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Overview on Performance Evaluation / External Evaluation of In vitro Diagnostic Medical Device (IVDMD)

Draft for Public Comment

Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health and Family Welfare
Government of India

Central Drugs Standard Control Organization

(In-Vitro Diagnostic Division)

Guidance Document

Title : Overview on Performance Evaluation / External Evaluation of In vitro Diagnostic Medical Device (IVDMD)

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Notice:

This Guidance document is aimed only for creating public awareness about In-Vitro Diagnostic Devices Regulation by CDSCO and is not meant to be used for legal or professional purposes. The readers are advised to refer to the statutory provisions of Medical Device Rules, 2017 and subsequent amendments and clarifications issued by CDSCO time to time for all their professional needs.

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1. INTRODUCTION

In vitro diagnostic medical devices are used to conduct tests outside of the human body to provide valuable information regarding a person's health or physiological status. They include tests and related devices, such as test strips and reagents, using specimens such as blood, tissue or urine etc., to carry out screening, diagnosis, prognosis, predictive testing, and monitoring of conditions. In-vitro Diagnostics medical devices are regulated under the Medical Devices Rules, 2017 notified by The Ministry of Health and Family Welfare, Government of India under the provisions of the Drugs and Cosmetics Act, 1940. These Rules came into force effective 1st January, 2018 to regulate the manufacture, import, sale and distribution of notified medical devices and In-vitro diagnostics (IVD) medical devices in the country.

Under the said rules, for grant of licence to manufacture or import Class B, Class C or Class D IVDs, applicant required to submit copy of performance evaluation report along with application. As per the proviso of Clause (h), Paragraph (ii), part II of Fourth Schedule of Medical Devices Rules 2017, where in, it is stated that "In case of in-vitro diagnostic medical devices, performance evaluation report by the manufacturer shall be submitted by the applicant. Provided that when the State Licensing Authority specifically requires for Class B or the Central Licence Authority for Class B, Class C and Class D in-vitro diagnostic medical devices, as the case may be, applicant shall submit the report issued by the central medical devices testing laboratory or a medical device testing laboratory registered under rule 83 or by any laboratory accredited by the National Accreditation Board for Testing and Calibration Laboratories or by any hospital accredited by National Accreditation Board for Hospitals and Healthcare Providers or by any Central Government or State Government Laboratory of any hospital or of any institute, specified by the concerned State Licensing Authority or the Central Licensing Authority".

In this regard CDSCO has issued guidance document on "Guidance on Performance Evaluation of In-vitro Diagnostic Medical Devices" dated 07/08/2018 and subsequently revised for updating list of the laboratories dated 07/08/2019, 24.02.2020 and 05.05.2022 and it will be updated in the website of

CDSCO as on when it is required . Accordingly, currently, SLA/ CLA may require the Performance Evaluation Report for the following In-vitro Diagnostics 1.HIV, 2. HBV, 3. HCV, 4. Blood Grouping reagent, 5. Cancer, 6. Tuberculosis, 7. Malaria, 8. Dengue, 9.Chikungunia, 10.Syphlis, 11.Typhoid, 12.Influenza, 13.ToRCH (Toxoplasma gondii, Rubella virus, Cytomegalovirus, Herpes simplex virus) 14.Chlamydia 15.Pneumonia, 16.Methicilline-Resistant Staphylococcus Aureus, 17.Entero virus, 18.Marker for congenital disorder e.g. Screen test for Down's Syndrome 19.Sexually transmitted agent i.e. Treponema pallidum, Neisseria gonorrhoeae, Human Papilloma Virus, Herpes Virus 20.Other life threatening Infections / agent.

