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MEDICAL DEVICE GUIDANCE DOCUMENT

COMMON SUBMISSION DOSSIER TEMPLATE (CSDT) OF IN- VITRO DIAGNOSTIC (IVD) MEDICAL DEVICE

Medical Device Authority
MINISTRY OF HEALTH MALAYSIA

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Preface

This Guidance Document was prepared by the Medical Device Authority (MDA) to help the industry and healthcare professionals in their quest to comply with the Medical Device Act (Act 737) and the regulations under it.

This Guidance Document shall be read in conjunction with the current laws and regulations used in Malaysia, which include but not limited to the following-

a) Medical Device Act 2012 (Act 737); and

b) Medical Device Regulations 2012.

In this Guidance Document, the following verbal forms are used:

- “shall” indicates a requirement;

- “should” indicates a recommendation;

- “may” indicates a permission; and

- “can” indicates a possibility or a capability.

Irrespective of the requirements of this Guidance Document, MDA has the right to request for information or material, or define conditions not specifically described in this document that is deemed necessary for the purpose of regulatory control.

MDA has put much effort to ensure the accuracy and completeness of this guidance document. In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.

MDA reserves the right to amend any part of the guidance document from time to time.

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Introduction

This guidance document provides recommendations on the content of Common Submission Dossier Template (CSDT) to be assembled and submitted to Authority or Conformity Assessment Body. It shall enable a manufacturer to prepare a CSDT and provide different Regulatory Authority or Conformity Assessment Body with the same body of documentary evidence that its In Vitro Diagnostic (IVD) medical device conforms to the Essential Principles. The use of the CSDT shall reduce costs for the manufacturer and reviewer, remove barriers to trade and facilitate timely international access to IVD medical devices.

This document is adopted from ASEAN CSDT and must be read in conjunction with the Guidance to Medical Device Product Registration. Sections of the ASEAN CSDT for which guidance has not been provided are taken to be self-explanatory.

COMMON SUBMISSION DOSSIER TEMPLATE (CSDT) OF IN-VITRO DIAGNOSTIC (IVD) MEDICAL DEVICE

1 Purpose

This document aims to provide guidance on the preparation of a product registration application for (IVD) medical devices using the ASEAN (CSDT). In particular, this document serves to clarify the information to be submitted in each section of the CSDT and the format that this information is to be submitted in.

2 Scope

This document applies to products that fall within the definition of an IVD medical device, as defined in MDA/GD/0006: Definition of Medical Device, including those used for the in vitro examination of specimens derived from the human body.

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1 Calibrator

Any substance, material or article intended by its product owner to be used in the calibration of a measuring instrument or measuring system.

3.2 Control material

Any substance, material or article intended by its product owner to verify the performance of an IVD medical device.

3.3 Instrument

Any equipment or apparatus intended by the manufacturer to be used as IVD Medical Device.

3.4 In Vitro Diagnostic (IVD) medical device

refer to MDA/GD/0006: Definition of Medical Device

3.5 Lay person

Any individual that does not have formal training in a specific field or discipline.

3.6 Manufacturer

a) any person who is responsible for —

(i) the design, production, fabrication, assembly, processing, packaging and labelling of a medical device whether or not it is the person, or a subcontractor acting on the person's behalf, who carries out these operations; and

(ii) assigning to the finished medical device under his own name, its intended purpose and for ensuring the finished product meets the regulatory requirement; or

b) any other person who —

(i) assembles, packages, processes, fully refurbishes, reprocess or labels one or more ready-made medical devices; or

(ii) assigning to the ready-made medical device under his own name, its intended purpose and ensuring the finished products meets the regulatory requirement,

but shall not include the following persons:

a) any person who assembles or adapts the medical device in the market that is intended for individual patients; and

b) any person who assembles, packages or adapts the medical device to which the assembling, packaging or adaptation does not change the purpose intended for the medical devices.

3.7 Near patient testing

Any testing performed outside a laboratory environment by qualified personnel, generally near to, or at the side of, the patient. Also known as Point-of-Care (POC).

3.8 Performance evaluation

Review of the performance of a medical device based upon data already available, scientific literature and, where appropriate, laboratory, animal or clinical investigations.

3.9 Reagent

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

3.10 Registrant

The person who applied for and obtained the registration of the IVD medical device.

3.11 Self-testing

Testing performed by laypersons.

3.12 Specimen receptacle

A device, whether vacuum-type or not, specifically intended by their manufacturers for the primary containment of specimens derived from the human body.

4 Preparation of a product registration submission based on the ASEAN CSDT

4.1 The registrant shall take note of the following pointers when preparing a CSDT dossier for submission to Medical Device Authority (MDA):

a) the prepared CSDT dossier must contain all sections, i.e. sections 5.0 to 6.6.1. Where there are sections not applicable to the medical device, the reason for the non-applicability shall be provided under the section heading;

b) the CSDT dossier must be prepared in English;

c) copies of labelling, certificates and reports that are referenced within the CSDT submission shall be submitted as annexes to the CSDT;

d) all reports submitted as part of the CSDT shall be signed-off by the manufacturer;

e) where supporting documents such as reports or certificates are provided, every document must be submitted in full, i.e. all the pages of a document must be submitted;

f) all copies of labelling, certificates, reports and other documents submitted must be legible;

g) all certificates submitted must be within its validity period (when a validity period is indicated).

