IMDRF International Medical Device Regulators Forum

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Preface

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators from around the world. The document has been subject to consultation throughout its development.

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Introduction

The purpose of this IMDRF guidance is to provide harmonized Essential Principles that should be fulfilled in the design and manufacturing of medical devices and IVD medical devices to ensure that they are safe and perform as intended. The worldwide adoption of a common set of fundamental design and manufacturing requirements for medical devices that, when met, provide assurance the device is safe and performs as intended, offers significant benefits to, among others, manufacturers, users, patients/consumers, and to Regulatory Authorities. Reducing differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

This document has been developed to encourage and support global convergence of regulatory systems. It is intended for use by Regulatory Authorities (RAs), Conformity Assessment Bodies (CABs), industry, and other stakeholders, and will provide benefits in establishing, in a consistent way, an economic and effective approach to the control of medical devices in the interest of public health. It seeks to strike a balance between the responsibilities of RAs to safeguard the health of their citizens and their obligations to avoid placing unnecessary burdens upon the industry.

The manufacturer of a medical device and in vitro diagnostic (IVD) medical device is expected to design and manufacture a product that is safe and effective throughout its life-cycle. This guidance document describes fundamental design and manufacturing requirements, referred to as 'Essential Principles of Safety and Performance' that, when met, provide assurance that a medical device and IVD medical device is safe and performs as intended, by the manufacturer. Essential principles of safety and performance provide broad, high-level, criteria for design, production, and postproduction throughout the life-cycle of all medical devices and IVD medical devices, ensuring their safety and performance. Compliance with the Essential Principles of Safety and Performance, via the use of applicable standards throughout a product's lifecycle, including where appropriate a pre-market review, is an acceptable approach for applying controls relative to a device's safety and performance by the RAs with Jurisdiction. Depending on the RA having jurisdiction and the particular medical device or IVD medical device there may be additional requirements that may need to be met. Where standards are being considered as part of regulatory compliance, their development can benefit from these Essential Principles of Safety and Performance.

As used within the context of this document to encourage compliance with the Essential Principles of Safety and Performance, "should" indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but is not prohibited. "May" is used to indicate that a course of action is permissible within the limits of the standard. "Can" is used as a statement of possibility and capability. Finally, "must" is used only to describe "unavoidable" situations, including those mandated by government regulation.

This document supersedes an earlier version produced under the Global Harmonization Task Force (GHTF) with the same title dated November 2, 2012 (GHTF/SG1/N68:2012).

1.0 Scope

This document applies to all medical devices and IVD medical devices and is intended to identify and describe essential principles of safety and performance which should be considered during the design and manufacturing process. Depending on the particular medical device or IVD medical device, some of the essential principles of safety and performance do not apply. In those cases, justifications should be provided for their exclusion.

2.0 References

- IMDRF/GRRP WG/N040:2017 *Competence, Training, and Conduct Requirements for Regulatory Reviewers*
- IMDRF/SaMD WG/N41FINAL:2017 *Software as a Medical Device (SaMD): Clinical Evaluation*
- IMDRF/SaMD WG/N23 FINAL:2015 *Software as a Medical Device (SaMD): Application of Quality Management System*
- IMDRF/SaMD WG/N12 FINAL:2014 *"Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations*
- IMDRF/SaMD WG/N10 FINAL:2013 *Software as a Medical Device (SaMD): Key Definitions*
- GHTF/SG1/N78:2012 *Principles of Conformity Assessment for Medical Devices.*
- IMDRF/GRRP WG/N52 *Principles of Labeling for Medical Devices and IVD Medical Devices*
- GHTF/SG1/N044:2008 *Role of Standards in the Assessment of Medical Devices.*
- GHTF/SG1/N055:2009 *Definitions of the Terms Manufacturer, Authorised Representative, Distributor and Importer*
- GHTF/SG1/N046:2008 *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*
- GHTF/SG1/N071:2012 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*
- GHTF/SG5/N1R8:2007 *Clinical Evidence – Key Definitions and Concepts*
- GHTF/SG5/N2R8:2007 *Clinical Evaluation*
- GHTF/SG5/N3:2010 *Clinical Investigations*
- GHTF/SG5/N6:2012 *Clinical Evidence for IVD Medical Devices - Key Definitions and Concepts*
- GHTF/SG5/N7:2012 *Clinical Evidence for IVD Medical Devices - Scientific Validity Determination and Performance Evaluation*.
- GHTF/SG5/N8:2012 *Clinical Performance Studies for In Vitro Diagnostic Medical Devices*
- Declaration of Helsinki

Standards

The standards below were consulted in the writing of this document and may be useful in meeting the essential principles discussed herein. This list is not intended as a required or complete list of standards that can be used to meet the essential principles.

- ISO 14971 *Medical Devices – Application of Risk Management to Medical Devices*
- ISO 13485 *Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes*
- ISO 11135 *Sterilization of Health-Care Products -- Ethylene oxide -- Requirements for the Development, Validation and Routine Control of a Sterilization Process for Medical Devices*
- ISO 11137 *Sterilization of Health Care Products -- Radiation*
- ISO 11138 *Sterilization of Health Care Products -- Biological indicators*
- ISO 11140 *Sterilization of Health Care Products -- Chemical indicators*
- ISO 11607 *Packaging for Terminally Sterilized Medical Devices*
- ISO 11737 *Sterilization of Medical Devices -- Microbiological Methods*
- ISO 17665 *Sterilization of Health Care Products - Moist Heat*
- ISO 14937 *Sterilization of Health Care Products - General Requirements for Characterization of a Sterilizing Agent and the Development, Validation and Routine Control of a Sterilization Process for Medical Devices*
- ISO 13408 *Aseptic Processing of Health Care Products*
- ISO 10993 *Biological Evaluation of Medical Devices*
- ISO 23640 *In Vitro Diagnostic Medical Devices - Evaluation of stability of in vitro diagnostic reagents*
- ISO 14155 *Clinical Investigation of Medical Devices for Human Subjects - Good clinical practice*
- ISO 14644 *Cleanrooms and Associated Controlled Environments*
- ISO 17664 *Processing of Health Care Products - Information to be Provided by the Medical Device Manufacturer for the Processing of Medical Devices*
- ISO 80369 *Small-Bore Connectors for Liquids and Gases in Healthcare Applications*
- ISO 22442 *Medical Devices Utilizing Animal Tissues and their Derivatives*
- IEC 60601 Medical Electrical Equipment
- IEC 61010 *Safety Requirements for Electrical Equipment for Measurement, Control, and Laboratory Use*
- IEC 62366-1 *Medical Devices - Part 1: Application of Usability Engineering to Medical Devices*
- IEC 62366-2 *Medical Devices - Part 2: Guidance on the Application of Usability Engineering to Medical Devices*
- IEC 80001 *Application of Risk Management for IT Networks Incorporating Medical Devices*
- IEC 62304 *Medical device software - Software Life Cycle Processes*
- CLSI EP05 *Evaluation of Precision of Quantitative Measurement Procedures*
- CLSI EP06 *Evaluation of the Linearity of Quantitative Measurement Procedures*
- CLSI EP07 *Interference Testing in Clinical Chemistry*

- CLSI EP12 *User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline*
- CLSI EP17 *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline*
- CLSI EP21 *Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures*
- CLSI EP25 *Evaluation of Stability of In Vitro Diagnostic Reagent*
- CLSI EP28 *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory*

3.0 Definitions

3.1 *Active Medical Device*: Any medical device, operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices. Standalone software is considered to be an active medical device. (GHTF/SG1/N77:2012)

3.2 *Analytical Performance of an IVD Medical Device:* The ability of an IVD medical device to detect or measure a particular analyte. (GHTF/SG5/N6:2012)

3.3 *Appropriately Reduce [Risks]:* The reduction of risk to an acceptable level as determined by the manufacturer and regulatory authority (reducing risk as low as reasonably practicable, reducing risk as low as reasonably achievable, or reducing risk as far as possible) without adversely affecting the benefit-risk ratio.

