

MEDICINES CONTROL COUNCIL



MEDICAL DEVICES and IVDs ESSENTIAL PRINCIPLES of SAFETY & PERFORMANCE

This guideline is intended to provide recommendations to applicants wishing to sell medical devices and IVDs in South Africa. It represents the Council's current thinking on the safety, quality and performance of medical devices and IVDs and the applicable essential principles relating to these products. It is not intended as an exclusive approach. The council reserves the right to request any additional information to establish the safety, quality and performance of a medical device or IVD in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The Council is committed to ensure that all medical devices and IVDs will be of the required quality, safety and performance. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar and the website.

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REGISTRAR OF MEDICINES and MEDICAL DEVICES

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The Essential Principles of Safety and Performance

INTRODUCTION

The Essential Principles of Safety and Performance of medical devices and IVDs set out the requirements relating to the safety and performance characteristics of medical devices and IVDs.

For a medical device to be supplied in South Africa, it must be demonstrated that the relevant Essential Principles have been met. ~~The regulatory framework provides flexibility for manufacturers and caters for technological advances and changes in the development of new medical devices by not dictating how a manufacturer must prove that they have met the Essential Principles.~~

It is the manufacturer's or distributor's responsibility to demonstrate compliance with the Essential Principles of Safety and Performance for their medical devices.

There are six general Essential Principles of Safety and Performance that apply to all medical devices. There are a further nine Essential Principles of Safety and Performance about design and construction that apply to devices on a case-by-case basis.

1 General Principles

- 1.1 Use of medical devices not to compromise health and safety
- 1.2 Design and construction of medical devices to conform to safety principles
- 1.3 Medical devices to be suitable for intended purpose
- 1.4 Long-term safety
- 1.5 Medical devices not to be adversely affected by transport or storage
- 1.6 Benefits of medical devices to outweigh any side effects

2 Principles about design and construction

- 2.1 Chemical, physical and biological properties
- 2.2 Infection and microbial contamination
- 2.3 Construction and environmental properties
- 2.4 Medical devices with a measuring function
- 2.5 Protection against radiation
- 2.6 Medical devices connected to or equipped with an energy source
- 2.7 Information to be provided with medical devices.
- 2.8 Clinical evidence
- 2.9 Principles applying to IVD medical devices only

3 Demonstrating compliance with the Essential Principles of Safety and Performance

A checklist that manufacturers may complete to demonstrate how they have complied with the Essential Principles of Safety and Performance for a particular medical device will be compiled.

Once a design specification that minimises the identified risks has been defined, the manufacturer will need to decide how to demonstrate that it meets the relevant Essential Principles of Safety and Performance. In many instances this will be achieved through implementation, maintenance and regular inspection of a quality management system by the device manufacturer.

Manufacturers can demonstrate that the Essential Principles of Safety and Performance have been met for a medical device in many ways. Some examples include:

- a documented and detailed risk analysis
- the results of testing of the medical device
- literature searches
- copies of the label, packaging and Instructions for Use to demonstrate that information requirements have been met
- expert opinion
- the design dossier, if applicable.

This information must be held and maintained by the manufacturer and must be made available to the Council upon request or at time of application, depending on the class of the medical device or IVD.

4 Standards

The most common way to demonstrate compliance with the Essential Principles of Safety and Performance is to meet a standard published by a South African or International Standards Agency, a Pharmacopoeia, or a similar standard. If the manufacturer chooses to use other voluntary standards they must provide evidence that the chosen standard is applicable to the manufacturer's quality system and that its application satisfies the requirements of the Regulations. The use of such standards is not mandatory.

To comply with Essential Principle 2, the design and construction of a medical device must conform with safety principles, having regard to the 'generally acknowledged state-of-the-art'. Published standards for medical devices are developed through a process of consensus, and therefore are accepted to reflect the generally acknowledged state-of-the-art. This is why standards need to be considered by a manufacturer, even though compliance with any given standard is not compulsory under the legislation.

To ensure that a medical device continues to conform to the state-of-the-art, it is important for the manufacturer to regularly update the risk analysis of the device to account for changes and advances in knowledge. The expectation is that manufacturers will consider the application of standards as part of maintaining their quality management systems.

An update or change to a standard should trigger the manufacturer to undertake a risk assessment of complying or not with the latest standard or version. The outcome of the risk assessment will be a decision to apply the new standard or to not.

4 Standards - continued

If the manufacturer decides to:

- update to the latest version of the standard, the Council would expect a plan to be put in place for how and when compliance with the standard will be achieved
- not update to the latest version of the standard, the Council would expect the manufacturer to hold justification for not complying.

When choosing which standards to apply to each device manufacturers should take into consideration the:

- intended purpose of the device
- environment in which it is likely to be used
- likely users of the device
- generally acknowledged state-of-the-art

Standards that are commonly used by medical device manufacturers are:

ISO 14971—Application of risk management to medical devices

ISO 13485—Quality management systems: Requirements for regulatory purposes

ISO 10993—Biological evaluation of medical devices

ISO 60601—Medical electrical equipment

ISO 10282—Single-use sterile rubber surgical gloves

If a standard is used, the manufacturer should include in the technical file for the medical device:

- identification of the standards used
- for each standard used, a statement:
 - that all requirements are met, except for non-applicable requirements, or deviations noted separately
 - of any requirements that are not applicable to the device
 - describing any deviations to the standard that were applied in relation to the device
 - information on any ways in which the standard may have been adapted for application to the particular device (for example, if alternative tests are allowed, which ones are performed in relation to that device).

Manufacturers of medical devices must ensure that their devices comply with all applicable rules and regulations that relate to the operation or supply of their device in South Africa, regardless of whether the requirements directly relate to medical device regulatory aspects or not. For example, a manufacturer of an electrically powered medical device that has radio communications functionality must comply with each of the appropriate electrical, spectrum, communications, customs, medical, etc. requirements that apply nationally.

5 Standards orders

The South African National Accreditation System (SANAS) is recognised by the South African Government as the single National Accreditation Body that gives formal recognition that Laboratories, Certification Bodies, Inspection Bodies, Proficiency Testing Scheme Providers and Good Laboratory Practice (GLP) test facilities are competent to carry out specific tasks in terms of the Accreditation for Conformity Assessment, Calibration and Good Laboratory Practice Act (Act 19 of 2006). SANAS's purpose is to instil confidence and peace of mind to companies and individuals through accreditation which is required for economic and social well-being for all.

Local and international standards can be used to demonstrate compliance with the Essential Principles of Safety and Performance or conformity assessment procedures.

Compliance with international harmonised standards, as published in the Official Journal of the European Communities and including the monographs of the European Pharmacopoeia, is not mandatory, but is the preferred way to establish compliance with Essential Principles of Safety and Performance. The standards cover topics such as:

- Clinical evidence
- Risk management
- Medical devices required to be sterile
- Quality management systems and quality assurance techniques
- Sterility
- Biological Safety and biocompatibility

6 Risk management

When developing a medical device, the Essential Principles of Safety and Performance relevant to the device must be considered. For example, Essential Principles 1, 3, 4 and 6 require that the medical device achieve its intended performance during normal conditions of use as specified by the manufacturer, and the known and foreseeable risks and any undesirable effects are minimised and acceptable when weighed against the benefits of the intended performance.

These principles in particular require that the device concept be first evaluated using a risk analysis that starts by considering any known patient- or user- related medical hazard (for example, blood loss, electric shock). *ISO 14971¹ can provide further guidance on this, but is not a mandatory standard that must be used.*

For each hazard, the analysis should list all potential causes and determine the probability and severity of their occurrence. Risk mitigation strategies should then be examined and tested. This type of analysis can and should be performed before beginning product development as it generates the safety requirements for the design specification.

¹ISO 14971 specifies a process for a manufacturer to identify the hazards associated with medical devices to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls. The requirements are applicable to all stages of the life-cycle of a medical device.

MEETING THE ESSENTIAL PRINCIPLES OF SAFETY AND PERFORMANCE—GENERAL PRINCIPLES**PRINCIPLE 1 - Use of medical devices not to compromise health and safety****1.1 Description**

A medical device is to be designed and produced in a way that ensures that:

- the device will not compromise the clinical condition or safety of a patient, or the safety and health of the user or any other person, when the device is used on a patient under the conditions and for the purposes for which the device was intended and, if applicable, by a user with appropriate technical knowledge, experience, education or training; and
- any risks associated with the use of the device are:
 - (a) acceptable risks when weighed against the intended benefit to the patient; and
 - (b) compatible with a high level of protection of health and safety.

1.2 How to demonstrate compliance

A fundamental concept in the design and production of a medical device is how the device is intended to be safely used and by whom. A manufacturer is required to undertake a well-reasoned and documented analysis of the foreseeable risks that could occur by using the device and compare these with a well-reasoned and documented analysis of the benefits that would be provided for the patient or user of the medical device. These analyses have to recognise that a patient or user's safety is paramount.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- a documented review of relevant published literature
- a documented review of manufacturer's experience with device
- assessing and documenting compliance of the device and its packaging with specifications and standards
- reviewing and documenting the labelling and Instructions for Use provided with the device
- reviewing and documenting final release procedures

PRINCIPLE 2 - Design and construction of medical devices to conform with safety principles**2.1 Description**

- (1) The solutions adopted by the manufacturer for the design and construction of a medical device must conform with safety principles, having regard to the generally acknowledged state of the art.