4.2 The level of detail of information to be provided under each CSDT section will depend on the IVD medical device class and the evaluation route, i.e. abridged or full evaluation. Registrants are advised to refer to the Guidance on Product Registration for details on the data requirements for each IVD medical device class and evaluation route.

5 Executive summary

An executive summary shall be provided with the CSDT, which shall include the following information-

a) an overview, e.g., introductory descriptive information on the medical device, the intended uses and indications for use of the medical device, any novel features and a synopsis of the content of the CSDT;

b) commercial marketing history;

c) intended uses and indications in labelling;

d) list of regulatory approval or marketing clearance obtained;

e) status of any pending request for market clearance from USFDA, EU, TGA, MHLW (Japan), Canada;

f) important safety / performance related information.

Table 1. Market Clearance by Five Founding Members

Country / Region	**Approval Type**
Australia	Therapeutic Goods Administration (TGA) Licence
Canada	Health Canada Licence
European Union (EU)	Annex IV i.e. Section 4 and 6 of IVDD (for List A IVD) Annex IV i.e. Section 4 and 6 or Annex V coupled with Annex VII (for List B and self-testing IVD) *[Note: Classification for IVD medical device in Singapore is according to GHTF and is different from EU IVD Directive. IVD medical device products without EU approval as above-mentioned will be subjected to full evaluation route*.]
Japan	Ministry of Health, Labour and Welfare (MHLW) Licence
United States of America (USA)	• FDA 510(K) clearance letter *[Note: 510(K) exempted products do not qualify for abridged evaluation route.]*; or • FDA PMA approval letter

Guidance:

(a) If the medical device contains any novel features, e.g. nanotechnology, a description of the novel feature is to be provided.

(b) For commercial marketing history, the list of countries where the medical device is marketed and the year of introduction into each country is to be provided.

i) Copies of certificates or approval letters from each reference agency for the IVD medical device are to be provided as an annex to the CSDT submission. For CE marked devices, the declaration of conformity by the manufacturer / AR must be submitted, in addition to the EC certificate issued by the notified bodies.

ii) declaration on labelling, packaging and instructions for use (IFU):

- if the labelling, packaging and IFU of the IVD medical device for sale in Malaysia is identical to that approved by the reference agency, a declaration that the labelling, packaging and IFU of the IVD medical device for sale in Malaysia is identical to that approved by each reference agency is to be provided.

- if the labelling, packaging and IFU of the IVD medical device for sale in Malaysia is not identical to that approved by the reference agency, the differences between Malaysia's labelling, packaging and IFU and each reference agency's approved labelling, packaging and IFU is to be described. The reason for the differences must also be provided.

(c) For important safety / performance related information, the following information is to be provided:

(i) summary of reportable adverse events and field safety corrective actions (FSCA) for the IVD medical device for the past 5 years. This is to be provided in a tabular format as given below. If there have not been adverse events or FSCAs to date, an attestation that this is the case is required.

For reported adverse events:

Description of adverse event	Frequency of occurrence (number of reports / total units sold) in the period of dd/mm/yyyy to dd/mm/yyyy (5 years))

For reported field safety corrective actions (FSCAs):

Date of FSCA	Reason for FSCA	Countries where FSCA was conducted

6 Elements of the common submission dossier template

6.1 Relevant essential principles and method used to demonstrate conformity

The CSDT should identify the Essential Principles of Safety and Performance of Medical Devices that are applicable to the device. The CSDT should identify the general method used to demonstrate conformity to each applicable Essential Principle. The methods that may be used include compliance with recognized or other standards, state of the art or internal industry methods, comparisons to other similar marketed devices, etc.

The CSDT should identify the specific documents related to the method used to demonstrate conformity to the Essential Principles.

6.1.1 Essential principles and evidence of conformity

The evidence of conformity can be provided in tabular form with supporting documentation available for review as required. A sample of the essential principles conformity checklist is included in Appendix A.

For example, a completed Essential Principles conformity checklist can be used to demonstrate that a recognized test standard was used as part of the method to demonstrate conformity to one Essential Principle. As such, CSDT would then include a declaration of conformity to the standard, or other certification permitted by the Regulatory Authority, and a summary of the test data, if the standard does not include performance requirements. When the manufacturer uses international or other standards to demonstrate conformity with the Essential Principles, the CSDT should identify the full title of the standard, identifying numbers, date of the standard, and the organization that created the standard. When the manufacturer uses other means, such as internal standards, the CSDT should describe the means.

Not all the essential principles will apply to all devices and it is for the manufacturer of the device to assess which are appropriate for his particular device product. In determining this, account must be taken of the intended purpose of the device.