Central Medical Device (IVDs) Testing Laboratory:

In pursuance of the powers conferred by sub-rule (2) of rule 19 of the Medical Devices Rules, 2017, the Central Government vide notification S.O. 2237(E) dated 01/06/2018 designated the National Institute of Biologicals, Noida having facilities for carrying out test and evaluation of following Category of medical device (IVDs) In-Vitro Diagnostics for human Immunodeficiency virus, Hepatitis B Surface Antigen and Hepatitis C Virus, Blood Grouping sera, Glucose Test Strip, Fully Automated Analyser Based Glucose Reagent, as Central Medical Device Testing Laboratory for the purposes of —

(a) Testing and evaluation;

(b) Functioning as an appellate laboratory; and

(c) To carry out any other function as may be specifically assigned to it by the Central Government,

2. PURPOSE

IVDs are fundamentally different from other medical devices because they perform their function outside of the body on specimens taken from the human body. Human subjects are typically not exposed to risks with the performance testing of IVD medical devices, except for the risk associated with specimen collection procedures or when they obtained information is used for patient management. The specimens are obtained via normal body functions (e.g. urine) or through the use of invasive medical devices to allow for the specimen to be obtained (e.g. biopsy). The specimens are never reintroduced into the human

body. These differences make the performance and risk characteristics of IVD medical devices different and unique from other medical devices.

To understand the Performance evaluation at Independent / External laboratory of IVDs it must be taken into account that IVD medical devices differ from other medical devices, in that the risks and benefits they pose are related to impact on patient management rather than direct contact between the device and the patient. A significant percentage of all healthcare decisions rely on information provided by clinical laboratory tests and these decisions can profoundly influence diagnosis and management of the patient and will be influenced by the risk to the patient of an incorrect result from the IVDs.

Performance evaluations at Independent / External laboratory are performed using samples resulting from the remnants of specimens taken for purposes of standard of care (leftover or archived). In these studies, there is no risk for the subjects arising from either the information provided by the IVD medical device or from the collection procedure of the specimen. This document is not intended for clinical performance evaluation studies as these studies involve specimens taken from the human body not from leftover or archived specimens.

Performance evaluation at Independent / External laboratory of in vitro diagnostics (IVDs) are required, to verify certain performance claims that are considered essential by which data are assessed and analyzed to demonstrate the performance of IVDs for the intended use as stated by the manufacturer.

The purpose of this guidance is to facilitate the manufacturers/ importers / Testing laboratories of IVDs in our country; this document may also serve to sensitize the interested stakeholders to the concepts of performance Evaluation / External evaluation.

3. SCOPE

This document is applicable to manufacturers/ importers / Testing laboratories of IVDs in India.

4. DEFINITIONS

Definitions that do not indicate they are set out in the Regulations are intended as guidance in this document. These definitions are not taken verbatim from the

above legislation and should not be used in any legal context. These definitions are meant to provide guidance in layman terms.

Central Licensing Authority: Central Licensing Authority means the Drugs Controller General of India appointed by the Central Government;

Licensing Authorities : Licensing Authorities.— The Central Licensing Authority shall be the competent authority for enforcement of MDR 2017 in matters relating to,-

(i) Import of all Classes of IVDs;

(ii) Manufacture of Class C and Class D medical devices;

(iii) Clinical performance evaluation and approval of new in vitro diagnostic medical devices and;

(v) co-ordination with the State Licensing Authorities.

(2) The State Drugs Controller, by whatever name called, shall be the State Licensing Authority and shall be the competent authority for enforcement of MDR2017 in matters relating to,-

(i) manufacture for sale or distribution of Class A or Class B IVDs;

(ii) sale, stock, exhibit or offer for sale or distribution of IVDs of all classes.

Central medical devices testing laboratory: central medical devices testing laboratory means a medical devices including IVD laboratory established or designated by the Central Government under rule 19 of MDR 2017 and shall be deemed to be a Central Drug Laboratory established for the purpose of section 6 of the Act;

(1) The Central Government may, by notification, establish Central medical devices testing laboratory for the purpose of,—

(a) Testing and evaluation of medical devices; or

(b) Functioning as an appellate laboratory; or

(c) To carry out any other function as may be specifically assigned to it.