Principle 2 - continued

- (2) Without limiting subsection (1), in selecting appropriate solutions for the design and construction of a medical device so as to minimise any risks associated with the use of the device, the manufacturer must:
- (a) first, identify hazards and associated risks arising from the use of the device for its intended purpose, and foreseeable misuse of the device; and
 - (b) second, eliminate, or reduce, these risks as far as possible by adopting a policy of inherently safe design and construction; and
 - (c) third, if appropriate, ensure that adequate protection measures are taken, including alarms if necessary, in relation to any risks that cannot be eliminated; and
 - (d) fourth, inform users of any residual risks that may arise due to any shortcomings of the protection measures adopted.

2.2 How to demonstrate compliance

The design and construction processes for a medical device need to take account of any foreseeable risks or hazards that may exist, or could be created by the device when it is used as intended by the manufacturer. The design and construction of the device should, wherever possible, eliminate the identified risks or hazards. Where risks or hazards cannot be avoided methods must be established to alert and inform users of the medical device.

As for Essential Principle 1, a well-reasoned and documented risk analysis should be developed to demonstrate compliance with Essential Principle 2. It is also important to regularly update the risk analysis of the device to account for changes in knowledge or advances in the field to ensure that the design and construction of the medical device continues to conform to safety principles.

Compliance with the relevant South African and international standards are generally accepted as meeting subsection design, construction and testing. If the device does not comply with any relevant South African and/or international standards, justification should be provided to explain why the manufacturer has made this decision.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- a documented review of manufacturer's experience with device
- documented compliance and/or consideration of relevant product safety and performance standards

PRINCIPLE 3 - Medical devices to be suitable for intended purpose**3.1 Description**

A medical device must:

- perform in the way intended by the manufacturer; and
- be designed, produced and packaged in a way that ensures that it is suitable for one or more of the purposes mentioned in the definition of medical device in ~~section 1~~ in the Medicines and Related Substances Act, 1965 (Act 101 of 1965).

Principle 3 - continued

3.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- appropriate test protocols and results to demonstrate that the design, production and packaging of the device enables it to perform as intended
- where the manufacturer makes specific claims in relation to, for example, antimicrobial efficacy of the medical device, appropriate data should support the claims
- where the manufacturer is operating an appropriate and certified quality system, this Essential Principle will be partly addressed by that certification

PRINCIPLE 4 - Long-term safety**4.1 Description**

A medical device must be designed and produced in a way that ensures that if:

- the device is used within the period, indicated by the manufacturer, in which the device can be safely used; and
- the device is not subjected to stresses that are outside the stresses that can occur during normal conditions of use; and
- the device is regularly maintained and calibrated in accordance with the manufacturer's instructions;
- the characteristics and performances mentioned in clauses 1, 2 and 3 are not adversely affected.

4.2 How to demonstrate compliance

The manufacturer needs to have evidence that the design and production practices used for their medical device have taken into account the following to ensure that the device continues to comply with Essential Principles 1, 2, and 3:

- the expected lifetime of the device
- identified stresses experienced by the medical device during normal use
- any regular maintenance and calibration requirements

Any adverse effects of these stresses must be considered and included in a well-reasoned and documented risk assessment.

The lifetime of a device is considered to include the period prior to first use, and the period (or number of uses) expected or recommended by the manufacturer. Assessment of this can be done by bench testing, simulated shelf life testing and clinical evaluation.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- assessment of lifetime of the device including bench testing, simulated shelf life testing and clinical evaluation
- a documented review of complaint history
- clinical evidence

PRINCIPLE 5 - Medical devices not to be adversely affected by transport or storage**5.1 Description**

A medical device must be designed, produced and packed in a way that ensures that the characteristics and performance of the device when it is being used for its intended purpose will not be adversely affected during transport and storage that is carried out taking account of the instructions and information provided by the manufacturer.

5.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- documented evidence of testing to demonstrate that the design, production and packaging of the device ensure that the device characteristics and performance is not adversely effected during transport and storage
- a documented review of complaint history

PRINCIPLE 6 - Benefits of medical devices to outweigh any undesirable effects**6.1 Description**

The benefits to be gained from the use of a medical device for the performance intended by the manufacturer must outweigh any undesirable effects arising from its use.

6.2 How to demonstrate compliance

To comply with this Essential Principle it is necessary, as part of a well-reasoned risk analysis, to identify and document any undesirable effects from using the device and compare these with the benefits expected to be achieved through the use of the device.

In addition to the risk analysis, manufacturers should provide evidence that the outcomes or conclusions of the risk analysis have been acted on.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- a documented review of the manufacturer's experience with device

MEETING THE ESSENTIAL PRINCIPLES - PRINCIPLES ABOUT DESIGN AND CONSTRUCTION**PRINCIPLE 7 -Chemical, physical and biological properties****Principle 7.1 - Choice of materials****7.1.1 General**

In ensuring that the requirements of the General Principles are met in relation to a medical device, particular attention must be given to:

- the chemical and physical properties of the materials used in the device; and
- the compatibility between the materials used and biological tissues, cells, body fluids and specimens;
- having regard to the intended purpose of the device.

7.1.2 How to demonstrate compliance

A manufacturer must be able to demonstrate that the materials used in the medical device are appropriate, given the intended purpose of the device. For example, a well-reasoned risk analysis should consider toxicity, flammability and biocompatibility risks, and examine if particular labelling or instructions could mitigate any residual risks.

Historical data on materials used in similar devices should be reviewed and included in the documented analysis.

A biological evaluation, based on relevant standards, should be made. It may be possible to limit any testing by considering the results of previous and relevant tests on the same or similar materials used in the same or similar applications.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- documented analysis and review of historical data on materials used in similar devices
- conducting a biological evaluation based on relevant standards. ISO 10993² can provide further guidance on this, but is not a mandatory standard that must be used.

Principle 7.2 - Minimisation of risks associated with contaminants and residue**7.2.1 Description**

A medical device must be designed, produced and packed in a way that ensures that any risks associated with contaminants and residues that may affect a person who is involved in transporting, storing or using the device, or a patient, are minimised, having regard to the intended purpose of the device.

² ISO 10993 is a multi-part standard for the biological evaluation of medical devices. Each part covers a different aspect of the evaluation.

Principle 7.2 - continued

In minimising risks, particular consideration must be given to the likely duration and frequency of any tissue exposure associated with the transportation, storage or use of the device.

7.2.2 How to demonstrate compliance

The contaminants and residues could include solvents, process and sterilisation residues, mould release agents, particulate contamination and fluid spillage. It may be necessary to use particular labelling or instructions supplied with the device to reduce or mitigate some risks if they cannot be eliminated.

Particular attention must be paid to the tissues exposed and to the duration and frequency of exposure.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- if necessary, demonstrating that the labelling and Instructions for Use supplied with the device inform users of how to reduce or mitigate risks associated with contaminants and residues that cannot be eliminated.

Principle 7.3- Ability to be used safely with materials**7.3.1 Description**

A medical device must be designed and produced in a way that ensures that the device can be used safely with any material, substance or gas with which the device may come into contact during normal use or use in routine procedures.

If the device is intended to be used to administer medicine, it must be designed and produced in a way that ensures that the device:

- is compatible with the provisions and restrictions applying to the medicine to be administered; and
- allows the medicine to perform as intended.

7.3.2 How to demonstrate ability to be used safely with materials

The analysis should also consider any specified materials that may be required to clean, disinfect or sterilise the medical device, as well as the effects of these materials during these procedures.

It may be necessary to use particular labelling or Instructions for Use supplied with the device to reduce or mitigate some risks associated with the interactions of these materials, substances or gases with the device.

Warnings are required if it is foreseeable that an interaction between the device and incompatible materials could occur. These warnings should be included in the labelling or Instructions for Use included with the device.

If the device is intended to administer medicine, the design, production and packaging processes should take into account any provisions or restrictions for the medicine as well as ensuring that the medicine can perform as intended.

Principle 7.3 – continued

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- if necessary, demonstrating that the labelling and Instructions for Use supplied with the device informs users of how to reduce or mitigate risks associated with the use of the device with materials that cannot be eliminated
- labelling and Instructions for Use to include warnings relating to a foreseeable interaction between a device and an incompatible material
- if the device is to administer a medicine, demonstrating that the design, production and packaging of the device take into account any provisions or restrictions for the medicine.

Principle 7.4 - Verification of incorporated substance**7.4.1 Description**

If a medical device incorporates, or is intended to incorporate, as an integral part, a substance that, if used separately, might be considered to be a medicine that is intended to act on a patient in a way that is ancillary to the device:

- the safety and quality of the substance must be verified in accordance with the requirements for medicines; and
- the ancillary action of the substance must be verified having regard to the intended purpose of the device.