Guidance:

The Essential Principles (EP) conformity checklist is to be prepared based on the list of EPs found in the Regulations. The IVD medical device to which the EP conformity checklist is applicable shall be identified on the checklist itself. Where applicable, the various configurations of the IVD medical device covered by the checklist are to be identified in the checklist. The columns in the recommended format for the checklist shall be completed as follows-

(a) *Applicable to the IVD medical device?*

(i) Either a ‘Yes’ or ‘No’ answer is required. If the answer is ‘No’ this shall be briefly explained. For example: For an IVD medical device that does

not incorporate biological substances, the answer to EP 9.2 would be 'No – The IVD medical device does not incorporate biological substances.'

(b) *Method of conformity*

(i) State the title and reference of the standard(s), industry or in-house test method(s), comparison study(ies) or other method used to demonstrate compliance. For standards, this shall include the date of the standard and where appropriate, the clause(s) that demonstrates conformity with the relevant EP. Where a standard is referred to more than once in the checklist, the reference number and date can be repeated.

(c) *Identity of specific documents*

(i) This column shall contain the reference to the actual technical documentation that demonstrates compliance to the EP, i.e. the certificates, test reports, study reports or other documents that resulted from the method used to demonstrate compliance, and its location within the technical documentation.

6.2 Device description

6.2.1 Device description and features

Besides a general description of the device, a more detailed description of the device attributes is necessary to explain how the device functions, the basic scientific concepts that form the fundamentals for the device, the component materials and accessories used in its principles of operation as well as packaging. A complete description of each functional component, material or ingredient of the device should be provided, with labelled pictorial representation of the device in the form of diagrams, photographs or drawings, as appropriate.

Guidance:

The following information shall be submitted to meet the requirements of this section:

(a) A general description of the principle of assay method or instrument principles of operation.

(b) A description of all components of the IVD medical device, including but not limited to-

(i) antibodies, antigens, nucleic acid primers;

(ii) buffers, assay controls and calibrators;

(iii) substrates used to detect antigen-antibody complexes; and

(iv) reagents provided with the IVD medical device or recommended for use.

(c) A description of the specimen collection and transport materials provided with the IVD medical device or recommended for use.

(d) For automated assays, a description of the appropriate instrumentation characteristics or dedicated instrumentation.

(e) A description or complete list of various configurations of the IVD medical device to be registered as a family or group, if applicable. For example, a family of pregnancy rapid test can consist of device available in different configurations, such as a test strip or in a cassette. Refer to Appendix B.

(f) A description of the accessories, other IVD medical devices and other products that are not IVD medical devices, which are intended to be used in combination with the IVD medical device. For example, a lancet, which is a medical device and not an IVD medical device that is provided in the package to the user to perform a test.

Note: Supporting documents, in CSDT format, must be provided for the medical device accompanying the IVD medical device.

(g) Risk class and the applicable classification rule for the IVD medical device according to the *Regulations*.

6.2.2 Intended use

This means the use for which the medical device is intended, for which it is suited according to the data supplied by the manufacturer in the instructions as well as the functional capability of the device.

Guidance:

The intended use of an IVD medical device shall include information on the following-

(a) Type of analyte or measurand of the assay.

(b) Whether the test is quantitative or qualitative.

(c) Role of the test in the clinical use e.g. screening, diagnostic or detection, aid to diagnostic, monitoring.

(d) Disease or condition that the test is intended for.

(e) Type of specimen to be used e.g. serum, plasma etc.

(f) The intended users (e.g. self-testing by lay person, near-patient by trained personnel or professionals).

(g) Assay type e.g. immunoassay, chemistry, cytochemistry, image analysis, immunohistochemistry.

(h) The specific name of the instrument required for the assay, if any.

For instruments, the intended use shall also include the modes of operation for instruments e.g., random access, batch, stat, open tube, closed tube, automatic, manual.

6.2.3 Instructions of use

These are all necessary information from the manufacturer including the procedures, methods, frequency, duration, quantity and preparation to be followed for safe use of the medical device. Instructions needed to use the device in a safe manner should, to the extent possible, be included on the device itself and/or on its packaging by other formats / forms.

Note: There is no specific guidance for this section of the ASEAN CSDT.

6.2.4 Limitations

This is a general description of the disease or condition and the patient population for which the device should not be used for the purpose of diagnosing, treating, curing or mitigating.

Guidance:

For example, a limitation of an assay using specimens from patients who have received preparations of mouse monoclonal antibodies for therapy when tested with assay kits which employed mouse monoclonal antibodies. It may show either falsely elevated or depressed values.

6.2.5 Warnings

This is the specific hazard alert information that a user needs to know before using the device.

Guidance:

For products containing biological material, radioactive material, explosive material and any other hazardous material, safety warnings must be included.

