

- (vi) ensure that their auditors possess required qualification and expertise in the relevant field for carrying out assessments of manufacturing site and medical device that they are undertaking;
- (vii) establish and maintain procedure and record which demonstrate its compliance with quality management system.

### 3. Procedure for audit:

The notified body shall carry out the audit in the following manner,-

- (i) technical review of respective documents as prescribed in the Fourth Schedule;
- (ii) on-site audit of the manufacturer's quality management system to establish conformity by examination of objective evidence, and that of sub-contractor wherever applicable, the requirements of the Fifth Schedule;
- (iii) establish conformity by examination and provision of objective evidences to the essential principles laid down by the Central Government from time to time. ;
- (iv) establish design conformity by review of the design documents during assessment of medical device to ensure its quality, safety, and performance;
- (v) record post approval changes, if any;
- (vi) assess conformity to the product and process standards as per provisions of these rules;
- (vii) inform the manufacturer about the observed noncompliances during audit, if any, and provide a copy of the audit report to the manufacturer;
- (viii) when any major non-compliance is observed during audit by the notified body which may affect quality of the device, it may provide reasonable time to rectify the non-compliance followed by compliance verification of the manufacturing site;
- (ix) The Notified Body, after assessment and verification, shall submit detailed report giving its findings on each aspect of audit along with its recommendations after completion of audit to the State Licensing Authority and a copy of the same to the manufacturer.

#### Fourth Schedule

[See rule 20(2), 21(2), 34(2), 34(4), 63(1) and 64(1)]

#### Documents required for grant of licence to manufacture for sale or for distribution or import

##### Part I

##### Power of Attorney

(To be authenticated in India either by a Magistrate of First Class or by Indian Embassy in the country of origin or by an equivalent authority through apostille)

##### Power of Attorney to accompany an application for issuance of import licence

I ..... working as ..... authorised to sign this Power of Attorney, on behalf of M/s ..... (full address/ telephone no., e-mail) having manufacturing site at ..... (full address, telephone no., e-mail), hereby delegate Power of Attorney to M/s....., (full address, as per wholesale licence or manufacturing licence, with telephone, fax and e-mail address), hereinafter to be known as authorised agent, intends to apply for import licence under the provisions of these rules, to import into India for the following medical devices manufactured at below manufacturing site.

Sr. No.	Name & address of foreign manufacturer (full address with telephone, fax and e-mail address)	Name & address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)

Following are the details of medical device proposed to be imported (A separate list may be annexed, if required in below given format).

S. No.	Generic name	Brand Name (if any)	Model No. (if any)	Dimension	Intended use	Shelf life	Sterile or Non sterile	Class of medical device

(2) Our Authorised agent shall,-

- (a) act as the official representative for obtaining import licence in India.
- (b) submit all necessary documents, as defined in the Fourth Schedule, for the import licence of medical device.
- (3) I shall comply with all the conditions imposed on the import licence and with provisions of the Medical Devices Rules, 2017.
- (4) I declare that M/s ..... is carrying on the manufacture of the listed medical device at the manufacturing site specified above.
- (5) I shall allow the Central Licensing Authority or any person authorized by it in that behalf to enter and inspect or audit the manufacturing premise and to examine the process, procedure and documents in respect of any manufacturing site or to take sample of listed medical device for which the application for import licence has been made.
- (6) In case of any violation of Drugs and Cosmetics Act, 1940 (23 of 1940) and the Medical Devices Rules, 2017, the authorised agent shall continue to be responsible even after withdraw of this Power of Attorney for the devices imported in India.
- (7) I do hereby state and declare that all the photocopies or scanned copies in the application are true copies of the original documents.
- (8) I do hereby state and declare that all the documents submitted by the undersigned are true and correct.

**Place:**

**Date:**

**Signature of the manufacturer  
(Name and Designation)  
Seal/Stamp**

**Undertaking from the authorised agent**

I ....., age....., working as ..... at M/s ..... (Full address/ telephone no., e-mail) agrees to act upon the Power of Attorney as the authorized agent on behalf of M/s ..... (Full address/ telephone no., e-mail) having manufacturing site at ..... (Full address, telephone no., e-mail).

**Place:**

**Date:**

**Signature of the authorised agent  
(Name and Designation)  
Seal/Stamp**

**Part II**

**(i) Documents to be submitted with the application for grant of Import Licence or licence to manufacture for sale or for distribution of a Class A medical device,-**

(a) The applicant shall submit documents as specified in the Table below.-

S.N.	For medical devices other than <i>in vitro</i> diagnostic medical device	For <i>in vitro</i> diagnostic medical device
1.	device description, intended use of the device, specification including variants and accessories;	device description, intended use of the device, specification including variants and accessories;
2.	material of construction;	a summary of analytical technology, relevant analytes and test procedure;
3.	working principle and use of a novel technology (if any);	working principle and use of a novel technology (if any);

4.	labels, package inserts (IFU, etc.), user manual, wherever applicable,	labels and package inserts (IFU, etc.), user manual, wherever applicable;
5.	summary of any reported Serious Adverse Event in India or in any of the countries where device is marketed and action taken by the manufacturer and National Regulatory Authority concerned;	analytical performance summary including sensitivity and specificity;
6.	site or plant master file as specified in Appendix I of this Schedule;	site or plant master file as specified in Appendix I of this Schedule;
7.	constitution details of the firm (of domestic manufacturer or authorised agent);	constitution details of the firm (of domestic manufacturer or authorised agent);
8.	essential principles checklist for demonstrating conformity to the essential principles of safety and performance of the medical device;	essential principles checklist for demonstrating conformity to the essential principles of safety and performance of the <i>in vitro</i> medical device;
9.	undertaking signed by the manufacturer stating that the manufacturing site is in compliance with the provisions of the Fifth Schedule;	undertaking signed by the manufacturer stating that the manufacturing site is in compliance with the provisions of the Fifth Schedule;

(b) In case of application for import licence, the authorised agent shall submit

- A. notarized copy of overseas manufacturing site or establishment or plant registration, by whatever name called, in the country of origin issued by the competent authority and Free Sale Certificate issued by the National Regulatory Authority or equivalent competent authority of the country concerned as referred under rule 36.
- B. notarised copy of Quality Management System certificate or Full Quality Assurance certificate or Production Quality Assurance certificate issued by the competent authority, in respect of the manufacturing site.
- C. self-attested copy of valid whole sale licence or manufacturing licence issued under these rules.
- D. copy of latest inspection or audit report carried out by Notified bodies or National Regulatory Authority or Competent Authority within last 3 years, if any.

