AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

Draft

African Medical Devices Forum

Guidelines on regulatory requirements for issuance of market authorization of medical devices including in-vitro diagnostic medical devices

CONTENTS

ABBREVIATIONS

AMDF	African Medical Devices Forum
GHTF	Global Harmonization Task Force
IMDRF	International Medical Devices Regulators Forum
ISO	International Organization for Standardization
IVD	in-vitro diagnostic device
NRA	national regulatory authority
SOP	standard operating procedure
STED	summary technical documentation
ToC	IMDRF Table of Contents
WHO	World Health Organization

TERMS AND DEFINITIONS

Abridged assessment: assessment including performance evaluation, manufacturing site inspection of abridged scope and labelling review.

Accessory: an article which is intended specifically by its manufacturer to be used together with a parent device to enable that device to be used in accordance with its intended use as an IVD or to augment or extend the capabilities of the parent device in fulfilment of its intended use as an IVD, and therefore should be considered an IVD (1).

Act: The <Relevant NRA> Act or <Name of Authority> Act, Chapter <XXX>.
Analytical performance: ability of an IVD to detect or measure a particular analyte (2, 3).

Applicant: any person or institution or company that applies formally to get market authorization for a medical device.

Assay: investigative (analytical) procedure in a laboratory for qualitatively assessing or quantitatively measuring the presence, amount or functional activity of a target entity (analyte).

Authority: the <Relevant NRA> or the acronym “NRA” established under section <XXX> of the Act.
Calibrator: any substance, material or article intended by its manufacturer/owner to be used in the calibration of a measuring instrument or measuring system.

Certified copy: a true copy of the original document certified by a person registered to practise law in the manufacturer’s country of origin and endorsed with the legal practitioner’s official stamp and signature.
Change/variation: significant change means a change that could reasonably be expected to affect the safety or effectiveness of a medical device. It includes a change to any of the following:

a) the manufacturing process, facility or equipment;
b) the manufacturing quality control procedures, including the methods, tests or procedures used to control the quality, purity and sterility of the device or of the materials used in its manufacture;

c) the design of the device, including its performance characteristics, principles of operation and specifications of materials, energy source, software or accessories; and
d) the intended use of the device, including any new or extended use, any addition or deletion of a contraindication for the device, and any change to the period used to establish its expiry date.

Clinical performance: ability of an IVD to yield results that are correlated with a particular clinical condition/ physiological state in accordance to target population and intended use (4, 5).

Conformity assessment: the systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Authority, to determine that an IVD is safe and performs as intended by the manufacturer and therefore conforms to the Essential principles of safety and performance of in vitro medical devices (5,6,7,8).

Conformity assessment body (CAB): a body engaged in procedures for determining whether the relevant requirements in technical regulations or standards are fulfilled. A CAB is authorized to undertake specified conformity assessment activities by a regulatory authority that will ensure that performance of the CAB is monitored and, if necessary, withdraw designation (6, 7).

Dossier review: review and assessment of documentation including data, protocols, reports, procedures, etc., to support the quality, safety and performance of a product for the purpose of NRA registration.

Dossier screening: systematic process to ensure that all requisite sections of the product dossier are submitted.

Full assessment: assessment process of a diagnostic product, including dossier review, performance evaluation, inspection of manufacturing site(s) and labelling review.
High dose hook effect: incorrect low measurement of analyte(s) that are present in the specimen in a very high concentration.

Inspection of manufacturing site(s): quality assessment of the manufacturing site(s) of the product undergoing assessment.

Intended use: the objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.

In-vitro diagnostic medical device (IVD): a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes (9).

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.
Label: any written, printed or graphic representation that appears on, or is attached to, the IVD or active

ingredient or any part of its packaging and includes any informational sheet or leaflet that accompanies the in-vitro diagnostic or active ingredient when it is being supplied (10).

Labelling review: review and assessment of the instructions for use and product labels.

Layperson: any individual who does not have formal training in a relevant field or discipline.
Local responsible person: a natural person residing in the country, or cooperate body registered in the country, who has received a legal mandate from the Applicant to act on his behalf with regard to matters pertaining to registration of devices in in the country (11).

Manufacturer: any natural or legal person with responsibility for the design and/or manufacture of a medical device with the intention of making the medical device available for use, under its name; whether or not such a medical device is designed and/or manufactured by that person, or on that person's behalf, by another person(s) (11).

Medical device(s): any instrument, apparatus, laboratory equipment and reagents, implement, machine, appliance, implant, in-vitro reagent or calibrator, software, material or other similar or related article which is intended by manufacturer to be used, alone or in combination for human beings or other animals for one more of the specific purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of diseases or compensation for an injury;
- investigation, replacement, modification or support or the anatomy or of a physiological process;
- supporting or sustaining life;
- control of conception;
- disinfection of medical devices;
- providing information for medical or diagnostic purposes by means of in-vitro examination or specimens derived from the human body or other animal; and
- does not achieve its primary intended action in or on the human body by pharmacological, immuno logical or metabolic means, but which may be assisted in its intended function by such means (9).

National standard: a standard as prescribed by the country's bureau of standards.

Near-patient testing: any testing performed outside the laboratory environment by qualified personnel, generally near to or at the side of the patient, also known as point-of-care testing (1).

Objective evidence: information that can be proved true, based on facts obtained through observation, measurement, testing or other means (12).

Performance evaluation: assessment and analysis of data to establish or verify the performance (analytical performance and where applicable, clinical performance) of an IVD (2, 3).

Process validation: confirmation by objective evidence that a process consistently produces a result or product meeting its predetermined requirements (13).

Risk assessment: overall process comprising a risk analysis and a risk evaluation (14).
Quality audit: the process of systematic examination of a quality system of IVD manufacturing facilities carried out by the Authority to demonstrate conformity for regulatory purposes.
Quality management system: collection of business processes aim to direct and control an organization

with regard to quality, from establishing quality policy, quality objectives and implementing and maintaining quality system (15).

Reagent: any chemical, biological or immunological component, solution or preparation intended by the manufacturer to be used as IVD.

Rebranded product: a rebranded product is identical in every respect to the product manufactured by the original manufacturer, except that the product is labelled with the “rebranded” product name and product code and bears the rebrander’s name.

Rebrander: a manufacturer of a rebranded IVD.

Recall: any action taken by the manufacturer, importer, supplier or registrant of a medical device to remove it from the market or to retrieve the medical device from any person to whom it has been supplied, because the medical device may: be hazardous to health; fail to conform to any claim made by its manufacturer or importer relating to its quality, safety or performance.

Recognized standards: national or international standards deemed to offer the presumption of conformity to specific Essential principles of safety and performance.

Registrant: the person who applied for and obtained the registration of the medical device, including IVD, under the medical device regulations.

Regulatory version: relates to the information associated with a submission for approval by a regulatory authority. The submitted version is defined by all of the documentation related to development, manufacture and intended use, labelling and post-market surveillance of the product and all the documented evidence supporting the safety and performance claims associated with that submission. If any aspect of this documentation differs in any way between the submissions to different regulatory authorities or assessment bodies (e.g. United States Food and Drug Administration, Health Canada, a Notified Body for Conformité Européenne (CE) marking, etc.), it is considered to be a different regulatory version.

Risk: combination of the probability of occurrence of harm and the severity of that harm (1, 2, 6, 14, 16).

Self-testing: testing performed by oneself.

Specimen receptacles: devices, whether vacuum-type or not, specifically intended by their manufacturer for the primary containment and preservation of specimens derived from the human body and other animals for the purpose of IVD examination.

Technical documentation: documented evidence, normally an output of the quality management system, that demonstrates compliance of a device with the Essential principles of safety and performance of IVD.

Validation: confirmation by examination and provision of objective evidence that the requirements for a specific intended use have been fulfilled (17).

Verification: confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled (17).

1. INTRODUCTION

<Name of Authority> (XXX) was established under the <Name of Authority> Act, <Reference number> of <Year> with the mandate to regulate all health products, including medical devices. The registration process of medical devices is an official authorization to market a medical device following successful assessment of quality, safety and performance. In order to regulate health products successfully, <Name of Authority> has set up a framework for regulating medical devices in <Name of country>.

Adherence to these guidelines will ensure that all relevant information is provided in the application submitted for registration. This will facilitate efficient and effective evaluation, as well as the approval process. It will also help to avoid queries leading to unnecessary delay in giving approvals. This is in accordance with provisions of the <Name of Authority> Act, Chapter <XXX> and its corresponding guidelines for devices in <Name of country>.

As part of the registration process, <Name of Authority> will assess medical devices, including in-vitro diagnostic devices (IVDs), to verify compliance with national requirements. The assessment will be based on requirements provided in this document, based on requirements defined by the Global Harmonization Task Force/International Medical Device Regulators Forum (GHTF/IMDRF), International Organization for Standardization (ISO) standards, Clinical Laboratory Standards International guidelines, World Health Organization (WHO) guidelines and other guidance documents. The Authority will take a risk-based approach when regulating medical devices. In addition, this guideline has adapted key elements of the IMDRF Table of Contents (ToC) in line with the need for global convergence of regulatory systems for medical devices. A risk-based abridged assessment procedure will be considered and adopted for medical devices including IVDs, which have been prequalified by WHO or other well established jurisdictions to avoid duplications and accelerate registration of such products.

The assessment of the medical device by the national regulatory authority (NRA) can cover all regulatory components, i.e. product dossier, manufacturing site inspection and performance evaluation or clinical investigation and labelling review. This type of assessment is usually extensive, done over several months and requires financial and technical resources which often lack in many resource limited settings. Abridged assessment using reliance and recognition principles as elaborated in WHO global model regulatory framework for medical devices including in-vitro diagnostic medical devices (18) and the Collaborative Registration Procedure can be considered when such products have been assessed by WHO or matured NRA. In abridged assessment, the assessment reports from the stringent NRA or WHO are reviewed using established templates, but also considering country specific requirements such as translations and country specific labelling requirements. **Reliance and recognition are also advocated during epidemic situation**s.

Applicants are encouraged to familiarize themselves with these guidelines and follow them when preparing and submitting their applications for registration of medical devices. However, the requirements highlighted are a minimum; if there is additional information, you are invited to submit it to <Name of the Authority>.

1.1 Risk classification of medical devices

Regulatory controls are intended to safeguard the health and safety of patients, users and other persons by ensuring that manufacturers of medical devices, including in-vitro diagnostics, follow specified procedures during design, manufacture and marketing. These controls should be propor-

tionate to the level of risk associated with a medical device, whereby the level of regulatory control increases with an increasing degree of risk, while taking into account the benefits offered by use of the device. Annexes 1 and 2 provide details on the risk classification rules for medical devices. As an example, risk classification of IVDs is guided by several rules, including the risk to the individual and the public when using the IVD. Risk classification during the assessment of an IVD is based on IMDRF recommendations, using the following criteria:

a) the intended use and indications for use, as specified by the manufacturer (specific disorder, condition or risk factor for which the test is intended);
b) the technical/scientific/medical expertise of the intended user (layperson or professional);
c) the importance of the information for reaching a diagnosis (sole determinant or one of several), taking into consideration the natural history of the disease or dis order, including presenting signs and symp toms which may guide a physician/veteri narian; and
d) the impact of the result (true or false) on the individual and/or public health.

IVDs are classified into four (4) risk classes, A, B, C or D, using classification rules. If more than one classification rule is applicable to the device, the rules resulting in the highest risk classification shall be applied. However, the Authority reserves the right to make the final decision on the class of the device. Based on the risk class, the degree of conformity assessment of the IVDs will increase from class A, having minimal oversight, to classes C and D, where the Authority is expected to assess the product more critically to ensure safety, quality and performance.

2. SCOPE AND PURPOSE

These guidelines are intended to provide manufacturers or their local representative with an overview of the harmonized processes and requirements for market authorization of medical devices, including IVDs, applicable in <Name of country>. Manufacturers wishing to apply for <Name of Authority> assessment of their product(s) should read this document before submitting their application.

3. ROLES AND RESPONSIBILITIES

Applicants, including manufacturers and or their authorized representatives, are the main actors involved in the assessment of medical devices including IVDs. Their roles and responsibilities are described below.

3.1 Applicant

Applications for registration of medical devices, including IVDs, can be made by the manufacturer of the device or their representative or by a person who orders the medical devices, including IVDs, to be manufactured for sale in <Name of country>. The Applicant shall be responsible for the product, information supplied in support of the application for registration, renewal and variations thereof. An Applicant who is not a resident of <Name of country> shall nominate a local responsible person. A certified copy of power of attorney, formal agreement or any other official authorization shall be submitted by an Applicant as official proof of nomination of a local responsible person. The manufacturer or local responsible person shall:

a) submit the application for market authorization and support the Authority in the whole process;
b) monitor the device on the market and inform the Authority immediately after the detection of any problem relating to a registered device, such as serious manufacturing defects, which may endanger personal or public health;
c) facilitate communication between the Applicant and the Authority on matters relating to the product;
d) handle implementation of device recalls;
e) provide technical support and service maintenance for registered device(s);
f) collect and submit post-market surveillance data on behalf of the manufacturer.

4. APPLICATION PROCESS

An application consists of documentation in hard copy and/or electronic form, samples and fees. The Applicant should have the following information before submitting the application to <Name of Authority>.

a) class of the device;
b) intended purpose of the device;
c) Global Medical Devices Nomenclature code and term;
d) conformity assessment certification; and
e) declaration of conformity.

There are several stages in the process of assessment of medical devices, including IVD, depending on the risk class and currently available data on the performance of the medical devices, including IVD. They include submission of an application for market authorization, assessment of the product dossier or technical file, assessment of the manufacturer quality management system through manufacturing site inspection, performance evaluation and labelling review.

4.1 Application form

A completed application form (see Annex 3) provides summary information about the product, its regulatory version and the manufacturer. The details provided in this form will inform the Authority in its decision on whether or not the product submitted is eligible for assessment and, if so, whether or not the assessment can be abridged. The information contained in the application is also used to determine the plan for each of the components of the assessment process. It is therefore important for the manufacturer to ensure that the information supplied in the application form is accurate and complete.

For all medical devices, including all IVD risk classes, the Applicant will submit the application form <together with dossier (technical file)> which has

been compiled according to the IMDRF Table of Contents format (ToC) which has recently replaced the summary technical documentation (STED) format (19) (Annexes 4 and 5). ToC has been adopted by many jurisdictions including WHO (20). All documents will be in <English> and must be submitted, preferably electronically. The manufacturer will pay an application fee, following the fee payment structure of the Authority. Bank details and payment procedures must also be clearly indicated.

The application form, supporting documentation including proof of payment will be reviewed by the Authority against the established eligibility criteria to determine the product's eligibility for registration assessment. If necessary, the manufacturer may receive a communication from the Authority requesting additional information and/or clarifications to assist it in the eligibility decision. The manufacturer must provide the Authority with the information and/or clarifications so requested within the time frame prescribed by the Authority. The Authority will inform the manufacturer in writing of its decision whether or not the product is eligible for assessment.

4.2 Product dossier submission

The product dossier shall be prepared according to established <Name of Authority> instructions for compilation of the product dossier based on IMDRF ToC (Annexes 4 and 5) associated checklist which will help the manufacturer to ensure that all sections have been included in the product dossier. Manufacturers must ensure that the contents of the product dossier are consistent with the information submitted in the application form and that any changes in the information submitted in, or as part of, the presubmission form are promptly notified in writing to the Authority. When a similar product (same regulatory version) has been assessed by a stringent regulatory authority, the manufacturer will be encouraged to submit a copy of the dossier, the dossier assessment and the manufacturing site inspection reports for possible recognition or reliance.

4.2.1 Product dossier review

The Authority will review the product dossier to assess the evidence in support of safety and performance of the product and assess the product design and manufacture. The assessment of product dossiers will be conducted in accordance with standard operating procedures (SOPs) and checklists established by the Authority for that purpose, so as to ensure uniformity in evaluation and timeliness of assessment activities (see also ( ) and Annex 6). Any deficiencies in the documentation submitted and/or in the data identified in the product dossier review will be communicated in writing to the manufacturer by the Authority.

A corrective action plan that details the amendments needed to correct the deficiencies (e.g. responses to comments; documentation and/or data that is missing) and deadlines for their submission must be provided by the manufacturer to the Authority.

The manufacturer will have the opportunity to submit up to <two (2)> corrective action plans and, provided that the corrective action plan is accepted by the Authority, only <one (1)> amendment to the original product dossier will be permitted. The assessment procedure will be suspended (i.e. the Authority will not undertake any further action) until a corrective action plan has been submitted by the manufacturer and accepted by the Authority. In certain cases, the Authority may agree, at its sole discretion, to permit the manufacturer to correct specific nonconformities after registration of the product, provided that the manufacturer commits itself in writing to correcting them by an agreed deadline. Such a "commitment to registration" will be reflected in the Authority registration report and will be verified during the reinspection. Failure to comply with registration commitments within the agreed deadline will result in the delisting from the Authority list of the registered medical device(s), including IVD(s).

The manufacturer may request a hearing or meeting with the Authority to clarify issues identified during dossier review. The Authority may provide technical guidance and specifications to manufacturers to facilitate compliance with the Authority

requirements. WHO has published several specifications and technical series, which can be used as guidance (22,23).

If the product successfully meets the Authority registration requirements, a summary of the product dossier review will be included in the Authority registration report. In the case of abridged assessment, the Authority registration report may also include the manufacturer's commitments to registration to resolve findings from the manufacturing site inspection relating to the technical documentation.

4.3 Inspection of manufacturing sites

The inspection of the manufacturing site(s) will be conducted to assess compliance of the manufacturer's quality management system and manufacturing practices with international standards, such as the quality management standard ISO 13485:2016 Medical devices – Quality management systems. Requirements for regulatory purposes and other relevant international standards and guidelines produced by IMDRF, including NRA technical guidelines (24). Therefore, customer-related issues that may be covered only in general terms in ISO 13485:2016 will be inspected in detail, based on prepared SOPs for conducting manufacturing site inspections. The Global Harmonization Working Party has published excellent guidance on the requirements for medical device auditing organizations for regulatory authority recognition (25,25).

Generally, there are four types of inspections: initial inspection, reinspection, special inspection and inspection under abridged assessment. Initial inspection is usually performed in two stages: Stage 1 inspection, usually a desk audit, will evaluate the documentation related to the quality management system to establish readiness for a Stage 2 inspection. General information about the documented quality management system, including the quality manual and manufacturing processes, organigram, workflows, critical suppliers and floor plan, will be reviewed. Any issues of concern will be communicated to the manufacturer. A satisfactory Stage 1 inspection is a precondition for proceeding to the Stage 2 inspection. The Stage 2 inspection will comprehensively evaluate the effective implementation of the quality management system and implemented production processes through one or more on-site inspections.

The manufacturing site may be reinspected when this is required by the Authority to ensure ongoing compliance with the registration requirements. This will be either a partial inspection (also known as a surveillance inspection) or a full inspection depending on, for example, the type of product, results of inspections by a recognized NRA, feedback from the market such as recalls or complaints and/or changes to the quality management system, manufacturing site or product(s) since the last inspection. Routine reinspections shall typically occur every <three to five (3–5)> years after market authorization of the product by the Authority, unless an earlier reinspection is deemed necessary by the Authority.

A special inspection may be required when the effective implementation of corrective actions to prevent the recurrence of nonconformities needs to be verified in a follow-up inspection; prior to registration; or when substantial changes are made to the medical device's design, composition, safety and/or performance. Other reasons include cases where serious concerns have been raised about the ongoing quality of the medical devices, including IVDs; when production has been suspended and then resumed; and/or when there is a significant change in the quality management system.

The Authority will document the eligibility for the inspection with an abridged scope based on the documentation provided with the presubmission form. If the product qualifies for an inspection with an abridged scope, the manufacturer will not have to submit the full quality management system documentation for a Stage 1 inspection. The manufacturer must, however, submit upon request by the Authority a defined-information package that will assist the Authority in preparing for inspection of the manufacturing site(s). The on-site inspection time will be limited and calculated for selected product(s) and key processes for that site (e.g. risk

management, in-use stability of the medical device under poorly controlled conditions, impact on stability of transportation, information gathered from the market, etc., user training and materials). An inspection with an abridged scope will not necessarily include a review of all quality management system procedures and processes that are usually inspected, as it will take into consideration the findings of the most recent regulatory audit reports (full and surveillance). There will be limited sampling of some of the general quality management processes and a follow-up or clarification of individual findings identified in the previous report.

Evidence will be collected on-site through examination of documents, including SOPs and records; visual observation of activities; visual observation of environmental conditions; it may include random sampling of the product for laboratory quality control testing. During the inspection, the quality records and reports that support the data submitted with the product dossier for the Authority assessment will be sampled. This material may include, but is not limited to, data recorded for the batches submitted for the Authority performance evaluation or testing, trial data collected in performance studies (internal and independent external), quality control data and batch manufacturing records. The manufacturer must ensure that the entire product dossier submitted to the Authority is available on-site.