3.4 *Conformity Assessment Body (CAB):* A body other than a Regulatory Authority engaged in determining whether the relevant requirements in technical regulations or standards are fulfilled. (IMDRF/GRRP WG/N040:2017)

3.5 *Clinical Data:* Safety and/or performance information that are generated from the clinical use of a medical device. (GHTF/SG5/N1R8:2007)

3.6 *Clinical Evaluation:* The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer. (GHTF/SG5/N1R8:2007)

3.7 *Clinical Evidence:* The clinical data and the clinical evaluation report pertaining to a medical device. (GHTF/SG5/N1R8:2007)

3.8 *Clinical Evidence for an IVD Medical Device:* All the information that supports the scientific validity and performance for its use as intended by the manufacturer. (GHTF/SG5/N6:2012)

3.9 *Clinical Investigation:* Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device. Explanation: This term is synonymous with ‘clinical trial’ and ‘clinical study’. (GHTF/

SG5/N1R8)

3.10 *Clinical Performance:* The ability of a medical device to achieve clinical outcome(s) in its intended purpose as claimed by the manufacturer. (Modified from GHTF/SG5/N1R8:2007)

3.11 *Clinical Performance of an IVD Medical Device:* The ability of an IVD medical device to yield results that are correlated with a particular clinical condition/physiological state in accordance with target population and intended user. (Modified from GHTF/SG5/N6:2012)

NOTE 1: Clinical performance can include diagnostic sensitivity and diagnostic specificity based on the known clinical/physiological state of the individual, and negative and positive predictive values based on the prevalence of the disease.

3.12 *Effective:* The ability of a medical device or IVD medical device to provide clinically significant results in a significant portion of the target population.

NOTE: This ability is assessed in situations where the medical device or IVD medical device is used for its intended uses and conditions of use and accompanied by adequate directions for use and warnings against unsafe use.

3.13 *Expected Lifetime/Expected Service Life:* Time period specified by the manufacturer during which the medical device or IVD medical device is expected to maintain safe and effective use.

NOTE 1: The expected lifetime can be determined by stability.

NOTE 2: Maintenance, repairs, or upgrades (e.g. safety or cybersecurity modifications) can be necessary during the expected lifetime.

3.14 *Expiry Date/Expiration Date:* Upper limit of the time interval during which the safety and performance characteristics of a material stored under specified conditions can be assured.

NOTE 1: This also applies to medical devices whose physical, chemical or functional properties are maintained during a specified and known period, such as for capital equipment.

NOTE 2: Expiry dates are assigned to IVD reagents, calibrators, control materials and other components by the manufacturer, based on experimentally determined stability properties.

(Modified from ISO 18113-1:2009)

3.15 *Harm:* Injury or damage to the health of people, or damage to property or the environment. (ISO/IEC Guide 51:2014)

3.16 *Hazard:* Potential source of harm. (ISO/IEC Guide 51:2014)

3.17 *Indications for Use:* A general description of the disease or condition the medical device or IVD medical device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the medical device or IVD medical device is intended.

3.18 *Intended Use / Intended Purpose*: The objective intent regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer. (Modified from GHTF/SG1/N77:2012)

NOTE: The intended use can include the indications for use.

3.19 *Instructions for Use:* Information provided by the manufacturer to inform the device user of the medical device's intended purpose and proper use and of any precautions to be taken. (GHTF/SG1/N70:2011)

NOTE: Instructions for use can also be referred to as "package insert."

3.20 *In Vitro Diagnostic (IVD) Medical Device:* 'In Vitro Diagnostic (IVD) medical device' means a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.

NOTE 1: IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.

NOTE 2: In some jurisdictions, certain IVD medical devices may be covered by other regulations.

(GHTF/SG1/N071:2012)

3.21 *Label:* Written, printed, or graphic information either appearing on the medical device itself, or on the packaging of each unit, or on the packaging of multiple devices. (GHTF/SG1/N70:2011)

NOTE: The definition above refers to the human readable label.

3.22 *Labeling:* the label, instructions for use, and any other information that is related to identification, technical description, intended purpose and proper use of the medical device, but excluding shipping documents. (GHTF/SG1/N70:2011)

NOTE 1: Labeling can also be referred to as "information supplied by the manufacturer."

NOTE 2: Labeling can be in printed or electronic format and may either physically accompany the medical device or direct the user to where the labeling information can be accessed (such as through a website).

3.23 *Lay User:* Individual who does not have formal training in a relevant field or discipline. (Modified from GHTF/SG1/N045:2008)

NOTE 1: Principles for lay person(s) may also apply to self-testing for a medical device or IVD medical device.

NOTE 2: For an IVD medical device used outside of a laboratory setting, the user of the

IVD medical device will be considered a lay user.

NOTE 3: For an IVD medical device for self-collection/self-testing, a self-tester is considered a lay user.

3.24 *Life-Cycle:* All phases in the life of a medical device, from the initial conception to final decommissioning and disposal. (ISO/IEC Guide 51:2014)

3.25 *Manufacturer:* "Manufacturer" means any natural or legal person[1] with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use, under their name; whether or not such a medical device is designed and/or manufactured by that person themselves or on their behalf by another person(s). (GHTF/SG1/N055:2009)

NOTE 1: This 'natural or legal person' has ultimate legal responsibility for ensuring compliance with all applicable regulatory requirements for the medical device in the countries or jurisdictions where it is intended to be made available or sold, unless this responsibility is specifically imposed on another person by the Regulatory Authority (RA) within that jurisdiction.

NOTE 2: The manufacturer's responsibilities are described in other GHTF guidance documents. These responsibilities include meeting both pre-market requirements and post-market requirements, such as adverse event reporting and notification of corrective actions.

NOTE 3: 'Design and/or manufacture', as referred to in the above definition, may include specification development, production, fabrication, assembly, processing, packaging, repackaging, labeling, relabeling, sterilization, installation, or remanufacturing of a medical device; or putting a collection of devices, and possibly other products, together for a medical purpose.

NOTE 4: Any person who assembles or adapts a medical device that has already been supplied by another person for an individual patient, in accordance with the instructions for use, is not the manufacturer, provided the assembly or adaptation does not change the intended use of the medical device.