**(ii) Documents to be submitted with the application for grant of licence to manufacture or import Class B, Class C or Class D medical device,-**

The domestic manufacturer or authorised agent shall submit the duly signed following information pertaining to Manufacturing site.

- (a) Constitution details of domestic manufacturer or authorised agent;
- (b) Site or plant master file as specified in Appendix I of this Schedule;
- (c) Device master file as specified in Appendix II for medical devices other than *in vitro* diagnostic medical devices, or Appendix III for *in vitro* diagnostic medical devices of this Schedule;
- (d) Essential Principles checklist for demonstrating conformity to the Essential Principles of Safety and Performance of the Medical Device including *in vitro* diagnostic medical device;
- (e) Test licence obtained for testing and generation of quality control data (for domestic manufacturers only), if any;
- (f) Undertaking signed stating that the manufacturing site is in compliance with the provisions of the Fifth Schedule.
- (g) Documents as specified in the clause (b) of paragraph (i) of this part.
- (h) In case of *in vitro* diagnostic medical devices, a copy of performance evaluation report issued by the central medical device testing laboratory or medical device testing laboratory registered under sub-rule (3) of rule 83.

**Part III**  
**Appendix I**

**Contents of a site or plant master file**

The manufacturer shall prepare a succinct document in the form of site master file containing specific information about the production and/or control of device manufacturing carried out at the premises. It shall contain the following information,-

**1. General Information:**

- (i) brief information on the site (including name and address), relation to other sites;
- (ii) manufacturing activities;
- (iii) any other operations carried out on the site
- (iv) name and exact address of the site, including telephone, fax numbers, web site URL and e-mail address;
- (v) type of medical devices handled on the site and information about specifically toxic or hazardous substances handled, mentioning the way they are handled and precautions taken;
- (vi) short description of the site (size, location and immediate environment and other activities on the site);
- (vii) number of employees engaged in production, quality control, warehousing, and distribution;
- (viii) use of outside scientific, analytical or other technical assistance in relation to the design, manufacture and testing;
- (ix) short description of the quality management system of the company;
- (x) devices details registered with foreign countries;
- (xi) brief description of testing facility;

**2. Personnel:**

- (i) organisation chart showing the arrangements for key personnel
- (ii) qualifications, experience and responsibilities of key personnel;
- (iii) outline of arrangements for basic and in-service training and how records are maintained;
- (iv) health requirements for personnel engaged in production
- (v) personnel hygiene requirements, including clothing.

**3. Premises and Facilities:**

- (i) layout of premises with indication of scale;
- (ii) nature of construction, finishes/fixtures and fittings;
- (iii) brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (including schematic drawings of the systems). Classification of the rooms used for the manufacture of sterile products should be mentioned;
- (iv) special areas for the handling of highly toxic, hazardous and sensitizing materials;
- (v) brief description of water systems (schematic drawings of the systems are desirable) including sanitation;
- (vi) maintenance (description of planned preventive maintenance programmes for premises and recording system);

**4. Equipment:**

- (i) Brief description of major production and quality control laboratories equipment (a list of the equipment is required);
- (ii) maintenance (description of planned preventive maintenance programmes and recording system);
- (iii) qualification and calibration, including the recording system. Arrangements for computerized systems validation.

**5. Sanitation :**

Availability of written specifications and procedures for cleaning the manufacturing areas and equipment.

**6. Production:**

- (i) Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters ;
- (ii) arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage;
- (iii) arrangements for reprocessing or rework;
- (iv) arrangements for the handling of rejected materials and products;
- (v) brief description of general policy for process validation.
- (vi) Brief description of sterilisation facility;

**7. Quality Assurance:**

Description of the quality assurance system and of the activities of the quality assurance department. Procedures for the release of finished products.

**8. Storage :**

Policy on the storage of medical device.

**9. Documentation :**

Arrangements for the preparation, revision and distribution of necessary documentation, including storage of master documents.

**10. Medical Device Complaints and Field Safety Corrective Action:**

- (i) Arrangements for the handling of complaints ;
- (ii) Arrangements for the handling of field safety corrective action.

**11. Internal Audit:**

Short Description of the internal audit system.

**12. Contract Activities:**

Description of the way in which the compliance of the contract acceptor is assessed.

**Appendix II****DEVICE MASTER FILE FOR MEDICAL DEVICES OTHER THAN *IN VITRO* DIAGNOSTIC MEDICAL DEVICES****EXECUTIVE SUMMARY:**

**1.** An executive summary shall be provided by the manufacturer and shall contain:

- 1.1 Introductory descriptive information on the medical device, the intended use and indication for use, class of device, novel features of the device (if any), shelf life of the device and a synopsis on the content of the dossier.
- 1.2 Information regarding sterilization of the device (whether it is sterile or non-sterile; if sterile, mode of sterilization).
- 1.3 Risk Management Plan, Risk Analysis, evaluation and control documents.
- 1.4 Clinical Evidence and evaluation (if applicable).
- 1.5 Regulatory status of the similar device in India (approved or not approved in India).
- 1.6 Design Examination Certificate, Declaration of Conformity, Mark of Conformity Certificate, Design Certificate (if applicable). Copy of such certificate(s) shall be enclosed.
- 1.7 Marketing history of the device from the date of introducing the device in the market.
- 1.8 Domestic price of the device in the currency followed in the country of origin.
- 1.9 List of regulatory approvals or marketing clearance obtained (submit respective copies of approval Certificates):