If serious or critical nonconformities of public health concern are identified in connection with an inspection, the Authority reserves the right to use, publish, issue and/or share them with relevant authorities. The manufacturer should carefully read the information set out in the Authority document information for manufacturers on the inspection of manufacturing site(s) for more information on the requirements of inspection, reports and nonconformities.

4.3.1 Report on the inspection of the manufacturing site(s)

The Global Harmonization Working Party has an excellent publication on the process of grading on nonconformities during manufacturing site inspection (25). A preliminary nonconformity report detailing issues of concern (if any) will be issued to the manufacturer on the final day of the inspection. A final inspection report including the graded nonconformities will be issued to the manufacturer after the inspection of the manufacturing site(s).
All nonconformities must be corrected by the manufacturer through suitable corrective actions addressing the root cause of each nonconformity. The manufacturer will have the opportunity to submit up to <two (2)> corrective action plans. Depending on the nature and number of nonconformities, objective evidence of the effective implementation of proposed corrective actions may be required.

The Authority will assess the information provided and decide whether the corrective action plan can be accepted. Conformity with the Authority requirements will be established on the basis of assessment of such information. In some instances, the number and criticality of nonconformities may require the effective implementation of proposed corrective actions to be verified in a follow-up inspection, before the nonconformities can be closed off.
A summary of the findings of the inspection of the manufacturing site(s) will be included in the Authority public report, if the product successfully meets the Authority's requirements. In certain cases, the Authority may agree, at its sole discretion, to permit the manufacturer to correct specific nonconformities after registration of the product, provided that the manufacturer commits itself in writing to addressing them by an agreed deadline. Such a "commitment to registration" will be reflected in the Authority public report and will be verified during the reinspection.

Failure to comply with registration commitments within agreed deadlines will result in the delisting from the Authority list of the registered medical device(s) concerned. If the manufacturer does not meet the Authority's requirements, the application will be cancelled.

4.4 Performance evaluation or clinical trials of medical devices

Performance evaluation or a clinical trial of a medical device is an essential assessment component for independent verification of the performance claims and operational characteristics of an IVD submitted for registration. It also allows the Authority to verify performance and operational characteristics that are considered essential for use in <Name of country>. In case of other medical devices, limited clinical trials may be performed under supervision of the Authority. The data obtained complement the verification and validation data submitted by the manufacturer in the product dossier. The performance evaluation of IVDs is a component of both the full assessment and the abridged assessment. The performance evaluation of the product is carried out by a specified Authority-appointed laboratory with established laboratory quality management system certification.

The Authority may coordinate the performance evaluation, while the manufacturer is required to oversee clinical trials. The performance evaluation must be carried out in accordance with a publicly available Authority analyte-specific protocol developed in collaboration with national laboratory experts. The manufacturer will be requested to send sufficient quantities from at least < two (2)> different lots of the product. For the purposes of the Authority's performance evaluation, a lot is defined as "The amount of material that is uniform in its properties and has been produced in one process or series of processes. The material can be either starting material, intermediate material or finished product" (27). Furthermore, the <two (2)> lots must be sourced from a representative production run and not produced especially for the purpose of the Authority performance evaluation. Detailed shipping instructions (e.g. number of test kits and/or instruments, number of lots, etc.) will be communicated in due time to the manufacturer by the evaluating site(s).

The manufacturer must send to the evaluating site(s) the requisite quantities and lots of the product (test kits and/or instruments) on "free domicile" terms, in accordance with the aforementioned detailed shipping instructions, free of charge, and delivered with all customs declarations, customs duties and transport and other charges paid for by the manufacturer. If necessary, special equipment needed to perform the assay must be made available by the manufacturer at no charge to the evaluating site (e.g. customs declaration and payment of customs duties, transport, installation, training, etc.) for the duration of the assessment process. The Authority will have absolute, exclusive, unfettered control over the manner in which the assessment is carried out (including the performance evaluation and/or the publication of results of the assessment, regardless of the outcome).

Without prejudice to the foregoing and in agreement with the Authority, the manufacturer may wish to visit the specified evaluating site (s) or clinical trial sites to observe the operator performing the test procedure on the manufacturer's product(s) before commencing the performance or clinical evaluation. No changes should, however, be made to the test procedure as outlined in the instructions for use. If such changes are desired, the manufacturer must notify the Authority in writing, and the performance evaluation will be suspended.

The Authority will send the draft performance evaluation or clinical trial report, including the data, to the manufacturer, which will have the opportunity to review and comment on the report and results. The Authority will take reasonable account of any comments by the manufacturer on the draft performance evaluation report, provided that such comments are submitted by the manufacturer in writing to the Authority within <one (1)> month of the manufacturer's receipt of the draft performance evaluation or clinical trial results. For the avoidance of doubt: the Authority will maintain full and exclusive control over the data analysis, the reporting of the performance evaluation results and the form and content of any publication thereof. After such <one (1)> month period, the performance evaluation report will be considered final.

A summary of the performance evaluation or clinical trial report will be included in the Authority public report if the product successfully meets the Au-

thority's requirements.

4.5 Labelling review

Product labelling is considered a critical element of the evidence submitted for assessment. Only clear and comprehensive labelling will effectively communicate the product information to the intended user and ensure the safe use of the registered medical device. The version of the instructions for use or instrument manual for the product which is submitted with the presubmission form will be considered during the assessment. The manufacturer must obtain the Authority's written agreement prior to implementing any changes to this version of the instructions for use; otherwise, the application may be cancelled.

The product labelling will be reviewed as part of the presubmission form, product dossier, performance evaluation/clinical trial and inspection of manufacturing site(s). The instructions for use or instrument manuals will be reviewed for clarity, correctness, consistency with the information submitted in the product dossier and in the technical documentation, and with international guidance (28) and requirements, and suitability for the target user group in <Name of country>. The overall feedback on the labelling review will be sent to the manufacturer after all assessment components have been completed. If so requested by the Authority, the manufacturer must amend the labelling before the product can be registered. The agreed product labelling will be included in the public report.

4.6 Outcome of the assessment

Each dossier review report, manufacturing site(s) inspection report, clinical trial/performance evaluation report and labelling review report will be finalized according to the relevant SOPs and format established by the Authority, describing the findings and including requests and recommendations to the manufacturer. The assessment reports will be communicated in writing to the manufacturer.

If any additional information is required, or if corrective action has to be taken by the manufacturer, the Authority will postpone its decision on the acceptability of the product and/or manufacturing site(s) concerned until, as applicable:

a) such information has been provided by the manufacturer, assessed and found satis factory by the Authority, and/or
b) such corrective action has been taken by the manufacturer and found satisfactory by the Authority, in light of the specified standards.

As the Authority is responsible for the assessment process, the ownership of the reports arising from or relating to the assessment process lies with the Authority. Thus, the Authority shall be entitled to use and publish such reports, subject always, however, to the protection of any commercially sensitive, confidential information of the manufacturer. Confidential information in this context means:

a) confidential intellectual property, know-how and trade secrets (formulae, processes or information contained or embodied in a product, unpublished aspects of trade marks, patents, etc.); and
b) commercial confidences (e.g. structure and development plans of a company).

Subject to the protection of commercially sensitive confidential information, the Authority will publish on its website and make publicly available the following information in connection with the assessment process:

a) the names of products and of manufactur ers that have applied for registration, the product code(s) submitted for registration and the registration status of each applica tion;
b) an Authority public report summarizing the findings of the assessment; and
c) any negative outcomes of the assessment, including product alerts such as Authority information notices for users or Authority notices of suspension.

4.7 Notices of concern

Notwithstanding any of the foregoing, the Authority reserves the right to use, publish, issue and/or share information with relevant authorities in Africa and other relevant intergovernmental organiza-

tions. The Authority may make publicly available (in each case, in accordance with the provisions of this document, including provisions regarding the protection of any commercially sensitive information of the manufacturer) any outcomes, reports, notices and/or results— whether in draft or final form, and whether positive or negative— of the assessment process. This may include, but is not limited to, the dossier review, performance evaluation and/or manufacturing site inspection and includes any confidential information to which the Authority may gain access in the course of the assessment process.

5. SUCCESSFUL ASSESSMENT

Once the Authority is satisfied that the assessment process is complete for the relevant product, and that the product meets the Authority's requirements, the product bearing a specific product name, product code(s) and regulatory version, as manufactured at the specific manufacturing site(s) inspected, will be included in the Authority list of registered medical devices. The Authority list of registered medical devices will be compiled in accordance with an SOP established by the Authority for final decision-making on inclusion in that list. The list will be published on the Authority website and will specify the registered product name, respective product code(s), regulatory version, manufacturer's name, manufacturing site(s), product packaging and year in which the product was registered.

The manufacturer will receive a letter of approval for registration of its product from the Authority, informing it of the outcome of the overall assessment of the product. Once the product is included in the Authority list of registered medical devices, the manufacturer will be responsible for:

a) fulfilling registered commitments;
b) annual reporting;
c) reporting of changes;
d) post-market surveillance obligations;
e) receiving reinspections; and
f) continued compliance with the Authority technical specifications.

The decision to include the product in the Authority list of registered medical devices is made based upon information available to the Authority at the time of the assessment, including information obtained as a result of the product dossier review, performance evaluation/clinical trial, the inspection of manufacturing site(s) and/or the labelling review conducted by the Authority. This decision is subject to change on the basis of new information that may become available to the Authority.

5.1 Correcting nonconformities identified during assessment and registration commitments

Nonconformities identified as part of any component of the assessment must be corrected by the manufacturer within the deadlines agreed with the Authority. All critical nonconformities must be corrected before the product is registered. In certain cases, the Authority may agree, at its sole discretion, to permit the manufacturer to correct specific nonconformities after registration occurs, provided that the manufacturer commits itself in writing to correcting them by an agreed deadline. Such commitments to registration must be fulfilled by the manufacturer within the agreed deadlines in order to maintain the registration status of the product. Failure to fulfil all registration commitments within the agreed deadlines will lead to delisting of the product from the Authority list of registered medical devices.

6. CANCELLATION OF THE APPLICATION

The Authority reserves the right to cancel the application for a specific product at any time or stage of the assessment procedure if:

a) the product dossier or, in the case of an abridged assessment the technical doc umentation, does not contain all the required information or does not meet the Authority requirements; and/or

b) the manufacturer is not able to, or fails to, provide the required or requested informa tion within a specified deadline; and/or

c) the product does not meet the acceptance criteria for the performance evaluation or clinical trial; and/or

d) the manufacturer is not able to, or fails to, implement any corrective actions which the Authority may require within a specified deadline; and/or

e) the information supplied is inadequate to allow completion of the assessment in a timely manner.

In this case, the manufacturer will not be allowed to reapply for the Authority assessment for a period of time determined by the Authority, usually <one (1)> year from the date of notification of cancellation, unless otherwise agreed by the Authority.

7. WITHDRAWAL FROM THE ASSESSMENT

The Authority will give the manufacturer the right to withdraw its application for assessment at any time or stage of the application. To exercise this right of withdrawal, the manufacturer must provide the Authority with a written notice specifying the product(s) to be withdrawn. In this case, the manufacturer will not be allowed to reapply for Authority assessment of the withdrawn product for a period of time determined by the Authority, usually <one (1)> year from the date of notification of withdrawal, unless otherwise agreed by the Authority.

8. FEES

The cost of the activities required to assess a medical device for registration will be covered by the manufacturer. The non-refundable assessment fee will contribute to the costs associated with review of the presubmission form for determining eligibility for assessment, product dossier screening and review, performance evaluation, inspection of manufacturing site(s), labelling review and dissemination of assessment information. The fee schedule is summarized in Table 1 below.

Table 1. Fee schedule for different assessments

Stage of assessment	Full assessment	Abridged assessment
Presubmission form		
Dossier		
Performance evaluation		
Minor changes		
Major changes		
Annual maintenance		

Manufacturers should note that the Authority reserves the right to decide, based on the assessment findings, whether a product meets the requirements to become registered. Therefore, payment of the assessment fees does not guarantee that the product will be registered and/or that, if registered, the product will retain its registration status for any minimum length of time. If the assessment of a change to a registered medical device or the quality management system is required, the manufacturer may need to pay an additional fee. Once fees have been paid to the Authority, they are non-refundable.

9. DURATION OF VALIDITY OF THE STATUS

The Authority will reassess products included in the Authority list of registered medical devices and their associated manufacturing sites at intervals determined by the Authority, using a risk-based approach. If, as a result of this reassessment, it is found that a product and/or specified manufacturing site(s) no longer meets the Authority's requirements, such products will be removed from the list. Failure of a manufacturer to participate in the reassessment procedure will also lead to delisting of the product from the Authority list of registered medical devices.

10. FULFILMENT OF REGISTRATION COMMITMENTS

Commitments related to registration must be fulfilled by the manufacturer within the agreed deadlines in order to maintain the registration status of the product. Failure to meet registration commitments within the agreed deadlines will lead to delisting of the product(s) from the Authority list of registered medical devices.

11. ANNUAL REPORTING

For all registered products, the manufacturer must submit to the Authority an annual report that details sales data and all categories of complaints in a summarized form (Annex 7). The annual report, in the format prescribed by the Authority, must be submitted by the manufacturer to the Authority every <xxx> year(s) after registration. The manufacturer will receive a letter from the Authority requesting submission of the annual report, together with the prescribed report format. The information provided in the annual report will inform the Authority 's decision on the frequency of reinspections.

12. SUBMISSION OF CHANGES TO A REGISTERED MEDICAL DEVICE

The Authority will register a medical device as it is submitted to it and assessed at a particular point in time. To meet the Authority's requirements, the manufacturer must establish, maintain and implement a procedure for categorizing and documenting any changes to the product and/or the quality management system. This procedure must be available as part of the product dossier and during the inspection of the manufacturing site(s).

The manufacturer of product(s) included in the Authority list of registered medical devices must comply with the duties and responsibilities set out by the Authority which include, but are not limited to (Annex 8):

a) changes to the registered product or its design, labelling or manufacture;
b) changes to the quality management system under which the product was designed and manufactured; and/or
c) other reportable administrative changes.

To determine whether a change to the product, including its design, labelling and manufacture, or to the quality management system, requires reporting to the Authority, the manufacturer should evaluate the potential effect the change may have on the safety, quality or performance of the product. For all reportable changes to a registered product, the manufacturer must submit to the Authority a variation form for any Authority-registered medical device, supporting documentation and, in some cases, a new application.

The manufacturer must communicate to the Authority its intent to introduce a change well in advance (i.e. early in the process of designing and validating the change), in order to allow sufficient time for the Authority to assess the change before its implementation. The Authority will not approve any changes without due assessment. Depending on the type of change, the assessment may also include an inspection of the manufacturing site(s) and/or a performance evaluation.

Once the change report form and supporting documentation are received by the Authority, they will be screened for completeness and, provided all the required information has been supplied, they will undergo assessment by the Authority. If any aspect of the change report form or the supporting documentation is incomplete, the manufacturer will be informed in writing and requested to complete it within a specified deadline set by the Authority. If the manufacturer fails to complete the aspect within the specified deadline, the product may be removed from the list of registered products.

The Authority will inform the manufacturer in writing of the outcome of its assessment of the change. The manufacturer will also be notified if the Authority deems (based on the nature of the change and its potential impact on the quality, safety and/or performance of the product), that an inspection of the manufacturing site(s) and/or performance evaluation is also required. Once the Authority is satisfied that the change assessment of a product is complete and provided that the overall findings demonstrate, as determined by the Authority, that the product continues to meet all requirements, then the Authority list of registered medical devices will be updated, as necessary, to reflect the relevant change accepted by the Authority.

In some cases, changes affect the safety and performance of the product to such a degree that a new application for Authority assessment is required. This will be the case where it is deemed that the changes have resulted in product or application information that are substantially different from the information previously registered. In these cases, the Authority will notify the manufacturer that a new application for Authority assessment is required.

If the submitted documentation supporting the change of the medical device does not meet the

Authority's requirements, or if all the requested information is not provided by the manufacturer within the specified deadline, the Authority will reject the change. The impact of such a decision on the registration status of the registered medical device will be communicated to the manufacturer in writing by the Authority.

13. APPEALS

National regulatory authorities shall make provision for appeals by and Applicant that is not satisfied with the decision of the Authority.

14. POST-MARKET AND MARKET SURVEILLANCE OF REGISTERED MEDICAL DEVICES

Post-market and market surveillance of registered products monitors the continued compliance of the registered products with Authority requirements. The post-market and market surveillance system includes proactive collection of information on quality, safety and performance of the medical device after it has been registered, as well as reactive reporting for the notification and evaluation of complaints, enabling appropriate action to be taken.

As soon as a medical device is accepted into the Authority assessment process, and as long as that medical device is included in the Authority list of registered medical devices, the manufacturer must comply with the manufacturer's obligations to undertake the following post-market and market surveillance activities, namely to notify the Authority of any events relating to the medical device that have affected (or could have affected) the performance of the medical device, safety of the person being tested, safety of users of the medical device or safety of any person associated with the medical device, including:

a) any serious adverse effect (should be reported to the Authority immediately but no later than 48 hours after the event);
b) any moderate adverse event or any change in the trend of mild adverse events (should be reported to the Authority immediately but no later than 10 calendar days after the event); and
c) all complaints (as well as all serious, moderate and mild adverse events) (must be reported to the Authority immediately, but no later than 30 calendar days after the complaint is received).

In the case of a complaint, the Authority will request the manufacturer to provide further information relating to the complaint; upon receiving such a request, the manufacturer must promptly supply the requested information to the Authority, including details of its investigation and any corrections and corrective actions taken:

a) to activate the manufacturer's com plaint-handling system, to inform the Au thority of reportable adverse events, and to encourage end users to report on problems experienced in the use of the medical device;
b) to notify the Authority of all events that require field-safety corrective actions, such as withdrawal of products from sale or dis tribution, physical return of the medical device to the manufacturer or destruction of the product (e.g. recall), product ex change, product modification(s) or provi sion of additional advice to customers to ensure that the product continues to func tion as intended; and
c) if required, to supply sufficient quantities of the registered product to the Authority, or to laboratories designated by the Au

thority, free of charge and delivered du ty-paid, for post-market and market surveil lance lot verification testing.

The Authority will investigate any complaint concerning a registered medical device that is communicated to the Authority by end users or by manufacturers. First, the Authority will notify the manufacturer and, depending on the nature of the complaint, may also notify any interested partner State and/or interested United Nations agencies. The Authority reserves the right to use, publish, issue, share with relevant authorities of partner States, United Nations agencies and other relevant intergovernmental organizations, and/or make publicly available (in each case, pursuant to the provisions of this document, including provisions regarding the protection of any commercially sensitive information of the manufacturer) any outcomes, reports and/or results—whether in draft or final form, and whether positive or negative – of:

a) any investigation relating to a complaint concerning any registered product;
b) any field-safety corrective action;
c) any Authority notices of concern, notices of suspension or information notices for users;
d) any manufacturer-issued field-safety notices; and
e) any confidential information to which the Authority may gain access in the course of any of the foregoing.

The Authority will review the investigation conducted by the manufacturer to ensure that it complies with scientific principles and is in accordance with international guidance and standards. The Authority reserves the right to request a special inspection to verify that corrections and corrective actions have been implemented.

15. ROUTINE REINSPECTION

Routine reinspections will be conducted to ensure continued compliance with registration requirements. Routine reinspections will typically take place every <three (3)> and up to <five (5)> years after registration of a product, unless an earlier reinspection is deemed necessary by the Authority.

16. CONFIDENTIALITY

The Authority assessors, inspectors and the designated evaluating sites will treat all information to which they gain access during the assessments, inspections and evaluations, or otherwise in connection with the discharge of their responsibilities in regard to this assessment procedure, as confidential and proprietary to the Authority or parties collaborating with the Authority, in accordance with the terms set forth below. The Authority assessors, inspectors and designated evaluating sites will take all reasonable measures to ensure that confidential information:

a) is not used for any purpose other than the assessment, inspection and evaluation activities described in this document; and
b) is not disclosed or supplied to any person who is not bound by similar obligations of confidentiality and non-use as are contained herein.

The Authority assessors, inspectors and evaluating sites will not, however, be bound by any obligation of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

a) was known to them prior to any disclosure by or on behalf of the Authority (including disclosure by the manufacturers); or
b) was in the public domain at the time of dis closure by or on behalf of the Authority

(including disclosure by the manufacturers); or

c) has become part of the public domain through no fault of theirs; or

d) has become available to them from a third party not in breach of any legal obligations of confidentiality; or

e) was subsequently and independently developed by or on behalf of the Authority, as shown by written records, by persons who had no knowledge of such confidential information; or

f) is required to be disclosed by law, provided that the Authority shall, in such a case, immediately notify the manufacturer in writing of such an obligation and shall provide adequate opportunity for the manufacturer to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by the Authority and/or submits the Authority to any national court jurisdiction).