NOTE 5: Any person who changes the intended use of, or modifies, a medical device without acting on behalf of the original manufacturer and who makes it available for use under his own name, should be considered the manufacturer of the modified medical device.

NOTE 6: An authorised representative, distributor or importer who only adds its own address and contact details to the medical device or the packaging, without covering or changing the existing labeling, is not considered a manufacturer.

NOTE 7: To the extent that an accessory is subject to the regulatory requirements of a medical device[2], the person responsible for the design and/or manufacture of that accessory is considered to be a manufacturer.

[1] The term "person" that appears here and in the other definitions of this document, includes legal entities such as a corporation, a partnership or an association.

[2] See GHTF/SG1/N29 *Information Document Concerning the Definition of the Term "Medical Device"*

3.26 *Medical Device*: Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
- investigation, replacement, modification, or support of the anatomy, or of a physiological process,
- supporting or sustaining life,
- control of conception,
- cleaning, disinfection or sterilization of medical devices,
- providing information by means of in vitro examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological, or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.

NOTE 1: Products which may be considered to be medical devices in some jurisdictions but not in others include:

- disinfection substances,
- aids for persons with disabilities,
- devices incorporating animal and/or human tissues,
- devices for in-vitro fertilization or assisted reproduction technologies.

(Modified from GHTF/SG1/N071:2012)

NOTE 1: For clarification purposes, in certain regulatory jurisdictions, devices for cosmetic/aesthetic purposes are also considered medical devices.

NOTE 2: For clarification purposes, in certain regulatory jurisdictions, the commerce of devices incorporating human tissues is not allowed.

3.27 *Near-Patient Testing:* Testing that is performed near a patient and outside of centralized laboratory testing facilities.

NOTE 1: Users of near-patient testing can include lay or professional users.

NOTE 2: This is not intended to refer to sample collection procedures.

NOTE 3: In certain regulatory jurisdictions, this is also referred to as Point of Care Testing.

3.28 *Normal Use*: operation, including routine inspection and adjustments by any user, and stand-by, according to the instructions for use or in accordance with generally accepted

practice for those medical devices or IVD medical devices provided without instructions for use. (modified from ISO 62366-1:2015).

NOTE 1: Normal use should not be confused with intended use. While both include the concept of use as intended by the manufacturer, intended use focuses on the medical purpose while normal use incorporates not only the medical purpose, but maintenance, transport, etc. as well.

NOTE 2: Use error can occur in normal use.

NOTE 3: Medical devices and IVD medical devices that can be used safely without instructions for use are exempted from having instructions for use by some authorities with jurisdiction.

3.29 *Packaging*: Product to be used for the containment, protection, handling, delivery, storage, transport and presentation of goods, from raw materials to processed goods, from the producer to the user or consumer, including processor, assembler or other intermediary. (ISO 21067-1:2016)

3.30 *Patient:* An individual under the care of a healthcare provider who may benefit from the action of a medical device. A patient may also be a user of a medical device.

3.31 *Performance:* The ability of a medical device to achieve its intended purpose as stated by the manufacturer. Performance may include both clinical and technical aspects.

3.32 *Performance Evaluation of an IVD Medical Device:* Assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of an IVD medical device.

3.33 *Performance of an IVD Medical Device:* The ability of an IVD medical device to achieve its intended use/intended purpose as claimed by the manufacturer. The performance of an IVD medical device consists of the analytical and, where applicable, the clinical performance supporting the intended use of the IVD medical device. (GHTF/SG5/N6:2012)

3.34 *Regulatory Authority (RA):* A government body or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and that may take enforcement action to ensure that medical products marketed within its jurisdiction comply with legal requirements. (IMDRF/GRRP WG/N040:2017)

3.35 *Risk:* Combination of the probability of occurrence of harm and the severity of that harm. (ISO/IEC Guide 51:2014)

3.36 *Risk Analysis:* Systematic use of available information to identify hazards and to estimate the risk. (ISO/IEC Guide 51:2014)

3.37 *Risk Assessment:* Overall process comprising a risk analysis and a risk evaluation. (ISO/IEC Guide 51:2014)

3.38 *Risk Evaluation:* Procedure based on the risk analysis to determine whether tolerable risk

has been exceeded. (ISO/IEC Guide 51:2014)

3.39 *Safety:* Freedom from unacceptable risk. (ISO/IEC Guide 51:2014)

3.40 *Self-Testing:* A medical device or IVD medical device used by a lay user who is responsible for collecting the data or specimen, by themselves and on themselves, relying solely on the instructions provided by the manufacturer. This use can also include performing the test and interpreting the results by themselves and on themselves.

3.41 *Shelf-Life*: Period of time until the expiry date during which a medical device in its original packaging maintains its stability under the storage conditions specified by the manufacturer.

NOTE: Stability (3.38) and expiry date (3.11) are related concepts

(Modified from ISO 18113-1:2009)

3.42 *Stability*: Ability of a medical device and IVD medical device to maintain its safety and performance characteristics within the manufacturer's specifications over a specified period of time.

NOTE 1: Stability applies to

- Sterile and non-sterile medical devices whose physical, chemical or functional properties may be altered or compromised over a stated time interval;
- IVD reagents, calibrators and controls, when stored, transported and used in the conditions specified by the manufacturer,
- Reconstituted lyophilized materials, working solutions and material removed from sealed containers, when prepared, used and stored according to the manufacturer's instructions for use,
- Measuring instruments or measuring systems after calibration.

NOTE 2: Stability of an IVD reagent or measuring system is normally quantified with respect to time and specified conditions,

- In terms of the duration of a time interval over which a measured property changes by a stated amount or
- In terms of the change of a property under specified conditions.

(Modified from ISO 18113-1:2009)

3.43 *State of the Art:* Developed stage of technical capability at a given time as regards products, processes and services, based on the relevant consolidated findings of science, technology and experience.

NOTE1: The state of the art embodies what is currently and generally accepted as good practice in technology and medicine. The state of the art does not necessarily imply the most technologically advanced solution. The state of the art described here is sometimes referred to as the "generally acknowledged state of the art". (Modified from ISO/IEC Guide 2:2004)

3.44 *User:* The person, professional or lay, who uses a medical device. The patient may be that user. (GHTF/SG1/N070:2011)

4.0 Safety and Performance of Medical Devices – General Essential Principles

A manufacturer of a medical device or IVD medical device is expected to design and manufacture a product that is safe and performs as intended throughout its life cycle. This guidance document describes fundamental design and manufacturing requirements, referred to as 'Essential Principles of Safety and Performance', to ensure this outcome. This document is structured to provide essential principles that apply to all medical devices including IVD medical devices (Section 5) and is then separated into two sections, one for essential principles applying to medical devices other than IVD medical devices (Section 6) and the other for essential principles that only apply to IVD medical devices (Section 7).

The medical device and IVD medical device manufacturer's design and manufacturing activities should be under the control of its quality management system. Conformity of the device to all the applicable Essential Principles will be demonstrated and assessed according to procedures designated by the Regulatory Authority and described in other GHTF and IMDRF guidances.