6.2.6 Precautions

This alerts the user to exercise special care necessary for the safe and effective use of the device. They may include actions to be taken to avoid effects on patients / users that may not be potentially life-threatening or result in serious injury, but about which the user should be aware. Precautions may also alert the

user to adverse effects on the device of use or misuse and the care necessary to avoid such effects.

Note: There is no specific guidance for this section of the ASEAN CSDT.

6.2.7 Materials

This section must include complete details of material specifications, including raw materials.

a) All components of the IVD medical device shall be listed and chemically and biologically characterised, including antibodies, antigens, assay controls, substrates used to detect antigen-antibody complexes, and test reagents. Appropriate references shall be cited.

b) If synthetic peptides are used, the peptide sequence shall be provided.

c) If components are of biological origin or recombinant, the source must be indicated and details on production must be provided. These details would include the strain of the virus, the cell line for cultivation of the virus, sequences of relevant nucleic acids and amino acids, etc., used in the manufacturing process of viral lysate, purified proteins, recombinant and synthetic proteins.

d) If applicable, process validation results to be provided to substantiate that manufacturing procedures are in place to minimise biological risks, in particular, with regard to viruses and other transmissible agents. This also includes inactivation of infectious organisms in reagents and the production of reagents.

e) if applicable, information to be provided on irradiating components, nonionising or ionising (e.g. Iodide-131 in the Radioimmunoassay kit, radio-labelled Phosphorus-32 DNA probes in Southern blots)

f) if applicable, information to be provided on the poison or controlled substance (e.g. Buprenorphine in drug assay kit).

6.2.8 Other relevant specifications

The functional characteristics and technical performance specifications for the device including, as relevant, accuracy, sensitivity, specificity of measuring and diagnostic medical devices, reliability and other factors; and other specifications including chemical, physical, electrical, mechanical, biological, software, sterility, stability, storage and transport, and packaging to the extent necessary to demonstrate conformity with the relevant Essential Principles.

Guidance:

A list of the features, dimensions and performance characteristics of the IVD medical device that would typically appear in the package insert and instruction manual, will satisfy the requirements of this section.

6.2.9 Other descriptive information

Other important descriptive characteristics not detailed above, to the extent necessary to demonstrate conformity with the relevant Essential Principles.

Note: There is no specific guidance for this section of the CSDT.

6.3 Product verification and validation documents

This section includes data from pre-clinical and clinical studies. The data required is to the extent appropriate to the complexity and risk class of the device.

Guidance:

For all aspects of verification and validation described in this section, where no testing was undertaken for the IVD medical device, a rationale for that decision must be provided. Evidence to support the rationale shall be provided.

The suitability of the IVD medical device for each of the intended specimen type, such as serum, plasma, whole blood etc, shall be verified and validated through both preclinical and clinical evidence. If specimens containing anti-coagulants are recommended for use, study shall be included.

6.3.1 Pre-clinical studies

The Information on preclinical studies to establish the safety and performance of the IVD medical device for its intended use must be provided. The pre-clinical studies provided should include information on study design, complete test or study protocols, methods of data analysis, data summaries and study conclusions. The most common characteristics that must be validated should include but are not limited to-

- Analytical Sensitivity
- Analytical Specificity and Interference
- Precision (Repeatability / Reproducibility)
- Linearity / Assay’s Measuring (Reportable) Range
- Traceability and Expected Values

- Cut-off Value
- Trueness
- Stability of reagent
- Specimen stability
- Performance Characteristics for Instrument (if applicable):
- Accuracy
- Precision / Reproducibility
- Linearity
- Carryover
- Interfering Substances
- Projected useful life
- Software Verification and Validation Studies

Guidance:

(a) *Analytical Sensitivity*

Data on analytical sensitivity shall include information on the following-

(i) the specimen type and preparation including matrix, analyte levels, and how levels were established;

(ii) the number of replicates (runs, days, instruments, and operators, as appropriate) included at each concentration tested;

(iii) the statistical method used;

(iv) the results of the analytical limits at low levels (e.g., limit of detection, functional sensitivity);

(v) the definition / calculation used to determine assay sensitivity. For example-

- Number of standard deviations above the mean value of the sample without analyte. Include mean and standard deviation; and
- Lowest concentration at which %CV and accuracy are within specified criteria and describe the evaluations to determine they were met;

(vi) For qualitative assay, include the percent of replicates that test positive at each concentration and evaluate the 95% interval for cut-off and limit of detection.

(b) *Analytical Specificity and Interference*

Data on analytical specificity shall include information on the following-

(i) a description of study design and statistical methods;

(ii) the specimen description and preparation including matrix, analyte levels present in the sample, how these levels were established; and

(iii) a list of the potentially cross-reactive and interfering substances tested including those where a similar syndrome can be associated with more than one analyte / agent / organism. Also include the concentrations at which these substances were present in the samples (indicate highest concentration tested and / or lowest concentration at which an effect was observed). Finally, include the number of replicates tested for each substance.