17. CONFLICT OF INTEREST

Before undertaking the work, each external inspector, assessor and representative of the evaluating site will also (in addition to the above-mentioned confidentiality undertaking) be required to complete and sign the Authority's declaration of interest form. If, based on the above-mentioned declaration of interests, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the assessor or inspector in question to undertake the work, then he/she will discharge his/her functions exclusively as adviser to the Authority. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify the Authority of any change in this information.

All inspectors furthermore agree that, at the manufacturer's request, the Authority will advise the manufacturer, in advance, of the identity of each inspector and the composition of the team performing the manufacturing site inspection and provide the curriculum vitae of the inspector. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to the Authority before the inspection visit. If such concerns cannot be resolved in consultation with the Authority, the manufacturer may object to a team member's participation in the manufacturing site visit. Such an objection must be made in writing by the manufacturer to the Authority within <ten (10)> days of receipt of the proposed team composition. In the event of such an objection, the Authority reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

18. DISPUTES – PRIVILEGES AND IMMUNITIES OF THE AUTHORITY

In the event of any dispute or disagreement between the manufacturer and the Authority arising from or relating to the assessment process, an SOP established by the Authority for the handling of such disputes and disagreements will be followed in order to discuss and resolve the issue.

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AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

Annex 1:
Risk Classification of Medical Devices including Classification Rules

1. Definitions

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. (Source - European Directive 93/42/EEC)

Active therapeutic device: Any active medical device, whether used alone or in combination with other medical devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or handicap. (Source - European Directive 93/42/EEC)

Active device intended for diagnosis: Any active medical device, whether used alone or in combination with other medical devices, to supply information for detecting, diagnosing, monitoring or to support in treating physiological conditions, states of health, illnesses or congenital deformities. (Source – based on European Directive 93/42/EEC)

Central circulatory system: For the purpose of this document, central circulatory system means the major internal blood vessels including the following: pulmonary veins, pulmonary arteries, cardiac veins, coronary arteries, carotid arteries (common, internal and external), cerebral arteries, brachiocephalic artery, aorta (includes all segments of the aorta), inferior and superior vena cava and common iliac arteries.

Central nervous system: For the purpose of this document, central nervous system means brain, meninges and spinal cord. (Source - European Directive 93/42/EEC)

Duration of use

Transient: Normally intended for continuous use for less than 60 minutes.

Short term: Normally intended for continuous use for between 60 minutes and 30 days.

Long term: Normally intended for continuous use for more than 30 days.

NOTE: For the purpose of this document, continuous use means:

a) The entire duration of use of the device without regard to temporary interruption of use during a procedure or, temporary removal for purposes such as cleaning or disinfection of the device.

b) The accumulated use of a device that is intended by the manufacturer to be replaced immediately with another of the same type.
(Source - European Directive 93/42/EEC - modified)

Harm: Physical injury or damage to the health of people or damage to property or the environment. (Source – ISO/IEC Guide 51:1999)

Hazard: Potential source of harm. (Source – ISO/IEC Guide 51:1999)

Immediate danger: A situation where the patient is at risk of either losing life or an important physiological function if no immediate preventative measure is taken.

Intended use / purpose: The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.

Invasive devices

Invasive device: A device, which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.

Body orifice: Any natural opening in the body, as well as the external surface of the eyeball, or any permanent

artificial opening, such as a stoma or permanent tracheotomy.

Surgically invasive device: An invasive device which penetrates inside the body through the surface of the body, with the aid or in the context of a surgical operation.
NOTE: Devices other than those referred to in the previous subparagraph and which produce penetration other than through an established body orifice, should be treated as surgically invasive devices.

Implantable device: Any device, including those that are partially or wholly absorbed,
which is intended: -

- to be totally introduced into the human body or,

- to replace an epithelial surface or the surface of the eye,

by surgical intervention which is intended to remain in place after the procedure.

Any device intended to be partially introduced into the human body through surgical

intervention and intended to remain in place after the procedure for at least 30 days is also

considered an implantable device.
(Source - European Directive 93/42/EEC)

Life supporting or life sustaining: A device that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

Medical device: See GHTF guidance document: Information Document Concerning the Definition of the Term 'Medical Device' (GHTF/SG1/N29:2005).

Reusable surgical instrument: Instrument intended for surgical use by cutting, drilling, sawing, scratching, scraping, clamping, retracting, clipping or other surgical procedures, without connection to any active medical device and which are intended by the manufacturer to be reused after appropriate procedures for cleaning and/or sterilisation have been carried out. (Source - European Directive 93/42/EEC – modified)

Risk: Combination of the probability of occurrence of harm and the severity of that harm. (Source – ISO/IEC Guide 51:1999)

2. Introduction

This guidance document is intended to assist a manufacturer to allocate its medical device to an appropriate risk class using a set of harmonized principles. Regulatory Authorities have the responsibility of ruling upon matters of interpretation for a particular medical device. Once assigned, such classification will prescribe how the manufacturer will demonstrate that its device complies with other documents in the series and, in particular, with those entitled Essential Principles of Safety and Performance of Medical Devices and Labelling for Medical Devices should it be required or requested so to do by a Regulatory Authority, Conformity Assessment Body, user or third party. It seeks to strike a balance between the responsibilities of Regulatory Authorities to safeguard the health of their citizens and their obligations to avoid placing unnecessary burdens upon the industry.

This document should be read in conjunction with the GHTF document on Principles of Conformity Assessment for Medical Devices that recommends conformity assessment requirements appropriate to each of the four risk classes proposed herein. This link between documents on classification and conformity assessment is important to ensure a consistent approach across all countries/regions adopting the global regulatory model recommended by the IMDRF/GHTF, so that premarket approval for a particular device may become acceptable globally.

This document is intended for use by Regulatory Authorities, Conformity Assessment Bodies and industry, 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.

Regulatory Authorities that are developing classification schemes or amending existing ones are encouraged to consider the adoption of the system described in this document, as this will help to reduce the diversity of schemes worldwide and facilitate the process of harmonization.

3. Scope

This document applies to all products that fall within the definition of a medical device that appears within the GHTF document Information Document Concerning the Definition of the Term 'Medical Device', other than those used for the in vitro examination of specimens derived from the human body for which a separate document is being developed.

4. General Principles of risk classification

Regulatory controls are intended to safeguard the health and safety of patients, users and other persons by ensuring that manufacturers of medical devices follow specified procedures during design, manufacture and marketing.

The GHTF guidance documents Essential Principles of Safety and Performance of Medical Devices and Labelling for Medical Devices apply to all devices whatever their risk class.

Regulatory controls should be proportional to the level of risk associated with a medical device. The level of regulatory control should increase with increasing degree of risk, taking account of the benefits offered by use of the device. At the same time, the imposition of regulatory controls should not place an unnecessary burden on regulators or manufacturers.

Therefore:

- there is a need to classify medical devices based on their risk to patients, users and other persons; and

- there is benefit for manufacturers and Regulatory Authorities if a globally harmonized classification system is developed.

The risk presented by a particular device depends substantially on its intended purpose and the effectiveness of the risk management techniques applied during design, manufacture and use.

The risk presented by a device also depends, in part, on its intended user(s), its mode of operation, and/or technologies. In general, the classification rules are intended to accommodate new technologies. Without prejudice to these rules, Regulatory Authorities may wish to require the notification of new devices being placed on the market in their jurisdictions. Such notification may be used in assessing the evidence requirements for use in the conformity assessment process. It may also be used to consider the need, if any, for possible re-classification and/or changes in these harmonized classification rules.

5. Recommendations

5.1 Primary Recommendations

- Regulatory Authorities should work towards the establishment of a global classification system.
- This system should consist of four risk classes. Based on experience of GHTF Founding Members, this is sufficient to accommodate all medical devices and allows an efficient and graduated system of conformity assessment controls.

- The initial determination of class should be based on a set of rules derived from those features of devices that create risk. In most cases the initial rules based classification will also be the final classification.
- These rules should be sufficiently clear that manufacturers may readily identify the class of their medical devices, subject, as required, to final classification by the Regulatory Authority.
- The rules should be capable of accommodating future technological developments.
- The manufacturer should document its justification for placing its product into a particular risk class, including the resolution of any matters of interpretation where it has asked a Regulatory Authority and/or Conformity Assessment Body for a ruling.

- Decisions on final classifications, which deviate from the initial rules-based classification, should be weighed against the disadvantages of disharmonized international classification.

5.2 Factors Influencing Device Classification

A number of factors, including for example the duration of device contact with the body, the degree of invasiveness, whether the device delivers medicinal products or energy to the patient, whether they are intended to have a biological affect on the patient and local versus systemic effects (e.g. conventional versus absorbable sutures) may, alone or in combination, affect device classification.

If, based on the manufacturer's intended purpose, two or more classification rules apply to the device, the device is allocated the highest level of classification indicated.

Where one medical device is intended to be used together with another medical device, that may or may not be from the same manufacturer, (e.g. a physiological monitor and a separate recorder, or a general purpose syringe and a syringe driver), the classification rules should apply separately to each of the devices.

Classification of an assemblage of medical devices that individually comply with all regulatory requirements depends on the manufacturer's purpose in packaging and marketing such a combination of separate devices. For example:

- If the combination results in a product that is intended by the manufacturer to meet a purpose different

from that of the individual medical devices that make it up, the combination is a new medical device in its own right and should be classified according to the new intended use.

- If the combination is for the convenience of the user but does not change the intended uses of the individual medical devices that make it up (e.g. a customised kit that provides all the devices necessary to carry out a particular surgical procedure), the classification allocated to the assemblage for the purpose of a Declaration of Conformity is at the level of the highest classified device included within it.

If one or more of the medical devices that is in the assemblage has yet to comply with all the relevant regulatory requirements, the combination should be classified as a whole according to its intended use.

Accessories intended specifically by manufacturers to be used together with a 'parent' medical device to enable that medical device to achieve its intended purpose, should be subject to all the GHTF guidance documents as apply to the medical device itself (e.g. Essential principles for Safety and Performance, post-market surveillance etc.). For classification purposes an accessory may be classified as though it is a medical device in its own right.

While most software is incorporated into the medical device itself, some is not. Provided such standalone software falls within the scope of the definition for a 'medical device', it should be classified as follows:

- Where it drives or influences the use of a separate medical device, it should be classified according to the intended use of the combination.

- Where it is independent of any other medical device, it is classified in its own right using the rules in Section 8.0 of this document.
- Standalone software (to the extent it falls within the definition of a medical device) is deemed to be an active device.

Experience gained from the clinical use of a particular type of medical device may suggest that the rules appearing in Section 8.0 of this document are inappropriate. Current GHTF procedures require that all GHTF documents be reviewed at regular intervals. Such a review of this document will provide any participant with an opportunity to suggest a change of text that, in his/her opinion, will address any shortcoming.

The purpose of risk classification is to make sure that the regulatory controls applied to a medical device are proportionate to risk. Statutory conformity assessment authority provides Regulatory Authorities methods to assure compliance with regulatory controls. At this time, conformity assessment requirements and other regulatory controls assigned to each class of device by different Regulatory Authorities have yet to be harmonized and may vary. While Study Group 1 of GHTF continues to support and encourage regulatory harmonization, it recognises that some Regulatory Authorities may have to reflect different local needs or social considerations when they introduce new regulations on classification, for example, in the application of devices covered by the Additional Rules 13 to 16. Study Group 1 hopes any such differences will disappear in the course of time.

5.3 Proposed General Classification System for Medical Devices

Figure 1 indicates the four risk classes of devices. The examples given are for illustration only and the manufacturer must apply the classification rules to each medical device according to its intended purpose.

Figure 1: Proposed general classification system for medical devices

CLASS	RISK LEVEL	DEVICE EXAMPLES
A	Low Risk	Surgical retractors / tongue depressors
B	Low-moderate Risk	Hypodermic Needles / suction equipment
C	Moderate-high Risk	Lung ventilator / bone fixation plate
D	High Risk	Heart valves / implantable defibrillator

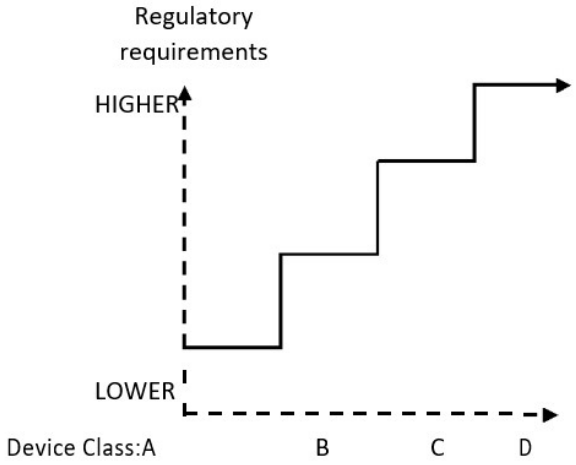
Figure 2 shows a conceptual illustration of increasing levels of regulatory requirements as the device risk class increases. These regulatory controls may include, for example: -

- operation of a quality system (recommended for all devices);

- technical data;
- product testing using in-house or independent resources;
- documentation of clinical evidence to support the manufacturer's claims;
- the need for and frequency of independent external audit of the manufacturer's quality system; and
- independent external review of the manufacturer's technical data.

The concept is expanded in the GHTF guidance document entitled Principles of Conformity Assessment for Medical Devices.

Figure 2: Conceptual illustration of regulatory controls increasing with device risk class



6. The Determination of Device Class using this Rules-based System

The manufacturer should:

1. Decide if the product concerned is a medical device, using the appropriate definition.

NOTE: Medical devices that are used for the in vitro examination of specimens derived from the human body are not covered by the classification rules within this document (see Scope).

2. Document the intended use of the medical device.

3. Take into consideration all the rules that follow in order to establish the proper classification for the device, noting that where a medical device has features that place it into more than one class, classification and conformity assessment should be based on the highest class indicated.

4. Determine if the device is subject to special national rules that apply within a particular jurisdiction.

NOTES:

- Once a rules-based system has been adopted, modifications may occasionally be required. For example, where through post-market experience, a level of risk for a type of medical device, classified using the criteria found in this guidance document is no longer appropriate, consideration should be given to re-classification of the device type by a change to the rules.

- Similarly, the historical knowledge of a device may necessitate a different class than the one assigned by the initial classification. Unlike the principle of reclassification after post-market experience with a device, this principle of historical knowledge should be applied immediately when the initial classification yields an inappropriate result.

- Where special national rules are applied, resulting in a device class other than that suggested by the present rules, then a different conformity assessment procedure may be indicated. This may have an effect on the acceptability of such devices for free movement in countries where these present rules have been adopted unless other, or additional, conformity assessment procedures are carried out.

7. Initial Classification Rules

RULE	ILLUSTRATIVE EXAMPLES OF DEVICES THAT MAY CONFORM WITH A RULE S
Rule 1. All non-invasive devices which come into contact with injured skin: - are in Class A if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates only, i.e. they heal by primary intent; - are in Class B if they are intended to be used principally with wounds which have breached the dermis, including devices principally intended to manage the microenvironment of a wound. **unless** they are intended to be used principally with wounds which have breached the dermis and can only heal by secondary intent, in which case they are in Class C.	Devices covered by this rule are extremely claim sensitive. Examples: simple wound dressings; cotton wool. Examples: non-medicated impregnated gauze dressings. Devices used to treat wounds where the subcutaneous tissue is as least partially exposed and the edges of the wound are not sufficiently close to be pulled together. To close the wound, new tissue must be formed within the wound prior to external closure. The device manufacturer claims that they promote healing through physical methods other than 'primary intent'. Examples: dressings for chronic ulcerated wounds; dressings for severe burns
Rule 2. All non-invasive devices intended for channelling or storing • body liquids or tissues, • liquids or • gases for the purpose of eventual infusion, administration or introduction into the body are in Class A, **unless** they may be connected to an active medical device in Class B or a higher class, in which case they are Class B; **unless** they are intended for use of • channeling blood, or • storing or channeling other body liquids, or • for storing organs, parts of organs or body tissues, in which case they are Class B. **unless** they are blood bags, in which case they are Class C.	Such devices are 'indirectly invasive' in that they channel or store liquids that will eventually be delivered into the body (see comment for Rule 4). Examples: administration sets for gravity infusion; syringes without needles. Examples: syringes and administration sets for infusion pumps; anaesthesia breathing circuits. **NOTE:** "Connection" to an active device covers those circumstances where the safety and performance of the active device is influenced by the non-active device and *vice versa*. Examples: tubes used for blood transfusion, organ storage containers. Example: Blood bags that do not incorporate an anti-coagulant. **NOTE:** in some jurisdictions, blood bags have a special rule that places them within a different risk class.
Rule 3. All non-invasive devices intended for modifying the biological or chemical composition of •	Such devices are indirectly invasive in that they treat or modify substances that will eventually be delivered into the body (see note to comment for Rule 4). They are normally used in conjunction

blood, • other body liquids, or • other liquids intended for infusion into the body are in Class C, **unless** the treatment consists of filtration, centrifuging or exchanges of gas or of heat, in which case they are in Class B.	with an active device within the scope of either Rule 9 or 11. Examples: haemodializers; devices to remove white blood cells from whole blood. **NOTE**: for the purpose of this part of the rule, 'modification' does not include simple, mechanical filtration or centrifuging which are covered below. Examples: devices to remove carbon dioxide; particulate filters in an extracorporial circulation system.
Rule 4. All other non-invasive devices are in Class A.	These devices either do not touch the patient or contact intact skin only. Examples: urine collection bottles; compression hosiery; non-invasive electrodes, hospital beds.
INVASIVE DEVICES	

Rule 5. All invasive devices with respect to body orifices (other than those which are surgically invasive) and which: • are not intended for connection to an active medical device, or • are intended for connection to a Class A medical device only. those which are surgically invasive) and which: • are not intended for connection to an active medical device, or • are intended for connection to a Class A medical device only. - are in Class A if they are intended for	Such devices are invasive in body orifices and are not surgically invasive (refer to definition in Section 4). Devices tend to be diagnostic and therapeutic instruments used in ENT, ophthalmology, dentistry, proctology, urology and gynaecology. Classification depends on the duration of use and the sensitivity (or vulnerability) of the orifice to such invasion. Section 4). Devices tend to be diagnostic and therapeutic instruments used in ENT, ophthalmology, dentistry, proctology, urology and gynaecology. Classification depends on the duration of use and the sensitivity (or vulnerability) of the orifice to such invasion. Examples: examination gloves; enema devices. Examples: urinary catheters, tracheal tubes. Examples: dentures intended to be removed by the patient; dressings for nose bleeds. Example: urethral stent; contact lenses for long-term continuous use (for this device, removal of the lens for cleaning or maintenance is considered as part of the continuous use). Examples: orthodontic wire, fixed dental prosthesis. Examples: tracheal tubes connected to a ventilator; suction catheters for stomach drainage; dental aspirator tips. **NOTE:** independent of the time for which they are invasive.

Rule 6. All surgically invasive devices intended for transient use are in Class B, **unless** they are reusable surgical instruments, in which case they are in Class A; or **unless** intended to supply energy in the form of ionizing radiation, in which case they are in Class C; or **unless** intended to have a biological effect or be wholly or mainly absorbed, in which case they are in Class C; or **unless** intended to administer medicinal products by means of a delivery system, if this is done in a manner that is potentially hazardous taking account of the mode of application, in which they are in Class C; or **unless** they are intended specifically for use in direct contact with the central nervous system, in which case they are in Class D; or **unless** intended specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class D.	A majority of such devices fall into several major groups: those that create a conduit through the skin (e.g. syringe needles; lancets), surgical instruments (e.g. single-use scalpels; surgical staplers; single-use aortic punch); surgical gloves; and various types of catheter/sucker etc. **NOTE**: a surgical instrument (other than those in Class D) is in Class A if reusable and in Class B if supplied sterile and intended for single use. Also, a surgical instrument connected to an active device is in a higher class than A. **NOTE:** if the device incorporates a medicinal substance in a secondary role refer to Rule 13. Examples: Manually operated surgical drill bits and saws. Example: catheter incorporating/containing sealed radioisotopes. **NOTES**: (a) the 'biological effect' referred to is an intended one rather than unintentional. The term 'absorption' refers to the degradation of a material within the body and the metabolic elimination of the resulting degradation products from the body. (b) This part of the rule does not apply to those substances that are excreted without modification from the body. Example: Insufflation gases for the abdominal cavity. Example: insulin pen for self-administration. **NOTE**: the term 'administration of medicines' implies storage and/or influencing the rate/volume of medicine delivered not just channelling. The term 'potentially hazardous manner' refers to the characteristics of the device and not the competence of the user. Examples: angioplasty balloon catheters and related guide wires; dedicated disposable cardiovascular surgical instruments.