(2) Without prejudice to sub-rule (1), the Central Government may also designate any laboratory having facility for carrying out test and evaluation of medical devices as central medical devices testing laboratory for the purposes specified in sub-rule (1): Provided that no medical devices testing laboratory, shall be so

designated unless it has been duly accredited by the National Accreditation Body for Testing and Calibration Laboratories.

Medical devices testing laboratory: Medical devices testing laboratory means any institute, organisation registered under sub-rule (3) of rule 83 of MDR 2017 for carrying out testing or evaluation of any medical device including IVDs on behalf of a licencee for manufacture for sale the list of MDTL is available in the CDSCO website;

Performance Evaluation : performance evaluation" in relation to in vitro diagnostic medical device means any systematic investigation by which data is assessed and analysed to establish or verify performance of the in vitro diagnostic medical device for its intended use;

Clinical performance evaluation: clinical performance evaluation means the systematic performance study of a new in vitro diagnostic medical device on a specimen collected from human participants to assess its performance;

Intended purpose: The use for which the device is intended according to the data supplied by the manufacturer on the label, in the instruction for use and/or in the promotional material.

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

Note: Aspects that are considered in the intended use include

- what is detected
- its function (e.g. screening, monitoring, diagnosis or aid to diagnosis);
- the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;
- whether it is automated or not; whether it is qualitative or quantitative;

- the type of specimen(s) required (e.g. serum, plasma, whole blood, tissue biopsy, urine);
- testing population ;
- the intended user (e.g. lay person, highly trained laboratory professional, minimally trained health care worker, self-testing);
- the intended setting of use (e.g. point of care, reference or diagnostic laboratory setting, primary health care setting)

User error: an act or omission of an act, that has a different result to that intended by the manufacturer or expected by the operator of the medical device.

User: the health care institution, professional, patient using or maintaining medical devices.

Lot: "The amount of material that is uniform in its properties and has been produced in one process or series of processes. The material can be either starting material, intermediate material or finished product". Furthermore, lots must be sourced from a representative production run and not produced especially for the purpose of the performance evaluation.

Point-of-Care/ Home Use tests: Point of Care tests are simple, in vitro Diagnostics medical devices that can be performed at the bedside in a hospital setting, at the physician's chamber or at home by the patient. **Examples include:** Glucometer with strips for the estimation of glucose levels in the blood, rapid coagulation tests (PT/INR) , rapid cardiac marker tests, drugs of abuse screening tests, urine strip tests, pregnancy test, fecal occult blood test, food pathogens screening test, hemoglobin test, infectious disease tests and cholesterol screening test amongst others.

Specimen: Discrete portion of a body fluid or tissue taken for examination, study, or analysis of one or more quantities or characteristics to determine the character of the whole

Leftover specimens: unadulterated remnants of human derived specimens collected as part of routine clinical practice and after all standard analysis has been performed. Such specimens/samples would be otherwise discarded as there is no remaining clinical need for them. This can include specimens collected for research or other purposes not connected to the clinical performance study in question.

Archived Specimen: specimen was collected in the past and is obtained from repositories (e.g. tissue banks, commercial vendor collections)

Qualitative tests: qualitative tests are tests that provide information that can not actually be measured. They provide information in the form of 'yes' (positive) or 'no' (negative) results.

e.g. ELISA and rapid card tests for HIV, HCV, HBsAg, Malaria, Dengue etc.

Quantitative tests: quantitative tests provide information about quantities; that is, information that can be measured in numbers.

e.g.: End point or kinetic biochemistry tests, Complete Blood Count etc.

In vitro diagnostic (IVD) : A device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software and related instruments or apparatus or other articles.