5.0 Essential Principles Applicable to all Medical Devices and IVD Medical Devices

The essential design and manufacturing principles listed in this Section are applicable to medical devices and IVD medical devices.

5.1 General

5.1.1 Medical devices and IVD medical devices should achieve the performance intended by their manufacturer and should be designed and manufactured in such a way that, during intended conditions of use, they are suitable for their intended purpose. They should be safe and perform as intended, should have risks that are acceptable when weighed against the benefits to the patient, and should not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons.

5.1.2 Manufacturers should establish, implement, document and maintain a risk management system to ensure the ongoing quality, safety and performance of the medical device and IVD medical device. Risk management should be understood as a continuous iterative process throughout the entire lifecycle of a medical device and IVD medical device, requiring regular systematic updating. In carrying out risk management manufacturers should:

a) establish and document a risk management plan covering each medical device and IVD medical device;

b) identify and analyze the known and foreseeable hazards associated with each medical device and IVD medical device;

c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse;

d) eliminate or control the risks referred to in point (c) in accordance with the requirements of points 5.1.3 and 5.1.4 below;

e) evaluate the impact of information from the production and postproduction phases, on the overall risk, benefit-risk determination and risk acceptability. This evaluation should include the impact of the presence of previously unrecognized hazards or hazardous situations, the acceptability of the estimated risk(s) arising from a hazardous situation, and changes to the generally acknowledged state of the art**.**

f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of points 5.1.3 and 5.1.4 below.

5.1.3 Risk control measures adopted by manufacturers for the design and manufacture of the medical device and IVD medical device should conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, manufacturers should control risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, manufacturers should, in the following order of priority:

a) eliminate or appropriately reduce risks through safe design and manufacture;

b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and

c) provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users.

5.1.4 The manufacturer should inform users of any relevant residual risks.

5.1.5 In eliminating or reducing risks related to use, the manufacturer should:

a) appropriately reduce the risks related to the features of the medical device and IVD medical device and the environment in which the medical device and IVD medical device are intended to be used (e.g. ergonomic/usability features, tolerance to dust and humidity) and

b) give consideration to the technical knowledge, experience, education, training and use environment and, where applicable, the medical and physical conditions of intended users.

5.1.6 The characteristics and performance of a medical device and IVD medical device should not be adversely affected to such a degree that the health or safety of the patient and the user and, where applicable, of other persons are compromised during the expected life of the device, as specified by the manufacturer, when the medical device and IVD medical device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained and calibrated (if applicable) in accordance with the manufacturer's instructions.

5.1.7 Medical devices and IVD medical devices should be designed, manufactured and

packaged in such a way that their characteristics and performance, including the integrity and cleanliness of the product and when used in accordance with the intended use, are not adversely affected by transport and storage (for example, through shock, vibrations, and fluctuations of temperature and humidity), taking account of the instructions and information provided by the manufacturer. The performance, safety, and sterility of the medical device and IVD medical device should be sufficiently maintained throughout any shelf-life specified by the manufacturer.

5.1.8 Medical devices and IVD medical devices should have acceptable stability during their shelf-life, during the time of use after being opened (for IVDs, including after being installed in the instrument), and during transportation or dispatch (for IVDs, including samples).

5.1.9 All known and foreseeable risks, and any undesirable side-effects, should be minimized and be acceptable when weighed against the evaluated benefits arising from the achieved performance of the device during intended conditions of use taking into account the generally acknowledged state of the art.

5.2 Clinical Evaluation

5.2.1 Where appropriate and depending on jurisdictional requirements, a clinical evaluation may be required. A clinical evaluation should assess clinical data to establish that a favorable benefit-risk determination exists for the medical device and IVD medical device in the form of one or more of the following:

- clinical investigation reports (for IVDs, clinical performance evaluation reports)
- published scientific literature/reviews
- clinical experience

5.2.2 Clinical investigations should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. These principles protect the rights, safety and well-being of human subjects, which are the most important considerations and shall prevail over interests of science and society. These principles shall be understood, observed, and applied at every step in the clinical investigation. In addition, some countries may have specific regulatory requirements for pre-study protocol review, informed consent, and for IVD medical devices, use of leftover specimens.

5.3 Chemical, Physical, and Biological Properties

5.3.1 Regarding chemical, physical, and biological properties of a medical device and IVD medical device, particular attention should be paid to the following:

a) the choice of materials and substances used, particularly with respect to:

- toxicity;
- biocompatibility; and

-flammability;

b) the impact of processes on material properties;

c) where appropriate, the results of biophysical or modelling research whose validity of which has been demonstrated beforehand;

d) the mechanical properties of the materials used, reflecting, where appropriate, matters such as strength, ductility, fracture resistance, wear resistance and fatigue resistance;

e) surface properties; and

f) the confirmation that the device meets any defined chemical and/or physical specifications.

5.3.2 Medical devices and IVD medical devices should be designed, manufactured and packaged in such a way as to minimize the risk posed by contaminants and residues to users and patients, taking account of the intended purpose of the medical device and IVD medical device, and to the persons involved in the transport, storage and use of the medical device and IVD medical device. Particular attention should be paid to tissues of users and patients exposed to those contaminants and residues and to the duration and frequency of exposure.

5.3.3 The medical device and IVD medical device should be designed and manufactured in such a way as to appropriately reduce the risks posed by substance egress (including leaching and/or evaporation), degradation products, processing residues, etc. Special attention should be given to leaking or leaching of substances, which are carcinogenic, mutagenic or toxic to reproduction.

5.3.4 The medical device and IVD medical device should be designed and manufactured in such a way as to appropriately reduce the risks posed by the unintentional ingress of substances into the device, taking into account the medical device and IVD medical device and the nature of the environment in which it is intended to be used.

5.3.5 Medical devices and IVD medical devices and their manufacturing processes should be designed in such a way as to eliminate or to appropriately reduce the risk of infection to users and all other persons who may come in contact with the medical device and IVD medical device. The design should:

a) allow for easy and safe handling;

b) appropriately reduce any microbial leakage from the medical device and IVD medical device and/or microbial exposure during use;

c) prevent microbial contamination of the medical device and IVD medical device or its content (e.g., specimens); and/or

d) appropriately reduce the risks from unintended exposure (e.g., cuts and pricks (such as needle stick injuries), eye splashes, etc.).

5.4 **Sterilization and Microbial Contamination**

5.4.1 Where necessary, medical devices and IVD medical devices should be designed to facilitate their safe cleaning, disinfection, sterilization, and re-sterilization by the user, as appropriate.

5.4.2 Medical devices and IVD medical devices labeled as having a specific microbial state should be designed, manufactured and packaged to ensure that they remain in that state when placed on the market and remain so under the transport and storage conditions specified by the manufacturer.

5.4.3 Medical devices and IVD medical devices, delivered in a sterile state should be designed, manufactured and packaged in accordance with appropriate procedures, to ensure that they are sterile when placed on the market and that, unless the packaging which is intended to maintain their sterile condition is damaged, they remain sterile, under the transport and storage conditions specified by the manufacturer, until that packaging is opened at the point of use. It should be ensured that the integrity of that packaging is clearly evident to the final user (for example, through the use of tamper-proof packaging).