Rule 7. All surgically invasive devices intended for short-term use are in Class B, **unless** they are intended to administer medicinal products, in which case they are in Class C; or **unless** they are intended to undergo chemical change in the body (except if the devices are placed in the teeth), in which case they are in Class C; or **unless** they are intended to supply energy in the form or ionizing radiation, in which case they are in Class C; or **unless** they are intended to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class D; or **unless** they are intended specifically for use in direct contact with the central nervous system, in which case they are in Class D; **unless** they are intended specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class D.	Such devices are mostly used in the context of surgery or post-operative care, or are infusion devices, or are catheters of various types. Examples: infusion cannulae; temporary filling materials; non-absorbable skin closure devices; tissue stabilisers used in cardiac surgery. **NOTE:** includes devices that are used during cardiac surgery but do not monitor or correct a defect. **NOTE:** if the device incorporates a medicinal substance in a secondary role refer to Rule 13. **NOTE**: the term 'administration of medicines' implies storage and/or influencing the rate/volume of medicine delivered not just channelling. Example: surgical adhesive. Example: brachytherapy device. Example: absorbable suture; biological adhesive. **NOTE**: the 'biological effect' referred to is an intended one rather than unintentional. The term 'absorption' refers to the degradation of a material within the body and the metabolic elimination of the resulting degradation products from the body. Example: neurological catheter. Examples: cardiovascular catheters; temporary pacemaker leads; carotid artery shunts. Example: rechargeable non-active drug delivery system.

Rule 8. All implantable devices, and long-term surgically invasive devices, are in Class C, **unless** they are intended to be placed into the teeth, in which case they are in Class B; or **unless** they are intended to be used in direct contact with the heart, the central circulatory system or the central nervous system, in which case they are in Class D; or **unless** they are intended to be life supporting or life sustaining, in which case they are in Class D; or **unless** they are intended to be active implantable medical devices, in which case they are Class D; or **unless** they are intended to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class D; or **unless** they are intended to administer medicinal products, in which case they are in Class D; or **unless** they are intended to undergo chemical change in the body (except if the devices are placed in the teeth), in which case they are in Class D; or **unless** they are breast implants, in which case they are in Class D.	Most of the devices covered by this rule are implants used in the orthopaedic, dental, ophthalmic and cardiovascular fields. Example: maxilla-facial implants; prosthetic joint replacements; bone cement; non-absorbable internal sutures; posts to secure teeth to the mandibula bone (without a bioactive coating). **NOTE:** if the device incorporates a medicinal substance in a secondary role refer to Rule 13. Examples: bridges; crowns; dental filling materials. Examples: prosthetic heart valves; spinal and vascular stents. Example: pacemakers, their electrodes and their leads; implantable defibrillators. Example: implants claimed to be bioactive. **NOTE**: hydroxy-apatite is considered as having biological effect only if so claimed and demonstrated by the manufacturer.
ACTIVE DEVICES.	

Rule 9(i). All active therapeutic devices intended to administer or exchange energy are in Class B, **unless** their characteristics are such that they may administer or exchange energy to or from the human body in a potentially hazardous way, including ionizing radiation, taking account of the nature, the density and site of application of the energy, in which case they are in Class C. **Rule 9(ii).** All active devices intended to control or monitor the performance of active therapeutic devices in Class C, or intended directly to influence the performance of such devices, are in Class C.	Such devices are mostly electrically powered equipment used in surgery; devices for specialised treatment and some stimulators. Examples: muscle stimulators; TENS devices; powered dental hand pieces; hearing aids; neonatal phototherapy equipment; ultrasound equipment for physiotherapy. Examples: lung ventilators; baby incubators; electrosurgical generators; external pacemakers and defibrillators; surgical lasers; lithotriptors; therapeutic X-ray and other sources of ionizing radiation. **NOTE**: the term 'potentially hazardous' refers to the type of technology involved and the intended application. Examples: external feedback systems for active therapeutic devices.
Rule 10(i). Active devices intended for diagnosis are in Class B: - if they are intended to supply energy which will be absorbed by the human body (except for devices used solely to illuminate the patient's body, with light in the visible or near infra-red spectrum, in which case they are Class A), or - if they are intended to image *in vivo* distribution of radiopharmaceuticals, or - if they are intended to allow direct diagnosis or monitoring of vital physiological processes, **unless** they are specifically intended for: a) monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac performance, respiration, activity of central nervous system, or b) diagnosing in clinical situations where the patient is in immediate danger, in which case they are in Class C. **Rule 10(ii).** Active devices intended to emit ionizing radiation and intended for diagnostic and/or interventional radiology, including devices which control or monitor such devices, or those which directly influence their performance, are in Class C.	Such devices include equipment for ultrasonic diagnosis/imaging, capture of physiological signals, interventional radiology and diagnostic radiology. Examples: magnetic resonance equipment; diagnostic ultrasound in non-critical applications; evoked response stimulators. Example: gamma/nuclear cameras. Example: electronic thermometers, stethoscopes and blood pressure monitors; electrocardiographs. Example: monitors/alarms for intensive care; Example: ultrasound equipment for use in interventional cardiac procedures. Example: these include devices for the control, monitoring or influencing of the emission of ionizing radiation.

Rule 11. All active devices intended to administer and/or remove medicinal products, body liquids or other substances to or from the body are in Class B, **unless** this is done in a manner that is potentially hazardous, taking account of the nature of the substances involved, of the part of the body concerned and of the mode and route of administration, in which case they are in Class C.	Such devices are mostly drug delivery systems or anaesthesia equipment. Examples of Class B devices: suction equipment; feeding pumps; jet injectors for vaccination; nebuliser to be used on conscious and spontaneously breathing patients where failure to deliver the appropriate dosage characteristics is not potentially hazardous. Examples: infusion pumps; anaesthesia equipment; dialysis equipment; hyperbaric chambers; nebuliser where the failure to deliver the appropriate dosage characteristics could be hazardous.
Rule 12. All other active devices are in	Examples: examination lamps; surgical microscopes; powered hospital beds & wheelchairs; powered equipment for the recording, processing, viewing of diagnostic images; dental curing lights.
ADDITIONAL RULES	
Rule 13. All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, and which is liable to act on the human body with action ancillary to that of the devices, are in Class D..	These medical devices incorporate medicinal substances in an ancillary role. Examples: antibiotic bone cements; heparin-coated catheters; wound dressings incorporating antimicrobial agents to provide ancillary action on the wound; blood bags incorporating an anti-coagulant. **NOTE:** Such medical devices may be subject to additional conformity assessment procedures according to the regional or national requirements of medicinal product Regulatory Authorities.

Rule 14. All devices manufactured from or incorporating animal or human cells/tissues/derivatives thereof, whether viable or non-viable, are Class D, **unless** such devices are manufactured from or incorporate non-viable animal tissues or their derivatives that come in contact with intact skin only, where they are in Class A.	**NOTE:** In some jurisdictions such products: - are considered to be outside the scope of the medical device definition; - may be subject to different controls. It is likely the regulations controlling these devices will be the subject of future harmonization efforts. Examples: porcine heart valves; catgut sutures. Examples: leather components of orthopaedic appliances.
Rule 15. All devices intended specifically to be used for sterilising medical devices, or disinfecting as the end point of processing, are in Class C. **unless** they are intended for disinfecting medical devices prior to end point sterilisation or higher level disinfection, in which case they are in Class B; or **unless** they are intended specifically to be used for disinfecting, cleaning, rinsing or, when appropriate, hydrating contact lenses, in which case they are in Class C.	Examples: devices for disinfecting or sterilising endoscopes; disinfectants intended to be used with medical devices. **NOTE:** This rule does not apply to products that are intended to clean medical devices by means of physical action e.g. washing machines. Example: washer disinfectors. In some jurisdictions solutions for use with contact lenses: - are considered to be outside the scope of the medical devices definition; - may be subject to different controls.
Rule 16. All devices used for contraception or the prevention of the transmission of sexually transmitted diseases are in Class C, **unless** they are implantable or long-term invasive devices, in which case they are in Class D.	Examples: condoms; contraceptive diaphragms. Example: intrauterine contraceptive device

Decision trees illustrating how these rules may be used to classify specific devices are shown in Appendix A

7.1 Rationale for the inclusion of the Additional Rules into this document

There are a small number of products that fall within the scope of the definition of a medical device and which may need to be classified to take account of factors other than those covered by the general rules (Rules 1 to 12). For the understanding of those countries that are not Founding Members of GHTF, it is felt important to offer guidance on the classification of such devices (see Clause 6.2, above). Therefore, four Additional Rules are provided (Rules 13 to 16).

Matters that may need to be considered are:

Rule 13: Devices incorporating a medicinal product

- The regulations applying to medicinal products require different acceptance procedures to those for medical devices.

- The behavior of a medicinal product used in conjunction with a medical device may differ from that covered by its approved use as a medicinal product alone.

Rule 14: Devices incorporating animal or human tissues

- There is an absence of global regulatory controls for such devices.

- Classification needs to acknowledge the diversity of opinions on such devices, globally.
- The possible risks associated with the transmission of infectious agents through materials used in such devices, e.g. Bovine Spongiform Encephalopathies (BSE) and Creutzfeldt-Jacob disease (CJD), demand classification at a higher risk level.

- The particular concerns relating to those disinfectants that are used with contact lenses, due to sensitivity and vulnerability of the eye.

Rule 16 Contraceptive devices

- The risks associated with unwanted pregnancy if caused by mechanical failure of the device.

- The need to safeguard public health through the use of condoms to reduce the prevalence of sexually transmitted diseases.

- User expectation that contraceptive devices are perfectly reliable and safe despite published data to the contrary.

8. References

GHTF final documents

GHTF/SG1/N12:2000 Role of Standards in the Assessment of Medical Devices.

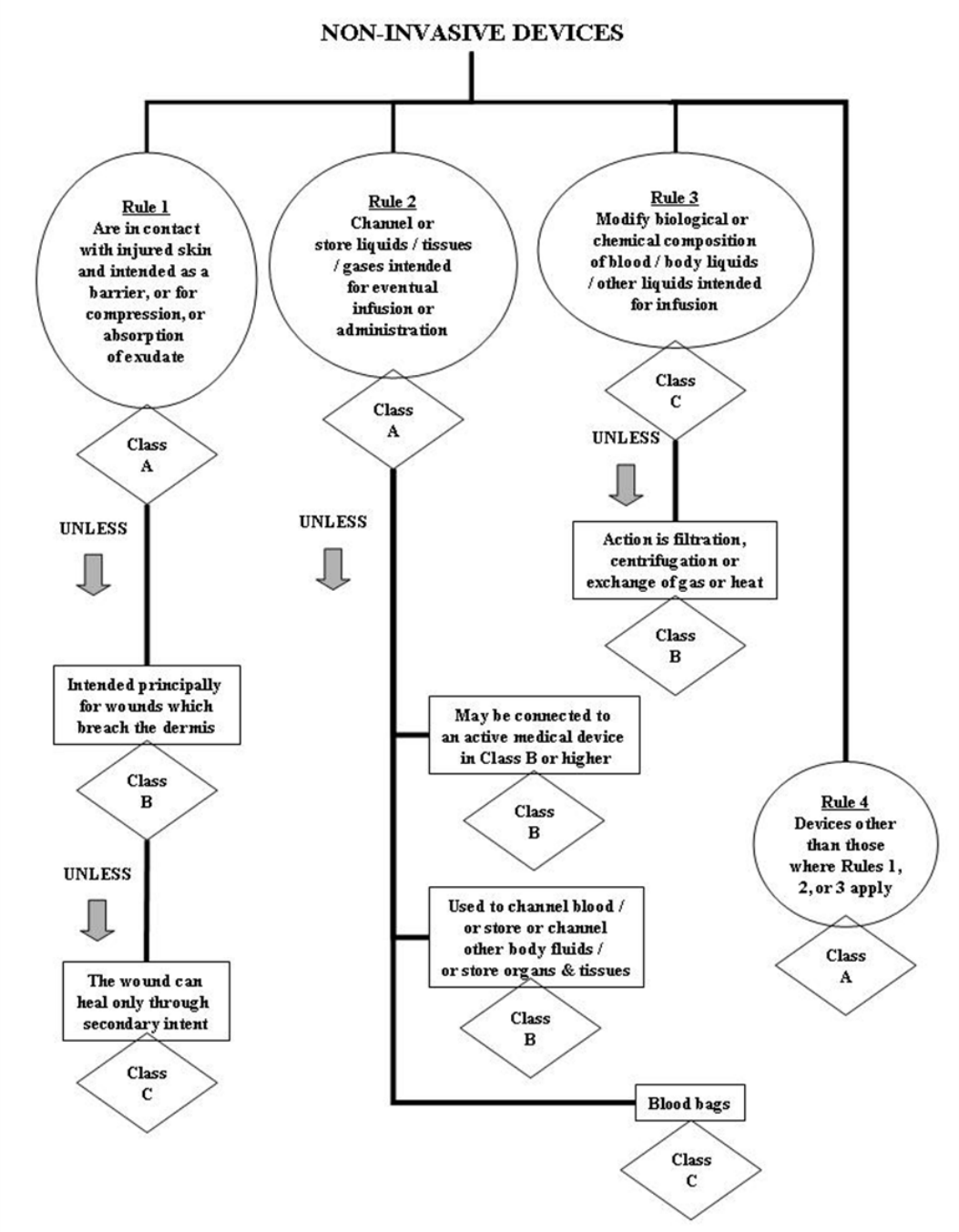
GHTF/SG1/N29:2005 Information Document Concerning the Definition of the Term ‘Medical Device’.

GHTF/SG1/N40:2006 Principles of Conformity Assessment for Medical Devices.

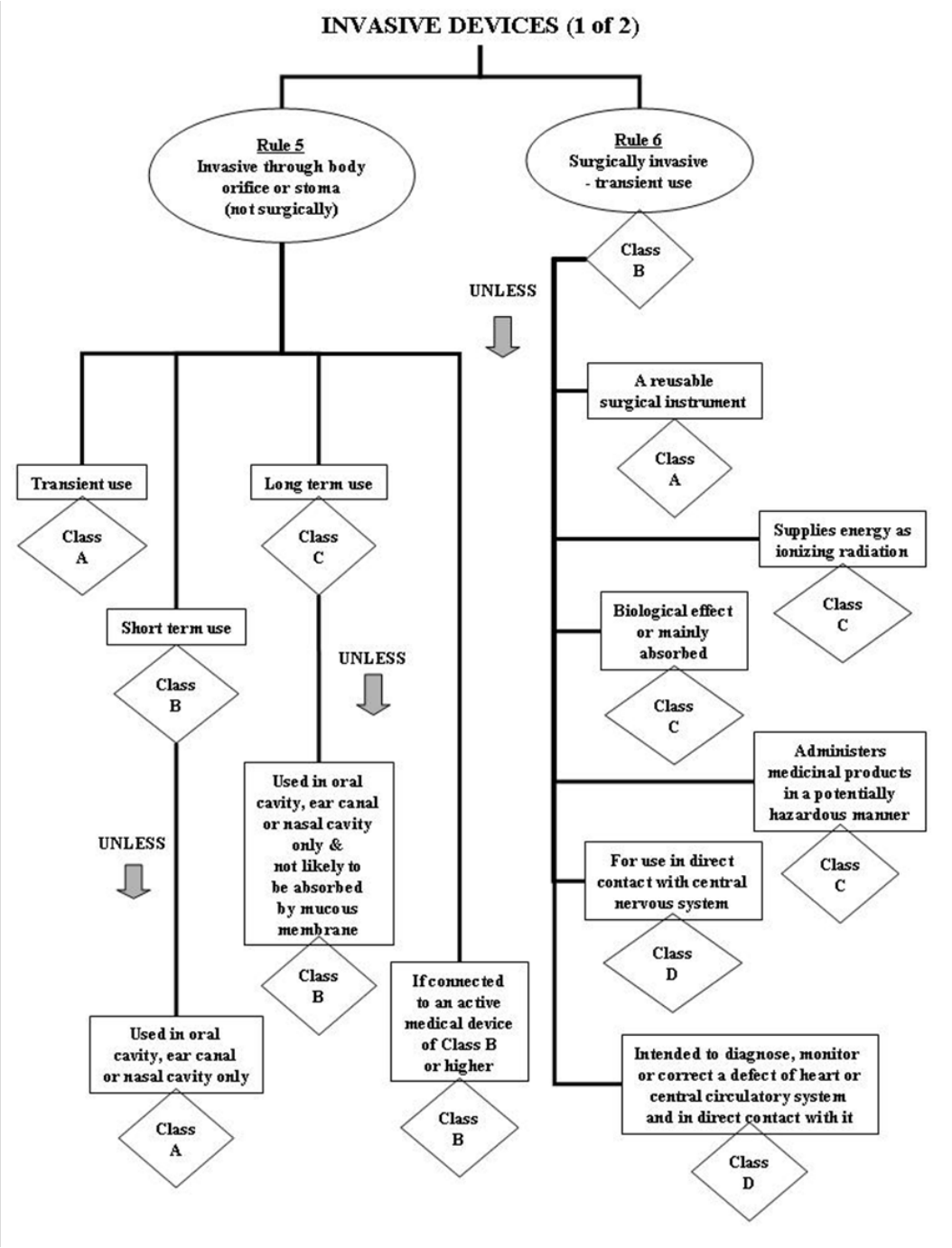
GHTF/SG1/N41:2005 Essential Principles of Safety and Performance of Medical Devices.

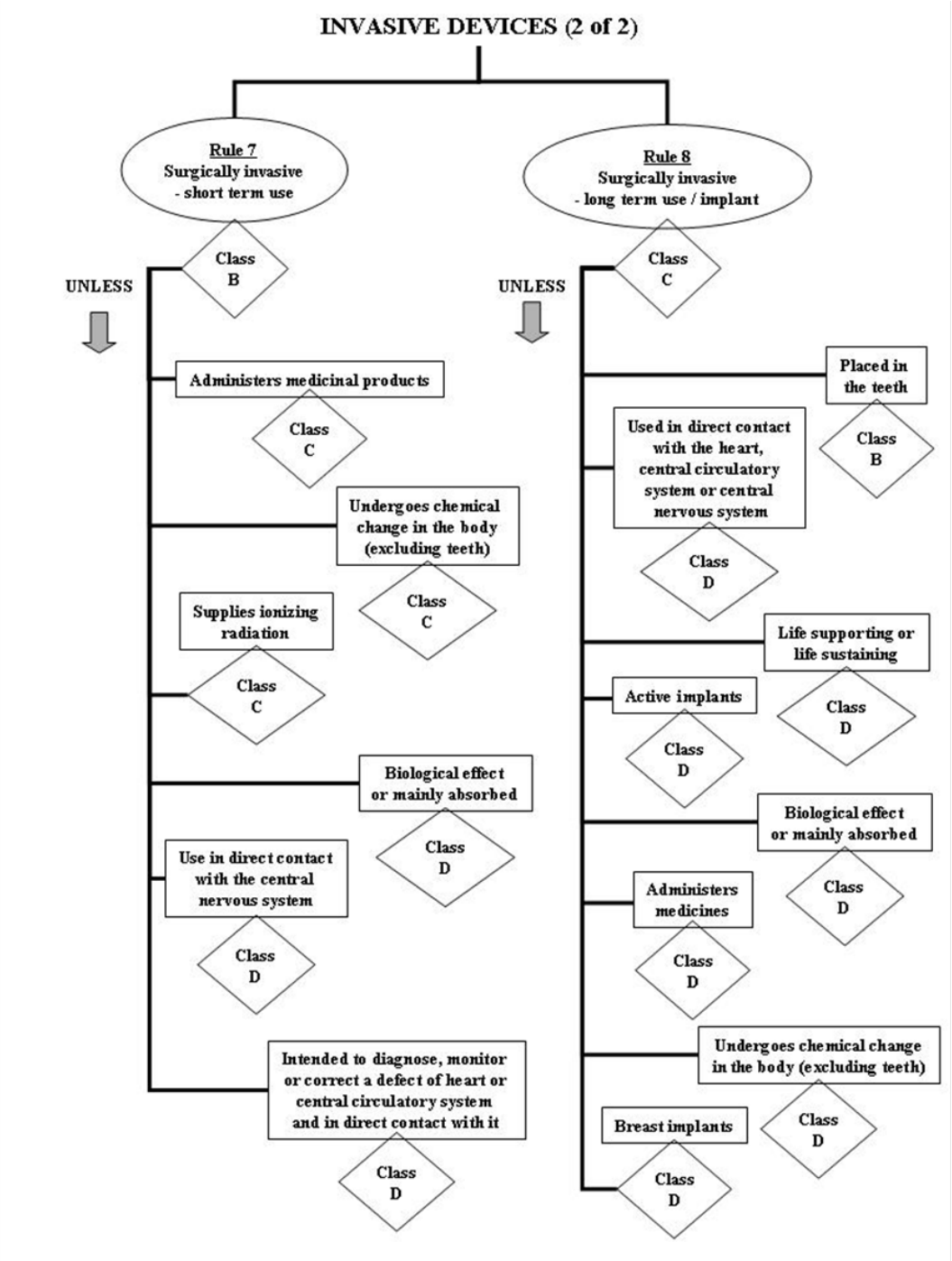
GHTF/SG1/N43:2005 Labelling for Medical Devices.