7.4.2 How to demonstrate compliance

A manufacturer of a medical device that contains a medicine as an integral part must show that the device component and the medicinal substance function together to achieve the intended purpose.

In addition, the manufacturer will need to provide evidence that the medicine meets all the necessary regulatory requirements as prescribed by the MCC to be supplied as a medicine.

For more information, see the General Guideline sections on medical devices incorporating a medicine and medical devices containing materials of animal, microbial or recombinant origin.

The work undertaken by the manufacturer could involve, but is not restricted to:

- evidence to demonstrate that the 'substance-device combination' works together as intended (for example, device specific tests to establish drug elution profile, coating integrity, device performance, degradation, particulate release)
- evidence of stability of the medicinal substance establishing that 'substance' incorporated in the device remains stable during manufacturing, transportation and storage (for example, sustained activity of regulated substance, evidence of tracking relevant characteristics during storage)
- evidence that the scheduled substance to be incorporated meets current relevant South African regulatory requirements. The device manufacturer should include evidence of quality of manufacture and safety of the scheduled substance.

Principle 7.5 - Minimisation of risks associated with leaching substances**7.5.1 Description**

A medical device must be designed and produced in a way that ensures that any risks associated with substances that may leach from the device are minimised.

7.5.2 How to demonstrate compliance

This Essential Principle deals specifically with leaching, which in this context means the removal of the soluble contents of a medical device by running water, another liquid or body fluids, leaving the insoluble portion behind and related to the use of the device. Examples of leachables are:

- additives
- sterilant residues
- process residues
- degradation products
- solvents
- plasticisers
- lubricants
- colouring agents
- fillers
- monomers

The design and production processes should take into account the outcomes or conclusions from a well-reasoned and documented risk analysis that has identified and analysed the significance of any foreseeable effects of a substance that could leach from a medical device, and the effects it could have on users of the device and other people who may come into contact with the device, during the intended use of the device as specified in the *Instructions for Use*.

Please note: This is different from Essential Requirement 7.5 in the European Essential Requirements, which deals specifically with leaking—the escape, entry, or passage of something through a breach or flaw.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis addressing issues such as:
 - Does the medical device come into contact with water or another liquid?
 - Does the medical device contain any substances capable of leaching?
 - Are any of the substances that are capable of leaching from the device hazardous to humans?
 - Is the concentration of the leached hazardous substances like to approach the limit for toxic effects?
- biological evaluation including testing. i.e. ISO 109933 can provide further guidance on this.

³ISO 10993 is a multi-part standard for the biological evaluation of medical devices. Each part covers a different aspect of the evaluation.

Principle 7.5 - continued

- *in vivo* toxicokinetic studies where relevant. i.e. ISO 109933 Part 16 and 17 can provide further guidance on this.
- *in vitro* testing of the medical device (e.g. assessing the kinds and levels of compounds leached from the medical device by physiologic media that contacts the device during normal use, such as blood).

Principle 7.6- Minimisation of risks associated with ingress or egress of substances**7.6.1 Description**

A medical device must be designed and produced in a way that ensures that any risks associated with unintentional ingress of substances into, or unintentional egress or leaking of substances out of, the device are minimised, having regard to the nature of the environment in which the device is intended to be used.

7.6.2 How to demonstrate minimisation of risks associated with ingress or egress of substances

Unintentional ingress means substances that are not intended to enter the device and unintentional egress means substances that are not intended to leave the device.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- a preclinical study evaluating the biological safety of the device
- biological evaluation including testing. ISO 10993 can provide further guidance on this, but is not a mandatory standard that must be used
- *in vitro* testing of the medical device (e.g. assessing the kinds and levels of compounds leached from the medical device by physiologic media that contacts the device during normal use, such as blood).

PRINCIPLE 8 - Infection and microbial contamination**Principle 8.1 - Minimisation of risk of infection and contamination****8.1.1 Description**

A medical device must be designed and produced in a way that ensures that the risk of infection to a patient, a user, or any other person, is eliminated or minimised.

The device must be designed in a way that:

- allows it to be easily handled; and
- if appropriate, minimises contamination of the device or specimen by the patient, user or other person by the device or specimen.

8.1.2 Minimisation of risk of infection and contamination

The work undertaken by the manufacturer could involve, but is not restricted to:

Principle 8.1 - continued

- a well-reasoned and documented risk analysis
- compliance with the Standards for Medical Devices Required to be Sterile
- sterilisation validation reports, bioburden data and evidence demonstrating the control of tissue of animal origin
- preservative efficacy reports for multi-dose, preserved medical devices (for example contact lens solutions) to demonstrate effectiveness of the preservative system, and to verify the expiry date and the open (in-use) shelf life assigned to the device
- verification of the integrity of the packaging system for medical devices packaged in a manner that minimises the risk of in-use microbial contamination, to verify the expiry date and the open (in-use) shelf life assigned to the device
- if the device is to be reprocessed, manufacturers must include instructions for the reprocessing in the Instructions for Use—for more information see Essential Principle 13.4: Instructions for use.

Principle 8.2 - Control of animal, microbial or recombinant tissues, tissue derivatives, cells and other substances**8.2.1 Description**

This section applies to a medical device that contains:

- (a) Tissues, tissue derivatives, cells or substances of animal origin that have been rendered non-viable; and
- (b) tissues, tissue derivatives, cells or substances of microbial or recombinant origin.

If the tissues, tissue derivatives, cells or substances originated from animals, the animals must have been subjected to appropriate veterinary controls and supervision, having regard to the intended use of the tissues, cells or substances.

If the medical device contains tissues, tissue derivatives, cells or substances of animal origin, a record must be kept of the country of origin of each animal from which the tissues, tissue derivatives, cells or substances originated.

The processing, preservation, testing and handling of tissues, tissue derivatives, cells or substances of animal, microbial or recombinant origin must be carried out in a way that ensures the highest standards of safety for a patient, the user of the device, and any other person.

In particular, the production process must implement validated methods of elimination, or inactivation, in relation to viruses and other transmissible agents.

8.2.1 Control of animal, microbial or recombinant tissues, tissue derivatives, cells and other substances

The work undertaken by the manufacturer could involve, but is not restricted to:

- evidence of the various controls, supervisory procedures, records and processing requirements

Principle 8.2 – continued

For animal sources i.e. ISO 22442⁴ can provide further guidance on this, but is not a mandatory standard that must be used.

- providing sufficient detail in the sourcing, handling and manufacturing process to demonstrate minimisation of the risk of transmitting Transmissible Spongiform Encephalopathies (TSEs)—refer to the MCC guidelines available in relation to minimising the risk of transmitting TSEs
- for microbial and recombinant sources, detailing the materials used in the manufacturing process including confirmation or not of those materials that are known to be sourced from both animal and non-animal sources.

Principle 8.3 - Medical devices to be supplied in a sterile state**8.3.1 Description**

Medical devices that are intended by the manufacturer to be supplied in a sterile state must be designed, produced and packed in a way that ensures that the device is sterile when it is supplied, and will remain sterile, if stored and transported in accordance with the directions of the manufacturer, until the protective packaging is opened or damaged.

The device must be produced and sterilised using an appropriate validated method.

The device must be produced in appropriately controlled conditions.

8.3.1 How to demonstrate medical devices supplied in a sterile state

The work undertaken by the manufacturer could involve, but is not restricted to:

- compliance with the appropriate clean room standards for the manufacturing premises in which the device is manufactured
- compliance with packaging standards and/or results of package strength and integrity testing, as appropriate for the device
- protocols for validation of the sterilisation cycle in accordance with the specific standards for the sterilisation method used and reports of testing to demonstrate compliance with the protocols and acceptable outcomes of the validation process.

Principle 8.4 - Medical devices to be supplied in a non-sterile state**8.4.1 Description**

A medical device that is intended by the manufacturer to be supplied in a non-sterile state must be packed in a way that ensures that the device maintains the level of cleanliness stipulated by the manufacturer.

If the device is intended to be sterilised before it is used, the device must be packed in a way that:

- (a) ensures that the risk of microbial contamination is minimised; and
- (b) is suitable, having regard to the method of sterilisation that the manufacturer indicates is to be used for the device.

The device must be produced in appropriately controlled conditions.

⁴ ISO 22442 is a multi-part standard for medical devices utilising animal tissues and their derivatives. Each part covers a different aspect of the evaluation.

8.4.1 How to demonstrate medical devices to be supplied in a non-sterile state

The work undertaken by the manufacturer could involve, but is not restricted to:

- compliance with the appropriate standards for air quality of the manufacturing premises in which the device is manufactured
- compliance with packaging standards and/or results of package strength and integrity testing, as appropriate for the device, to ensure that the initial cleanliness of the device prior to sterilisation is maintained
- results of studies demonstrating that the packaging can withstand the sterilisation process, and/or is permeable to the sterilising agent, and capable of maintaining sterility for a defined period after the sterilisation process.