Country	Approved Indication	Approved Shelf life	Class of Device	Date of First Approval
USA				
Australia				
Japan				
Canada				
European Union				
Others*				

\*Optional

Status of market clearance pending, rejected or withdrawn

Regulatory Agency of the country	Indication for use	Registration status and date	Reason for rejection/ withdrawal, if any

1.10 Safety and performance related information on the device:

- (a) Summary of reportable event and field safety corrective action from the date of introduction:-

**For Serious Adverse Event:**

S.N.	Serious Adverse Event (SAE)	Duration		Number of the SAE reported	Total Units sold	Lot/Batch No.
		From	To			

**For Field Safety Corrective Action (FSCA):**

Date of FSCA	Reason for FSCA	Countries where FSCA was conducted	Description of the action taken

- (b) If the device contains any of the followings, then descriptive information on the following need to be provided.
1. Animal or human cells tissues or derivatives thereof, rendered non-viable (e.g. Porcine Heart Valves).
  2. Cells, tissues or derivatives of microbial recombinant origin (e.g. Dermal fillers based on Hyaluronic acid derived from bacterial fermentation process).
  3. Irradiating components, ionising or non-ionizing.

**2. Device description and product specification, including variants and accessories****2.1 The dossier should contain the following descriptive information for the device:-**

- (a) A general description including its generic name, model name, model no., materials of construction, intended use, indications, instructions for use, contraindications, warnings, precautions and potential adverse effects;
- (b) the intended patient population and medical condition to be diagnosed or treated and other considerations such as patient selection criteria;
- (c) principle of operation or mode of action, accompanied by animation or videos (if available);
- (d) an explanation of any novel features;
- (e) a description of the accessories, other medical device and other product that are not medical device, which are intended to be used in combination with it and it should also be clarified whether these accessories or device are supplied as a system or separate components;
- (f) a description or complete list of the various configurations or variants of the device that will be made available;
- (g) a general description of the key functional elements, e.g. its parts or components (including software if appropriate), its formulation, its composition, its functionality and where appropriate, this will include: labeled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts or components, including sufficient explanation to understand the drawings and diagrams;
- (h) a description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body, e.g., during extracorporeal circulation of body fluids. Complete chemical, biological and physical characterization of the material (s) of the medical device;
- (i) for medical devices intended to emit ionizing radiation, information on radiation source (e.g. radioisotopes) and the material used for shielding of unintended, stray or scattered radiation from patients, users and other persons shall be provided.

**2.2 Product Specification:**

The dossier should contain a list of the features, dimensions and performance attributes of the medical device, its variants and accessories, that would typically appear in the product specification made available to the end user, e.g. in brochures, catalogues etc.

**2.3 Reference to predicate or previous generations of the device:**

Where relevant to demonstrating conformity to the essential principles, and to the provision of general background information, the dossier should contain an overview of:

- (a) the manufacturer's previous generation of the device, if such exist;
- (b) predicate devices available on the local and international markets; and
- (c) comparative analysis to prove substantial equivalence to the predicate device(s) as claimed.

**3.0 LABELLING:**

The dossier should typically contain a complete set of labeling associated with the device as per the requirements of Chapter VI of these rules. Information on labelling should include the following:-

- (a) Copy of original label of the device, including accessories if any, and its packaging configuration;

- (b) Instructions for use (Prescriber's manual);
- (c) Product brochure; and
- (d) Promotional material.

#### 4. DESIGN AND MANUFACTURING INFORMATION:

##### 4.1 Device Design:

The dossier should contain information to allow the reviewer to obtain a general understanding of the design stages applied to the device. The information may take in form of flow chart. Device design validation data should be submitted.

##### 4.2 Manufacturing Processes:

The dossier should contain information to allow the reviewer to obtain a general understanding of the manufacturing processes. The information may take the form of flow chart showing an overview of production, manufacturing environment, facilities and controls used for manufacturing, assembly, any final product testing, labelling and packaging and storage of the finished medical device. If the manufacturing process is carried out at multiple sites, the manufacturing activities at each site should be clearly specified.

#### 5. ESSENTIAL PRINCIPLES CHECKLIST:

- (i) The dossier should contain the following:-
  - (a) the essential principles;
  - (b) whether each essential principle applies to the device and if not, why not;
  - (c) the method used to demonstrate conformity with each essential principle that applies;
  - (d) a reference for the method employed (e.g., standard); and
  - (e) the precise identity of the controlled document that offers evidence of conformity with each method used.
- (ii) Methods used to demonstrate conformity may include one or more of the following:
  - (a) conformity with standards as referred to in rule 7;
  - (b) conformity with an in-house test method;
  - (c) the evaluation of pre-clinical and clinical evidence;
  - (d) comparison to a similar device already available on the market.
- (iii) The essential principles checklist should incorporate a cross-reference to the location of such evidence both within the full technical documentation held by the manufacturer and within the dossier. A template for a checklist is shown in as under:

Essential Principle	Relevant Yes/No	Specification/standard Sub-clause/reference	Complies Yes/No	Document Reference Justification and/or comments

#### 6. Risk analysis and control summary:

The dossier should contain a summary of the risks identified during the risk analysis process and how these risks have been controlled to an acceptable level. This risk analysis should be based on prescribed standards and be part of the manufacturer's risk management plan based on complexity and risk class of the device. The technique used to analyse the risk must be specified, to ensure that it is appropriate for the medical device and risk involved. The risks and benefits associated with the use of the medical device should be described. The risk analysis submitted shall have periodic updation of the risks identified as per risk management plan.