(c) *Precision (Repeatability / Reproducibility)*

Data on precision shall include information on the following-

(i) description of studies and results to evaluate estimates of total variability for each specimen type. Include, as appropriate, repeatability (within-run) and reproducibility such as between-day, between-run, within-day, between-sites, between-lots, between instrument, and between operator(s), etc;

(ii) description of specimens (samples) used to study variability including matrix, sample type (e.g., patient samples, spiked samples, control material), and preparation, including analyte levels and how they were established. The relationship between the analyte levels to measuring (reportable) range and medical decision points must also be described;

(iii) description of sources of variability examined (e.g., runs, instruments, operators, days; sites at which variability studies were performed; reagent lots and instruments studies with identifying information);

(iv) description of statistical methods used to analyse data; include any model assumptions;

(v) for quantitative or qualitative assays with numerical values, the number of measurements, mean, standard deviation, and %CV for each parameter tested and for each level tested; and

(vi) For qualitative assays, the number of replicates, the concentration of the sample, the number of positive and negative results, and the number of invalid or equivocal results, if applicable. For reproducibility studies on qualitative tests, an estimation of the precision of the method at analyte concentrations near the cut-off.

(d) *Linearity / Assay's Measuring (Reportable) Range*

Data on linearity / assay's measuring shall include information on the following-

(i) the linear range, measuring (reportable) range and information on how these were established. For quantitative and semi-quantitative assays, the analytical data to support linearity and the description on the recovery of the assay in graphic and tabular form;

(ii) the linear range and measuring (reportable) range. Include the measure of deviation from linearity, if applicable;

(iii) description of how reportable range is determined including acceptable criteria or results for accuracy, precision, or other characteristics within this range;

(iv) description of specimen type and preparation including information on matrix, analyte levels, and the methods used to determine the target levels;

(v) the number of samples, the number of replicates, and the statistical methods used;

(vi) the results such as estimates of slope, intercept with confidence intervals, and R2 value of regression;

(vii) provide the range of percent recovery at each concentration (observed value / target value);

(viii) description on how results outside the measuring (reportable) range are reported to the user;

(ix) description on the validation of instructions for out-of-range specimens, if applicable; and

(x) discussion of possible high-dose hook effect, if applicable.

(e) *Traceability & Expected Values (Controls, Calibrators, Methods)*

Data on traceability and expected values shall include information on the following-

(i) where applicable, summary information about traceability of calibrators and trueness control material. Include for examples, methods and acceptable criteria for traceability to reference material and description of value assignment and validation; and

(ii) a description on how the recommended calibration and control testing frequency were established, validation of the standard curve by replicate analysis of calibrators, and validation of quality control, as appropriate (e.g., novel, internalised quality control).

Note: *Precision control material used for establishing reproducibility does not require traceability to reference material.*

(f) *Cut-off Value*

Data on cut-off value shall include information on the following-

(i) the rationale for the units, cut-off and/or categories of the results;

(ii) a description of specimen preparation including analyte levels, matrix, and how the level was established;

(iii) the statistical method used (e.g., Receiver Operator Characteristic Analysis); and

(iv) a definition of equivocal zone, if applicable.

(g) *Trueness*

Data on trueness shall include information on the following-

(i) the measure of trueness in the closeness of agreement between the average value obtained from a large series of test results and an accepted reference value; and

(ii) bias of the measurement procedure shall be determined by a suitable recovery or comparison of procedures experiments, and provides the methodology and the rational of its use.

(h) *Stability of reagent*

Data on stability of reagent shall include information on the recommended shelf life or storage conditions for in use or opened and unopened IVD medical device, and also taking into consideration of variable conditions including temperature, freeze / thaw cycle and its duration during usage (including for on-board use), and for transportation. The studies shall be provided from at least 3 lots or batches. If real-time stability is not available, an accelerated study is acceptable

for initial shelf life claim while continuing real time studies to be performed. Statistical method used also to be provided. The final real time study report must be submitted when completed.

(i) *Specimen stability*

Data on specimen stability shall include information on the following-

(i) description of the recommended method for the specimen's collection, storage and transportation; and

(ii) the specimen stability validation studies for the collection, storage and transportation methods. Elements to be validated would include but not limited to storage duration, temperature limits, and freeze / thaw cycle.

(j) *Performance Characteristics for Instrument (if applicable)*:

Data to support the performance characteristics for instruments shall include information on the following:

(i) *Accuracy*

Comparison information on each test parameter to either a reference method or an IVD medical device with the same intended use. The testing pool shall contain samples representative of the appropriate population, including an equal number of males and females for which samples span the reportable range. Specimens that are close to the clinically critical decision point(s) must be included. Data to be presented using linear regression, including 95% confidence intervals for the slope and y-intercept and scatter plots.

(ii) *Precision / Reproducibility*

Estimation of intra, inter, lot-to-lot, operator-to-operator, and total imprecision for each measurand parameter of the IVD medical device using samples that span the testing range.

(iii) *Linearity*

Information on how linearity was established and indication on whether this conformed to any available reference or methodology.