Clinical sensitivity: The number of true positive specimens identified by a given assay as positive divided by the number of specimens identified by the reference assays as positive, expressed as a percentage.

$$\text{Sensitivity (\%)} = \frac{\text{True Positives}}{\text{True Positives + False Negatives}} \times 100$$

Clinical specificity: The number of true negative specimens identified by a given assay as negative, divided by the number of specimens identified by the reference assays as negative, expressed as a percentage.

$$\text{Specificity (\%)} = \frac{\text{True Negatives}}{\text{True Negatives + False Positives}} \times 100$$

Reference standard: The best available method for establishing the presence or absence of the target analyte; the reference standard can be a single test or method, or a combination of methods and techniques, including clinical follow-up.

Diagnostic accuracy: The extent of agreement between the outcome of the IVD's tested and the reference standard

False negative result: A negative test result for a specimen in which the target analyte is present (as determined by the designated reference standard).

False positive result: A positive test result for a specimen in which the target analyte is absent (as determined by the designated reference standard).

True negative result: A negative test result for a specimen in which the target analyte is absent (as determined by the designated reference standard).

True positive result: A positive test result for a specimen in which the target analyte is present (as determined by the designated reference standard).

Component: Any raw material, substance, piece, part, software, firmware, labelling, or assembly which is intended to be included as part of the finished, packaged, and labelled device.

Confidence intervals: The 95% confidence intervals are calculated for both sensitivity and specificity in order to assess the level of uncertainty introduced by

sample size, etc. Exact 95% confidence intervals for binomial proportions were calculated from the F-distribution.

Prevalence: The frequency of a condition of interest at a given point in time expressed as a fraction of the number of individuals in a specified group with the condition of interest compared to the total number of individuals (those with the condition plus those without the condition of interest) in the specified group; pretest probability of the condition of interest in a specified group

Positive predictive value (PPV) :

The probability that when the test is reactive that the specimen does contain target analyte. PPVs were calculated using the formula.

$$PPV = \frac{(\text{prevalence})(\text{sensitivity})}{(\text{prevalence})(\text{sensitivity}) + (\text{prevalence})(1 - \text{sensitivity})}$$

Negative predictive value (NPV):

The probability that when the test is negative that a specimen does not have contain target analyte. NPVs were calculated using the formula.

$$NPV = \frac{(1 - \text{prevalence})(\text{specificity})}{(1 - \text{prevalence})(\text{specificity}) + (\text{prevalence})(1 - \text{sensitivity})}$$

The probability that a test result will accurately determine the true infection status of a person being tested varies with the prevalence of infection in the population from which the person comes. In general, the higher the prevalence of infection in the population, the greater the probability that a person testing positive is truly infected (i.e., the greater the positive predictive value [PPV]). Thus, with increasing prevalence, the proportion of individuals testing false-positive decreases; conversely, the likelihood that a person whose test result is negative is truly uninfected (i.e., the negative predictive value [NPV]), decreases as

prevalence increases. Therefore, as prevalence increases, so does the proportion of individuals testing false-negative.

The PPV and NPV are calculated at prevalences of 0.1%, 1% and 5%.

5. Testing Facilities

The laboratory premises shall be air conditioned so as to maintain the accuracy and functioning of laboratory instruments or to enable the performance of special tests such as, microbiological tests, etc; The laboratory shall provide adequate space having regard to the nature and number of samples of IVDs proposed to be tested and evaluated: Provided that the HOD shall determine from time to time whether the space provided continues to be adequate;

The laboratory shall provide and maintain suitable equipment having regard to the nature and number of samples of IVDs intended to be tested which shall be adequate in nature. The testing and evaluation of IVDs shall be under active direction of a person whose qualification and experience is considered adequate and who shall be held responsible for reports of test or evaluation issued. The laboratory shall provide standards recognised under the provisions of the Drugs and cosmetic and MDR 2017 and such standards of reference as may be required in connection with the testing or evaluation of the IVDs for the testing of which approval has been applied for.