#### 7. Verification and validation of the medical device

##### 7.1 General:

- (A) The dossier should contain product verification and validation documentation. The dossier should summarize the results of verification and validation studies undertaken to demonstrate conformity of the device with the essential principles that apply to it. Such information would typically cover wherever applicable:
  - (a) engineering tests;
  - (b) laboratory tests;
  - (c) simulated use testing;
  - (d) any animal tests for demonstrating feasibility or proof of concept of the finished device;
  - (e) any published literature regarding the device or substantially similar devices.
- (B) Such summary information may include:
  - (i) declaration or certificate of conformity to a recognised standard and summary of the data if no acceptance criteria are specified in the standard;
  - (ii) declaration or certificate of conformity to a published standard that has not been recognised, supported by a rationale for its use, and summary of the data if no acceptance criteria is specified in the standard;

- (iii) declaration or certificate of conformity to a professional guideline, industry method, or in-house test method, supported by a rationale for its use, a description of the method used, and summary of the data in sufficient detail to allow assessment of its adequacy;
  - (iv) a review of published literature regarding the device or substantially similar devices.
- (C) In addition, where applicable to the device, the dossier should contain detailed information on:
- (a) biocompatibility studies data as per prescribed standards;
  - (b) medicinal substances incorporated into the device, including compatibility of the device with the medicinal substance;
  - (c) biological safety of devices incorporating animal or human cells, tissues or their derivatives;
  - (d) sterilisation;
  - (e) software verification and validation;
  - (f) animal studies that provide direct evidence of safety and performance of the device, especially when no clinical investigation of the device was conducted;
  - (g) clinical evidence.
- (D) Detailed information will describe test design, complete test or study protocols, methods of data analysis, in addition to data summaries and test conclusions. Where no new testing has been undertaken, the dossier should incorporate a rationale for that decision, e.g. biocompatibility testing on the identical materials was conducted when these were incorporated in a previous, legally marketed version of the device. The rationale may be incorporated into the Essential Principle checklist.

### **7.2 Biocompatibility:**

- (i) The dossier should contain a list of all materials in direct or indirect contact with the patient or user.
- (ii) Where biocompatibility testing has been undertaken (as per prescribed standards) to characterize the physical, chemical, toxicological and biological response of a material, detailed information should be included on the tests conducted, standards applied, test protocols, the analysis of data and the summary of results. At a minimum, tests should be conducted on samples from the finished, sterilized (when supplied sterile) device.
- (iii) Depending on nature and intended use of the investigational medical device, device performance for its actions (including mechanical, electrical, thermal, radiation and any other of this type) and safety should be assessed in healthy or diseased animal model (intended to be treated by such medical device), as appropriate, demonstrating reaction to active and basic parts of the devices on absolute tissue, local tissue as well as whole organ, clearly recording local, general and systemic adverse reactions, risks or potential risks and performance of device in line with intended use. Wherever possible, histopathology, pathophysiology and path anatomy should be carried out.
- (iv) ISO-10993, Biological Evaluation of Medical Devices, should be followed for conducting bio-compatibility study for invasive medical devices should be carried out. A report of biocompatibility study along with rationale for selecting specific tests carried out should be prepared including conclusion of the study.

### **7.3 Medicinal substances:**

Where the medical device incorporates a medicinal substance, the dossier should provide detailed information concerning that medicinal substance, its identity and source, the intended reason for its presence, and its safety and performance in the intended application.

### **7.4 Biological safety:**

- (i) The dossier should contain a list of all materials of animal or human origin used in the device. For these materials, detailed information should be provided concerning the selection of sources or donors; the harvesting, processing, preservation, testing and handling of tissues, cells and substances of such origin should also be provided. Process validation results should be included to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents. Transmissible Spongiform Encephalopathies (TSE) or Bovine Spongiform Encephalopathy (BSE) Certificates should also be submitted.
- (ii) The system for record-keeping to allow traceability from sources to the finished device should be fully described.

### **7.5 Sterilization:**

- (i) Where the device is supplied sterile, the dossier should contain the detailed information of the initial sterilization validation including sterilizer qualification, bioburden testing, pyrogen testing, testing for sterilant residues (if applicable) and packaging validation as per prescribed standards. Typically, the detailed validation information should include the method used, sterility assurance level attained, standards applied, the sterilization protocol developed in accordance with prescribed standards, and a summary of results.

- (ii) Evidence of the ongoing revalidation of the process should also be provided. Typically this would consist of arrangements for, or evidence of, revalidation of the packaging and sterilization processes.

#### 7.6 Software verification and validation:

The dossier should contain information on the software design and development process and evidence of the validation of the software, as used in the finished device. This information should typically include the summary results of all verification, validation and testing performed both in-house and in a simulated or actual user environment prior to final release. It should also address all of the different hardware configurations and, where applicable, operating systems identified in the labelling.

#### 7.7 Animal studies:

- (i) Where studies in an animal model have been undertaken to provide evidence of conformity with the Essential Principles related to functional safety and performance, detailed information should be contained in the dossier.
- (ii) The dossier should describe the study objectives, methodology, results, analysis and conclusions and document conformity with Good Laboratory Practices. The rationale (and limitations) of selecting the particular animal model should be discussed.

#### 7.8 Stability data:

If available, real-time aging data shall be submitted to support the claimed shelf life. However, if real-time data is not available, accelerated stability data shall be submitted to support the claimed shelf life. Such a provisional claimed shelf life may be approved provided that the manufacturer immediately initiates real-time stability testing to validate the proposed shelf life. After completion of the real time stability analysis, real-time stability data shall be submitted in support of the claimed shelf life.

#### 7.9 Clinical evidence:

The dossier should contain the clinical evidence that demonstrates conformity of the device with the Essential Principles that apply to it. It needs to address the elements contained in the Clinical Investigation, as specified under the Seventh Schedule. If a predicate device is available, the manufacturer needs to submit the substantial equivalence evaluation along with relevant published literature in accordance with these rules.