(iv) *Carryover*

Studies to demonstrate lack of over estimation of results due to the carryover effect. The testing pool shall consist of samples at clinically meaningful levels. For investigation of potential carry-over, at least five runs with alternating high-positive and negative specimens shall be performed during robustness studies. The high positive samples shall comprise of samples with naturally occurring high virus titres.

(v) *Interfering Substances*

Studies to show possible interference of substances such as lipids, haemoglobin, bilirubin, etc.

(vi) *Projected useful life*

For IVD medical device that does not have expiry dates, the projected useful life of the IVD medical device must be provided. Manufacturer may refer to TS/ISO 14969 (Medical devices – Quality management systems – Guidance on the application of ISO 13485:2003) for information on how to determine the projected useful life.

(vii) *Software Verification and Validation*

The correctness of a software product is a critical product characteristic that cannot be fully verified in a finished product. The manufacturer must provide evidence that validates the software design and development process. This information shall include the results of all verification, validation and testing performed in-house and in a user's environment prior to final release, for all of the different hardware configurations identified in the labelling, as well as representative data generated from both testing environments.

6.3.2 Clinical evidence

This section should indicate how any applicable requirements of the EPs for clinical evaluation of the device have been met. Where applicable, this evaluation may take the form of a systematic review of existing bibliography, clinical experience with the same or similar medical devices, or by clinical investigation. Clinical investigation is most likely to be needed for higher risk class medical devices, or for medical devices where there is little or no clinical experience.

Guidance:

The clinical evidence to be provided shall include the information mentioned in this section.

For any IVD medical device, if discrepant test results are identified as part of an evaluation, these results shall be resolved as far as possible, using one or more of the following approaches-

- by evaluation of the discrepant sample in further test systems;
- by use of an alternative method or marker;
- by a review of the clinical status and diagnosis of the patient; and

- by the testing of follow-up-samples.

(a) Clinical (Diagnostic) Sensitivity

Data on clinical (diagnostic) sensitivity shall include information on the following-

(i) the methodology including its statistical method, results, discussion and conclusion for the study;

(ii) the total individual positive specimens and the sero-conversion panels used in the study. For positive specimens, where different virus subtypes and genotypes are available, studies of these subtypes specimens must be included. For Class D IVD medical device, when testing the sero-conversion specimens, the diagnostic sensitivity during the early infection phase (sero-conversion) has to represent the state of the art;

(iii) the probability that the IVD medical device gives a positive result in the presence of the target marker; and

(iv) Negative predictive values to be included in the calculation.

(b) Clinical (Diagnostic) Specificity

Data on clinical (diagnostic) specificity shall include information on the following-

(i) the methodology including its statistical method, results, discussion and conclusion for the study;

(ii) the total individual negative specimens in the study. Negative specimens used in a performance evaluation shall be defined so as to reflect the target population for which the test is intended, for example blood donors, clinical samples or hospitalised patients including pregnant women, and potentially interfering samples;

(iii) the probability that the IVD medical device gives a negative result in the absence of the target marker; and

(iv) Positive predictive values to be included in the calculation.

(c) Comparison Studies Using Clinical Specimens

Comparison studies using clinical specimens shall include information on the following-

(i) Method comparison: All performance evaluations shall be carried out in direct comparison with an established state of the art IVD medical device. The established product for comparison must have obtained

marketing clearance from the reference agencies, namely Australia TGA, Canada TPP, Europe, Japan MHLW, and US FDA.

Study design shall include-

- description on the test methods,
- information on the comparator(s) (e.g., reference IVD medical device, reference method),
- the sample type(s) (e.g., unaltered patient specimens, spiked or diluted patient specimens, spiked patient pools, and control material), matrix, number of samples, sample range,
- when appropriate, number / types of sites, sample selection methods, inclusion / exclusion criteria, overall demographic description of patients represented by the samples (e.g., age, gender, race, how/whether samples represent the intended use population), number of individuals represented, and
- statistical methods used to generate results (e.g., regression methods, data exclusion, number of observation represented by each data point).

Results shall include-

- Description on the overall results and / or results from specific sites and patient groups, as appropriate,
- For quantitative tests, information such as slope and intercept (with confidence intervals), correlation coefficient, measure of scatter around the regression line, measure of bias at medical decision levels.
- In some cases, a graph (x-y graph or bias plot) can be included, and
- For qualitative or semi-quantitative tests, percent agreement with comparator for positive / negative samples, confidence intervals.

(ii) Matrix comparison

Study design shall include-

- for each matrix in the intended use, the method for comparison or determination of accuracy, and
- sample types tested, number of samples, sample range or target concentrations tested and calculations / statistical methods.

Results / Acceptance criteria shall include-

- the accuracy of the new matrix or results of the matrix comparison.

(d) Clinical Cut-off

This information shall include-

(i) the established cut-off and its validation for the new IVD medical device; and

(ii) if applicable, the “equivocal zone” is to be defined, and include a description of how results within this zone are reportable to the user.