Principle 8.5 - Distinction between medical devices supplied in sterile and non-sterile state**8.5.1 Description**

If a medical device is supplied in both a sterile state and a non-sterile state, the information provided with the device must clearly indicate whether the device is in a sterile state or a non-sterile state.

8.5.1 How to demonstrate distinction between medical devices supplied in a sterile and non-sterile state

The work undertaken by the manufacturer could involve, but is not restricted to:

- the labelling and Instructions for Use provided with the sterile and non-sterile device must clearly indicate in which state the device is supplied
- labelling should be in compliance with Essential Principle 13.

PRINCIPLE 9 - Construction and environmental properties**Principle 9.1 - Medical devices intended to be used in combination with other devices or equipment****9.1.1 General**

A medical device that is intended by the manufacturer to be used in combination with another medical device or other equipment (including a connection system) must be designed and produced in a way that ensures that:

- (a) the medical device, and any other device or equipment with which it is used, operate in a safe way; and
- (b) the intended performance of the device, and any other device or equipment with which it is used, is not impaired.

Any restrictions on use must be indicated on the label or in the instructions for use.

9.1.2 How to demonstrate medical devices intended to be used in combination with other medical equipment

The work undertaken by the manufacturer could involve, but is not restricted to:

Principle 9.1 - continued

- well-reasoned and documented risk analysis considering all the other devices meant to be used for the intended purpose of the device
- documenting how the device is designed for use with other medical devices and evidence of appropriate testing procedures that demonstrate that the combination of medical devices allows all medical devices to operate safely and without any impairment to the intended performance
- addressing the use of the device in combination with another medical device as part of the clinical evidence
- providing all the information for the use of the device in combination with another medical device as a part of the Instructions for Use
- for medical electrical systems, IEC 60601-1-1⁵ can provide further guidance, but is not a mandatory standard that must be used

Principle 9.2 - Minimisation of risks associated with use of medical devices**9.2.1 General**

A medical device must be designed and produced in a way that ensures that, as far as practicable, the following risks are removed or minimised:

- (a) the risk of injury arising from the physical features of the device;
- (b) any risks associated with reasonably foreseeable environmental conditions;
- (c) the risk of reciprocal interference involving other devices that are normally used in an investigation or treatment of the kind for which the device is intended to be used;
- (d) any risks arising if maintenance or calibration of the device is not possible;
- (e) any risks associated with the ageing of materials used in the device;
- (f) any risks associated with loss of accuracy of any measuring or control mechanism of the device;
- (g) the risk of fire or explosion occurring during normal use of the device, and in the event of a single fault condition, especially if the device is intended to be exposed to flammable substances or substances that can cause combustion;
- (h) the risks associated with disposal of any waste substances.

9.2.2 How to demonstrate minimisation of risks associated with the use of medical devices

The design and production processes should take account of the outcomes or conclusions a well-reasoned and documented risk analysis that has identified and analysed the significance of any of the listed foreseeable risks when the device is used.

For each risk, the analysis should list all potential causes and determine the probability and severity of their occurrence. Risk-mitigation strategies should then be examined and tested.

The most common way to demonstrate compliance with the Essential Principles is to meet a standard published by a South African or International Standards Agency, a Pharmacopoeia, or a similar standard.

⁵ IEC 60601-1-1 is a standard relating to medical electrical equipment and safety requirements for medical electrical systems.

Principle 9.2 - continued

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- documented compliance or consideration of relevant product safety and performance standards

PRINCIPLE 10 - Medical devices with a measuring function**10.1 Description**

A medical device that has a measuring function must be designed and produced in a way that ensures that the device provides accurate, precise and stable measurements within the limits indicated by the manufacturer and having regard to the intended purpose of the device.

The measurement, monitoring and display scale of the device must be designed and produced in accordance with ergonomic principles, having regard to the intended purpose of the device.

The measurements made by the device must be expressed:

- (a) in South African legal units of measurement; or
- (b) if the device measures a physical quantity for which no South African legal unit of measurement has been prescribed under the requirements of the Trade Metrology Act and Regulations, 1973 (Act 77 of 1973), and the Measuring Units and National Measuring Standards Act, 1973 (Act 76 Of 1973).

10.2 How to demonstrate compliance

Essential Principle 10 only applies to medical devices with a measuring function. Other kinds of measurement are not covered by Essential Principle 10. For examples and details please see Section ~~3 Classification of medical devices~~ in the General Information guideline.

The device must perform a measuring function that provides an absolute quantitative measurement (legal units or reference to a fixed reference) of a physiological/anatomical parameter (or energy/substance delivered/removed from the body) in which the accuracy is critical for the intended purpose of the device.

Manufacturers are expected to consider product specific standards, pharmacopoeial monographs, and applicable guidance documents in order to ensure the device is designed and produced in an appropriate way. For example, the manufacturer of a measuring cup or spoon might refer to the relevant pharmacopoeial monograph in order to determine the specification and accuracy of the device. Manufacturers may also refer to production process controls that ensure the measuring function is accurate and reliable. This will normally involve calibration against an appropriate reference standard.

Ergonomic principles concerned with how a user of the device interprets the outputs from the device and uses the device must be incorporated in the design and production processes for the device. The usability standards: i.e. *IEC 62366: Medical devices—Application of usability engineering to medical devices*, and *IEC 60601-1-6: Medical electrical equipment—Part 1-6: General requirements for basic safety and essential performance—Collateral standard: Usability* is directly relevant.

The measurement outputs must be in South African legal or otherwise approved units.

PRINCIPLE 11 -Protection against radiation**Principle 11.1 - Minimisation of exposure to radiation****11.1.1 General**

This Essential Principle is intended to cover all forms of radiation.

A medical device must be designed and produced in a way that ensures that the exposure of a patient, the user, or any other person, to radiation is minimised, having regard to the levels of radiation required to enable the device to perform its therapeutic and diagnostic functions and the intended purpose of the device.

11.1.2 How to demonstrate compliance

South African and international standards related to radiation exposure limits and other applicable legislation (for example, South African Radiation Protection and Nuclear Safety Agency (ARPANSA) and South African Communications and Media Authority (ACMA) requirements and state/territory radiation protection legislation) are also relevant to Essential Principle 11.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis
- evidence of appropriate radiation shielding
- additional information is also provided on active medical devices in the General Information guideline.

Principle 11.2 - Medical devices intended to emit radiation**11.2.1 General**

This applies to a medical device that is intended by the manufacturer to emit hazardous levels of visible or invisible radiation because the emission is necessary for a specific medical purpose, the benefit of which is considered to outweigh the risks inherent in the emission.

The device must be designed and produced in a way that ensures that the user can control the level of the emission.

The device must be designed and produced in a way that ensures the reproducibility and tolerance of relevant variable parameters.

If practicable, the device must be fitted with a visual indicator or an audible warning, or both, that operates if potentially hazardous levels of radiation are emitted.

11.2.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis

Principle 11.2 - continued

- demonstrating that appropriate control and indicator mechanisms have been incorporated into the device to ensure the operational consistency of variable parameters relevant to the emission of the radiation and the operation of the device
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis.

Principle 11.3 - Minimisation of exposure to unintended radiation**11.3.1 General**

A medical device must be designed and produced in a way that ensures that the exposure of a patient, the user, or any other person, to the emission of unintended, stray or scattered radiation is minimised.

11.3.1 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 11.4 - Operating instructions**11.4.1 General**

The operating instructions for a medical device that emits radiation must include detailed information about the following matters:

- (a) the nature of the radiation emitted;
- (b) the means by which patients and users can be protected from the radiation;
- (c) ways to avoid misusing the device;
- (d) ways to eliminate any risks inherent in the installation of the device

11.4.1 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- the *Instructions for Use* for the device must include particular information about the emitted radiation, appropriate protection measures, foreseeable misuse of the device and eliminating foreseeable risks arising from the installation of the device

Principle 11.5 - Medical devices intended to emit ionising radiation - additional requirements**11.5.1 General**

In addition to clauses 11.1 to 11.4, the device must be designed and produced in a way that ensures that, if practicable, the quantity, geometry and energy distribution (or quality) of radiation emitted can be controlled and varied, having regard to the intended purpose of the device.

If the device is intended to be used for diagnostic radiology, the device must be designed and produced in a way that ensures that, when used in relation to a patient for a purpose intended by the manufacturer:

- (a) the device achieves an appropriate image or output quality for that purpose; and
- (b) the exposure of the patient, or the user, to radiation is minimised.

If the device is intended to be used for therapeutic radiology, the device must be designed and produced in a way that ensures that the delivered dose of radiation, the type and energy of the radiation beam and, if appropriate, the energy distribution of the radiation beam can be reliably controlled and monitored.

11.5.1 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

PRINCIPLE 12 - Medical devices connected to or equipped with an energy source

South African and international standards related to electro medical safety, electromagnetic compatibility, medical device software and active implantable medical devices are also relevant to Essential Principle 12.