#### 7.10 Post Marketing Surveillance data (Vigilance reporting):

The dossier should contain the Post Marketing Surveillance or Vigilance Reporting procedures and data collected by the manufacturer encompassing the details of the complaints received and corrective and Preventive actions taken for the same.

##### NOTE:

1. All reports submitted as a part of the dossier should be signed and dated by the responsible person.
2. Batch Release Certificates and Certificate of Analysis of finished product for minimum 3 consecutive batches should be submitted.
3. All certificates submitted must be within the validity period.
4. Any information which is not relevant for the subject device may be stated as 'Not Applicable' in the relevant Sections/Columns of the above format, and reasons for non-applicability should be provided.

### Appendix III

#### DEVICE MASTER FILE FOR *IN VITRO* DIAGNOSTIC MEDICAL DEVICES

##### 1. EXECUTIVE SUMMARY:

An executive summary shall be provided by the manufacturer and shall contain:

- 1.1 Introductory descriptive information on the *in vitro* diagnostic medical device, the intended use and risk Class of *in vitro* diagnostic medical device, novel features (if any), claimed shelf life and a synopsis on the content of the dossier.
- 1.2 Regulatory status of the similar device in India (approved or new *in vitro* diagnostic medical device).
- 1.3 Domestic price of the *in vitro* diagnostic medical device in the currency followed in the country of origin.
- 1.4 Marketing history of the *in vitro* diagnostic medical device from the date of introducing the *in vitro* diagnostic medical device in the market.
- 1.5 List of regulatory approvals or marketing clearance obtained in below format (submit respective copy of approval certificate).

S.N.	Name of the country	Approved indication	Approved shelf life	Composition	Risk Class	Date of first approval

## 1.6 Status of pending request for market clearance

Regulatory Agency of the country	Intended use	Indication for use	Registration status and date	Reason for rejection/withdrawal, if any

1.7 Safety and performance related information on the *in vitro* diagnostic medical device:

## (a) Summary of reportable events and field safety corrective action from the date of introduction

For adverse event (false diagnosis or any other hazard during its use)

Adverse event (false diagnosis)	Frequency of occurrence during the period (number of report/total units sold)

For Field Safety Corrective Action (FSCA)

Date of FSCA	Reason for FSCA	Countries where FSCA was conducted	Description of the action taken

(b) If the *in vitro* diagnostic medical device contains any of the following then descriptive information on the following need to be provided.

- (1) Animal or human fluids or derivatives thereof, rendered non-viable.
- (2) Cells, tissues and/or derivatives of microbial recombinant origin.

**2. Description and specification, including variants and accessories of the *in vitro* diagnostic medical device****2.1 Description**

The device master file should include the following device descriptive information:

- (a) it may include:-
  - (1) what is detected;
  - (2) its function (for example screening, monitoring, diagnostic or aid to diagnosis, staging or aid to staging of disease);
  - (3) the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;
  - (4) whether it is automated or not;
  - (5) whether it is qualitative or quantitative;
  - (6) the type of specimen required (eg. serum, plasma, whole blood, tissue biopsy, urine);
  - (7) testing population;
- (b) the intended user (lay person or professional);
- (c) a general description of the principle of the assay method;
- (d) the risk based Class of the device;
- (e) a description of the components (e.g. reagents, assay controls and calibrators) and where appropriate, a description of the reactive ingredients of relevant components (such as antibodies, antigens, nucleic acid primers) where applicable;
- (f) a description of the specimen collection and transport materials provided with the *in vitro* diagnostic medical device or descriptions of specifications recommended for use;
- (g) for instruments of automated assays; a description of the appropriate assay characteristics or dedicated assays;
- (h) for automated assays; a description of the appropriate instrumentation characteristics or dedicated instrumentation;

- (i) a description of any software to be used with the *in vitro* diagnostic medical device;
- (j) a description or complete list of the various configurations/variants of the *in vitro* diagnostic medical device that will be made available;
- (k) a description of the accessories, other *in vitro* diagnostic medical device and other products that are not *in vitro* diagnostic medical device, which are intended to be used in combination with the *in vitro* diagnostic medical device.

Reference to the manufacturer's previous device generation(s) or similar devices or device history.

#### **2.2 For a new *in vitro* diagnostic medical device:**

Where relevant to demonstrating conformity to the essential principles, and to provide general background information, the device master file may provide a summary of Clinical Performance Evaluation reports.

#### **2.3 For an *in vitro* diagnostic medical device already available on the market in India:**

- (i) This information may include a summary of the number of adverse event reports related to the safety and performance of this *in vitro* diagnostic medical device in relation to the number of *in vitro* diagnostic medical devices placed on the market.
- (ii) External certificates and documents which give written evidence of conformity with the essential principles may be annexed to the device master file.
- (iii) comparative analysis to prove substantial equivalence to the predicate device(s), if claimed in the application.

#### **3. Essential principles checklist:**

- (i) The device master file should include an essential principles checklist that identifies:
  - (a) the essential principles of safety and performance;
  - (b) whether each essential principle applies to the *in vitro* diagnostic medical device and if not, why not;
  - (c) the method used to demonstrate conformity with each essential principle that applies; and
  - (d) the reference to the actual technical documentation that offers evidence of conformity with each method used.
- (ii) The method used to demonstrate conformity may include one or more of the following:-
  - (a) conformity with recognized or other standards;
  - (b) conformity with a commonly accepted industry test method (reference method);
  - (c) conformity with appropriate in house test methods that have been validated and verified;
  - (d) comparison to an *in vitro* diagnostic medical device already available on the market.
- (iii) The essential principles checklist should include a cross-reference to the location of such evidence both within the full technical documentation held by the manufacturer and within the Device master file (when such documentation is specifically required for inclusion in the Summary Technical Documentation as outlined in this guidance).