(e) Reference Interval (Expected Values)

This information shall include-

(i) the reference interval for this measured and the method used to determine it;

(ii) the literature references establishing the reference intervals and justification for applying this range to the new IVD medical device;

(iii) a description of the methods for determining the reference intervals if they are not well established from the literature or if the range cannot be transferred to the new IVD medical device;

(iv) the description of the population studies (demographics, inclusion / exclusion criteria, number of individuals);

(v) any separate reference intervals for subclasses where clinically justified;

(vi) the method of clinical diagnosis of the reference population(s); and

(vii) the statistical method used to calculate the ranges.

(f) Additional requirements for IVD medical device for self-testing and near patient testing (if applicable)

The field evaluation report shall be provided. Study results and data shall:-

(i) show the handling suitability of the IVD medical device; and

(ii) determine the IVD medical device’s performance when used by the intended users following instructions provided in the labelling and without the assistance from the professionals.

Also, there shall be a study to show that the correct result can be obtained by the intended users, when compared to the laboratory professionals.

6.3.2.1. Use of existing bibliography

Copies are required of all literature studies, or existing bibliography, that the manufacturer is using to support safety and effectiveness. These will be a subset of the bibliography of references. General bibliographic references should be medical device-specific as supplied in chronological order. Care should be taken to ensure that the references are timely and relevant to the current application.

Clinical evidence of effectiveness may comprise device-related investigations conducted domestically or other countries. It may be derived from relevant publications in a peer-reviewed scientific literature.

The documented evidence submitted should include the objectives, methodology and results presented in context, clearly and meaningfully.

6.4 Device labelling

The device labelling refers to any written, printed or graphic representation affixed to a medical device or any part of its packaging, or accompanying a medical device, when the medical device is being supplied.

This section should summarize or reference or contain the following labelling data to the extent appropriate to the complexity and risk class of the device, which is generally considered as “labelling”-

- Labels on the device and its packaging;
- Instructions for use;
- Physician’s manual.

Any information and instructions given to the patient, including instructions for any procedure the patient is expected to perform (if applicable).

6.4.1 Samples of labels on the medical device and its packaging

This is the printed, written or graphic product information provided on or attached to one or more levels of packaging, including the outer packaging or the outside container wrapper. Any pack labelling, which is not provided on the outer packaging must be easily legible through this outer packaging.

If it is physically impossible to include samples of labels (e.g. large warning labels affixed onto an X-ray machine), alternative submission methods (e.g. photographs or technical drawings), to the extent appropriate, will suffice to meet the requirements of this section.

6.4.2 Instructions for use

The instructions for use is commonly referred to as the physician's manual, user manual, operator's manual, prescriber's manual or reference manual. It contains directions under which the physician or end-user can use a device safely and for its intended purpose. This should include information on indications, contraindications, warnings, precautions, potential adverse effects, alternative therapy and the conditions that should be managed during normal use to maintain the safety and effectiveness of the medical device.

Guidance:

The submission dossier shall typically contain a complete set of labelling associated with the IVD medical device as prescribed in the Regulation. The following information is to be provided:

(a) The labels

(i) The labels on the IVD medical device and its packaging are to be provided for the primary and secondary levels of packaging and shall be provided in the original colour. The labels can be provided in the form of artwork.

(ii) Labels provided must be in English.

(iii) Labels must be provided for all the components of an IVD medical device system, members of a IVD medical device family and accessories submitted for registration. Alternatively, a representative label may be submitted for variants, provided the variable fields on the artwork are annotated, and the range of values for the variable fields are indicated.

(b) The instructions for use shall contain information on the proper use of the IVD medical device, such as:-

(i) the intended use,

(ii) directions for use,

(iii) limitations,

(iv) warnings,

(v) precautions,

(vi) materials,

(vii) storage requirements,

(viii) expiration/stability dating,

(ix) specimen handling and its storage requirements,

(x) results (calculations, formulas, interpretation),

(xi) performance characteristics (summarise analytical and diagnostic sensitivity, specificity, reproducibility, etc.), and

(xii) study design (population studies, N, type of sample, matrix, dilution, target concentrations, etc.).

(c) Apart from IVD medical device labelling, the promotional material and product brochures shall be provided in this section to aid in the evaluation of the IVD medical device.

Note: Inclusion of promotional materials as part of the submission requirement for CSDT does not constitute approval by the Authority of the claims contained within the promotional materials.

6.5 Risk analysis

This section should summarize or reference or contain the results of the risk analysis. This risk analysis should be based upon international or other recognized standards and be appropriate to the complexity and risk class of the device.

6.5.1 Results of risk analysis

A list of possible hazards for these devices must be prepared. Indirect risks from medical devices may result from device-associated hazards, such as moving parts, which lead to sustained injury, or from user-related hazards, such as ionizing radiation from an X-ray machine. The evaluation of these risks against the claimed benefits of the device and the method(s) used to reduce risk to acceptable levels must be described. The individual or organization that carries out the risk analysis must be clearly identified. The technique used to analyze risk must be specified, to ensure that it is appropriate for the medical device and the risk involved.