Standards that may provide further guidance, but are not mandatory standards that must be used include:

- IEC 60601: a family of standards relating to the safety and performance of medical electrical equipment
- IEC 62304: Medical device software—Software life cycle processes
- AS ISO 9918: Capnometers for use with humans—Requirements
- AS ISO 9703: Anaesthesia and respiratory care alarm signals
- ISO 5356: Anaesthetic and respiratory equipment

~~Additional information on active medical devices is provided in the General Information guideline.~~

Principle 12.1 -Medical devices incorporating electronic programmable systems**12.1.1 General**

A medical device that incorporates an electronic programmable system must be designed and produced in a way that ensures that:

- (a) the performance, reliability, and repeatability of the system are appropriate for the intended purpose of the device; and
- (b) any consequent risks associated with a single fault condition in the system are minimised.

12.1.1 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 12.2 - Safety dependent on internal power supply**12.2.1 General**

This section applies to a medical device if the safety of a patient on whom the device is to be used will depend on an internal power supply for the device.

The device must be fitted with a means of determining the state of the power supply.

12.2.1 How to demonstrate compliance

This Essential Principle only applies if the safety of the patient will depend on the internal power supply for the device. If that is the case, there should be some sort of indication (if it is possible) on the device showing the state of the internal power supply. Moreover, there should be visual and/or audible alarms, if the state of the internal power supply goes below a certain range.

The work undertaken by the manufacturer could involve, but is not restricted to:

- addressing the safety issue as a part of the risk analysis and indicating what control measures are in place to reduce the risk
- documenting how the visual indication showing state of the internal power supply and alarms are designed and tested as a part of the technical documentation
- providing information about the visual indication of the internal power supply and alarms as a part of the *Instructions for Use*.

Principle 12.3 - Safety dependent on external power supply**12.3.1 General**

This section applies to a medical device if the safety of a patient on whom the device is to be used will depend on an external power supply for the device.

Principle 12.3 - continued

It applies if the safety of the patient will depend on the external power supply for the device. For example, if there is an external power supply to a ventilator or anaesthetic machine and a power failure occurs, there should be visual and audible alarms.

The device must be fitted with an alarm system that indicates whether a power failure has occurred.

External power supplies include:

- electrical
- battery powered
- gas powered
- pneumatic
- liquid or solid fuels

The work undertaken by the manufacturer could involve, but is not restricted to:

- addressing the safety issue as a part of the risk analysis and indicating what control measures are in place to reduce the risk to the patient
- documenting how the visual and audible alarms are designed and tested as a part of the technical documentation
- providing information about the visual and audible alarms as a part of the *Instructions for Use*

Principle 12.4 - Medical devices intended to monitor clinical parameters**12.4.1 General**

A medical device that is intended by the manufacturer to be used to monitor one or more clinical parameters of a patient must be fitted with an appropriate alarm system to warn the user if a situation has developed that could lead to the death of the patient or a severe deterioration in the state of the patient's health.

12.4.2 How to demonstrate compliance

Medical devices that monitor variations in cardiac performance, respiration and activity of the nervous system are relevant examples for this Essential Principle.

The work undertaken by the manufacturer could involve, but is not restricted to:

- as part of the risk analysis, indicating what control measures are in place to reduce the risk to the patient if the variations of any physiological parameters monitored are of a kind that could result in immediate danger to the patient
- documenting how the alarm system is designed and tested as a part of the technical documentation
- providing information about the alarm system as a part of the *Instructions for Use*. IEC 60601-1-8⁶ can provide further guidance.

⁶ IEC 60601-1-8 is a standard relating to medical electrical equipment and general requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems.

Principle 12.5 - Minimisation of risk of electromagnetic fields**12.5.1 General**

A medical device must be designed and produced in a way that ensures that the risk of an electromagnetic field being created that could impair the operation of other devices or equipment being used in the vicinity of the medical device is minimised.

12.5.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 12.6 - Protection against electrical risks**12.6.1 General**

A medical device must be designed and produced in a way that ensures that, as far as possible, when the device is installed correctly, and the device is being used for an intended purpose under normal conditions of use and in the event of a single fault condition, patients, users, and any other persons, are protected against the risk of accidental electric shock.

12.6.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 12.7 - Protection against mechanical risks**12.7.1 General**

A medical device must be designed and produced in a way that ensures that a patient, the user, and any other person, is protected against any mechanical risks associated with the use of the device.

12.7.2 How to demonstrate compliance

Mechanical risks may be connected with, for example, resistance, stability and moving parts.

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 12.8 - Protection against risks associated with vibration**12.8.1 General**

A medical device must be designed and produced in a way that ensures that any risks associated with vibrations generated by the device are minimised.

If vibrations are not part of the intended performance of the device, particular attention must be given to relevant technical progress, and the available means, for limiting vibrations, particularly at source.

12.8.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 12.9 - Protection against risks associated with noise**12.9.1 General**

A medical device must be designed and produced in a way that ensures that any risks associated with noise emitted by the device are minimised.

If noise is not part of the intended performance of the device, particular attention must be given to relevant technical progress, and the available means, for reducing the emission of noise, particularly at source.

12.9.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis of the significance of any foreseeable noise emitted by the device, either intentional or unintentional
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 12.10- Protection against risks associated with terminals and connectors**12.10.1 General**

A medical device that is intended by the manufacturer to be connected to an electric, gas, hydraulic, pneumatic or other energy supply must be designed and produced in a way that ensures that any risks to the user associated with the handling of a terminal or connector on the device, in relation to the energy supply, are minimised.

12.10.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 12.11 - Protection against risks associated with heat**12.11.1 General**

A medical device must be designed and produced in a way that ensures that, during normal use, any accessible part of the device (other than any part intended by the manufacturer to supply heat or reach a given temperature), and any area surrounding an accessible part of the device, does not reach a potentially dangerous temperature.

12.11.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 12.12- Protection against risks associated with administration of energy or substances**12.12.1 General**

This section applies in relation to a medical device that is intended by the manufacturer to be used to administer energy or a substance to a patient.

The device must be designed and produced in a way that ensures that:

- (a) the delivered rate and amount of energy, or of the substance, can be set and maintained accurately to ensure the safety of the patient and the user; and
- (b) as far as possible, the accidental release of dangerous levels of energy or of the substance is prevented.

The device must be fitted with a means of indicating or, if appropriate, preventing inadequacies in the rate and amount of energy, or of the substance, administered that might cause danger to the patient, the user or any other person.

The functions of each control and indicator on the device must be clearly specified on the device.

If the instructions for the operation of the device, or the operating or adjustment parameters for the device, are displayed by means of a visual system incorporated into the device, the instructions or parameters must be able to be understood by the user and, if appropriate, the patient.

12.12.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- a well-reasoned and documented risk analysis
- ensuring that operational information displayed by the device is clearly understandable
- evidence of appropriate testing to confirm the design and production decisions resulting from the risk analysis

Principle 12.13 - Active implantable medical devices**12.13.1 General**

An active implantable medical device must display a code that can be used to identify:

- (a) the type of device; and
- (b) the manufacturer of the device; and
- (c) the year of manufacture of the device.

The code must be able to be read without the need for surgery to the person in whom the device is implanted.

12.13.2 How to demonstrate compliance

The format of the code is determined by the manufacturer.

One way to display this code is to inscribe the device using radio-opaque materials that can be viewed on an x-ray of the patient. For example, to enable medical staff to re-program a patient's implantable pacemaker in an emergency situation, an X-ray of the patient can be taken to read the radio-opaque code shown on the pacemaker, and this code can be used to determine the make and model of a suitable programming device.

The work undertaken by the manufacturer could involve, but is not restricted to:

- documenting how a unique code is assigned to the device
- documenting how the code is affixed to the device during manufacture
- documenting how the code can be read without the need for surgery (possibly as part of the *Instructions for Use*)
- producing technical drawings showing the artwork for the code on the device

PRINCIPLE 13- Information to be provided with medical devices**Principle 13.1- General information to be provided with a medical device****13.1.1 General**

The following information must be provided with a medical device:

- (a) information identifying the device;
 - (b) information identifying the manufacturer of the device;
 - (c) information explaining how to use the device safely;
- having regard to the training and knowledge of potential users of the device.

In particular:

- (d) the information required by section 13.3 must be provided with a medical device; and
- (e) if *instructions for use* of the device are required under subsection 13.4, the information mentioned in subsection 13.4.1 must be provided in those instructions.

Principle 13.1 – continued

The information must be provided in English, and may also be provided in any other South African language.

The format, content and location of the information must be appropriate for the device and its intended purpose.

Any number, letter, symbol, or letter or number in a symbol, used in the information must be legible and at least 1 millimetre high.

If a symbol or identification colour that is not included in a medical device standard is used in the information provided with the device, or in the *instructions for Use* of the device, the meaning of the symbol or identification colour must be explained in the information provided with the device or the *instructions for use* of the device.

13.1.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- ensuring that the label, packaging, and Instructions for Use meet the information requirements
- copies of the label, packaging, and Instructions for Use should be kept with the documentation that a manufacturer assembles and maintains to demonstrate compliance with the Essential Principles.