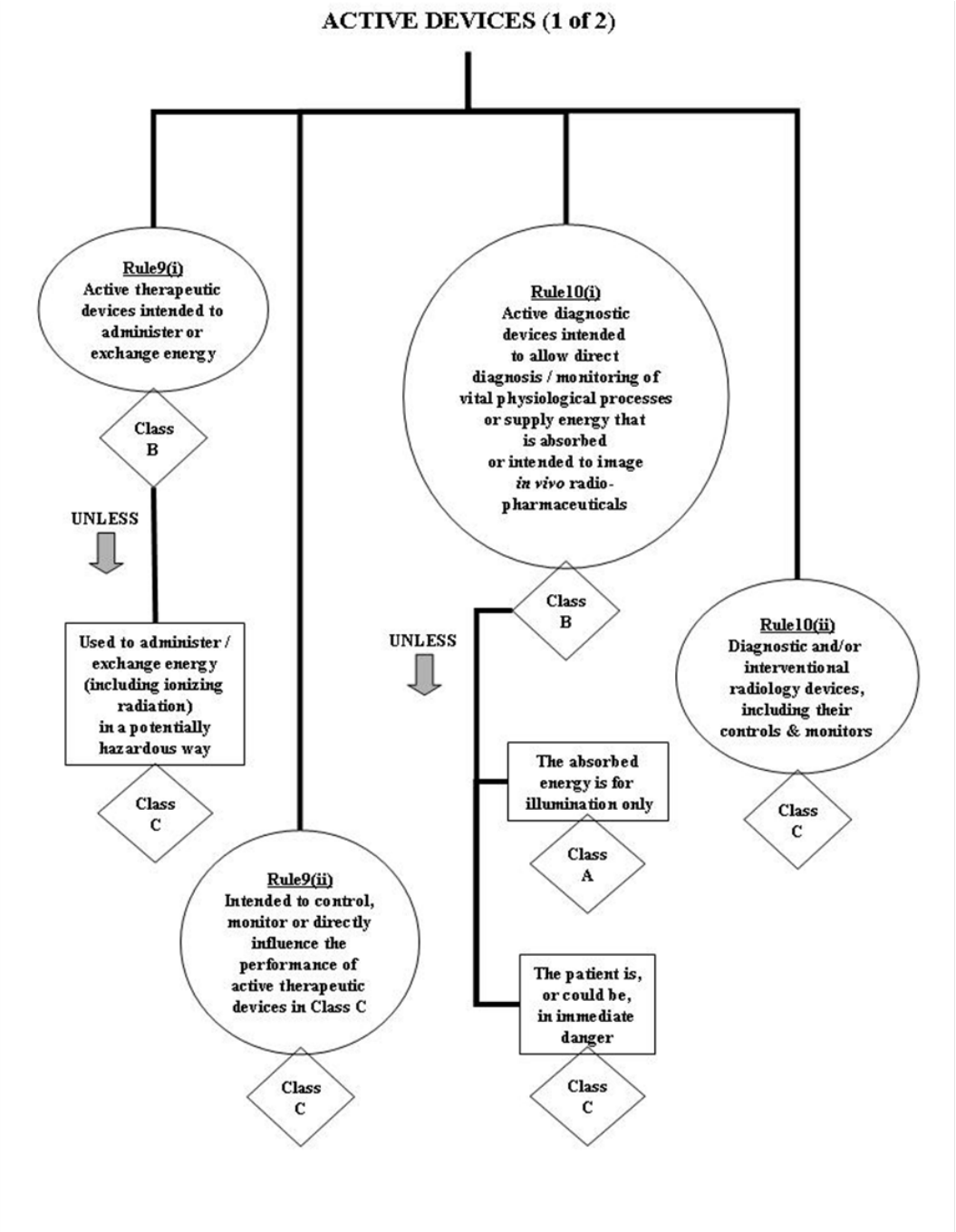
9. Appendix A: Decision trees to demonstrate how the rules may be used to classify specific devices.

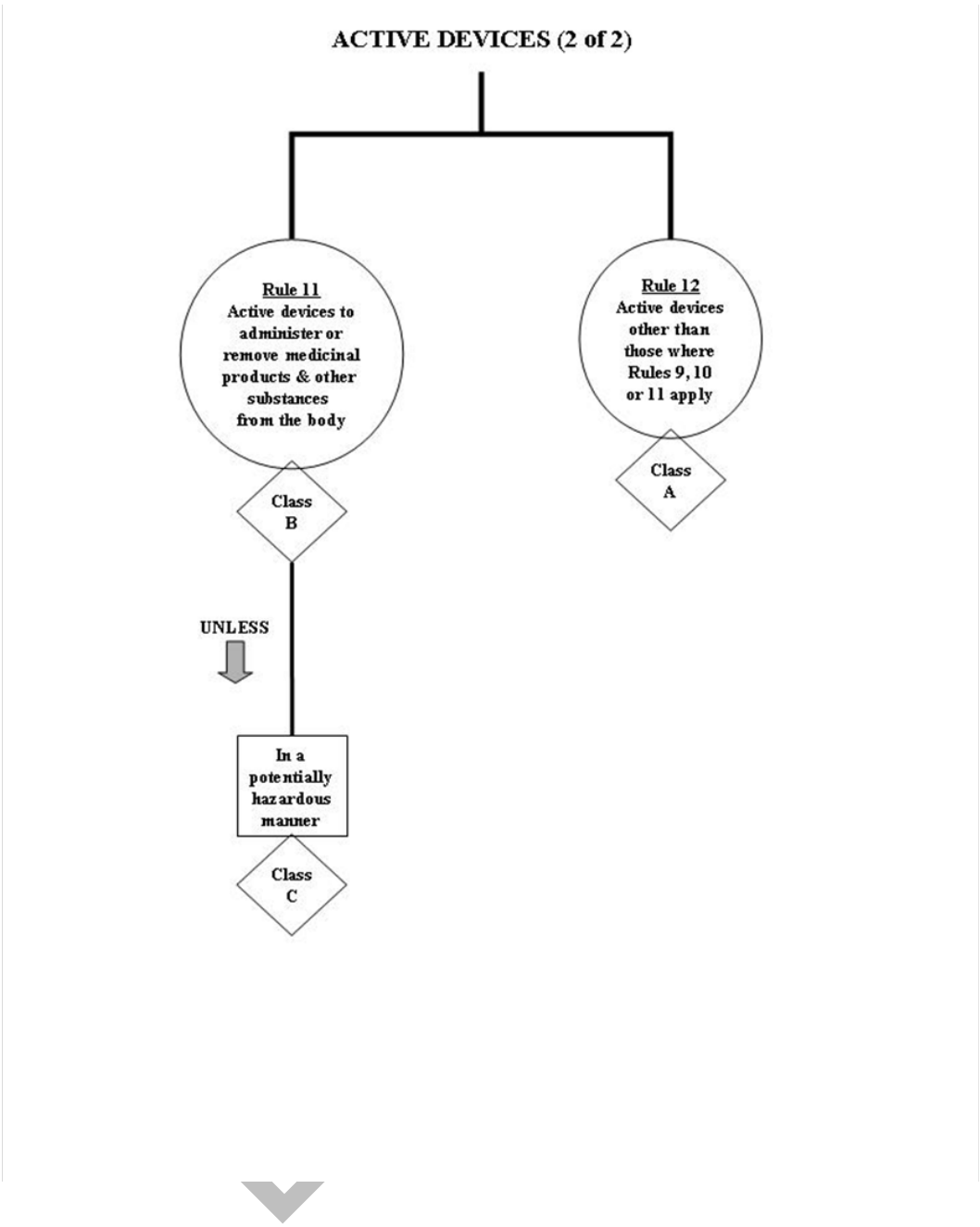


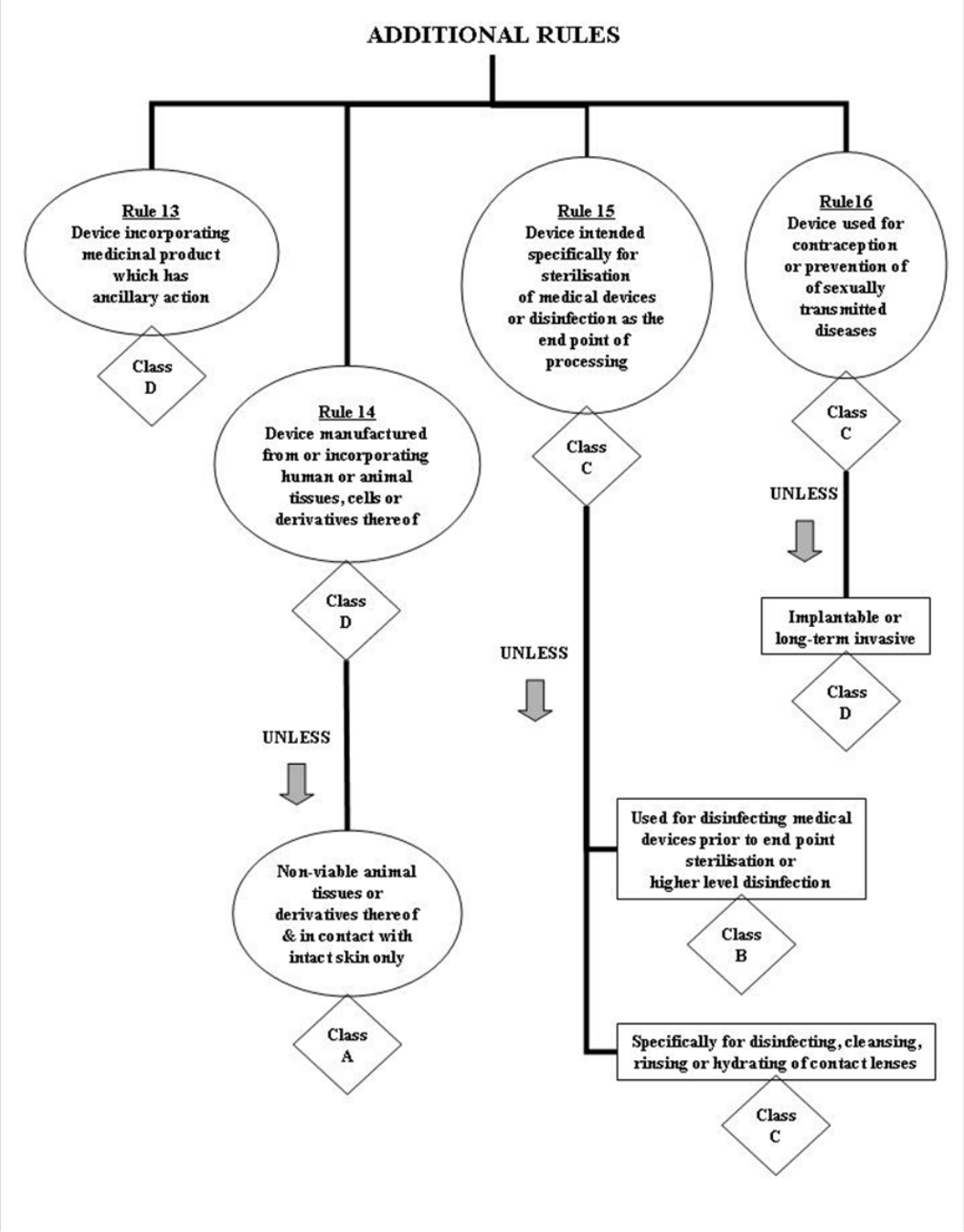
NOTE: This diagram and those that follow are for illustrative purposes only and the determination of risk class for a particular device should be made by referring to the rules themselves and not the decision trees. Where a medical device has features that place it into more than one class, conformity assessment should be based on the highest class indicated.


INVASIVE DEVICES (1 of 2)
Rule 5
Invasive through body orifice or stoma (not surgically)
Rule 6
Surgically invasive - transient use
Class B
UNLESS
A reusable surgical instrument
Class A
Supplies energy as ionizing radiation
Class C
Biological effect or mainly absorbed
Class C
Administers medicinal products in a potentially hazardous manner
Class C
For use in direct contact with central nervous system
Class D
Intended to diagnose, monitor or correct a defect of heart or central circulatory system and in direct contact with it
Class D
Transient use
Class A
Long term use
Class C
Short term use
Class B
UNLESS
Used in oral cavity, ear canal or nasal cavity only
Class A
UNLESS
Used in oral cavity, ear canal or nasal cavity only & not likely to be absorbed by mucous membrane
Class B
If connected to an active medical device of Class B or higher
Class B


INVASIVE DEVICES (2 of 2)
Rule 7
Surgically invasive
- short term use
Class
B
UNLESS
Administers medicinal products
Class
C
Undergoes chemical change in the body (excluding teeth)
Class
C
Supplies ionizing radiation
Class
C
Biological effect or mainly absorbed
Class
D
Use in direct contact with the central nervous system
Class
D
Intended to diagnose, monitor or correct a defect of heart or central circulatory system and in direct contact with it
Class
D
Rule 8
Surgically invasive
- long term use / implant
Class
C
UNLESS
Placed in the teeth
Class
B
Used in direct contact with the heart, central circulatory system or central nervous system
Class
D
Life supporting or life sustaining
Class
D
Active implants
Class
D
Biological effect or mainly absorbed
Class
D
Administers medicines
Class
D
Undergoes chemical change in the body (excluding teeth)
Class
D
Breast implants
Class
D


ACTIVE DEVICES (1 of 2)
Rule9(i)
Active therapeutic devices intended to administer or exchange energy
Class B
UNLESS
Used to administer / exchange energy (including ionizing radiation) in a potentially hazardous way
Class C
Rule9(ii)
Intended to control, monitor or directly influence the performance of active therapeutic devices in Class C
Class C
Rule10(i)
Active diagnostic devices intended to allow direct diagnosis / monitoring of vital physiological processes or supply energy that is absorbed or intended to image in vivo radio-pharmaceuticals
Class B
UNLESS
The absorbed energy is for illumination only
Class A
The patient is, or could be, in immediate danger
Class C
Rule10(ii)
Diagnostic and/or interventional radiology devices, including their controls & monitors
Class C


ACTIVE DEVICES (2 of 2)
Rule 11
Active devices to administer or remove medicinal products & other substances from the body
Class B
UNLESS
In a potentially hazardous manner
Class C
Rule 12
Active devices other than those where Rules 9, 10 or 11 apply
Class A


ADDITIONAL RULES
Rule 13
Device incorporating medicinal product which has ancillary action
Class D
Rule 14
Device manufactured from or incorporating human or animal tissues, cells or derivatives thereof
Class D
UNLESS
Non-viable animal tissues or derivatives thereof & in contact with intact skin only
Class A
Rule 15
Device intended specifically for sterilisation of medical devices or disinfection as the end point of processing
Class C
UNLESS
Used for disinfecting medical devices prior to end point sterilisation or higher level disinfection
Class B
Specifically for disinfecting, cleansing, rinsing or hydrating of contact lenses
Class C
Rule16
Device used for contraception or prevention of of sexually transmitted diseases
Class C
UNLESS
Implantable or long-term invasive
Class D

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Annex 2:
Principles of In Vitro Diagnostic (IVD) Medical Devices Classification

Table of Contents

1.0 Introduction

The objective of the Global Harmonization Task Force (GHTF) is to encourage convergence at the global level in the evolution of regulatory systems for medical devices in order to facilitate trade whilst preserving the right of participating members to address the protection of public health by regulatory means considered to be most suitable.

The primary way in which the Global Harmonization Task Force (GHTF) achieves its goals is through the production of harmonized guidance documents suitable for implementation or adoption by member Regulatory Authorities, as appropriate taking into account their existing legal framework, or by nations with developing regulatory programmes.

This guidance document is one of a series that together describe a global regulatory model for medical devices. Its purpose is to assist a manufacturer to allocate its In Vitro Diagnostic (IVD) medical device to an appropriate risk class using a set of harmonized principles. Regulatory Authorities have the responsibility of ruling upon matters of interpretation for a particular medical device.

This document should be read in conjunction with the GHTF document on Principles of Conformity Assessment for IVD medical devices that recommends conformity assessment requirements appropriate to each of the four risk classes proposed herein. The link between development of documents on classification and conformity assessment is important to ensure a consistent approach across all countries/regions adopting the global regulatory model recommended by the GHTF, so that premarket approval for a particular device may become acceptable globally. Regulatory Authorities who may have different classification procedures are encouraged to adopt this GHTF guidance as the opportunity permits.

This document has been developed to encourage and support global convergence of regulatory systems. It is intended for use by Regulatory Authorities, Conformity Assessment Bodies and industry, 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.

Regulatory Authorities that are developing classification schemes or amending existing ones are encouraged to consider the adoption of the system described in this document, as this will help to reduce the diversity of schemes worldwide and facilitate the process of harmonization.

The regulatory requirements of some countries do not, at this time, align fully with this guidance.

2.0 Rationale, Purpose and Scope

2.1 Rationale

This guidance document is one of a series that together describe a global regulatory model for medical devices. It provides guidance on the principles of classification of IVD medical devices.

Since the inter-relationship between device class and conformity assessment is critical in establishing a consistent approach to premarket approval across all countries/regions, it should be read in conjunction with the GHTF document on Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices that recommends procedures that may be used to demonstrate that an IVD medical device conforms to the Essential Principles of Safety and Performance for Medical Devices.

2.2 Purpose

The purpose of this document is to

- assist a manufacturer to allocate its IVD medical device to an appropriate risk class using a set of harmonized classification principles;
- base such classification principles on an IVD medical device's intended use ;
- allow Regulatory Authorities to rule upon matters of interpretation for a particular IVD medical device, when appropriate.

Subsequently, such classification will determine the conformity assessment route as described in the GHTF document on Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices.

2.3 Scope

This document applies to all products that fall within the definition of an IVD medical device. An IVD medical device is defined as a device which, whether used alone or in combination, is 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. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles. Note: International reference materials (e.g. WHO) and materials used for external quality assessment schemes are excluded.

3.0 Definitions

Accessory : an article which, is intended specifically by its manufacturer to:

- be used together with an IVD medical device to enable that device to be used in accordance with its intended use as an IVD medical device.
- or to augment or extend the capabilities of that device in fulfilment of its intended use as an IVD medical device.

and therefore should be considered an IVD medical device.

IVD medical device for Self-testing: any IVD medical device intended by the manufacturer for use by lay persons.

Examination: set of operations having the object of determining the value of a property.

Note: In the IVD medical device industry and in many laboratories that use IVD medical devices, examination of an analyte in a biological sample is commonly referred to as a test, assay or analysis.

Harm: physical injury or damage to the health of people or damage to property or the environment.

Hazard: potential source of harm.

Intended use / purpose: the objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.

Instrument: equipment or apparatus intended by the manufacturer to be used as an IVD medical device.

IVD medical device: a 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. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.

Note: In some jurisdictions, some IVD medical devices may be covered by separate regulations.

Reagent: chemical, biological or immunological components, solutions or preparations intended by the manufacturer to be used as IVD medical devices.

Lay person: individual that does not have formal training in a relevant field or discipline.

Near patient (testing): testing performed outside a laboratory environment by a healthcare professional not necessarily a laboratory professional , generally near to, or at the side of, the patient.

Risk: combination of the probability of occurrence of harm and the severity of that harm.

Self-testing: testing performed by lay persons.

Specimen receptacle: a device, whether vacuum-type or not, specifically intended by its manufacturer for the primary containment of specimens derived from the human body.

Transmissible agent: an agent capable of being transmitted to a person, as a communicable, infectious or contagious disease.

Transmission: the conveyance of disease to a person.

4.0 General Principles

Regulatory controls are intended to safeguard the health and safety of patients, users and other persons by ensuring that manufacturers of IVD medical devices follow specified procedures during design, manufacture and marketing.

The risk presented by a particular device depends substantially on its intended use.

The GHTF guidance documents Essential Principles of Safety and Performance of Medical Devices and Labelling for Medical Devices apply to all devices whatever their risk class.

Regulatory controls should be proportional to the level of risk associated with a medical device. The level of regulatory control should increase with increasing degree of risk, taking account of the benefits offered by use of the device. At the same time, the imposition of regulatory controls should not place an unnecessary burden on regulators or manufacturers.

The Classification of an IVD medical device is based on the following criteria:

- the intended use and indications for use as specified by the manufacturer (including but not limited to specific disorder, populations, condition or risk factor for which the test is intended)
- the technical/scientific/medical expertise of the intended user (lay person or healthcare professional)
- the importance of the information to the diagnosis (sole determinant or one of several), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a physician
- the impact of the result (true or false) to the individual and/or to public health

Certain jurisdictions may lower the classification of IVD medical devices for which traceability is established through the use of reference measurement procedures and/or available reference materials.

5.0 Recommendations and Factors Influencing IVD Medical Device Classification

• Regulatory Authorities should work towards the establishment of a global classification system specific to IVD medical devices.

• Such a system should be based upon common features of existing national requirements with the aim of future convergence.