#### **4. Risk analysis and control summary:**

The device master file should contain a summary of the risks identified during the risk analysis process and a description of how these risks have been controlled to an acceptable level. Preferably, this risk analysis should be based on recognised standards and be part of the manufacturer's risk management plan.

The summary should address possible hazards for the *in vitro* diagnostic medical device such as the risk from false positive or false negative results, indirect risks which may result from *in vitro* diagnostic medical device-associated hazards, such as instability, which could lead to erroneous results, or from user-related hazards, such as reagents containing infectious agents. The results of the risk analysis should provide a conclusion with evidence that remaining risks are acceptable when compared to the benefits.

#### **5. Design and manufacturing information:**

##### **5.1 Device design:**

The Device master file should contain information to allow a reviewer to obtain a general understanding of the design applied to the *in vitro* diagnostic medical device.

It should include a description of the critical ingredients of an assay such as antibodies, antigens, enzymes and nucleic acid primers provided or recommended for use with the *in vitro diagnostic* medical device,

This section is not intended to take the place of the more detailed information required for a QMS audit or other conformity assessment activity. If design takes place at multiple sites, a controlling site must be identified.

##### **5.2 Manufacturing processes:**

The device master file should contain information to allow a reviewer to obtain a general understanding of the manufacturing processes. It is not intended to take the place of the more detailed information required for a QMS audit or other conformity assessment activity. The information may take the form of a process flow chart

showing, for example, an overview of production including the technologies used, assembly, any in-process and final product testing, and packaging of the finished *in vitro* medical device.

### 5.3 Manufacturing sites:

The device master file should identify the sites where these activities are performed (this does not include the sites of all suppliers of raw materials but only the sites that are involved in critical manufacturing activities). If Quality Management System certificates, or the equivalent, exist for these sites, they may be annexed to the device master file.

### 6. Product validation and verification:

The information provided in the product validation and verification section of the device master file will vary in the level of detail as determined by the class of the device. The device master file should summarize the results of validation and verification studies undertaken to demonstrate conformity of the *in vitro* diagnostic medical device with the essential principles that apply to it. Where appropriate, such information might come from literature.

**For the purpose of the device master file document, summary and detailed information are defined as follows:**

#### (i) Summary information:

A summary should provide enough to assess the validity of that information by the regulatory authorities. This summary should contain a brief description of:

- (a) the study protocol;
- (b) the study results;
- (c) the study conclusion.

This summary may include:

- (a) Where a recognized standard exists, a declaration/certificate of conformity to a recognized standard can be provided with a summary of the data if no acceptance criteria are specified in the standard;
- (b) In the absence of a recognized standard, a declaration/certificate of conformity to a published standard that has not been recognized might be provided if it is supported by a rationale for its use, and summary of the data, and a conclusion, if no acceptance criteria are specified in the standard;
- (c) In the absence of a recognized standard and non-recognized published standards, a professional guideline, industry method, or in-house standard may be referred to in the summarized information. However, it should be supported by a rationale for its use, a description of the method used, a summary of the data in sufficient detail and a conclusion to allow assessment of its adequacy;
- (d) A review of relevant published literature regarding the device/analyte (measurand) or substantially similar *in vitro* diagnostic medical devices.

#### (ii) Detailed information:

Detailed information should include:

- (a) complete study protocol;
- (b) method of data analysis;
- (c) complete study report;
- (d) study conclusion.

For detailed information, when a recognized standard exists that contains the protocol and the method of data analysis, this information can be substituted by a declaration or certificate of conformity to the recognized standard along with a summary of the data and conclusions. Where appropriate, actual test result summaries with their acceptance criteria should be provided and not just pass/fail statements.

### 7. Analytical Studies:

The statements and descriptions in the following sections refer to all *in vitro* diagnostic medical devices. It must be noted however that there are applicability differences between instrumentation and reagent-based assays, and that the assays themselves may be quantitative, semi-quantitative or qualitative in nature. There may be limited applicability of some of the following subsections for qualitative or semi-quantitative assays. Where possible, comments regarding instrumentation or qualitative assays appear in the subsections.

### 8. Specimen type:

- (a) This section should describe the different specimen types that can be used. This should include their stability and storage conditions. Stability includes storage and where applicable transport conditions. Storage includes elements such as duration, temperature limits and freeze/thaw cycles.
- (b) This section should include summary information for each matrix and anticoagulant when applicable, including a description of the measurement procedure for comparison or determination of measurement accuracy. This

includes information such as specimen type tested, number of samples, sample range (using spiked samples as appropriate) or target concentrations tested, calculations and statistical methods, results and conclusions.

## 9. Analytical performance characteristics.

### 9.1 Accuracy of measurement:

This section should describe both trueness and precision studies.

*Explanation.*- The general term measurement accuracy is currently used to cover both trueness and precision, whereas this term was used in the past to cover only the one component now named trueness.

While measurement trueness, affected by systematic error, is normally expressed in terms of bias, measurement precision, affected by random error, is naturally expressed in terms of standard deviation,

Accuracy is affected by a combination of systematic and random effects that contribute as individual components of the total error of measurement.

### 9.2 Reproducibility:

This section should include reproducibility estimates and information about the studies used to estimate, as appropriate, variability between days, runs, sites, lots, operators and instruments. Such variability is also known as “Intermediate Precision”. Reproducibility data is obtained for instrumentation in conjunction with an appropriate assay.

*Note 1.*- Such studies should include the use of samples that represent the full range of expected analyte (measurand) that can be measured by the test as claimed by the manufacturer.

*Note 2.*- If a recognized standard is used, a declaration/certificate of conformity to the recognized standard along with a summary of the data and conclusions.