Principle 13.2 - Information to be supplied with medical devices - location**13.2.1 General**

Unless it is impracticable or inappropriate to do so, the information required to be provided with a medical device must be provided on the device itself.

If this is not practicable, the information must be provided:

- (a) on the package used for the device; or
- (b) in the case of devices that are packaged together because individual packaging of the devices for supply is not practicable – on the outer packaging used for the devices.

If it is not practicable to comply with either of the above, the information must be provided on a leaflet supplied with the device, or in a printed document or using other appropriate media.

13.2.2 How to demonstrate compliance

The work undertaken by the manufacturer could involve, but is not restricted to:

- ensuring that the label, packaging and Instructions for Use meet the information requirements
- copies of the label, packaging and Instructions for Use should be kept with the documentation that a manufacturer assembles and maintains to demonstrate compliance with the Essential Principles.

Principle 13.3 - Information to be supplied with medical devices – as a label**13.3.1 General**

Information to be provided with medical devices as a label where possible on the medical device or IVD, or on the packaging of each unit or on the packaging of multiple devices or IVDs

The information mentioned in the following table must be provided with a medical device.

Item	Information to be supplied
1	Name and trade name of the medical device or IVD
2	The manufacturer's name, or trading name, and business address
3	The applicant's name and business address
4	The approved intended purpose of the medical device or IVD where practical
5	The product catalogue code where applicable
6	The expiry date where applicable, or date of manufacture
7	The Batch code or number and or the lot number where applicable
8	The serial number where applicable. For accessories the serial number may be substituted with a control number, and for software it may be substituted with a version number
9	Sufficient information to enable a user to identify the device, or if relevant, the contents of packaging
10	Where appropriate, an indication that the device contains or incorporates a Scheduled or biological substance
11	The expiry date where applicable, and if there is no expiry date then the date of manufacture
12	Any particular handling or storage requirements applying to the device
13	If the device is supplied sterile, an indication of its sterile state and, where appropriate, the sterilization method.
14	Where relevant, an indication of the net quantity of contents, expressed in terms of weight or volume, numerical count, or any combination of these or other terms which accurately reflect the contents of the package
15	Any warnings, restrictions, or precautions that should be taken, in relation to use of the device
16	The performance intended where applicable
17	Any special operating instructions for the use of the device, special facilities , special training or particular qualifications of the medical device user or third parties
18	If applicable, an indication that the device is intended for a single use only
19	If applicable, an indication that the device has been custom-made for a particular individual and is intended for use only by that individual or health professional
20	If applicable, an indication that: (a) if the device is a medical device other than an IVD medical device—the device is intended for pre-market clinical investigation; or (b) if the device is an IVD medical device—the device is only intended for performance evaluation only (c) the device is intended for non-clinical research, teaching or testing purposes (d) the device is intended for presentation or demonstration purposes (e) the device is for <i>in vitro</i> diagnostic use
21	If the medical device is a reprocessed medical device; the name of the re-processor and identification that the device has been reprocessed

13.3.2 Particular requirements

The work undertaken by the manufacturer could involve, but is not restricted to:

- ensuring that the label, packaging, and *Instructions for Use* meet the information requirements
- copies of the label, packaging and Instructions for Use should be kept with the documentation that a manufacturer assembles and maintains to demonstrate compliance with the Essential Principles of Safety and Performance.

Principle 13.4 - Instructions for Use

13.4.1 Instructions for Use for a medical device

Information to be provided as *Instructions for Use* with the medical device or IVD, or on the packaging of each unit or on the packaging of multiple devices or IVDs.

Instructions for the use of a medical device must be provided with the device.

However, instructions for the use of a medical device need not be provided with the device, or may be abbreviated, if:

- the device is a Class A medical device and
- the device can be used safely for its intended purpose without instructions.

Instructions for the use of a medical device must include information mentioned in the following table that is applicable to the device.

Item	Information to be supplied
1	Name and trade name of the medical device
2	Name and business address of the manufacturer; where practical, the approved indication for use of the medical device or IVD including in the case of a medical device, the intended user
3	The performance intended, where practical
4	Where the manufacturer has included clinical investigations as part of premarket conformity assessment to demonstrate conformity to the safety and performance criteria, a summary of the investigation, outcome data and clinical safety information, or a reference as to where such information may be accessed
5	Any residual risks, contraindications and any expected and foreseeable side effects, including information to be conveyed to the patient in this regard
6	Specifications that the user requires to use the device appropriately (e.g. if the device has a measuring function, the degree of accuracy claimed for it)
7	If the device contains, or incorporates, a medicinal substance and/or material of biological origin: identification of that substance or material, as appropriate
8	Details of any preparatory treatment or handling of the device before it is ready for use (e.g. sterilization, final assembly, calibration)
9	Any requirements for special facilities, or special training, or particular qualifications of the device user and/or third parties
10	The information needed to verify whether the device is properly installed and is ready to perform safely and as intended by the manufacturer, together with, where relevant: details of the nature, and frequency, of preventative and regular maintenance, and of any

Item	Information to be supplied
	preparatory cleaning or disinfection;
11	Identification of any consumable components and how to replace them
12	Information on any necessary calibration to ensure that the device operates properly and safely during its intended life span; and methods of eliminating the risks encountered by persons involved in installing, calibrating or servicing medical devices.
13	An indication of any special storage and/or handling condition that applies
14	If the device is supplied sterile, instructions in the event of the sterile packaging being damaged before use; If the device is supplied non-sterile with the intention that it is sterilized before use, the appropriate instructions for sterilization
15	If the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of re-sterilization including information to identify when the device should no longer be reused (e.g. signs of material degradation or the maximum number of allowable reuses);
16	For devices intended for use together with other medical devices and/or general purpose equipment: (i) information to identify such devices or equipment, in order to obtain a safe combination; and/or (ii) information on any known restrictions to combinations of medical devices and equipment;
17	If the device emits hazardous, or potentially hazardous levels of radiation for medical purposes: (i) detailed information as to the nature, type and where appropriate, the intensity and distribution of the emitted radiation; and (ii) the means of protecting the patient, user, or third party from unintended radiation during use of the device
18	Information that allows the user and patient to be informed of warnings, precautions, measures to be taken and limitations of use regarding the medical device which information must cover, where appropriate (i) warnings, precautions and measures to be taken in the event of malfunction of the medical device or changes in its performance that may affect safety; (ii) warnings, precautions and measures to be taken in regard to the exposure to reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, radiation associated with diagnostic or therapeutic procedures, pressure, humidity, or temperature; (iii) warnings ,precautions and limitations related to the scheduled substance or biological substance that is incorporated into the medical device as an integral part of the medical device; and (iv) precautions and measures to be taken in regard to the risks of interference posed by the reasonably foreseeable presence of the medical device during specific diagnostic investigations, evaluations, therapeutic treatment or use (e.g. electromagnetic interference emitted by the medical device affecting other equipment) (v) precautions related to materials incorporated into the medical device that are carcinogenic, mutagenic or toxic, or could result in sensitisation or allergic reaction of the patient or user.

Item	Information to be supplied
19	Warnings and precautions to be taken related to the disposal of the medical device, its accessories and the consumables used with it, if any. This information must cover, where appropriate- (i) infection or microbial hazards (e.g. explants, needles or surgical equipment contaminated with potentially infectious substances of human origin); (ii) environmental hazards (e.g. batteries or materials that emit potentially hazardous levels of radiation); and (iii) physical hazards (e.g. from sharps)
20	For medical devices intended for use by a lay-person, the circumstances when the user must consult with a healthcare professional;
21	The date of issue or latest revision of the instructions for use and, where appropriate, an identification number; and
22	Appropriate service and maintenance instructions for technical equipment and medical devices, where applicable.