• This system should consist of four risk classes. Based on experience of GHTF Founding Members, this is sufficient to accommodate all IVD medical devices and allows an efficient and defined conformity assessment system.

• The determination of classification for an IVD medical device should be based on a set of rules derived from those features that create risk.

• The set of rules should be sufficiently clear that manufacturers may readily identify the class of their IVD medical device, subject, when appropriate, to confirmation by the Regulatory Authority of compliance to the relevant rule.

• The manufacturer should document its justification for placing its product into a particular risk class, including the resolution of any matters of interpretation where it has asked a Conformity Assessment Body and/or Regulatory Authority for a ruling.

• The rules should be capable of accommodating future technological developments.

• Decisions on final classifications, which deviate from the initial rules-based classification, should be weighed against the disadvantages of disharmonized international classification.

• Where more than one of the classification rules applies to the IVD medical device, the device should be allocated to the highest class indicated.

• Accessories should be classified separately using this guidance document.

• Calibrators intended to be used with an IVD reagent should be placed in the same class as the IVD reagent.

• Stand alone control materials with quantitative or qualitative assigned values intended for one specific analyte or multiple analytes should be placed in the same class as the IVD reagent(s).

• Stand alone control materials with no assigned values intended for use with multiple or single analytes should not be placed in the same class as the IVD reagent(s).

• While most software is incorporated into the IVD medical device itself, some is not. Provided such standalone software falls within the scope of the definition for an 'IVD medical device', it should be classified as follows:
- Where it controls or influences the intended output of a separate IVD medical device, it will have the same class as the device itself.
- Where it is not incorporated in an IVD medical device, it is classified in its own right using the rules in Section 9.0 of this document.

Note 1: Performance of software or instrument that is specifically required to perform a particular test will be assessed at the same time as the test kit.
Note 2: The interdependence of the instrument and test methodology prevents the instrument from being assessed separately, even though the instrument itself is still classified as Class A.

Study Group 1 of GHTF continues to support and encourage regulatory harmonization. It recognises that some Regulatory Authorities may have to reflect different local needs when they introduce new regulations on classification. Study Group 1 hopes any such differences will disappear in the course of time.

6.0 Proposed General Classification System for IVD Medical Devices

A four class system is proposed. The use of an alphabetical system in this document is chosen as a distinctive format for GHTF.

Figure 1 indicates the four risk classes of devices. The examples given are for illustration only; the manufacturer must apply the classification rules to each IVD medical device according to its intended use.

Figure 1: Proposed general classification system for IVD medical devices.

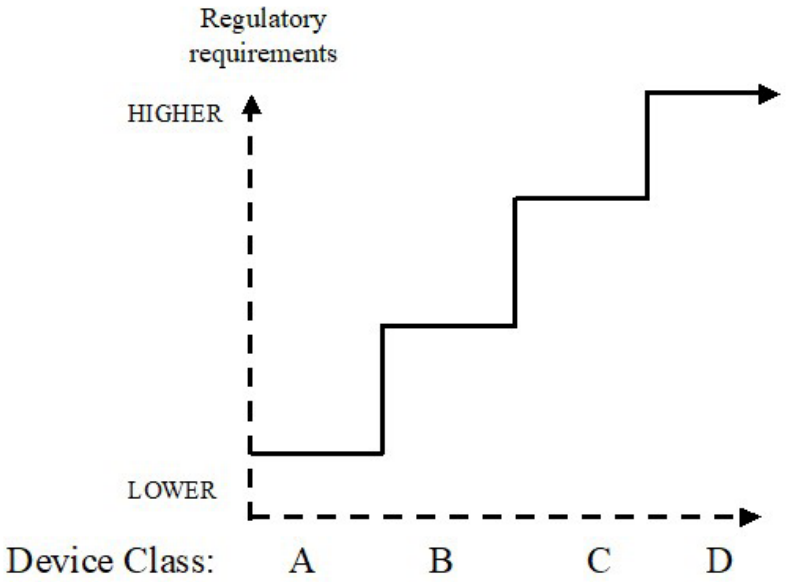
CLASS	RISK LEVEL	EXAMPLES
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyser, prepared selective culture media
B	Moderate Individual Risk and/or Low Public Health Risk	Vitamin B12, Pregnancy self-testing, Anti-Nuclear Antibody, Urine test strips
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self-testing, HLA typing, PSA screening, Rubella
D	High Individual Risk and High Public Health Risk	HIV Blood donor screening, HIV Blood diagnostic

Figure 2 shows a conceptual illustration of increasing levels of regulatory requirements as the device risk class increases. These may include, for example:

- operation of a quality system (recommended for all devices);
- documentation of clinical evidence to support the manufacturer's specified intended use;
- the need for technical data;
- product testing using in-house or independent resources;
- the need for and frequency of independent external audit of the manufacturer's quality system; and
- independent external review of the manufacturer's technical data.

The concept is expanded in the GHTF guidance document entitled Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices.

Figure 2: Conceptual illustration of regulatory requirements increasing with device risk class.



7.0 The Determination of Device Class

The manufacturer should:

1. Decide if the product concerned is an IVD medical device based on the intended use and the indications for use using the definition in section 4.0 of this document.

2. Take into consideration all the rules as listed in section 9.0 in order to establish the proper classification for the device. Where an IVD medical device has multiple intended uses as specified by the manufacturer, which place the device into more than one class, it will be classified in the higher class.

3. Where more than one of the classification rules applies to the IVD medical device, it should be allocated to the highest class indicated, e.g. a self-testing for HIV would be a class D under rule 1 and not a class C under rule 4.

4. Determine that the device is not subject to special national rules that apply within a particular jurisdiction.

NOTE: Where special national rules are applied, resulting in a device class other than that suggested by the present rules, then a different conformity assessment procedure may be indicated. This may have an effect on the acceptability of such devices for free movement in a global context unless other, or additional, conformity assessment procedures are carried out. For example, where such special national rules result in the lower classification of a particular IVD medical device than that indicated in the rules indicated below, and as a consequence, a less vigorous conformity assessment procedure is carried out, this may be unacceptable to other jurisdictions.

8.0 Classification Rules

Rule 1: IVD medical devices intended for the following purposes are classified as Class D:

• Devices intended to be used to detect the presence of, or exposure to, a transmissible agent in blood, blood components, blood derivatives, cells, tissues or organs in order to assess their suitability for transfusion or transplantation, or

• Devices intended to be used to detect the presence of, or exposure to, a transmissible agent that causes a life-threatening, often incurable, disease with a high risk of propagation

Rationale: The application of this rule as defined above should be in accordance with the rationale that follows: Devices in this Class are intended to be used to ensure the safety of blood and blood components for transfusion and/or cells, tissues and organs for transplantation. In most cases, the result of the test is the major determinant as to whether the donation/product will be used. Serious diseases are those that result in death or long-term disability, that are often incurable or require major therapeutic interventions and where an accurate diagnosis is vital to mitigate the public health impact of the condition.

Examples: Tests to detect infection by HIV, HCV, HBV, HTLV. This Rule applies to first-line assays, confirmatory assays and supplemental assays.

Rule 2: IVD medical devices intended to be used for blood grouping, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation, are classified as Class C, except for ABO system [A (ABO1), B (ABO2), AB (ABO3)], rhesus system [RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e)], Kell system [Kel1 (K)], Kidd system [JK1 (Jka), JK2 (Jkb)] and Duffy system [FY1 (Fya), FY2 (Fyb)] determinations which are classified as Class D.

Rationale: The application of this rule as defined above should be in accordance with the rationale for this rule which is as follows: A high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation places the device into Class D. The rule divides blood grouping devices into two subsets, Class C or D, depending on the nature of the blood group antigen the IVD medical device is designed to detect, and its importance in a transfusion setting.

Examples: HLA, Duffy system (other Duffy systems except those listed in the rule as Class D are in Class C).

Rule 3: IVD medical devices are classified as Class C if they are intended for use:

• in detecting the presence of, or exposure to, a sexually transmitted agent. Examples: Sexually transmitted diseases, such as Chlamydia trachomatis, Neisseria gonorrhoeae.

• in detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation. Examples: Neisseria meningitidis or Cryptococcus neoformans.

• in detecting the presence of an infectious agent where there is a significant risk that an erroneous result would cause death or severe disability to the individual or fetus being tested. Examples: diagnostic assay for CMV, Chlamydia pneumoniae, Methycillin Resistant Staphylococcus aureus.

• in pre-natal screening of women in order to determine their immune status towards transmissible agents. Examples: Immune status tests for Rubella or Toxoplasmosis.

• in determining infective disease status or immune status, and where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient. Examples: Enteroviruses, CMV and HSV in transplant patients.

• in screening for selection of patients for selective therapy and management, or for or for disease staging, or in the diagnosis of cancer. Example: personalized medicine.

NOTE: those IVD medical devices where the therapy decision would usually be made only after further investigation and those used for monitoring would fall into class B under rule 6.

•in human genetic testing. Examples: Huntington's Disease, Cystic Fibrosis.

• to monitor levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient. Examples: Cardiac markers, Cyclosporin, Prothrombin time testing.

• In the management of patients suffering from a life-threatening infectious disease. Examples: HCV viral load, HIV Viral Load and HIV and HCV geno- and subtyping.

• In screening for congenital disorders in the fetus. Examples: Spina Bifida or Down Syndrome.

Rationale: The application of this rule as defined above should be in accordance with the rationale for this rule which is as follows: Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.

Rule 4: IVD medical devices intended for self-testing are classified as Class C, except those devices from which the result is not determining a medically critical status, or is preliminary and requires follow-up with the appropriate laboratory test in which case they are Class B.

IVD medical devices intended for blood gases and blood glucose determinations for near-patient testing would be Class C. Other IVD medical devices that are intended for near-patient should be classified in their own right using the classification rules.

Rationale: The application of this rule as defined above should be in accordance with the rationale for this rule which is as follows: In general, these devices are used by individuals with no technical expertise and thus the labelling and instructions for use are critical to the proper outcome of the test.

Example for self-testing class C: Blood glucose monitoring,

Example for self-testing class B: Pregnancy self test, Fertility testing, Urine test-strips.

Rule 5: The following IVD medical devices are classified as Class A:

• Reagents or other articles which possess specific characteristics, intended by the manufacturer to make them suitable for in vitro diagnostic procedures related to a specific examination.

• Instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures

• Specimen receptacles

Note: Any product for general laboratory use not manufactured, sold or represented for use in specified in vitro diagnostic applications are not deemed to be IVD medical devices, as defined in this document. However, in certain jurisdictions products for general laboratory use are considered to be IVD medical devices.

Rationale: The application of this rule as defined above should be in accordance with the rationale for this rule which is as follows: These devices present a low individual risk and no or minimal public health risk.

Examples: Selective/differential microbiological media (excluding the dehydrated powders which are considered not to be a finished IVD medical device), identification kits for cultured microorganisms, wash solutions,

instruments and plain urine cup.

Note 1: In certain jurisdictions there may be differences as to whether a device classified in this rule is considered an IVD medical device.

Note 2: The performance of software or an instrument that is specifically required to perform a particular test will be assessed at the same time as the test kit.

Note 3: The interdependence of the instrument and the test methodology prevents the instrument from being assessed separately, even though the instrument itself is still classified as Class A.

Rule 6: IVD medical devices not covered in Rules 1 through 5 are classified as Class B.

Rationale: The application of this rule as defined above should be in accordance with the rationale for this rule which is as follows: These devices present a moderate individual risk as they are not likely to lead to an erroneous result that would cause death or severe disability, have a major negative impact on patient outcome or put the individual in immediate danger. The devices give results that are usually one of several determinants. If the test result is the sole determinant however other information is available, such as presenting signs and symptoms or other clinical information which may guide a physician, such that classification into Class B may be justified. Other appropriate controls may also be in place to validate the results. This Class also includes those devices that present a low public health risk because they detect infectious agents that are not easily propagated in a population.

Examples: Blood gases, H. pylori and physiological markers such as hormones, vitamins, enzymes, metabolic markers, specific IgE assays and celiac disease markers.

Rule 7: IVD medical devices that are controls without a quantitative or qualitative assigned value will be classified as Class B.

Rationale: For such controls, the qualitative or quantitative value is assigned by the user and not the manufacturer.

9.0 References

GHTF final documents

GHTF/SG1/N044:2008 Role of Standards in the Assessment of Medical Devices.

GHTF/SG1/N029:2005 Information Document Concerning the Definition of the Term ‘Medical Device’.

GHTF/SG1/N041:2005 Essential Principles of Safety and Performance of Medical Devices.

GHTF/SG1/N043:2005 Labelling for Medical Devices.

GHTF/SG1/N046:2008 Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices

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Annex 3:

APPLICATION FORM FOR MARKET AUTHORIZATION OF IN VITRO DIAGNOSTIC MEDICAL DEVICES

How to complete this form

This form has been designed to assist Relevant NMRA to capture necessary information about a product submitted for NRA assessment. The information provided by the manufacturer in this form assists Relevant NMRA to determine the type of assessment (full or abridged) that the product will undergo. The information in this form is also used in the planning of each of the elements of the NRA assessment. Therefore, the manufacturer must complete the form with accuracy and completeness.

Type in text or tick boxes (□) as required for each field. Where information is not available, or the field is not applicable, type in N/A.

The manufacturer should sign and submit this form as a searchable PDF file or hard copies.

1. Applicant information

1.1.1	Name of Applicant	Click here to enter text.
1.1.2	Applicant physical address	Street Name and No.: Click here to enter text.
		City: Click here to enter text.
		Postcode: Click here to enter text. / Country: Click here to enter text.
1.1.3	Applicant postal address	Street Name and No.: Click here to enter text.
		Postal Office Box No.: Click here to enter text.
		City: Click here to enter text.
		Postcode: Click here to enter text. / Country: Click here to enter text.
1.1.4	Applicant telephone	Click here to enter text.
1.1.5	Applicant e-mail & web address	Click here to enter text.
1.1.6	Other important details of the applicant	Click here to enter text.

2. Manufacturer Information (if different from the applicant)

2.1 Manufacturer

2.1.1	Name of manufacturer	Click here to enter text.
2.1.2	Manufacturer physical address	Street Name and No.: Click here to enter text.
		City: Click here to enter text.
		Postcode: Click here to enter text. / Country: Click here to enter text.
2.1.3	Manufacturer postal address	Street Name and No.: Click here to enter text.
		Postal Office Box No.: Click here to enter text.
		City: Click here to enter text.
		Postcode: Click here to enter text. / Country: Click here to enter text.
2.1.4	Manufacturer telephone	Click here to enter text.
2.1.5	Manufacturer e-mail & web address	Click here to enter text.
2.1.6	Name of parent company	Click here to enter text.

2.2 Authorized contacts for the Applicant and manufacturer

2.2.1	Name of **applicant** authorized contact	Click here to enter text.
2.2.2	Authorized contact postal address	Department: Click here to enter text.
		Street Name and No.: Click here to enter text.
		City: Click here to enter text.
		Postcode: Click here to enter text. / Country: Click here to enter text.
2.2.3	Authorized contact telephone	Fixed line: Click here to enter text. / Mobile phone: Click here to enter text.
2.2.4	Authorized contact e mail	Click here to enter text.

2.2.5 Name of **manufacturer** authorized contact (if different from the applicant)	Click here to enter text.	
2.2.6 Authorized contact postal address	Department: Click here to enter text.	
	Street Name and No.: Click here to enter text.	
	City: Click here to enter text.	
	Postcode: Click here to enter text.	Country: Click here to enter text.
2.2.7 Authorized contact telephone	Fixed line: Click here to enter text.	Mobile phone: Click here to enter text.
2.2.8 Authorized contact e mail	Click here to enter text.	

3. Authorized local representative

3.1 Name authorized local representative	Click here to enter text.	
3.2 Authorized local representative postal address	Department: Click here to enter text.	
	Street Name and No.: Click here to enter text.	
	City: Click here to enter text.	
	Postcode: Click here to enter text.	Country: Click here to enter text.
3.3 Authorized local representative telephone	Fixed line: Click here to enter text.	Mobile phone: Click here to enter text.
3.4 Authorized local representative e mail	Click here to enter text.	

4. Product – Information

4.1 Product name and product code/catalogue number for NRA assessment

4.1.1 State product name: Click here to enter text.		
4.1.2 Provide the product code for each kit size submitted for NRA assessment:		
Contents of the kit [1], including accessories	Number of tests per kit: Click here to enter text. *Product code:* Click here to enter text.	Number of tests per kit: Click here to enter text. Product code: Click here to enter text. *if multiple kit sizes are available
Insert name of one component per line.Click here to enter text.	***Indicate*** Xx vial/device/bottle (xx volume)Click here to enter text.	Indicate Xx vial/device/bottle (xx volume) Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.
4.1.3 If reagents are supplied in more than one box, provide the reagent name, product code/catalogue number, and number of tests for each box of reagents		

[1] [**ATTACHMENT:** Attach photographs of all kit components (packaged and individually.]

Name of reagent for each box	Product code/catalogue number	Reagent box size (number of tests per kit)
Click here to enter text.	Click here to enter text.	Click here to enter text.

4.1.4 Does this product require dedicated instrumentation? If so, please provide the instrument or component name, product code/catalogue number, and other relevant information.		
Name of instrument or component	Product code/catalogue number	Other
Click here to enter text.	Click here to enter text.	Click here to enter text.

4.1.5 Is the regulatory version submitted for NRA assessment commercially available? (See section 6 below)	□ Yes Date product[2] was initially placed on the market: Click here to enter text.
	□ No Product[3] expected to be commercialized by: Click here to enter text.

4.2 Current instructions-for-use and user manual[3]

4.2.1 Instructions-for-use (IFU) version number (if different IFUs are provided with different kit sizes, please include each, and identify which product code applies to which IFU)	Click here to enter text.
4.2.2 If applicable, the user manual(s) version number for dedicated instrumentation	Click here to enter text.

4.3 Risk class of the IVD

4.3.1 Instructions-for-use (IFU) version number (if different IFUs are provided with different kit sizes, please include each, and identify which product code applies to which IFU)	Click here to enter text.
4.3.2 If applicable, the user manual(s) version number for dedicated instrumentation	Click here to enter text.

[2] Refers to the product holding the regulatory version submitted for NRA assessment

[3] [**ATTACHMENT:** Attach the English language version of the instructions-for-use to this application form. Instructions-for-use are also known as a package insert.]

4.4 Transport, storage and operating temperatures

4.4.1. List transport, storage and operating temperatures and shelf life					
Product name (If more than one box, provide the name for each reagent box)	Transport temperature range (min °C - max °C)	Storage temperature range (min °C - max °C)	Operating temperature range (min °C - max °C)	Shelf-life upon manufacture (months)	Indicative shelf life upon delivery (months)
Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
4.4.2. Describe any other storage conditions that are applicable to this product: Click here to enter text.					

5. Product - Disease Category, Analyte and Method

5.1 HIV

5.1.1 Select HIV sub-type	
□ HIV-1/HIV-2 discriminatory detection	□ HIV-1/2 combined detection
□ HIV + another analyte	Specify: Click here to enter text.
5.1.2 Select HIV analyte	
□ Antibody	□ Antigen
□ Ab/Ag combined detection	□ Ab/Ag discriminatory detection
□ Nucleic acid – qualitative	□ Nucleic acid - quantitative
□ Surrogate marker for viral load	

5.2 Malaria

5.2.1 Select malaria species	
□ *P. falciparum*	□ *P. vivax*
□ *P. ovale*	□ *P. malariae*
□ *P. knowlesi*	□ PAN - all malarial species

5.2.2 Select malarial analyte		
□ HRP2	□ pLDH	□ pLDH- *Pf* specific □ pLDH-PAN □ pLDH- *Pv* specific (non-HRP2)
□ Aldolase	□ Multiple/other: Specify: Click here to enter text.	

5.2.3 Select type of detection		
□ One line (one species detection)	□ One line (combine detection of 2 or more species)	□ 2 or more lines (discriminatory detection of 2 or more species)

5.3 Hepatitis

5.3.1 Select hepatitis C (HCV) analyte	
□ Antibody	□ Antigen

□	Ab/Ag combination	□	Nucleic acid
5.3.2	Select hepatitis B (HBV) analyte		
□	Surface antigen		

5.4 HPV

4.4.1	Select human papilloma virus (HPV) analyte		
□	HPV 16, 18	□	All high risk HPV
□	Other combination of high risk genotypes	Specify: Click here to enter text.	
4.4.2 Select method of analysis			
□	Genotype discrimination	□	Non-discrimination of genotypes

5.5 Other disease categories

5.5.1 Specify: Click here to enter text.

5.6 Assay format for serology and nucleic acid testing technologies

5.6.1.	Select the assay format		
□	Immunochromatographic (lateral flow)	□	Immunofiltration (flow through)
□	Agglutination	□	EIA (Enzyme immunoassay)
□	Recombinant immunoblot	□	Western blot
□	Antigen neutralization	□	Immunofluorescence
□	NAT (nucleic acid testing)	Specify NAT methodology:	
		□	NAT (qualitative)
		□	NAT (quantitative)
□	Other: Click here to enter text.		