5.4.4 Medical devices and IVD medical devices labelled as sterile should be processed, manufactured, packaged, and sterilized by means of appropriate, validated methods. The shelf-life of these medical devices and IVD medical devices should be determined by validated methods.

5.4.5 Medical devices and IVD medical devices intended to be sterilized, either by the manufacturer or user, should be manufactured and packaged in appropriate and controlled conditions and facilities.

5.4.6 Where the medical devices and IVD medical devices are provided non-sterile and are intended to be sterilized prior to use:

a) the packaging system should minimize the risk of microbial contamination and should be suitable taking account of the method of sterilization indicated by the manufacturer; and

b) the method of sterilization indicated by the manufacturer should be validated.

5.4.7 For medical devices and IVD medical devices placed on the market in both sterile and non-sterile conditions, the label should clearly distinguish between these versions.

5.5 Considerations of Environment and Conditions of Use

5.5.1 If the medical device or IVD medical device is intended to be used in combination with other medical devices or IVD medical devices and/or equipment, the whole combination, including the connection system should be safe and should not impair the specified performance of the medical device or IVD medical device. Any known restrictions on use applying to such combinations should be indicated on the label and/or in the instructions for use. Any connections which the user has to handle, such as fluid, gas transfer, electrical or mechanical coupling, should be designed and manufactured in such a way as

to remove or appropriately reduce all possible risks, including incorrect connections or safety hazards.

5.5.2 Medical devices and IVD medical devices should be designed and manufactured in consideration of the intended environment and conditions of use, and in such a way as to remove or appropriately reduce the:

a) risks of injury to the users or other persons in connection with its physical and ergonomic/usability features;

b) risks of user error due to the design of the medical device or IVD medical device user interface, ergonomic/usability features, and the environment in which the medical device or IVD medical device is intended to be used;

c) risks connected with 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, temperature, and/or variations in pressure and acceleration;

d) risks associated with the use of the medical device or IVD medical device when it comes into contact with materials, liquids, and substances, including gases, to which it is exposed during intended conditions of use;

e) risks associated with the possible negative interaction between software and the information technology (IT) environment within which it operates and interacts;

f) environmental risks from unexpected egress of substances from the medical device or IVD medical device during use, taking into account the medical device or IVD medical device and the nature of the environment in which it is intended to be used;

g) the risk of incorrect identification of specimens/samples/data and the risk of erroneous results due to, for example, confusing color and/or numeric coding on specimen receptacles, removable parts and/or accessories used to perform the analysis, test, or assay as intended; and

h) the risks of interference with other medical devices or IVD medical devices normally used in diagnosis, monitoring or treatment.

5.5.3 Medical devices and IVD medical devices should be designed and manufactured in such a way as to remove or appropriately reduce the risks of fire or explosion during normal use and in single fault condition. Particular attention should be paid to medical devices and IVD medical devices whose intended use includes exposure to or in association with flammable or explosive substances or substances which could cause combustion.

5.5.4 Medical devices and IVD medical devices should be designed and manufactured in such a way that adjustment, calibration, and maintenance can be done safely and effectively. Specifically,

a) When maintenance is not possible, for example, with implants, the risks from ageing of materials, etc. should be appropriately reduced.

b) When adjustment and calibration are not possible, for example, with certain kinds of thermometers, the risks from loss of accuracy of any measuring or control mechanism are appropriately reduced.

5.5.5 Medical devices and IVD medical devices that are intended to be operated together with other medical devices or IVD medical devices or products should be designed and manufactured in such a way that the interoperability and compatibility are reliable and safe.

5.5.6 Medical devices and IVD medical devices should be designed and manufactured in such a way as to appropriately reduce the risk of unauthorized access that could hamper the device from functioning as intended or impose a safety concern.

5.5.7 Any measurement, monitoring or display scale functions of medical devices and IVD medical devices should be designed and manufactured in line with ergonomic/usability principles, taking account of the intended purpose, users and the environmental conditions in which the medical devices and IVD medical devices are intended to be used.

5.5.8 Medical devices and IVD medical devices should be designed and manufactured in such a way as to facilitate their safe disposal or recycling and the safe disposal or recycling of related waste substances by the user, patient or other person. The instructions for use should identify safe disposal or recycling procedures and measures.

5.6 Protection against Electrical, Mechanical, and Thermal Risks

5.6.1 Medical devices and IVD medical devices should be designed and manufactured in such a way as to protect users against mechanical risks connected with, for example, resistance to movement, instability, and moving parts.

5.6.2 Medical devices and IVD medical devices should be designed and manufactured in such a way as to appropriately reduce the risks arising from vibration generated by the medical devices or IVD medical devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.

5.6.3 Medical devices and IVD medical devices should be designed and manufactured in such a way as to appropriately reduce the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.

5.6.4 Medical devices and IVD medical devices should be designed and manufactured in such a way as to appropriately reduce the risk related to the failure of any parts within the device that are intended to be connected or reconnected before or during use.

5.6.5 Accessible parts of medical devices and IVD medical devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings should not attain potentially dangerous temperatures under normal use.

5.7 Active Medical Devices and IVD Medical Devices and Medical Devices Connected to Them

5.7.1 For active medical devices and IVD medical devices, in the event of a single fault condition, appropriate means should be adopted to eliminate or appropriately reduce consequent risks.

5.7.2 Medical devices and IVD medical devices where the safety of the patient depends on an internal power supply should be equipped with a means of determining the state of the power supply and an appropriate warning or indication for when the capacity of the power supply becomes critical.

5.7.3 Medical devices and IVD medical devices where the safety of the patient depends on an external power supply should include an alarm system to signal any power failure.

5.7.4 Medical devices and IVD medical devices intended to monitor one or more clinical parameters of a patient should be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.

5.7.5 Medical devices and IVD medical devices should be designed and manufactured in such a way as to appropriately reduce the risks of creating electromagnetic interference which could impair the operation of any devices or equipment in the intended environment.

5.7.6 Medical devices and IVD medical devices should be designed and manufactured in such a way as to provide a level of intrinsic immunity to electromagnetic interference such that is adequate to enable them to operate as intended.

5.7.7 Medical devices and IVD medical devices should be designed and manufactured in such a way as to appropriately reduce the risk of accidental electric shocks to the user or any other person, both during normal use of the medical device or IVD medical device and in the event of a single fault condition in the medical device or IVD medical device, provided the medical device or IVD medical device is installed and maintained as indicated by the manufacturer.

5.8 Medical Devices and IVD Medical Devices that Incorporate Software or are Software as a Medical Device

5.8.1 Medical devices and IVD medical devices that incorporate electronic programmable systems, including software, or are software as a medical device, should be designed to ensure accuracy, reliability, precision, safety, and performance in line with their intended

use. In the event of a single fault condition, appropriate means should be adopted to eliminate or appropriately reduce consequent risks or impairment of performance.

5.8.2 For medical devices and IVD medical devices that incorporate software or are software as a medical device, the software should be developed, manufactured and maintained in accordance with the state of the art taking into account the principles of development life cycle (e.g., rapid development cycles, frequent changes, the cumulative effect of changes), risk management (e.g., changes to system, environment, and data), including information security (e.g., safely implement updates), verification and validation (e.g., change management process).