13.4.2 Instructions for use for an IVD

Each package of an IVD shall have an instruction for use of the IVD that must contain the following information with regard to the IVD in at least English:

Item	Information to be supplied
1	The name or trade name
2	Name and address of the manufacturer
3	The intended purpose/use, including but not limited to: (i) what is detected; (ii) its function (e.g. screening, monitoring, diagnosis or aid to diagnosis); (iii) the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate; (iv) whether it is automated or not; (v) whether it is qualitative or quantitative; (vi) the type of specimen(s) required (e.g. serum, plasma, whole blood, tissue biopsy, urine); and (vii) testing population;
4	An indication that it is for in vitro diagnostic use and the intended user
5	The intended purpose and use, including but not limited to- (i) what is detected; (ii) its function; (iii) the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate; (iv) whether it is automated or not; (v) whether it is qualitative or quantitative; (vi) the type of specimens required (e.g. serum, plasma, whole blood, tissue biopsy, urine); and (vii) testing population;
6	An indication whether the device is intended for self-testing or near-patient testing, for “point of care”, “self-testing” or “research use only”

Item	Information to be supplied
7	The test principle
8	A description of the reagent, calibrators and controls and any limitation upon their use (e.g. suitable for a dedicated instrument only) <i>Note:</i> IVD kits include individual reagents and articles that may be made available as separate IVDs. In this situation, where appropriate, these IVDs should comply with the instructions for use content in this section.
9	A list of materials provided and a list of special materials required but not provided;
10	For IVDs intended for use together with other IVDs or medical devices, and/or general purpose equipment: (i) information to identify such devices or equipment, in order to obtain a safe combination; and/or (ii) information on any known restrictions to combinations of medical devices and equipment
11	An indication of any special storage (e.g. temperature, light, humidity, etc.) and/or handling conditions that apply
12	In use stability which may include, the storage conditions, and shelf life following the first opening of the primary container, together with the storage conditions and stability of working solutions, where this is relevant
13	If the IVD is supplied as sterile, instructions in the event of the sterile packaging being damaged before use
14	Information that allows the user to be informed of warnings, precautions, measures to be taken and limitations of use regarding the IVD, which information must cover, where appropriate- (i) warnings, precautions and measures to be taken in the event of malfunction of the IVD or its degradation as suggested by changes in its appearance that may affect performance; (ii) warnings, precautions and measures to be taken with regard to the exposure to reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects , electrostatic discharge, radiation associated with diagnostic or therapeutic procedures, pressure, humidity, or temperature; (iii) warnings, precautions and measures to be taken with regard to the risks of interference posed by the reasonably foreseeable presence of the medical device during specific diagnostic investigations, evaluations, therapeutic treatment including electromagnetic interference emitted by the medical device affecting other equipment, where applicable; and (iv) precautions related to materials incorporated into the IVD that are carcinogenic, mutagenic or toxic, or could result in sensitisation or allergic reaction
15	Warnings and precautions related to potentially infectious material that is included in the IVD
16	Where relevant, requirements for special facilities including clean room environment, radiation safety or particular qualifications of the medical device user
17	Conditions for collection, handling, and preparation of the specimen
18	Details of any preparatory treatment or handling of the IVD before it is ready for use including reconstitution and calibration where applicable
19	The information needed to verify whether the IVD is properly installed and is ready to perform safely and as intended by the manufacturer, together with, where relevant-

Item	Information to be supplied
	(i) details of the nature, and frequency, of preventative and regular maintenance including cleaning and disinfection; (ii) identification of any consumable components and how to replace them; (iii) information on any necessary calibration to ensure that the IVD operates properly and safely during its intended life span; and (iv) methods of mitigating the risks encountered by persons involved in installing, calibrating or servicing an IVD
20	Where relevant, recommendations for quality control procedures
21	The metrological traceability of values assigned to calibrators and trueness-control materials, including identification of applicable reference materials and reference measurement procedures of higher order
22	Assay procedure including calculations and interpretation of results and where relevant if any confirmatory testing must be considered; analytical performance characteristics, such as sensitivity, specificity, and accuracy; where relevant, clinical performance characteristics, such as diagnostic sensitivity and diagnostic specificity; where relevant, reference intervals; information on interfering substances or limitations such as visual evidence of hyperlipidaemia or haemolysis, age of specimen that may affect the performance of the assay
23	Warnings or precautions to be taken related to the disposal of the medical device, its accessories, and the consumables used with it, if any, which information must cover, where appropriate-- (i) infection or microbial hazards; (ii) environmental hazards; and (iii) physical hazards; for an IVD intended for use by a lay person, the circumstances when the user must consult with a healthcare professional; where relevant, a bibliography; the date of issue or latest revision of the instructions for use and, where appropriate, an identification number; and appropriate maintenance instructions for technical IVD machines, where applicable.
24	Instructions for the use of an IVD must be included with the sale of each IVD, however, instructions for use for Class A IVDs must be included, where applicable.

13.4.3 How to demonstrate compliance with Instructions for Use

The work undertaken by the manufacturer could involve, but is not restricted to:

- ensuring that the label, packaging and Instructions for Use meet the information requirements
- copies of the label, packaging and Instructions for Use should be kept with the documentation that a manufacturer assembles and maintains to demonstrate compliance with the Essential Principles.

PRINCIPLE 14- Clinical evidence

Every medical device requires clinical evidence, appropriate for the use and classification of the device, demonstrating that the device complies with the applicable provisions of the Essential Principles.

14.1 General

The Council expects manufacturers to hold evidence that demonstrates that:

- the medical device achieves its intended purpose(s) during normal conditions of clinical use
- the known and foreseeable clinical risks and any adverse effects have been minimised
- the risk of using the medical device is acceptable when weighed against the benefits inherent in the intended purpose(s)
- any clinical claims about the device's performance and safety (for example on the label and the Instructions for Use) are supported by clinical data.

A properly developed risk analysis is crucial in determining what type of clinical data is required for a particular device. An outcome of the analysis is the identification of any residual risks. The clinical data are expected to quantify and address those risks.

14.2 The nature of clinical evidence

Clinical evidence may comprise:

- Full clinical study reports for the device in question used for the intended purpose(s) claimed, or reports for a similar device with reasoned argument as to why the safety and performance of that device may be extrapolated to the device under assessment—paying particular attention to the intended purpose(s). Full study reports mean complete reports, not publications.
- A literature review for such devices used for similar intended purpose(s) as the device under assessment, with a documented search strategy including databases searched, search terms used and any inclusion and exclusion criteria applied, in sufficient detail to enable the search to be reproduced if desired. This demonstrates an adequate review of current knowledge about a particular product or therapy in general. Then a critical discussion of the papers revealed by the search must be undertaken with particular emphasis on how the publications demonstrate safety and performance of the device under assessment for the indications claimed (i.e. in terms of similarity, predicates, the actual device, etc.).
- Post-market data of the specific device under assessment, or a similar or predicate device. These data may include adverse event or complaint information, for example.
- If there are no actual clinical data for the specific device, depending upon the nature of it, it may be possible to provide a full clinical justification for why clinical evidence is either not required, or only partially required. Typically, this involves referencing the performance of a predicate or similar marketed device and critically examining each change or difference in terms of materials, design, clinical use, and their likely impact on safety and performance. If it can be established via contention that the changes made should not pose any impact on safety and performance, a clinical justification can, in some circumstances, suffice for clinical evidence.

14.1 The nature of clinical evidence – continued

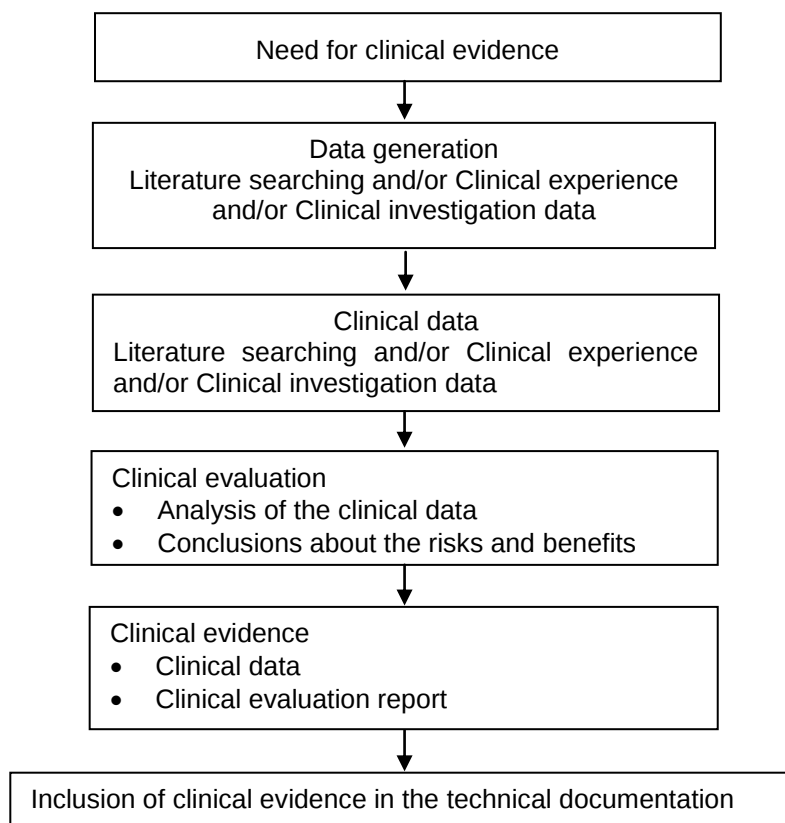
- All clinical reports should contain a critical review of all data presented, performed by a 'clinical expert' who should have appropriate clinical qualifications and experience to be able to provide an objective critical review of the clinical data for the device that is the subject of the submission. The appropriateness of this expert will clearly vary depending upon the nature of the device. A complete *curriculum vitae* for such an expert, or similar documentation, is also a necessary component of the clinical evidence submission.

14.3 How to conduct clinical evaluation

The stages in performing a clinical evaluation are:

- identification of any pertinent standards and the clinical data required to meet them
- objective appraisal of each individual data set as described under clinical evidence above, in terms of its relevance, applicability, quality, and clinical significance
- a subsequent analysis of all the data sets, whereby conclusions are reached about the performance, safety and presentational aspects (labelling, patient information and Instructions for Use) of the device. The evaluation should consolidate the findings of all clinical data and explain why such data demonstrate acceptable safety and performance of the device under assessment.