Guidance:

Information required in this section is to be provided in the form of a risk management report. It is recommended that the risk management activities be conducted according to ISO 14971. A risk management report will contain details of the risk analysis, risk evaluation, risk control conducted for the IVD medical device. The risks and benefits associated with the use of the IVD medical device shall be described.

6.6 Manufacturer information

This section should summarize or reference or contain documentation related to the manufacturing processes, including quality assurance measures, which is appropriate to the complexity and risk class of the medical device.

6.6.1 Manufacturing process

Manufacturing process for the medical device should be provided in the form of a list of resources and activities that transform inputs into the desired output.

EXAMPLE: The manufacturing process should include the appropriate manufacturing methods and procedures, manufacturing environment or condition, and the facilities and controls used for the manufacturing, processing, packaging, labelling, storage of the medical device. Sufficient detail must be provided to enable a person generally familiar with quality systems to judge the appropriateness of the controls in place. A brief summary of the sterilization method and processing should be included, if any.

If multiple facilities are involved in the manufacture of medical device, the applicable information (e.g. quality assurance certificates issued by an accredited third party inspection body) for each facility must be submitted. Firms that manufacture or process the medical device under contract to the manufacturer may elect to submit all or a portion of the manufacturing information applicable to their facility directly to the Regulatory Authority in the form of a master file. The manufacturer should inform these contractors of the need to supply detailed information on the medical device. However, it is not the intent of this section to capture information relating to the supply of sub-components (i.e. unfinished medical device) that contributes towards the manufacture of the finished medical device itself.

Guidance:

(a) Information on the manufacturing process shall be provided in sufficient detail to allow a general understanding of the manufacturing processes. Detailed proprietary information on the manufacturing process is not required. The information may be presented in the form of a process flow chart showing an overview of production, controls, assembly, in-process and final product testing, and packaging of the finished IVD medical device.

(b) If the manufacturing process is carried out at multiple sites, the manufacturing activities carried out at each site shall be clearly identified. For example:

    (i) If the manufacturing process of a product consists of a number of subassembly processes, the manufacturing sites where each of these subassembly processes are carried out must be identified, and the relationship between these processes must be shown; or

(ii) If multiple sites manufacture the same product, each of these sites must be identified. The sites (including contract manufacturers) where design and manufacturing activities are performed shall be identified.

(c) Quality Management System certificates are to be provided for the design and manufacturing sites (including contract manufacturers) as an annex to the CSDT submission. This requirement does not apply to raw material manufacturers (for example, contract manufacturers of sodium azide).

(d) For Class D IVD medical device, the batch release plan shall be provided to demonstrate that each batch consistently identifies the relevant antigens, epitopes, and antibodies. The batch release plan shall be provided as an annex, with detailed information on the establishment of the batch release panel, including the number of positive and negative panel.

Appendix A

Example of an Essential Principles Conformity Checklist

Essential Principle	Applicable to the device?	Method of Conformity	Identity of Specific Documents
1. Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.			

2. The solutions adopted by the product owner for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, the product owner shall control the risk(s) so that the residual risk(s) associated with each hazard is judged acceptable. The product owner shall apply the following principles in the priority order listed: ➢ Identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse, ➢ Eliminate risks as far as reasonably practicable through inherently safe design and manufacture, ➢ Reduce as far as is reasonably practicable the remaining risks by taking adequate protection measures , including alarms ➢ Inform users of any residual risks.			

Appendix B

List of Configurations of Medical Device to be Registered

Guidelines on completing the table below:

1. For the "Name as per Device Label" column-

   (a) For a medical device family, list the names of the constituent members in this column. Enter the identifier associated with each constituent member in the "Identifier" column.
   (b) For a medical device group, list the names of the constituent medical devices in this column. Enter the identifier associated with each constituent medical device in the "Identifier" column.
   (c) For a medical device system, list the names of every constituent component in this column. Enter the identifier associated with each constituent component in the "Identifier" column.

2. For the "Identifier" column, identifier refers to a unique series of letters or numbers or any combination of these or a bar code that is assigned to a medical device by the product owner and that identifies it and distinguishes it from similar devices. Examples of an identifier for a device are a barcode, catalogue, model or part number.

3. For the "Brief Description of Item" column, give a brief description of the key distinguishing attributes or specifications of each item. Examples of a brief description of a constituent member of a family include the following:

   For percutaneous transluminal coronary angioplasty (PTCA) catheters:
   10 mm balloon length and 2 mm balloon diameter.

4. A list of configurations is to be provided with each **SINGLE, FAMILY, IVD TEST KIT, and SYSTEM** and **SET** medical device application.

Name of Medical Device FAMILY/GROUP/SYSTEM:	
Proposed Grouping for Medical Device (SINGLE, FAMILY, IVD TEST KIT, SYSTEM and SET):	

Name as per Device Label	**Identifier**	**Brief Description of Item**

MEDICAL DEVICE AUTHORITY

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