>
</tr>
<tr>
<td>Vulnerability</td>
<td>Description</td>
<td>Detail</td>
<td>Examples</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>timings and volumes</td>
<td>not validated rigorously or not at all</td>
<td>Reading time not validated at beginning and end of assigned life</td>
<td></td>
</tr>
<tr>
<td>controls</td>
<td>not proven to warn of damaged IVD with lower performance</td>
<td>EIA controls set too high line controls fail to mirror state of active constituents</td>
<td></td>
</tr>
<tr>
<td>legibility poor</td>
<td>users and environments not considered</td>
<td>font too small type face unsuitable use of white space inappropriate ink smudges with time</td>
<td></td>
</tr>
<tr>
<td>intelligibility poor</td>
<td>no consideration of educational level of intended users in intended environment</td>
<td>complex language poor translations languages in text not appropriate for intended areas of use</td>
<td></td>
</tr>
<tr>
<td>symbols used</td>
<td>not in accord with (36) or absent</td>
<td>pictures inaccurate number of drops angle of addition different methods (times, volumes)</td>
<td></td>
</tr>
<tr>
<td>mismatches in instructions</td>
<td>IFU, “simple” method guide, training manuals differ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>product code</td>
<td>not present or not under version control</td>
<td>product changes not reflected in the product code</td>
<td></td>
</tr>
<tr>
<td>IFU content validation</td>
<td>not traceable through the change system</td>
<td>version of IFU provided not the same as, or untraceable to, that used in performance verification and validation</td>
<td></td>
</tr>
<tr>
<td>Regulation</td>
<td>ISO 18113 series</td>
<td>requirements not met</td>
<td>sections missing</td>
</tr>
<tr>
<td>Vulnerability</td>
<td>Description</td>
<td>Detail</td>
<td>Examples</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------------</td>
<td>-----------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>actual</td>
<td>manufacturer not clear</td>
<td>OEM, inadequate addresses,</td>
<td>contact details</td>
</tr>
<tr>
<td>supplier control</td>
<td></td>
<td>no audit of</td>
<td>printers specifications not appropriate or not checked</td>
</tr>
<tr>
<td>improvements</td>
<td></td>
<td>IFU not updated as</td>
<td>appropriate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAPA data not applied between IVD for different measurands</td>
</tr>
</tbody>
</table>

A spreadsheet related to a checklist like this could have further columns indicating what measures need to be taken and by whom.

6.6.2 Package labelling

Checklists and facilitated brainstorming (9) should be appropriate for managing risks related to package labelling for IVD because the hazards related to transport, storage and use of the IVD need to be well understood from its development processes. WHO PQ expects that package labelling will be suitable for users in environments that might be more extreme than in manufacturers' home countries and where transport operatives might not read English. It is particularly important that the labelling on the outer package for transport is clear, of a size providing easy legibility under all conditions and uses international symbols (36) appropriately and correctly. Restrictions related to handling and allowable temperatures must be very obviously displayed. Regulatory requirements for labelling are set out in the ISO 18113 (5) series and in (35). The following table lists some of the common, repeated failings of package labelling submitted to WHO PQ. It is intended as a resource for a manufacturer’s checklist but each IVD, in each pack size, must be risk managed individually by the manufacturer. Any statement on labelling (e.g. transport conditions, expiry dating) must be supported by evidence in the design history file of the IVD.
### Clarity

<table>
<thead>
<tr>
<th>Issue</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labels obscure</td>
<td>Font too small&lt;br&gt;Only English on shipping labels:&lt;br&gt;No symbols used&lt;br&gt;Symbols used incorrectly</td>
</tr>
<tr>
<td>Ink used not permanent</td>
<td>Ink poor quality and smears during transport or when handled in use&lt;br&gt;Ink fades in strong light</td>
</tr>
<tr>
<td>Labels detach from containers</td>
<td>Glue of poor quality: heat labile or water soluble</td>
</tr>
</tbody>
</table>

### Claims

<table>
<thead>
<tr>
<th>Issue</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability not valid</td>
<td>Evidence for stability only available for one bottle size although different kit sizes use different bottles&lt;br&gt;Shelf-life or transport studies performed using unlabelled materials</td>
</tr>
</tbody>
</table>