If the manufacturer concludes there is insufficient clinical evidence to be able to declare conformity with the Essential Principles, the manufacturer will need to generate additional data (for example, conduct a clinical investigation, or broaden the scope of literature searching) to address any deficiency. In this respect clinical evaluation can be an iterative process.



14.4 Sources of clinical data

Data generated during a clinical investigation program for the device, including:

- data from all formal clinical investigations carried out using finished products
- any other experimental use in humans using prototype devices or components for the purpose of developing or investigating their safety and performance

Note: There is no requirement that clinical investigations should be done in South Africa.

Data from clinical experience, including:

- manufacturer-generated post-market surveillance reports, registries or cohort studies (which may contain unpublished long-term safety and performance data)
- adverse events databases (held by either the manufacturer or regulatory authorities)
- data for the device in question generated from individual patients under Authorised Prescriber prior to marketing of the device
- details of clinically relevant field corrective actions (for example, recalls, notifications, hazard alerts)

Data obtained from a review of the literature:

- specifically about the device in question—where available, this must always be included in any review, and/or
- for comparative and well established devices including relevant post-market information. Adequate justification should be provided to explain how data for a similar device can establish the safety and performance of the device in question

For safety data, all reports, including individual case reports and overviews relevant to the device should be considered. This would include scientific reports not suitable for assessment of performance due to poor trial design or inadequate analysis but providing safety data about the device.

14.5 How to decide what type of data to use

The level and nature of the data considered in a clinical evaluation should be appropriate to the use and classification of the medical device. The data requirements will also vary according to the nature and clinical application of the technology used in or by the device.

Devices based on new or unproven technology and those that extend the intended purpose of an existing technology through a new clinical use must be supported with clinical investigation data.

Devices based on an existing technology and intended for an established and accepted use may rely on literature review.

14.6 Key elements of a literature review

A literature review consists of the following components:

- a compilation, using documented methodology, of the relevant currently available scientific literature regarding the intended purpose of the device and the design features, consisting of:
 - clinical study reports
 - review papers
 - expert opinion

14.6 Key elements of a literature review - continued

- a report, written by an expert in the relevant field, containing a critical appraisal of this compilation. Where the review relies in part or wholly on data for a comparable device, the report should also clearly justify how the devices described in the compiled literature are relevant to the safety and performance of the device in question.

It is important that the published literature be able to establish the clinical performance and safety of the device in question, and demonstrate a favourable risk profile.

A review must be supported by a detailed search of the literature, using a reproducible search strategy across a range of appropriate scientific databases. The methodology should be documented in a written report.

The search output (that is, the citations) should be assessed against clearly defined selection criteria. The report should also summarise how each citation did or did not fit the selection criteria for inclusion in the review.

When selecting papers to be included in the assessment of performance and safety, the following aspects should be considered:

- the quality of the literature articles
- the design of any clinical trials reported in the paper
- the quality of the data reported in the literature
- the clinical significance of the results of those trials

The quality of the paper can be judged by assessing its:

- scientific impartiality
- the completeness of reporting
- clarity and logic of argument
- the validity of any conclusions drawn in the article

14.7 Where clinical data can be found

Data relevant to the clinical evaluation may be:

- held by the manufacturer (i.e. manufacturer, Applicant pre- and post- market investigation reports and adverse event reports for the device in question)
- in the scientific literature (i.e. example, published articles of clinical investigations and adverse event reports for the device in question or for comparable devices)

The manufacturer is responsible for identifying data relevant to the device and determining the type(s) and amount of data needed for the clinical evaluation.

There may be situations where demonstration of compliance with the Essential Principles is not possible through evaluation of the published clinical data alone. This can occur because clinical data from clinical investigation and/or the published literature are either lacking or are of poor quality and therefore not sufficiently useful.

One option for the manufacturer will be to generate additional clinical investigation data by conducting a clinical trial. Alternatively, other forms of data can be considered.

14.7 Where clinical data can be found - continued

This can include data from device usage registries, post-market investigations, surveillance and adverse event reports. In the absence of any recent clinical data for simple devices of a traditional nature assessed to be low risk and safe, a justification as to why no clinical data is required.

14.8 Requirements for clinical investigations

There is no requirement that the dossier has to include clinical data generated from clinical investigations conducted within South Africa. However, where an investigation of a new medical device is conducted in South Africa, it must be conducted in accordance with South African legislative and regulatory requirements and South African ethical standards.

Clinical investigations conducted outside of South Africa are required to comply with relevant jurisdictional legislative and regulatory requirements and must be in accordance with the principles of the Declaration of Helsinki.

Clinical investigation design is an important consideration. The most desirable clinical investigation design is a randomised, double-blind, controlled investigation. This design has the lowest risk of bias that could potentially contribute to the outcomes observed in the investigation. In cases where there are numerous published reports of such investigations, it is possible to focus on these investigations at the expense of other studies, which, because of their design, will have higher levels of bias.

However, it may be difficult to conduct double-blind studies with medical devices, particularly for implantable devices, or to use comparator groups. It is more likely in such cases that these studies have greater potential for bias and/or that there are few published reports available to support the review. In this case, almost all papers retrieved by the search will need to be assessed. The issue of potential duplication of data in different papers will need to be addressed.

14.9 Details for an Importer or Distributor or Authorised Representative to look for in the manufacturer's technical dossier when checking to see if there is clinical evidence

There should be a section in the technical dossier clearly labelled 'Clinical Evidence' that includes:

- the clearly stated intended purpose(s) and application of the device identification of the Essential Principles relevant to the specific design of the device clinical data or justification as to why no clinical data are required
- a clinical evaluation report containing a comprehensive analysis of the clinical data relevant to the device, authored by a clinical expert competent in the appropriate field and able to give an objective assessment of the clinical data that are present

14.10 Where to find more information

The Council recognises that a flexible, case-by-case approach should be adopted so applicants are encouraged to discuss individual device requirements with the Council.

The International Medical Device Regulator's Forum (previously the Global Harmonization Task Force (GHTF)), an international body that was established to achieve greater uniformity between national medical device regulatory systems has developed a comprehensive guidance document on Clinical Evaluation: <<http://www.imdrf.org/>>.

14.10 Where to find more information - continued

In addition to general guidance, the document provides:

- a possible format for a literature search report
- a possible methodology for documenting the screening and selection of literature within a literature search report
- some examples to assist with the formulation of criteria for data appraisal
- a possible method of appraisal
- a possible format for a Clinical Evaluation Report

PRINCIPLE 15 - Principles applying to IVD medical devices only**15.1 General**

An IVD medical device must be designed and manufactured in a way in which the analytical and clinical characteristics support the intended use, based on appropriate scientific and technical methods.

An IVD medical device must be designed in a way that addresses accuracy, precision, sensitivity, specificity, stability, control of known relevant interference and measurement of uncertainty, as appropriate.

If performance of an IVD medical device depends in whole or part on the use of calibrators or control materials, the traceability of values assigned to the calibrators or control material must be assured through a quality management system.

An IVD medical device must, to the extent reasonably practicable, include provision for the user to verify, at the time of use, that the device will perform as intended by the manufacturer.

An IVD medical device for self-testing must be designed and manufactured so that it performs appropriately for its intended purpose, taking into account the skills and the means available to users and the influence resulting from variation that can reasonably be anticipated in the user's technique and environment.

The information and instructions provided by the manufacturer of an IVD medical device for self-testing must be easy for the user to understand and apply.

An IVD medical device for self-testing must be designed and manufactured in a way that reduces, to the extent practicable, the risk of error in the use of the device, the handling of the sample and the interpretation of results.

15.2 How to comply with principles applicable to IVD medical devices only

The manufacturer must have evidence, as demonstrated by appropriate testing protocols, that the IVD medical device (IVD) performs as intended.

There must be documented procedures in place to ensure that values assigned to controls and calibrators can be related to stated references through a chain of unbroken comparisons, thereby ensuring the ongoing accuracy of these materials.

15.2 How to comply with principles applicable to IVD medical devices only - continued

The design and construction process for an IVD medical device for self-testing needs to take account of the foreseeable risks which could exist for, or be created by, the device when used as intended. This should consider where the device is intended to be used, and by whom. Identified risks or hazards should be eliminated wherever possible, and methods established to alert and inform users of any residual hazards. Also, where possible, the manufacturer of an IVD should consider a mechanism whereby the validity of a test result can be confirmed. This must be simple to perform and interpret.

UPDATE HISTORY

Date	Reason for update	Version & publication
Aug 2014	First draft publication for comment	Version 1 for comment, Sept 2014
12 Dec 2014	Due date for comment	
July 2016	Version 1 for implementation Amendment of following sections: Introduction, 3, 4, 5, 6, 10.2, Principle 12, 13.3.1, 13.3.2, 13.4.1, 13.4.2	Version 1, July 2016
With implementation of the Medical Device Regulations	Implementation	