5.8.3 Software that is intended to be used in combination with mobile computing platforms should be designed and developed taking into account the platform itself (e.g. size and contrast ratio of the screen, connectivity, memory, etc.) and the external factors related to their use (varying environment as regards level of light or noise).

5.8.4 Manufacturers should set out minimum requirements concerning hardware, IT networks characteristics and IT security measures, including protection against unauthorized access, necessary to run the software as intended.

5.8.5 The medical device and IVD medical device should be designed, manufactured and maintained in such a way as to provide an adequate level of cybersecurity against attempts to gain unauthorized access.

5.9 Medical Devices and IVD Medical Devices with a Diagnostic or Measuring Function

5.9.1 Medical devices and IVD medical devices with a diagnostic or measuring (including monitoring) function should be designed and manufactured in such a way as to provide, among other performance characteristics, sufficient accuracy, precision and stability for their intended purpose, based on appropriate scientific and technical methods.

a) Where applicable, the limits of accuracy should be indicated by the manufacturer.

b) Whenever possible, values expressed numerically should be in commonly accepted, standardized units, and understood by users of the medical device or IVD medical device. While generally supporting the convergence on the global use of internationally standardized measurement units, considerations of safety, user familiarity and established clinical practice may justify the use of other recognized measurement units.

c) The function of the controls and indicators should be clearly specified on the medical device and IVD medical device. Where a medical device or IVD medical device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information should be understandable to the user and, as appropriate, the patient.

5.10 **Labeling**

The following principle is a general recommendation for labeling. For additional guidance on the contents of the labeling, please refer to IMDRF/GRRP WG/N52.

5.10.1 Medical devices and IVD medical devices should be accompanied by the information needed to distinctively identify the medical device or IVD medical device and its manufacturer. Each medical device and IVD medical device should also be accompanied by, or direct the user to any safety and performance information relevant to the user, or any other person, as appropriate. Such information may appear on the medical device or IVD medical device itself, on the packaging or in the instructions for use, or be readily accessible through electronic means (such as a website), and should be easily understood by the intended user.

5.11 **Protection against Radiation**

5.11.1 Medical devices and IVD medical devices should be designed, manufactured and packaged in such a way that exposure of users, other persons, or where appropriate, patients, to radiation is appropriately reduced in a manner that is compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for diagnostic and therapeutic purposes.

5.11.2 The operating instructions for medical devices and IVD medical devices emitting hazardous or potentially hazardous radiation should contain detailed information as to the nature of the emitted radiation, the means of protecting the users, other persons, or where appropriate, patients, and ways of avoiding misuse and of appropriately reducing the risks inherent to transport, storage and installation.

5.11.3 Where medical devices and IVD medical devices are intended to emit hazardous, or potentially hazardous, radiation, they should be fitted, where possible, with visual displays and/or audible warnings of such emissions.

5.11.4 Medical devices and IVD medical devices should be designed and manufactured in such a way that that the exposure of users, other persons, or where appropriate, patients, to the emission of unintended, stray or scattered radiation is appropriately reduced. Where possible and appropriate, methods should be selected which reduce the exposure to radiation of users, other persons, or where appropriate, patients, who may be affected.

5.11.5 For medical devices and IVD medical devices emitting hazardous or potentially hazardous radiation and that require installation, information regarding the acceptance and performance testing, the acceptance criteria, and the maintenance procedure should be specified in the operating instructions.

5.11.6 Where medical devices and IVD medical devices are intended to emit hazardous, or potentially hazardous, radiation, accessible to user, they should be designed and manufactured in such a way as to ensure that the quantity, geometry, energy distribution

(or quality), and other key characteristics of the radiation emitted can be appropriately controlled and adjusted and, where appropriate, monitored during use. Such medical devices and IVD medical devices should be designed and manufactured to ensure reproducibility of relevant variable parameters within an acceptable tolerance.

5.12 Protection against the Risks posed by Medical Devices and IVD Medical Devices intended by the Manufacturer for use by Lay Users

5.12.1 Medical devices and IVD medical devices for use by lay users (such as self-testing or near-patient testing intended for use by lay users) should be designed and manufactured in such a way that they perform appropriately for their intended use/purpose taking into account the skills and the means available to lay users and the influence resulting from variation that can be reasonably anticipated in the lay user's technique and environment. The information and instructions provided by the manufacturer should be easy for the lay user to understand and apply when using the medical device or IVD medical device and interpreting the results.

5.12.2 Medical devices and IVD medical devices for use by lay users (such as self-testing or near-patient testing intended for use by lay users) should be designed and manufactured in such a way as to:

a) ensure that the medical device and IVD medical device can be used safely and accurately by the intended user per instructions for use. When the risks associated with the instructions for use cannot be mitigated to appropriate levels, these risks may be mitigated through training.

b) appropriately reduce the risk of error by the intended user in the handling of the medical device or IVD medical device and, if applicable, in the interpretation of the results.

5.12.3 Medical devices and IVD medical devices for use by lay users (such as self-testing or near-patient testing intended for use by lay users) should, where appropriate, include means by which the lay user:

a) can verify that, at the time of use, the medical device or IVD medical device will perform as intended by the manufacturer, and

b) is warned if the medical device or IVD medical device has failed to operate as intended or to provide a valid result.

5.13 Medical Devices and IVD Medical Devices Incorporating Materials of Biological Origin

5.13.1 For medical devices and IVD medical devices that include tissues, cells, or substances of animal, plant, or bacterial origin or their derivatives, which are non-viable or rendered

non-viable the following should apply:

a) where appropriate, taking into account the animal species, tissues and cells of animal origin, or their derivatives, should originate from animals that have been subjected to veterinary controls that are adapted to the intended use of the tissues.

   Information on the geographical origin of the animals may need to be retained by manufacturers depending on jurisdictional requirements.

b) sourcing, processing, preservation, testing and handling of tissues, cells and substances of animal origin, or their derivatives, should be carried out so as to provide safety for patients, users and, where applicable, other persons. In particular, safety with regards to viruses and other transmissible agents should be addressed by implementation of validated state of the art methods of elimination or inactivation in the course of the manufacturing process, except when the use of such methods would lead to unacceptable degradation compromising the medical device or IVD medical device.

5.13.2 For Regulatory Authorities, which regulate products manufactured utilizing tissues, cells, or substances of human origin or their derivatives as medical devices or IVD medical devices, the following should apply:

a) donation, procurement and testing of the tissues and cells should be done in accordance with jurisdictional requirements; and

b) processing, preservation and any other handling of those tissues and cells or their derivatives should be carried out so as to provide safety for patients, users and, where applicable, other persons. In particular, safety with regard to viruses and other transmissible agents should be addressed by appropriate methods of sourcing and by implementation of validated state of the art methods of elimination or inactivation in the course of the manufacturing process.