5.7 CD4 counting technology[4]

5.7.1.	Select the best description of the CD4 instrument/method.		
□	Double platform flow cytometer	□	Single platform flow cytometer
□	Point-of-care technology	□	Other: Click here to enter text.
5.7.2.	Select the appropriate electricity power requirement		
□	Alternating current (110-220V)	□	Direct current (battery, solar power)
5.7.3.	Select the type of results obtained		
□	CD4 counts only	□	CD4 counts and percent
□	CD4 counts and hematology	□	CD4 counts, percent and hematology
□	CD4 counts semi-quantitative	□	CD4 counts semi-quantitative
□	CD4 qualitative		

5.8 Specimen type

5.8.1	Select the specimen type(s) to be used with the product		
□	Serum	□	Plasma
□	Venous whole blood	□	Capillary whole blood
□	Oral fluid	□	Dried blood spot
Other: Click here to enter text.			
□	50-100 tests/day per operator	□	> 100 tests/day per operator

[4] Section 3.6 applies only to CD4 technologies and should be left blank for other types of products.

5.9 Indicative cost

Indicate the approximate cost per Test (reagent)	Click here to enter text. USD
Indicate the approximate instrument(s)	Click here to enter text. USD

6. Regulatory and Commercial Status of the Product

6.1 Regulatory status of product

6.1.1 State the regulatory version of the product submitted for assessment (please tick and enter the approval period)[5]:		
Name of jurisdiction	Type of regulatory approval	Product name Product code Period of approval: Start (DD/MM/YY) - Expiry (DD/MM/YY)
Rest of world version	The product submitted for assessment is not approved in any of the jurisdictions listed below	
European Community (CE-mark) Directive 98/79/EC	□ Self-declared CE-mark, Annex III	Click here to enter text.
	□ Full quality assurance certificate, Annex IV.3	Click here to enter text.
	□ Product design examination certificate, Annex IV.4	Click here to enter text.
	□ Type examination certificate, Annex V	Click here to enter text.
	□ Production quality assurance certificate, Annex VII	Click here to enter text.
United States of America (FDA)	□ Premarket Approval (PMA)	Click here to enter text.
	□ 510(k) clearance	Click here to enter text.
	□ Certificate of Exportability to Foreign Government	Click here to enter text.
	□ Non-clinical Research Use Only Certificate	Click here to enter text.
	□ Other: Click here to enter text.	Click here to enter text.
Canada (Health Canada)	□ Medical device license and summary report for a Class III IVD	Click here to enter text.
	□ Medical device license and summary report for a Class IV IVD	Click here to enter text.
	□ Manufacturer's Certificate to Cover Export of Medical Devices (MCE)	Click here to enter text.
	□ Other: Click here to enter text.	Click here to enter text.

[5] If more than one regulatory version exists, and at least one regulatory version has undergone stringent regulatory assessment (CE; List A, Annex II, FDA; PMA or BLA, Health Canada; Class IV, TGA; Class 4, Japan; Minister's approval), please complete Annex 1 to determine if the product can undergo the abridged NMRA assessment.

Australia (TGA)	□	Click here to enter text.
	□ Australian Register of Therapeutic Goods (ARTG) Number (aka Medical Device Inclusion Number) Number	Click here to enter text.
	□ Conformity Assessment - Full quality assurance certificate	Click here to enter text.
	□ Conformity Assessment - Production quality assurance certificate	Click here to enter text.
	□ Other: Click here to enter text.	Click here to enter text.
	□ License for manufacturer	Click here to enter text.
Japan (JMHLW)	□ Recognized foreign manufacturer	Click here to enter text.
	□ Minister's approval	Click here to enter text.
	□ Other: Click here to enter text.	Click here to enter text.

6.1.2. Provide details of <u>any other</u> current regulatory approvals for this product (Do <u>not</u> include ISO 13485 certification details here. This is covered in question 7)		
Name of regulatory authority/jurisdiction	Type of regulatory approval	Product name Product code Period of approval: Start (DD/MM/YY) - Expiry (DD/MM/YY)
Click here to enter text.	Click here to enter text.	Click here to enter text.

6.2 Commercial agreements and re-branding[6]

6.2.1	Do you sell or supply this product or any of the components for re-branding [7]?	□	Yes
		□	No
6.2.2	Is this product or any of the major components sourced from another manufacturer?	□	Yes
		□	No
If you have answered yes to 7.2.1 or 7.2.2, please provide details: Click here to enter text.			

6.3 NMRA/EAC history of product

6.3.1	Has NMRA previously assessed this product?	□ Yes	Date Click here to enter text.

[6] Applications for NMRA assessment of IVDs are accepted only from the legal manufacturer of the product.

		□ No	
6.3.2	Has NMRA previously assessed this product under a different name?	□ Yes	Date Click here to enter text.
		□ No	
If you answered yes to 6.3.2, please provide the name of the previously assessed product: Click here to enter text.			
6.3.3 Is there any application for this product pending in any NMRA?			

7. Manufacturer - Quality Management System

7.1	Does the manufacturer have a quality management system in place for the design, development and production of this product? Submit a written declaration of conformity. The DoC should contain an attestation that a device complies with the applicable EPSP, has been classified accordingly and has met applicable conformity assessment elements	□ Yes □ No
7.2	Does this quality management system meet the requirements of *ISO 13485 Medical devices — Quality management systems — Requirements for regulatory purposes*?	□ Yes □ No
7.3	Does the quality management system meet the requirements of other similar standards e.g. those required by other jurisdictions? If yes, please provide details.	Click here to enter text.

8. Manufacturer – Quality Management System Certification

8.1 Please provide details regarding any certification held in respect to the quality management system used for the manufacture of this product.		
Type of QMS e.g. ISO 13485:2003 ISO 13485:2016	Name of certification body	Current period of certification Start (DD/MM/YY) - Expiry (DD/MM/YY)
Click here to enter text.	Click here to enter text.	Click here to enter text.

9. Manufacturer - Sites of Product Manufacture

9.1 Sites of manufacture (If different from Legal manufacturer)

9.1.1 List all sites that are involved in the manufacture of this product. Include all stages of manufacture		
Description of the stage of manufacture	Name of site	Physical address of site
Design & Development	Click here to enter text.	Click here to enter text.
Assembly of device (list **all** sites from raw materials to components to finished product)	Click here to enter text.	Click here to enter text.
Labelling	Click here to enter text.	Click here to enter text.
Packaging	Click here to enter text.	Click here to enter text.

Lot release QC	Click here to enter text.	Click here to enter text.
Release for supply	Click here to enter text.	Click here to enter text.
Other:	Click here to enter text.	Click here to enter text.

9.2 Key suppliers

9.2.1 List **all** key suppliers which supply products/components/services for the manufacture of this product (e.g. raw materials, enzymes, key components, bulk chemicals and reagents, instruments, etc.)		
Description of the component/product/service supplied	Name of supplier	Physical address of supplier
Click here to enter text.	Click here to enter text.	Click here to enter text.

10. Manufacturer Declaration

The undersigned duly authorized representative of the Manufacturer makes the following declarations on behalf of the Manufacturer and, in signing this pre-submission form, declares that he/she has the power and authority to bind the Manufacturer.

I declare that:

- I am authorized to represent the manufacturer specified in this Application form (the "Manufacturer") for the purposes of NRA assessment of the product specified in this pre-submission form (the "Product").
- All the information provided in this form is current, complete and correct.
- Any changes to the information provided in this form will be readily communicated by the Manufacturer to NMRA.
- The Manufacturer holds data in support of all claims made in this form.
- The Manufacturer understands and agrees that, in the event that NRA agrees to undertake assessment of the Product: (i) Submits technical file based on the format provided and must pay the assessment fees; (ii) NRA will have absolute, exclusive, unfettered control over the manner in which the assessment process is carried out (including the performance evaluation); and (iii) NRA reserves the right to share the results of the assessment and the full assessment and inspection reports, including any drafts thereof and including (subject to appropriate obligations of confidentiality) any confidential information to which NRA may gain access in the course of the assessment process, with the relevant authorities of any interested Member State and with relevant intergovernmental organizations.
- The Manufacturer understands and agrees that the validity of the registration status is dependent on the fulfilment of post-assessment requirements including:
    - registration commitments;

- annual reporting;
- reporting of changes;
- post-market surveillance obligations;
- receiving re-inspection; and
- ongoing compliance with product technical specifications.

Name of the Duly Authorized Representative of the Manufacturer: Click here to enter text.

Signature of the Duly Authorized Representative of the Manufacturer:_____

Date: Click here to enter text.

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Annex 4:
IMDRF In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC)

Table of Contents

1. INTRODUCTION

This document provides an internationally harmonized, modular, format for use when filing medical device submissions to regulatory authorities for market authorization. This document is comprehensive in scope in that it defines the location of both common (IMDRF) and regional content for all submission types. As a consequence, not all headings are required for all submission types and/or IMDRF jurisdictions.

The ToC documents are intended to work together with a separate document created for each participating jurisdiction – a classification matrix. The classification matrix defines whether for the given submissions type a heading is required, not required, optional, conditionally required, etc. The classification matrices are the published under the authority of participating authorities and are not products of IMDRF, please consult regional regulator websites for further information.

2. SCOPE

This document was developed for in-vitro diagnostics medical device (IVD) market authorization submissions. Market authorization submissions for combination products are out of scope; refer to each specific regulator for guidance regarding combination products. Submissions to request approval to conduct clinical trials are not within the scope of this document.

The document is intended to provide guidance for industry with flexibility to adapt to the variety of products and future products.

3. PURPOSE

To create a comprehensive submission structure that can be used as a harmonized international electronic submission format while minimizing regional divergences and indicating where regional variation exists. This document is intended to provide guidance regarding the location of submission elements. This document is intended to work together with a separate document created for each participating jurisdiction – a classification matrix.

This document is not intended to introduce any new regulatory requirements; however, by virtue of being more transparent, it may appear to be introducing new requirements.

4. CLASSIFICATION MATRICES

As this document is comprehensive in nature, not all headings are required for all submission types and/or jurisdictions. This document is intended to work together with a separate document created for each participating jurisdiction – a classification matrix. The classification matrix defines whether for the given submissions type a heading is required, not required, optional, conditionally required, etc. The classification matrices are to be made available on regional regulators websites.

5. DEFINITIONS

FULL REPORT - Typically includes a complete, detailed description of the objective of the assessment, the methods and procedures including when applicable why a regional or harmonized/recognized standard/guidance has or has not been complied with, study endpoint(s), pre-defined pass/fail criteria, deviations, results, discussion and conclusions, and may include data. Complete, detailed support of method selection, worst case justification, study endpoint selection, and pass/fail criteria should be included.

SUMMARY - A summary should include a brief synopsis of the (1) purpose, (2) methods, (3) acceptance criteria, (4) results and (5) discussion and conclusions. Outliers and deviations should be reported with the results. Results should be stated quantitatively with appropriate statistical context where applicable (e.g. value ± SD, confidence intervals, etc.).

The summary should specifically address:

1. Why the characteristic being evaluated is of interest;
2. Why the particular methods are being used to evaluate the characteristic, if applicable including why a regional or harmonized/recognized standard/guidance has or has not been complied with;
3. How the stated acceptance and sample size are scientifically supported;
4. What device was tested and how it relates to the devices that will be marketed;
5. Why the tested components are representative of the range of devices that will be marketed;
6. Whether the summary has been previously submitted and reviewed by the regulator, including identification of the device and the reference number for the

submission; and

7. The extent to which the duties and functions of a study (e.g. testing, monitoring, etc) have been conducted by an external organization (e.g. contract research organisation or individual contractor)

HEADING CLASS - Headings are classified as either IMDRF; IMDRF, RF; or Regional.

Heading classification is provided in this document to provide an indication of the relevance of any given heading to a particular jurisdiction. The classification matrices provide further requirement classification by jurisdiction and submission type and should be used as the final reference for information of this type.

IMDRF headings are used by most regulators and are therefore considered an IMDRF heading. Content of IMDRF heading contain common elements and may contain regional elements in addition to the common elements.

o Regional Focus (IMDRF, RF) – content needs to be considered with the specific region in mind and will likely need to be adapted for that region (e.g. regional approval numbers or regulatory history, regional variation in approved or requested intended use/indications for use)

o In cases where not all regulators use the heading, the applicable jurisdictions are listed following the heading classification (e.g. IMDRF (USFDA, HC, JP)).

Regional headings are those that contain no common elements. In this case the heading name is consistent amongst IMDRF members, but the content will be specific and different for each region. Headings are also classified as Regional if they are required by only one jurisdiction.

SUBMISSION – A regulatory submission can be any type of information related to a medical device regulatory process. This includes but is not limited to a request for approval/authorization to market a device, any communications relating to the original submission, and any request for modification to an existing approval. The submission types that will be accepted in the format described in this document will be dictated by regional policy.

6. NUMBERING OF HEADINGS

Numbering should remain consistent regardless of whether the heading is required or not. For example, if Heading 1.02 is not required for the submission type or jurisdiction, but Headings 1.01 and 1.03 are, then the numbering would remain 1.01 followed by 1.03.

7. QUALITY MANAGEMENT SYSTEM CHAPTERS (6A & 6B)

Chapter 6A & B of the ToC is written in terms of the quality management system language employed in ISO 13485. Chapter 6A is where the company places the standard operating procedures (SOPs) the company utilizes to implement its overall high level quality management system. Chapter 6B is where the company places the documents and records the company utilizes to implement the quality management system SOPs described in Chapter 6A.

8. LANGUAGE REQUIREMENTS

Each jurisdiction has its own language requirements. Regional guidance should be sought to ensure that content is provided in a language that is acceptable for the jurisdiction to which the submission will be submitted. Any translated material submitted should be verified for accuracy.

9. OTHER GENERAL NOTES

This outline of documentation is to support a smooth documentation process. It remains the applicant's responsibility to ensure all regulatory requirements are met, and that clear and transparent evidence of conformity to these requirements are provided.

Regional regulatory guidance will vary between the IMDRF member regulators and can be found in a variety of locations including the individual regulator's laws, directives, regulations, guidance documents, etc. When any requirements are conflicting between this document and regional documents (e.g. the regional laws, directives, regulations, guidance documents), the regional requirement will take precedence.

For the USFDA and ANVISA, regional regulatory guidance include the categories (1) special controls in a device specific regulation, (2) device-specific guidance document, (3) special controls guidance, (4) special controls guideline, and/or (5) statutory or regulatory criteria.

When submitting to the USFDA please refer to the current version of the following MDUFA IV guidance documents to ensure the content for each heading and the overall electronic format of the submission is sufficient to be accepted for review by the USFDA. For example:

1. Refuse to Accept Policy for 510(k)s: Guidance for Industry and Food and Drug Administration Staff
2. Acceptance and Filing Reviews for Premarket Approval Applications (PMAs): Guidance for Industry and Food and Drug Administration Staff
3. eCopy Program for Medical Device Submissions: Guidance for Industry and Food and Drug Administration Staff

For the EU, the latest EN ISO version and related Annex Z should be taken as reference to verify the correct presumption of conformity with the essential requirement of Medical Devices Directives.

Note: WHO participates as an Official Observer in the IMDRF and its working groups. Recommendations from WHO are based on the experience of Prequalification Team – Diagnostics Assessment, taking the needs of WHO Member States without strong regulatory systems into account.

ACRONYMS

ANVISA	National Health Surveillance Agency – Brazil
CAPA	Corrective Action and Preventive Action
EU	European Union
GMDN	Global Medical Device Nomenclature
HC	Health Canada
HSA	Health Sciences Authority – Singapore
IMDRF	International Medical Device Regulators Forum
JP	Japan
MDUFA	Medical Device User Fee Amendments
NB	Notified Body
NMPA	National Medical Products Administration – China
PMDA	Pharmaceuticals and Medical Devices Agency – Japan
RF	Regional Focus
TGA	Therapeutic Goods Administration – Australia
ToC	Table of Contents
USFDA	United States Food and Drug Administration
WHO PQ	World Health Organization Prequalification Team – Diagnostics Assessment

HIERARCHY PRESENTATION

The following is a hierarchical presentation of the submission structure. More detailed guidance regarding where elements belong is provided following this table.

CHAPTER 1 – REGIONAL ADMINISTRATIVE	
1.01	Cover Letter
1.02	Submission Table of Contents
1.03	List of Terms/Acronyms
1.04	Application Form/Administrative Information
1.05	Listing of Device(s)
1.06	Quality Management System, Full Quality System or other Regulatory Certificates
1.07	Free Sale Certificate/ Certificate of Marketing authorization
1.08	Expedited Review Documentation
1.09	User Fees
1.10	Pre-Submission Correspondence and Previous Regulator Interactions
1.11	Acceptance for Review Checklist
1.12	Statements/Certifications/Declarations of Conformity
1.12.01	Performance and Voluntary Standard
1.12.02	Environmental Assessment
1.12.03	Clinical Trial Certifications
1.12.04	Indications for Use Statement with Rx and/or OTC designation Enclosure
1.12.05	Truthful and Accurate Statement
1.12.06	Declaration of Conformity
1.13	Letters of Reference for Master Files
1.14	Letter of Authorization
1.15	Other Regional Administrative Information
CHAPTER 2 – SUBMISSION CONTEXT	
2.01	Chapter Table of Contents
2.02	General Summary of Submission
2.03	Summary and Certifications for Premarket Submissions
2.04	Device Description
2.04.01	Comprehensive Device Description and Principle of Operation
2.04.02	Material Specifications
2.04.03	Description of Device Packaging
2.04.04	History of Development
2.04.05	Reference and Comparison to Similar and/or Previous Generations of the Device
2.04.06	Substantial Equivalence Discussion
2.05	Indications for Use and/or Intended Use
2.05.01	Intended Use; Intended Purpose; Intended User; Indications for Use
2.05.02	Intended Environment/Setting for use
2.05.03	Pediatric Use
2.05.04	Contraindications for Use
2.06	Global Market History
2.06.01	Global Market History
2.06.02	Global Incident Reports and Recalls
2.06.03	Sales, Incident and Recall Rates
2.06.04	Evaluation/Inspection Reports
2.07	Other Submission Context Information
CHAPTER 3 – ANALYTICAL PERFORMANCE AND OTHER EVIDENCE	
3.01	Chapter Table of Contents
3.02	Risk Management
3.03	Essential Principles (EP) Checklist
3.04	Standards
3.04.01	List of Standards
3.04.02	Declaration and/or Certification of Conformity
3.05	Analytical Performance
3.05.01	Stability of Sample(s)
3.05.01.01	[Study description, study identifier, date of initiation, date of completion]
3.05.01.01.01	Summary
3.05.01.01.02	Full Report
3.05.01.01.03	Statistical Data
3.05.02	Validation of Specimens
3.05.02.01	[Study description, study identifier, date of initiation, date of completion]
3.05.02.01.01	Summary
3.05.02.01.02	Full Report

3.05.02.01.03	Statistical Data
3.05.03	Metrological traceability of calibrator and control material values
3.05.03.01	[Study description, study identifier, date of initiation, date of completion]
3.05.03.01.01	Summary
3.05.03.01.02	Full Report
3.05.03.01.03	Statistical Data
3.05.04	Accuracy of Measurement
3.05.04.01	Trueness
3.05.04.01.01	[Study description, study identifier, date of initiation, date of completion]
3.05.04.01.01.01	Summary
3.05.04.01.01.02	Full Report
3.05.04.01.01.03	Statistical Data
3.05.04.02	Precision (Repeatability and Reproducibility)
3.05.04.02.01	[Study description, study identifier, date of initiation, date of completion]
3.05.04.02.01.01	Summary
3.05.04.02.01.02	Full Report
3.05.04.02.01.03	Statistical Data
3.05.05	Analytical Sensitivity
3.05.05.01	[Study description, study identifier, date of initiation, date of completion]
3.05.05.01.01	Summary
3.05.05.01.02	Full Report
3.05.05.01.03	Statistical Data
3.05.06	Analytic Specificity
3.05.06.01	[Study description, study identifier, date of initiation, date of completion]
3.05.06.01.01	Summary
3.05.06.01.02	Full Report
3.05.06.01.03	Statistical Data
3.05.07	High Dose Hook Effect
3.05.07.01	[Study description, study identifier, date of initiation, date of completion]
3.05.07.01.01	Summary
3.05.07.01.02	Full Report
3.05.07.01.03	Statistical Data
3.05.08	Measuring Range of the Assay
3.05.08.01	[Study description, study identifier, date of initiation, date of completion]
3.05.08.01.01	Summary
3.05.08.01.02	Full Report
3.05.08.01.03	Statistical Data
3.05.09	Validation of Assay Cut-off
3.05.09.01	[Study description, study identifier, date of initiation, date of completion]
3.05.09.01.01	Summary
3.05.09.01.02	Full Report
3.05.09.01.03	Statistical Data
3.05.10	Validation of the Assay Procedure
3.05.10.01	[Study description, study identifier, date of initiation, date of completion]
3.05.10.01.01	Summary
3.05.10.01.02	Full Report
3.05.10.01.03	Statistical Data
3.06	Other Studies
3.06.01	Electrical Systems: Safety, Mechanical and Environmental Protection, and Electromagnetic Compatibility
3.06.01.01	[Study description, study identifier, date of initiation, date of completion]
3.06.01.01.01	Summary
3.06.01.01.02	Full Report
3.06.01.01.03	Statistical Data
3.06.02	Software/Firmware
3.06.02.01	Software/Firmware Description
3.06.02.02	Hazard Analysis
3.06.02.03	Software Requirement Specification
3.06.02.04	Architecture Design Chart
3.06.02.05	Software Design Specification
3.06.02.06	Traceability Analysis
3.06.02.07	Software Life Cycle Process Description

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Annex 5:

IMDRF Non-In Vitro Diagnostic Device Market Authorization Table of Contents (nIVD MA ToC)

Table of Contents

1. INTRODUCTION

The Regulated Product Submission (RPS) proposal was endorsed as a New Work Item (NWI) by IMDRF at its inaugural meeting in Singapore (March 2012). The proposal, as endorsed, included the objective of establishing a comprehensive harmonized structure for pre-market medical device submissions.