### Regulatory

<table>
<thead>
<tr>
<th>Issue</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not fully compliant with (36) and (5) or (35)</td>
<td>No product code&lt;br&gt;No lot number&lt;br&gt;No expiry date&lt;br&gt;No storage conditions&lt;br&gt;No single use symbol</td>
</tr>
<tr>
<td>Supplier audits inadequate</td>
<td></td>
</tr>
</tbody>
</table>

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### 6.7 Manufacturing

#### 6.7.1 Suppliers

Control of both suppliers and goods supplied have always been expectations according to ISO 13485; however ISO 13485:2016 now explicitly states that the criteria for their control and management must be proportionate to the risk associated with the medical device (19). Formal, documented risk management in relation to suppliers and goods (which should always include assessments of continuity of supply in addition to the assessment of quality of the goods supplied) is hence a regulatory requirement. The policies and procedures of the organization should specify how this risk management will be performed and documented, and these activities must form part of the design control of the IVD. The mechanisms for these risk management activities are as described previously, probably with an emphasis on ISO 31000 (8) and the methods it specifies.

Following from this assessment will be the documented rationale of the extent and frequency of supplier audits and the nature and methods of verifying the incoming goods against the specifications (The incoming goods QA specifications, developed to minimize effects of identified hazards.) As with all risk management, the process is iterative: once
controls have been developed, the system must be re-assessed to ensure that no new
hazards have been created. Then, once the system is operative, it must be continuously
reviewed to ensure that it is functional and does not need amendment.

In addition to the use of suppliers for basic materials for the manufacture of IVDs,
outsourcing of services and component manufacturing is increasingly common. Particular
hazards are associated with outsourcing of manufacturing processes of either subsystems
or complete systems. Good risk management can help maintain the balance between
quality and cost. This, together with the increased regulatory requirements of risk
management (19), make it essential to have a robust risk based approach for evaluating
new and existing suppliers.

The steps to be taken are as follows:

a. Use the already identified critical control points of the product noted.
b. Identify specifications that the supplier needs to meet. Document how these are
to be evaluated (for example initial product check, audit of supplier) and
monitored (for example incoming product QC data).
c. Prepare a qualification plan to:
   – assess the supplied product risk.
   – assess the supplier risk.
   – schedule audits.
   – ensure effective follow-up of nonconformities.
   – determine frequency of formal review of supplier.
d. Prepare supplier quality agreements (SQA). Note: SQA apply to both internal
suppliers (for example subsidiary providers under a single ownership) and to
external suppliers.

The SQA should indicate, for example:

- commitment by the supplier to quality.
- agreement on how quality will be monitored.
  - frequency and scope of audits defined; allow purchaser’s auditors
to review audit reports from other external auditors, especially
when related to QMS regulatory approvals.
• access to supplier QMS management review.
• change control notification obligation, for example timely notification of changes to product design, manufacturing equipment, critical personnel, QC changes, change in vendor of raw materials etc.
• the product acceptance criteria defined.
• for nonconforming product, a description of actions taken by the supplier within their QMS.
• complaints from other customers of the supplier
• field corrective actions – supplier’s involvement and responsibilities.
• environmental controls.
• distribution of product, for example shipping conditions (temperature, humidity, dust, vibration), packaging.

e. Use of tools.
   – use FMEA or other such tools.
   – develop supplier risk scorecards to rank suppliers based on past and current performance.
   – define key metrics and key performance indicators (KPIs)

f. Demonstrate compliance to auditors and/or regulators. Documentation and qualified personnel need to be available for interview to support the following:
   – qualification plan for each supplier (referred to in supplier audit plans).
   – approved supplier list that includes explanation of criticality of supplier, how this is determined and what impact this has on risk management.
   – supplier audits:
     ▪ that qualifications of auditors are suitable for the task.
     ▪ objective evidence that specific requirements for the manufacturer’s particular IVD have been met; compliance with relevant technical standards may also be required.
     ▪ well-documented audit findings (reports contain sufficient detail to illustrate thoroughness of audit).
supplier corrective action plan (CAP) or corrective action request (CAR) is documented and follow-up is completed in an appropriate time frame.

- triggers for action are defined – for example, critical nonconformities may initiate an immediate meeting with the supplier, an additional audit or cessation of supply. Justification for actions taken must be documented.

- Evidence that top management has been informed of findings (as required by the manufacturer’s QMS) and any decisions for action or no action were taken by qualified personnel.