5.13.3 For medical devices and IVD medical devices manufactured utilizing biological substances other than those referred to in Sections 5.13.1 and 5.13.2 (for example, materials of plant or bacterial origin), the processing, preservation, testing and handling of those substances should be carried out so as to provide safety for patients, users and, where applicable, other persons, including in the waste disposal chain. In particular, safety with regards to viruses and other transmissible agents should be addressed by appropriate methods of sourcing and by implementation of validated state of the art methods of elimination or inactivation in the course of the manufacturing process. Other requirements can apply in specific regulatory jurisdictions.

6.0 Essential Principles Applicable to Medical Devices other than IVD Medical Devices

The essential design and manufacturing principles listed in this Section of the document are

additional to the essential principles listed in Section 5. These essential principles are applicable to medical devices other than IVD medical devices.

6.1 Chemical, Physical and Biological Properties

6.1.1 With regards to chemical, physical, and biological properties of a medical device, particular attention should be paid to the compatibility between the materials and substances used and biological tissues, cells and body fluids, taking account of the intended purpose of the device and, where relevant (for example, for some absorbable products), absorption, distribution, metabolism and excretion.

6.1.2 Medical devices should be designed and manufactured in such a way that they can be used safely with the materials, substances, and gases, with which they enter into contact during their intended use; if the devices are intended to administer medicinal products they should be designed and manufactured in such a way as to be compatible with the medicinal products concerned in accordance with the provisions and restrictions governing those medicinal products and that the performance of both the medicinal products and of the devices is maintained in accordance with their respective indications and intended use.

6.1.3 Medical devices should be designed and manufactured in such a way as to appropriately reduce the risks linked to the size and the properties of particles which are or can be released into the patient's or user's body, unless they come into contact with intact skin only. Special attention should be given to nanomaterials.

6.2 Protection against Radiation

6.2.1 Medical devices emitting ionizing radiation intended for medical imaging should be designed and manufactured in such a way as to achieve an image and/or output quality that are appropriate to the intended medical purpose whilst minimizing radiation exposure of the patient, user, and other persons.

6.2.2 Medical devices emitting ionizing radiation should be designed to allow the accurate estimation (or monitoring), display, reporting, and recording of the dose from a treatment.

6.3 Particular Requirements for Implantable Medical Devices

6.3.1 Implantable medical devices should be designed and manufactured in such a way as to remove or appropriately reduce the risks associated with medical treatment, e.g. the use of defibrillators, high-frequency surgical equipment.

6.3.2 Active programmable implantable medical devices should be designed and manufactured in a manner that allows the unequivocal identification of the device without the need for a

surgical operation.

6.4 Protection against the Risks Posed to the Patient or User by Medical Devices Supplying Energy or Substances

6.4.1 Medical devices for supplying the patient with energy or substances should be designed and manufactured in such a way that the amount to be delivered can be set and maintained accurately enough to ensure the safety of the patient, user, and others.

6.4.2 Medical devices should be fitted with the means of preventing and/or indicating any inadequacies in the amount of energy delivered or substances delivered which could pose a danger. Devices should incorporate suitable means to appropriately reduce the risk of accidental release of dangerous levels of energy or substances from an energy and/or substance source.

6.5 Medical Devices Incorporating a Substance Considered to be a Medicinal Product/Drug

6.5.1 Where a medical device incorporates, as an integral part, a substance which, if used separately may be considered to be a medicinal product/drug as defined in the relevant legislation that applies in that Regulatory Authority and which is liable to act upon the body with action ancillary to that of the medical device, the safety and performance of the medical device as a whole should be verified, as well as the identity, safety, quality and efficacy of the substance in the specific combination product.[3]

7.0 Essential Principles Applicable to IVD Medical Devices

The essential design and manufacturing principles listed in this Section of the document are additional to the essential principles of safety and performance listed in Section 5. These essential principles are applicable to only IVD medical devices.

7.1 Chemical, Physical and Biological Properties

7.1.1 With regards to chemical, physical, and biological properties for IVD medical devices,

[3] This essential principle is not intended to provide definitions for combination products since these definitions are yet to be harmonized and how combination products are handled varies among different regulatory authorities.

attention should be paid to the possibility of impairment of analytical performance due to physical and/or chemical incompatibility between the materials used and the specimens, analyte or marker to be detected and measured (such as biological tissues, cells, body fluids and micro-organisms), taking account of the intended purpose of the device.

7.2 Performance Characteristics

7.2.1 IVD medical devices should achieve the analytical and clinical performances, as stated by the manufacturer that are applicable to the intended use/purpose, taking into account the intended patient population, the intended user, and the setting of intended use. These performance characteristics should be established using suitable, validated, state of the art methods. For example:

a) The analytical performance can include, but is not limited to,

   a. Traceability of calibrators and controls
   b. Accuracy of measurement (trueness and precision)
   c. Analytical sensitivity/Limit of detection
   d. Analytical specificity
   e. Measuring interval/range
   f. Specimen stability

b) The clinical performance, for example diagnostic/clinical sensitivity, diagnostic/clinical specificity, positive predictive value, negative predictive value, likelihood ratios, and expected values in normal and affected populations.

c) Validated control procedures to assure the user that the IVD medical device is performing as intended, and therefore the results are suitable for the intended use.

7.2.2 Where the performance of an IVD medical device depends on the use of calibrators or control materials, the traceability of values assigned to such calibrators or control materials should be ensured through available reference measurement procedures or available reference materials of a higher order.

7.2.3 Wherever possible, values expressed numerically should be in commonly accepted, standardized units and understood by the users of the IVD medical device.

7.2.4 The performance characteristics of the IVD medical device should be evaluated according to the intended use statement which may include the following:

a) intended user, for example, lay user, laboratory professional;

b) intended use environment, for example, patient home, emergency units, ambulances, healthcare centers, laboratory;

c) relevant populations, for example, pediatric, adult, pregnant women, individuals with signs and symptoms of a specific disease, patients undergoing differential

diagnosis, blood donors, etc. Populations evaluated should represent, where appropriate, ethnically, gender, and genetically diverse populations so as to be representative of the population(s) where the device is intended to be marketed. For infectious diseases, it is recommended that the populations selected have similar prevalence rates.

Appendices

Appendix A: Use of Standards in Meeting Essential Principles

Consensus standards that contain detailed requirements may be used to demonstrate conformance with the essential principles of safety and performance. Such consensus standards provide a greater level of detail and specificity than can be expressed in the essential principles. The essential principles of safety and performance and their related standards can be useful in the fulfilment of pre-market and post-market requirements throughout the lifecycle of medical devices and IVD medical devices. It is important to note that, the use of specific consensus standards, depends on the requirements of the Regulatory Authorities having jurisdiction. Use of these consensus standards is voluntary, and manufacturers may establish alternative ways to demonstrate that they meet the essential principles. In addition, some Regulatory Authorities may have additional requirements outside of these essential principles of safety and performance.

A. General Approach to Using Standards

The essential principles of safety and performance are the general, high-level criteria that when met play a major role in the determination that a medical device and IVD medical device is safe and effective. Regulatory requirements expect that a medical device and IVD medical device be safe and effective during its lifecycle and so conformity with the essential principles of safety and performance should be achieved throughout the lifecycle of the medical device and IVD medical device. This usually means that the medical device and IVD medical device should be:

a) designed to be safe and effective, complying with the essential principles of safety and performance,
b) manufactured to maintain the design characteristics, and
c) used in a way that maintains the design characteristics.