This document provides an internationally harmonized, modular, format for use when filing medical device submissions to regulatory authorities for market authorization. This document is comprehensive in scope in that it defines the location of both common (IMDRF) and regional content for all submission types. As a consequence, not all headings are required for all submission types and/or IMDRF jurisdictions.

The ToC documents are intended to work together with a separate document created for each participating jurisdiction – a classification matrix. The classification matrix defines whether for the given submissions type a heading is required, not required, optional, conditionally required, etc.

2. SCOPE

This document was developed for non-In-vitro diagnostics device (nIVD) market authorization submissions. Market authorization submissions for combination products are out of scope; refer to each specific regulator for guidance regarding combination products. Submissions to request approval to conduct clinical trials are not within the scope of this document.

The document is intended to provide guidance for industry with flexibility to adapt to the variety of products and future products.

3. PURPOSE

To create a comprehensive submission structure that can be used as a harmonized international electronic submission format while minimizing regional divergences and indicating where regional variation exists. This document is intended to provide guidance regarding the location of submission elements. This document is intended to work together with a separate document created for each participating jurisdiction – a classification matrix.

This document is not intended to introduce any new regulatory requirements; however, by virtue of being more transparent, it may appear to be introducing new requirements.

4. CLASSIFICATION MATRICES

As this document is comprehensive in nature, not all headings are required for all submission types and/or jurisdictions. This document is intended to work together with a separate document created for each participating jurisdiction – a classification matrix. The classification matrix defines whether for the given submissions type a heading is required, not required, optional, conditionally required, etc. The classification matrices are to be made available on regional regulators websites.

5. DEFINITIONS

FULL REPORT - Typically includes a complete, detailed description of the objective of the assessment, the methods and procedures including when applicable why a regional or harmonized/recognized standard/guidance has or has not been complied with, study endpoint(s), pre-defined pass/fail criteria, deviations, results, discussion and conclusions, and may include data. Complete, detailed support of method selection, worst case justification, study endpoint selection, and pass/fail criteria should be included.

SUMMARY - A summary should include a brief synopsis of the (1) purpose, (2) methods, (3) acceptance criteria, (4) results and (5) discussion and conclusions. Outliers and deviations should be reported with the results. Results should be stated quantitatively with appropriate statistical context where applicable (e.g. value ± SD, confidence intervals, etc.).

The summary should specifically address:

1. Why the characteristic being evaluated is of interest;
2. Why the particular methods are being used to evaluate the characteristic, if applicable including why a regional or harmonized/recog nized standard/guidance has or has not been complied with;
3. How the stated acceptance and sample size are scientifically supported;
4. What device was tested and how it relates to

the devices that will be marketed;

5. Why the tested components are representative of the range of devices that will be marketed;
6. Whether the summary has been previously submitted and reviewed by the regulator, includ ing identification of the device and the reference number for the submission; and
7. The extent to which the duties and functions of a study (e.g. testing, monitoring, etc) have been conducted by an external organization (e.g. contract research organisation or individual contractor)

HEADING CLASS - Headings are classified as either IMDRF; IMDRF, RF; or Regional.

Heading classification is provided in this document to provide an indication of the relevance of any given heading to a particular jurisdiction. The classification matrices provide further requirement classification by jurisdiction and submission type and should be used as the final reference for information of this type.

IMDRF headings are used by most regulators and are therefore considered an IMDRF heading. Content of IMDRF heading contain common elements and may contain regional elements in addition to the common elements.

o Regional Focus (IMDRF, RF) – content needs to be considered with the specific region in mind and will likely need to be adapted for that region (e.g. regional approval numbers or regulatory history, regional variation in approved or requested intended use/indications for use)

o In cases where not all regulators use the heading, the applicable jurisdictions are listed following the heading classification (e.g. IMDRF (USFDA, HC, JP)).

Regional headings are those that contain no common elements. In this case the heading name is consistent amongst IMDRF members, but the content will be specific and different for each region. Headings are also classified as Regional if they are required by only one jurisdiction.

SUBMISSION – A regulatory submission can be any type of information related to a medical device regulatory process. This includes but is not limited to a request for approval/authorization to market a device, any communications relating to the original submission, and any request for modification to an existing approval. The submission types that will be accepted in the format described in this document will be dictated by regional policy.

6. NUMBERING OF HEADINGS

Numbering should remain consistent regardless of whether the heading is required or not. For example, if Heading 1.02 is not required for the submission type or jurisdiction, but Headings 1.01 and 1.03 are, then the numbering would remain 1.01 followed by 1.03.

7. QUALITY MANAGEMENT SYSTEM CHAPTERS (6A & 6B)

Chapter 6A & B of the ToC is written in terms of the quality management system language employed in ISO 13485. Chapter 6A is where the company places the standard operating procedures (SOPs) the company utilizes to implement its overall high level quality management system. Chapter 6B is where the company places the documents and records the company utilizes to implement the quality management system SOPs described in Chapter 6A.

8. LANGUAGE REQUIREMENTS

Each jurisdiction has its own language requirements. Regional guidance should be sought to ensure that content is provided in a language that is acceptable for the jurisdiction to which the submission will be submitted. Any translated material submitted should be verified for accuracy.

9. OTHER GENERAL NOTES

This outline of documentation is to support a smooth documentation process. It remains the applicant's responsibility to ensure all regulatory requirements are met, and that clear and transparent evidence of conformity to these requirements are provided.

Regional regulatory guidance will vary between the IMDRF member regulators and can be found in a variety of locations including the individual regulator's laws, directives, regulations, guidance documents, etc. When any requirements are conflicting between this document and regional documents (e.g. the regional laws, directives, regulations, guidance documents), the regional requirement will take precedence.

For the USFDA and ANVISA, regional regulatory guidance include the categories (1) special controls in a device specific regulation, (2) device-specific guidance document, (3) special controls guidance, (4) special controls guideline, and/or (5) statutory or regulatory criteria.

When submitting to the USFDA please refer to the current version of the following MDUFA IV guidance documents to ensure the content for each heading and the overall electronic format of the submission is sufficient to be accepted for review by the USFDA. For example:

1. Refuse to Accept Policy for 510(k)s: Guidance for Industry and Food and Drug Administration Staff
2. Acceptance and Filing Reviews for Premarket Approval Applications (PMAs): Guidance for In dustry and Food and Drug Administration Staff
3. eCopy Program for Medical Device Submis sions: Guidance for Industry and Food and Drug Administration Staff

For the EU, the latest EN ISO version and related Annex Z should be taken as reference to verify the correct presumption of conformity with the essential requirement of medical Devices Directives.

10. ACRONYMS

ANVISA	National Health Surveillance Agency – Brazil
CAPA	Corrective Action and Preventive Action
EU	European Union
GMDN	Global Medical Device Nomenclature
HC	Health Canada
HSA	Health Sciences Authority – Singapore
IMDRF	International Medical Device Regulators Forum
JP	Japan
MDUFA	Medical Device User Fee Amendments
NB	Notified Body
NMPA	National Medical Products Administration – China
PMDA	Pharmaceuticals and Medical Devices Agency – Japan
RCT	Randomized Controlled Trial
RF	Regional Focus
SUD	Single Use Device
TGA	Therapeutic Goods Administration – Australia
ToC	Table of Contents
USFDA	United States Food and Drug Administration

11. HIERARCHY PRESENTATION

The following is a hierarchical presentation of the submission structure. More detailed guidance regarding where elements belong is provided following this table.

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1.10	Pre-Submission Correspondence and Previous Regulator Interactions
1.11	Acceptance for Review Checklist
1.12	Statements/Certifications/Declarations of Conformity
1.12.01	Performance and Voluntary Standard
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3.05.01.01	[Study description, study identifier, date of initiation]
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3.05.02	Chemical/Material Characterization
3.05.02.01	[Study description, study identifier, date of initiation]
3.05.02.01.01	Summary
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3.05.05.08	Software Verification and Validation
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3.05.09.02.01	[Study description, study identifier, date of initiation]
3.05.09.02.01.01	Summary
3.05.09.02.01.02	Full Report
3.05.09.02.01.03	Statistical Data
3.05.09.03	Residual Toxicity
3.05.09.3.01	[Study description, study identifier, date of initiation]
3.05.09.3.01.01	Summary
3.05.09.3.01.02	Full Report
3.05.09.3.01.03	Statistical Data
3.05.09.4	Cleaning and Disinfection Validation

3.05.09.4.01	[Study description, study identifier, date of initiation]
3.05.09.4.01.01	Summary
3.05.09.4.01.02	Full Report
3.05.09.4.01.03	Statistical Data
3.05.09.5	Reprocessing of Single Use Devices Validation Data
3.05.09.5.01	[Study description, study identifier, date of initiation]
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3.05.09.5.01.02	Full Report
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3.07.01.01	[Study description, study identifier, date of initiation]
3.07.01.01.01	Summary
3.07.01.01.02	Full Report
3.07.01.01.03	Statistical Data
3.07.02	Package Validation
3.07.02.01	[Study description, study identifier, date of initiation]
3.07.02.01.01	Summary
3.07.02.01.02	Full Report
3.07.02.01.03	Statistical Data
3.08	Other non-clinical Evidence
3.08.01	[Study description, study identifier, date of initiation]
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4.02.01	Clinical Evaluation Report
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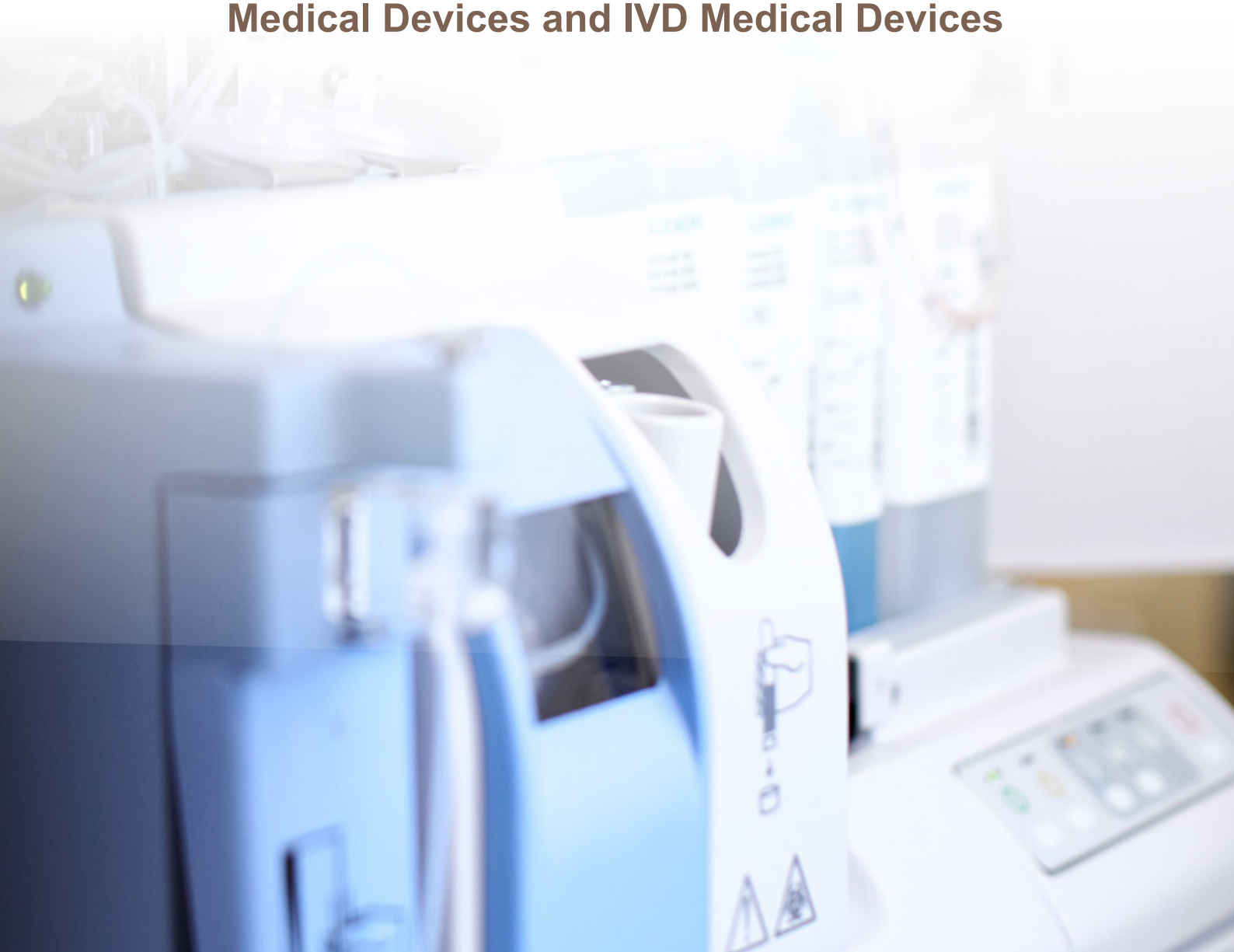
AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

Annex 6:
Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices



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1. 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.

2. 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.

3. DEFINITIONS

Active Medical Device: Any medical device, operation of which depends on a source of electri-cal 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)

Analytical Performance of an IVD Medical Device: The ability of an IVD medical device to detect or measure a

[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.

particular analyte. (GHTF/SG5/N6:2012)

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.

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)

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

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)

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

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)

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)

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)

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.

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.

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.

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)

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

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

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.

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.

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."

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)

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.

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).

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.

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)

Manufacturer: "Manufacturer" means any natural or legal person 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 med-

ical 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.

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 allevi¬ation of disease,
- diag¬nosis, monitoring, treatment, alleviation of, or com¬pensation for, an injury,
- inves¬tigation, replacement, modification, or support of the anatomy, or of a physiologi¬cal process,
- supporting or sustaining life,
- con¬trol 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 pharmaco¬logical, 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 re production 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.

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.

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

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

can be used safely without instructions for use are exempted from having instructions for use by some authorities with jurisdiction.

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)

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.

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.

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.

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)

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)

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

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

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

Risk Evaluation: Procedure based on the risk analysis to determine whether tolerable risk has been exceeded. (ISO/IEC Guide 51:2014)

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

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.

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)

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)

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.

NOTE 1: 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)

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

4. 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. 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 pro duction and postproduction phases, on the overall risk, benefit-risk determination and risk acceptability. This evaluation should include the impact of the presence of previously unrec ognized 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 re lation to risks that cannot be eliminated; and

c) provide information for safety (warnings/pre cautions/contra-indications) and, where appro priate, 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 med ical device and IVD medical device are intend ed to be used (e.g. ergonomic/usability fea tures, tolerance to dust and humidity) and

b) give consideration to the technical knowledge, experience, education, training and use envi ronment 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 pro-

tect 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 de fined 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 medi cal 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 de-

vices 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 exam ple, with implants, the risks from ageing of ma terials, etc. should be appropriately reduced.

b) When adjustment and calibration are not pos sible, for example, with certain kinds of ther mometers, the risks from loss of accuracy of any measuring or control mechanism are ap propriately 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, appro-

priate 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 numer ically should be in commonly accepted, stan dardized 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 mea surement units, considerations of safety, user familiarity and established clinical practice may justify the use of other recognized measure ment units.

c) The function of the controls and indicators should be clearly specified on the medical de vice and IVD medical device. Where a medi cal device or IVD medical device bears instruc tions required for its operation or indicates op erating or adjustment parameters by means of a visual system, such information should be understandable to the user and, as appropri ate, 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 med ical 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 in tended user in the handling of the medical de vice 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 an imal species, tissues and cells of animal ori gin, 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 ad dressed by implementation of validated state of the art methods of elimination or inactiva tion in the course of the manufacturing pro cess, except when the use of such methods would lead to unacceptable degradation com promising 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 tis sues and cells should be done in accordance with jurisdictional requirements; and

b) processing, preservation and any other han dling of those tissues and cells or their deriva tives should be carried out so as to provide safety for patients, users and, where applica ble, other persons. In particular, safety with re gard 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. 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.

7. 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, 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 pre cision)
   c. Analytical sensitivity/Limit of detection
   d. Analytical specificity
   e. Measuring interval/range
   f. Specimen stability
b) The clinical performance, for example diag nostic/clinical sensitivity, diagnostic/clinical specificity, positive predictive value, negative predictive value, likelihood ratios, and expect ed 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 suit able 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, laborato ry professional;
b) intended use environment, for example, patient home, emergency units, ambulances, healthcare

[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

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 do nors, etc. Populations evaluated should rep resent, 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 infec tious diseases, it is recommended that the populations selected have similar prevalence rates.

8. REFERENCES

- IMDRF/GRRP WG/N040:2017 Competence, Training, and Conduct Requirements for Reg ulatory Reviewers
- IMDRF/SaMD WG/N41FINAL:2017 Software as a Medical Device (SaMD): Clinical Evalua tion
- 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 Representa tive, Distributor and Importer
- GHTF/SG1/N046:2008 Principles of Confor mity 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 Cocepts
- GHTF/SG5/N7:2012 Clinical Evidence for IVD Medical Devices - Scientific Validity Determi nation and Performance Evaluation.
- GHTF/SG5/N8:2012 Clinical Performance Studies for In Vitro Diagnostic Medical Devices
- Declaration of Helsinki

9. STANDARDS

The standards below were consulted in the writing of this document and may be useful in meeting the essen- tial 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 Manage ment Systems – Requirements for Regulatory Purposes
- ISO 11135 Sterilization of Health-Care Prod ucts -- Ethylene oxide -- Requirements for the Development, Validation and Routine Control of a Sterilization Process for Medical Devices
- ISO 11137 Sterilization of Health Care Prod ucts -- 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 Charac terization of a Sterilizing Agent and the Devel opment, 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

10. 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 per-

formance,

b) manufactured to maintain the design charac teristics, and

c) used in a way that maintains the design char acteristics.

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 stan dard 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 require ments 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.

11. 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

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Annex 7:

POST MARKET SURVEILLANCE ANNUAL REPORT SUBMISSION FORM

PMS Number:

Market authorization holder details

Name	
Address	
Contact	
Other details	

Product details

Name	
Market authorization	
Manufacturer	
Manufacturing site	
Classification	

Post Market report

When did the product enter the market (date)	
Number of units sold	
Number of complaints	
Trend identified in relation to complaints (Y/N). If Yes provide details and data	
Number of adverse events	
Reports of unforeseen risks	
Number of vigilance reports reported to NMRA	
Number of reported incidents worldwide	
Corrective action taken (provide details)	
Provide details of CAPA, recalls, withdrawal	

Detailed description of complaints

Description of complaints:
Please indicate in each event reasons for complaints
1. User error 2. Procedure error 3. Malfunction 4. Harm caused to the patient or user of the device 5. Other ……

Vigilance reporting

Has any vigilance report (s) sent to NMRA (Y/N), If Yes provide details and dates of submission.
Provide copy (ies) of reports if not yet submitted to NMRA

Risk Management

Has the risk management policy and procedure (s) updated based on the reported events?
Provide copy (ies) if not yet submitted to NMRA
Does the benefit outweigh the risk?? (Y/N) If Yes provide details

……. **…….....**

Name of the authorized officer **signature and date**

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Annex 8:

8 REPORTING FORM FOR VARIATION OF IN VITRO DIAGNOSTIC MEDICAL DEVICE WHICH HAS BEEN ISSUED MARKET AUTHORIZATION

Name of the product
Market Authorization holder
Market Authorization Number/Ref
Intended use
Specify type of change/variation
Justification for change (provide sufficient details). If the space is not sufficient attach additional information
Current
Proposed change
Attach the artwork/model to demonstrate the change (s)
Details of market authorization holder Name: Business address Postal address Country Phone …… …….. …… **Name** **Date** **Signature and stamp**