## 10. Analytical sensitivity:

This section should include information about the study design and results. It should provide a description of specimen type and preparation including matrix, analyte (measurand) levels, and how levels were established. The number of replicates tested at each concentration should also be provided as well as a description of the calculation used to determine assay sensitivity. For example:

- (a) Number of standard deviations above the mean value of the sample without analyte (measurand), commonly referred to as limit of blank (LoB).
- (b) Lowest concentration distinguishable from zero, based on measurements of samples containing analyte (measurand), commonly referred to as limit of detection (LoD).
- (c) Lowest concentration at which precision and/or trueness are within specified criteria, commonly referred to as limit of quantitation (LoQ).

For Class C and D *in vitro* diagnostic medical devices, detailed information would be provided.

## 11. Analytical specificity:

- (i) This section should describe interference and cross reactivity studies to determine the analytical specificity, defined as the ability of a measurement procedure to detect or measure only the analyte (measurand) to be detected, in the presence of other substances/agents in the sample.
- (ii) Provide information on the evaluation of potentially interfering and cross reacting substances/agents on the assay. Information should be provided on the substance/agent type and concentration tested, sample type, analyte (measurand) test concentration, and results.
- (iii) Interferents and cross reacting substances/agents, which vary greatly depending on the assay type and design, could derive from exogenous or endogenous sources such as:
  - (a) substances used for patient treatment (e.g. therapeutic drugs, anticoagulants, etc.);
  - (b) substances ingested by the patient (e.g. over the counter medications, alcohol, vitamins, foods, etc.);
  - (c) substances added during sample preparation (e.g. preservatives, stabilizers);
  - (d) substances encountered in specific specimens types (e.g. hemoglobin, lipids, bilirubin, proteins);
  - (e) analytes of similar structure (e.g. precursors, metabolites) or medical conditions unrelated to the test condition including specimens negative for the assay but positive for a condition that may mimic the test condition (e.g. for a hepatitis A assay: test specimens negative for hepatitis A virus, but positive for hepatitis B virus).

*Explanation.*- Interference studies involve adding the potential interferent to the sample and determining any bias of the test parameter relative to the control sample to which no interferent has been added.

## 12. Metrological traceability of calibrator and control material values:

Where applicable, summarize the information about metrological traceability of values assigned to calibrators and trueness control materials. Include, for example, methods and acceptance criteria for the metrological

traceability to reference materials and/or reference measurement procedures and a description of value assignment and validation.

Precision control materials, used when establishing the reproducibility of a measurement procedure do not require the assessment of metrological traceability to a reference material or a reference method.

**13. Measuring range of the assay:**

This section should include a summary of studies which define the measuring range (linear and non-linear measuring systems) including the limit of detection and describe information on how these were established. This summary should include a description of specimen type, number of samples, number of replicates, and preparation including information on matrix, analyte (measurand) levels and how levels were established. If applicable, add a description of high dose hook effect and the data supporting the mitigation (e.g. dilution) steps.

**14. Definition of Assay Cut-off:**

This section should provide a summary of analytical data with a description of the study design including methods for determining the assay cut-off, including:

- (a) the population(s) studied (demographics / selection / inclusion and exclusion criteria / number of individuals included);
- (b) method or mode of characterization of specimens; and
- (c) Statistical methods e.g. Receiver Operator Characteristic (ROC) to generate results and if applicable, define gray-zone/equivocal zone.

**15. Stability (excluding specimen stability):**

This section should describe claimed shelf life, in use stability and shipping studies.

**16. Claimed Shelf life:**

This section should provide information on stability testing studies to support the claimed shelf life. Testing should be performed on at least three different lots manufactured under conditions that are essentially equivalent to routine production conditions (these lots do not need to be consecutive lots). Accelerated studies or extrapolated data from real time data are acceptable for initial shelf life claim but need to be followed up with real time stability studies. Such detailed information should describe:

- (a) the study report (including the protocol, number of lots, acceptance criteria and testing intervals);
- (b) when accelerated studies have been performed in anticipation of the real time studies, the method used for accelerated studies;
- (c) conclusions and claimed shelf life.

*Explanation,-* Shelf life can be derived from the lot with the longest real time stability data as long as accelerated or extrapolated data from all three lots are comparable.

**17. In use stability:**

This section should provide information on in use stability studies for one lot reflecting actual routine use of the device (real or simulated). This may include open vial stability and/or, for automated instruments, on board stability. In the case of automated instrumentation if calibration stability is claimed, supporting data should be included. Such detailed information should describe:

- (a) the study report (including the protocol, acceptance criteria and testing intervals);
- (b) conclusions and claimed in use stability.

**18. Shipping stability:**

This section should provide information on shipping stability studies for one lot to evaluate the tolerance of products to the anticipated shipping conditions. Shipping studies can be done under real and/or simulated conditions and should include variable shipping conditions such as extreme heat or cold. Such information should describe:

- (a) the study report (including the protocol, acceptance criteria);
- (b) method used for simulated conditions;
- (c) conclusion and recommended shipping conditions.

**19. Clinical Evidence:**

The device master file should contain the Clinical Evidence, Evaluation report that demonstrates conformity of the *in vitro* diagnostic medical device to the Essential Principles that apply to it.

**20. Labelling:**

The device master file should typically contain a complete set of labeling associated with the *in vitro* medical device as described in Chapter VI.

**21. Post marketing surveillance data (vigilance reporting):**

The dossier should contain the post marketing surveillance or vigilance reporting procedures and data collected by the manufacturer encompassing the details of the complaints received and corrective and Preventive actions taken for the same.