In the case of concerning findings while the medical device or IVD medical device is in the post-production phase (i.e., after marketing approval and manufacturing), the production and post-production information should be evaluated for relevancy to safety and performance and a redesign of the product might be needed to return the medical device or IVD medical device to compliance with the essential principles of safety and performance.

It is important to note that it is not possible to assure an acceptable level of safety and performance in the lifecycle by simply being compliant with one or more standards at one time. The requirements in a single standard typically do not meet all the specific parts of a given essential principle as related to a given medical device or IVD medical device. A process for continuous compliance is required and the expectation is that this is achieved through the use of a robust quality management system and a risk management process.

B. Use of Standards by Regulatory Authorities having Jurisdiction

In some countries, Regulatory Authorities having jurisdiction acknowledge the use of voluntary consensus standards as one means of demonstrating compliance with relevant essential principles of safety and performance of medical devices and IVD medical devices. In addition, use of consensus standards can promote harmonization among Regulatory Authorities in the regulation

of medical devices and IVD medical devices.

Standards suitable to address the essential principles should be based on:

a) a close relationship of the scope of the standard to one or more of the essential principles,
b) the clarity, effectiveness, and completeness of the technical requirements contained in the standard as it relates to a specific essential principle,
c) the existence of test methods for determining compliance with each of the technical requirements in the standard, and
d) the definition of clear acceptance criterion for determining that each technical requirement is met.

These standards should, wherever possible, be standards incorporating the thinking of the global marketplace and help support the development of consistent expectations between Regulatory Authorities having jurisdiction. In the absence of international consensus standards, it may be appropriate for Regulatory Authorities having jurisdiction to accept the use of regional or national consensus standards or industry standards. Regulatory Authorities having jurisdiction typically establish and maintain a list of accepted standards that they find suitable for demonstrating conformance to these essential principles.

C. Assessing the Conformity of a Medical Device and IVD Medical Device

Conformity assessment is performed by a Regulatory Authority or other party, and is a demonstration that a medical device or IVD medical device conforms to the essential principles as an assurance it is safe and performs as intended. Conformity assessment can include a variety of evaluation activities including examination of records and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority having jurisdiction. In assessing the conformity of a medical device with the essential principles, standards or parts of several standards may be utilized and combined in a way that is appropriate for the specific medical device or IVD medical device. In some cases, the use of parts of standards and/or combinations of standards should be acceptable for conformity assessment purposes.

If the combination of standards does not cover all the necessary essential principles of safety and performance for a specific medical device or IVD medical device, other means of demonstrating conformance to the essential principles should be used. In addition, the Regulatory Authority having jurisdiction may have additional requirements that are beyond those contained in the standard. In some cases, even if there is an available standard, other objective evidence acceptable to the regulatory authority may be used in lieu of using any standard to demonstrate conformance to the essential principles.

D. Risk Management within Consensus Standards

Risk management is increasingly becoming a key principle within standards. For example, many medical device consensus standards include risk management principles in the application of these standards during the medical device and IVD medical device lifecycle. The use of risk management principles in these consensus standards allows these standards to remain relevant and helpful as technology advances. Application of risk management principles within

consensus standards requires the medical device and IVD medical device manufacturer to consider the implications of design and manufacturing decisions made during the lifecycle of the medical device. Documentation of these risk management activities can provide a justification that manufacturers design and manufacturing decisions meet a Regulatory Authority's requirements for marketing a medical device and IVD medical device.

Appendix B: Guidance on Essential Principles

The table below is intended to provide general guidance for meeting the essential principles of safety and performance. The standards and guidances below are not intended to encompass all of the requirements to meet a particular essential principle, but rather provide some overarching guidance. Depending on the specific medical device or IVD medical device additional product specific standards may need to be used. In addition, the requirements of the particular Regulatory Authority having jurisdiction must also be taken into consideration.

Essential Principle	Guidances	Relevant Standards
5.1	GHTF/SG3/N18:2010 *Quality Management System –Medical Devices – Guidance on Corrective Action and Preventive Action and related QMS Processes* GHTF/SG3/N17:2008 *Quality Management System – Medical Devices – Guidance on the Control of Products and Services Obtained from Suppliers* GHTF/SG3/N99-10:2004 *Quality Management Systems - Process Validation Guidance* GHTF/SG3/N15R8 *Implementation of Risk Management Principles and Activities within a Quality Management System* ISO 13485:2016 Handbook	ISO 13485 ISO 14971 ISO 23640 ISO 24971 CLSI EP25
5.2	Declaration of Helsinki GHTF/SG5/N1R8:2007 *Clinical Evidence – Key Definitions and Concepts* GHTF/SG5/N2R8:2007 *Clinical Evaluation* GHTF/SG5/N3:2010 *Clinical Investigations* GHTF/SG5/N6:2012 *Clinical Evidence for IVD Medical Devices - Key Definitions and Concepts* GHTF/SG5/N7:2012 *Clinical Evidence for IVD Medical Devices - Scientific Validity Determination and Performance Evaluation*. GHTF/SG5/N8:2012 *Clinical Performance Studies for In Vitro Diagnostic Medical Devices*	ISO 14155
5.3		ISO 10993 IEC 60601 IEC 61010
5.4		ISO 11135 ISO 11137 ISO 11138 ISO 11140 ISO 11607 ISO 10993 ISO 11737 ISO 13408 ISO 14644 ISO 14937 ISO 14698 ISO 17664 ISO 17665

5.5		IEC 60601 IEC 61010 IEC 62366-1 IEC/TR 62366-2 IEC 80001 ISO 80369 IEC 62304
5.6		IEC 60601 IEC 61010
5.7		IEC 60601 IEC 61010
5.8	IMDRF/SaMD WG/N41FINAL:2017 *Software as a Medical Device (SaMD): Clinical Evaluation* IMDRF/SaMD WG/N23 FINAL:2015 *Software as a Medical Device (SaMD): Application of Quality Management System* IMDRF/SaMD WG/N12 FINAL:2014 *"Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations* IMDRF/SaMD WG/N10 FINAL:2013 *Software as a Medical Device (SaMD): Key Definitions*	IEC 62304
5.9		IEC 60601 IEC 61010 IEC 62366-1 IEC/TR 62366-2
5.10	IMDRF/GRRP WG/N52 *Principles of Labeling for Medical Devices and IVD Medical Devices*	ISO 15223-1 ISO 18113
5.11		IEC 60601 IEC 61010
5.12		IEC 62366-1 IEC/TR 62366-2
5.13		ISO 22442
5.14	Refer to jurisdictional requirements.	
6.1		ISO 10993 IEC 60601

6.2		IEC 60601
6.3	Requirements depend on the type of implantable device.	
6.4		IEC 60601
7.1		CLSI EP05 CLSI EP06 CLSI EP07 CLSI EP12 CLSI EP17 CLSI EP21 CLSI EP25 CLSI EP28 ISO 17511 ISO 23640
7.2		ISO 10993 IEC 61010