- Traceability at all steps is essential. Documentation must be readily accessible for each supplier. For example, although a spreadsheet of KPIs of all suppliers may be available, and all audit reports kept together, all data related to a single supplier must be readily available in an assembled single supplier-specific file for review by an external auditor for regulatory and compliance purposes. Note that by assembling all notifications of nonconforming material and other reports from a single supplier, trends may become evident.

- The risk to the manufacturer’s QMS posed by a poorly performing supplier must be considered broadly for example the problem could occur with another supplier and could thus be prevented.

- Evidence of good communication between the supplier and manufacturer must be available. That is, it should be shown that the supplier is quick to respond to the manufacturer’s quality concerns, for example with a corrective action plan; cooperative when scheduling audits; and readily provides evidence of QMS compliance, for example, certification and audit reports from EU notified bodies or the US Food and Drug Administration.

Comment: The work of external auditors, although becoming more harmonized, varies in quality. Regulatory approvals such as certification are not valuable unless they are supported by the review of the actual audit reports on which they are based. The manufacturer’s auditor can thus assess
the auditors’ skills and the thoroughness of the external audit and hence the validity of regulatory approvals provided by a supplier.

6.7.2 Manufacturing processes

Each manufacturing process should be risk assessed to ensure the safety of manufacturing staff together with the capability of the process to produce the planned results leading to a consistent, safe product. These top level assessments should take into account the local health and safety regulations as well as the expectations of ISO 14971 (1). There should also be an assessment of:

- the materials used in relation to safety, to local environmental regulations and possibly to ISO 14001 (32).

- equipment (purchase, maintenance and cleaning), training needs as communicated in the manufacturing section of the input documentation, and cost.

- the written procedures to be followed by the operators (legibility under manufacturing conditions, intelligibility, completeness, and the presence of any warnings and precautions).

- any in-process controls necessary to ensure consistency within the process and the methods for those controls.

- potential effects of differences in the scale of the process (especially in stability and specificity of the final IVD), and the necessity for validation of different scales of manufacture.

- the necessity for validation or verification of the product of the process, and the methods for performing those activities.

The mechanism for process risk management is most often an FMEA led by the manufacturing department with input at least from R&D and QA. A flow diagram of the process being evaluated is essential as is detailed technical knowledge of the materials being used, the capability of the manufacturing department (before and after any controls introduced as a result of the assessment) and the reasons for the specifications for the product of the process. Figure 5 shows fragments of the risk management
documentation for a manufacturing process. It shows only a part related to the actual manufacturing steps, not all the aspects listed above. Note that the work instructions are written in a structured fashion that relates easily to a flowsheet and then to the FMEA. This makes the process easy to manage, explain and update as necessary.

It should be possible to trace each control action back to the hazard that it controls and forward to the validation of the control and the test methods involved. (See the Test Method Validation guide, TGS-4 in this series (37))

Fragment of a process instruction showing the hierarchy of actions for a single step

Fragment of the flowchart for the same process, showing several steps
6.7.3 Safe documentation

It is essential that each procedure is assessed for the safety of the process concerned. This should be a priority of management of manufacturing and needs emphasis. In particular, appropriate warnings (about hazards to operator safety) and cautions (about hazards to equipment) must be included and evaluated.

6.7.4 Process changes in manufacturing

Any change to a process must be managed within the change control system of the QMS but the policies concerning change must also make reference to re-assessing the effect of any changes on the established risk profile. This applies even to minor changes to a manufacturing process. Such changes must be managed, details recorded and the risk management documents updated accordingly, even if the outcome is that there is no change to the risks.

Example: Nonconformities noted during WHO inspections of production lines have included the following:

- A lack of staff well trained in risk management techniques and hence the inadequate application of such techniques to the production line. This has resulted in observing unsafe practices of personnel, for example not
wearing hearing protection and unsafe handling of infectious materials, as well as hazard to product quality, for example inappropriate handling of labile biological materials.

- Well-structured and sufficiently detailed batch manufacturing records (BMRs) play an important role in reducing manufacturing risk. Analysis of BMRs by suitably qualified personnel was poorly performed leading to lost opportunities for preventive action to maintain quality. Quality control data in BMRs (checking of the output being within specifications and trend analysis of the data) were not adequately reviewed and thus trends towards failure modes were not detected.

- Reporting on deviations (products not meeting specifications) and appropriate follow-up actions were often inadequate.

References