**22. Information required to be submitted for the in vitro diagnostic medical device:**

- (1) The details of source antigen or antibody as the case may be and characterization of the same. Process control of coating of antigen or antibody on the base material like Nitrocellulose paper, strips or cards or ELISA wells etc. Detailed composition of the *in vitro* diagnostic medical device and manufacturing flow chart process of the *in vitro* diagnostic medical device showing the specific flow diagram of individual components or source of the individual components.
- (2) Test protocol of the *in vitro* diagnostic medical device showing the specifications and method of testing. In house evaluation report of sensitivity, specificity and stability studies carried out by the manufacturer.
- (3) In case of imported diagnostic *in vitro* diagnostic medical devices, the report of evaluation in details conducted by the National Control Authority of country of origin.
- (4) Specimen batch test report for at least consecutive 3 batches showing specification of each testing parameter.
- (5) The detailed test report of all the components used/packed in the finished *in vitro* diagnostic medical device.
- (6) Pack size and labeling.
- (7) Product inserts.
- (8) Specific evaluation report, if done by any laboratory in India, showing the sensitivity and specificity of the *in vitro* diagnostic medical device.
- (9) Specific processing like safe handling, material control, area control, process control, and stability studies, storage at quarantine stage and finished stage, packaging should be highlighted in the product dossier.

**NOTE:**

1. All the test reports submitted as a part of the dossier should be signed and dated by the responsible person.
2. Batch Release Certificates and Certificate of Analysis of finished product for minimum 3 consecutive batches should be submitted.
3. All certificates submitted must be within the validity period.
4. Any information which is not relevant for the subject *in vitro* diagnostic medical device may be stated as 'Not Applicable' in the relevant sections/columns of the above format, and reasons for non-applicability should be provided.

**Part IV****Information required to be submitted with the Application Form for import or manufacture of medical devices which does not have predicate device.****(a) Data to be submitted along with the application (for medical devices other than new *in vitro* diagnostic):-**

1. Design Analysis data including, (whichever applicable)-
  - (a) design input and design output documents;
  - (b) mechanical and electrical tests;
  - (c) reliability tests;
  - (d) validation of software relating to the function of the device;
  - (e) any performance tests;
  - (f) *in vitro* tests.
2. Bio-compatibility tests data, Report of bio-compatibility tests along with rationale for selecting these tests. Summary report of the biocompatibility study including the conclusion of the study.
3. Risk Management data;
4. Animal Performance study data;
5. Pilot or Pivotal Clinical Investigation data, including that carried out in other countries if any;
6. In case, if waiver from clinical investigation is claimed in accordance with the provisions of Medical Device Rules, 2017, the information or supporting data shall be submitted.
7. Regulatory status and Restriction on use in other countries (if any) where marketed or approved;
8. Proposed Instruction for use and labels.

**(b) Data to be submitted along with the application (for new *in vitro* diagnostic medical devices):-**

1. Device data including, (whichever applicable)-
  - (i) design input, design output documents, stability data;
  - (ii) device specification including specificity, sensitivity, reproducibility and reputability;
  - (iii) product validation and software validation relating to the function of the device (if any);
  - (iv) performance evaluation report from a laboratory designated under sub-rule (1) of rule 19.
2. Risk Management data.
3. Clinical Performance Evaluation data carried out in India and in other countries (if any).
4. Regulatory status and Restriction on use in other countries (if any) where marketed or approved.
5. Proposed Instruction for use and labels.

**Fifth Schedule**

[See rule 20(3), 20(5), 20(8), 22(i)]

**Quality Management System for medical devices and *in vitro* diagnostic medical devices****1. General Requirements:**

- 1.1. This schedule specifies requirements for a quality management system that shall be used by the manufacturer for the design and development, manufacture, packaging, labelling, testing, installation and servicing of medical devices and *in vitro* diagnostic medical devices. If the manufacturer does not carry out design and development activity, the same shall be recorded in the quality management system. The manufacturer shall maintain conformity with this Schedule to reflect the exclusions.
- 1.2. If any requirement in paragraph 7 (product realisation) of this Schedule is not applicable due to the nature of the medical device and *in vitro* diagnostic medical devices for which the quality management system is applied, the manufacturer does not need to include such a requirement in its quality management system.
- 1.3. The processes required by this Schedule, which are applicable to the medical device and *in vitro* diagnostic medical device, but which are not performed by the manufacturer are the responsibility of the manufacturer and are accounted for in the manufacturer's quality management system.
- 1.4. If a manufacturer engages in only some operations subject to the requirements of this part, and not in others, that manufacturer need only to comply with those requirements which are applicable to the operations in which it is engaged.
- 1.5. It is emphasized that the quality management system requirements specified in this Schedule are in addition to complementary to technical requirements for products.
- 1.6. Manufacturers of components or parts of finished devices and *in vitro* diagnostic medical devices are encouraged to use appropriate provisions of this schedule as guidance.

**2. Applicability:**

The provisions of this Schedule shall be applicable to manufacturers of finished devices, *in vitro* diagnostic medical devices, mechanical contraceptives (condoms, intrauterine devices, tubal rings), surgical dressings, surgical bandages, surgical staplers, surgical sutures and ligatures, blood and blood components collection bags with or without anticoagulants.

**3. Terms and definitions:**

- 3.1 **Active implantable medical device.-** Active medical device which is intended to be totally or partially introduced, surgically or medically, into the human or animal body or by medical intervention into a natural orifice and which is intended to remain after the procedure.
- 3.2 **Active medical device.-** Medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human or animal body or gravity.
- 3.3 **Advisory notice.-** Notice issued by the manufacturer, subsequent to delivery of the medical device and *in vitro* diagnostic medical devices, to provide supplementary information or to advise what action should be taken in or both in:-
  - (a) the use of a medical device and *in vitro* diagnostic medical devices;
  - (b) the modification of a medical device and *in vitro* diagnostic medical devices;
  - (c) the return of the medical device and *in vitro* diagnostic medical devices to the organization that supplied it; or
  - (d) the destruction of a medical device and *in vitro* diagnostic medical devices.
- 3.4 **Customer complaint.-** Written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device and *in vitro* diagnostic medical devices that has been placed on the market.
- 3.5 **Implantable medical device. -** Medical device intended:-
  - (a) to be totally or partially introduced into the human or animal body or a natural orifice; or
  - (b) to replace an epithelial surface or the surface of the eye;