To fulfil the tasks of testing IVDs, laboratory may employ / utilizes required scientists, technicians. Laboratory may ensure it has all necessary equipment and analysis machines are available for the testing of IVDs: For the testing of the IVDs, laboratory may require reference materials and international standards for the specified markers:

In addition, laboratory may require a considerable number of commercially available sample panels and own characterized samples which are used for performance assessment and the testing of specified IVDs.

6. Responsibility of Testing laboratory:

- ✓ Laboratory may provide and maintain necessary qualified staff, adequate premises and equipment;

- ✓ Laboratory may provide proper facilities for storage so as to preserve the properties of samples picked up for testing;
- ✓ Laboratory should maintain records of tests for evaluation and performance carried out on all samples of medical devices and the results thereof together with protocols of tests and the reports showing readings and calculations and such records shall be retained, in case of substances for which an expiry date is assigned, for a period of two years beyond the expiry date, and in the case of other substances, for a period of six years;
- ✓ Laboratory shall allow the medical device officer appointed under Drugs and cosmetics Act to enter, with or without prior notice, the premises where the testing is carried out and to inspect the premises and the equipment used for test and the testing procedures employed.
- ✓ Laboratory shall allow the medical device officer to inspect records maintained and shall make available such information as may be required for ascertaining whether the provisions of the Drugs and cosmetics Act
- ✓ Laboratory shall inform forthwith, any change of existing expert staff or person-in-charge of the testing or evaluation to the Central Licensing Authority
- ✓ In case, any sample of a IVDs is found on test, to be not of standard quality, HOD of the testing laboratory shall furnish a copy of the test or evaluation report on the sample with the protocols of tests applied to the concerned Licensing Authority;

7. Safety

HIV, hepatitis B and hepatitis C and other viruses are transmissible by blood and body fluids. Therefore, all types of specimens must be handled as potentially infectious. Appropriate precautions to minimize infectious hazards must be taken at all stages from the collection of specimens to the disposal of used materials from the laboratory. The applicable Guidelines on Safety Precautions and Guidelines should be strictly adhered to by the laboratory staff.

8. Procedure for dispatch of sample to testing laboratory

The sample of IVDs shall be sent by registered post or by courier or by hand in a sealed packet, enclosed with a covering letter along with necessary documents,

in an outer cover addressed to the HOD, of the testing laboratory. A copy of covering letter may be endorsed or acknowledged.

9. Procedure to be adopted by testing laboratory on receipt of sample.

On receipt of the sample package of IVDs, from a person for test or evaluation, testing laboratory shall note the condition of the sample package. After completion of test or evaluation, the testing laboratory shall forthwith furnish a report to the concerned authorised person. Samples of IVDs may be submitted by the Manufacturers or Importers or CDSCO or SLA. They are received by concerned laboratory through Sample Receipt. The samples are then sent to the IVD Laboratory for Quality Control evaluation.

A. PROCEDURE FOR RECEIVING THE SAMPLE IN THE LABORATORY

1. It is noted whether the cold chain has been maintained wherever it is required for a sample.

2. The samples are physically examined and the following details are documented in the 'Sample receipt register' of the laboratory.

Date of receiving in the laboratory

- Name /type of the sample
- Lot/ Batch No. and expiry of the IVDs
- Pack size
- No. of Test Strips submitted
- No. of instrument submitted and whether they are in working condition (if applicable)
- Details of manufacturer's 'Controls' preparation

3. Any deficiencies noted regarding 'sample submission' is intimated to the concerned person with the request to have the requirement fulfilled so as to enable the laboratory to initiate testing.

B. STORAGE BEFORE TESTING

1 .IVD and the components received are stored at recommended temperature.

2. Only those samples which are under testing/ planned for testing are stored in the laboratory.

C. STORAGE AFTER TESTING

1. Leftover IVDs are stored under stipulated storage conditions in the 'Store Room'.

2. Leftover manufacturer's Controls if any are stored in the designated place in the laboratory at recommended temperature.

D. CRITERIA FOR ACCEPTANCE OF SAMPLES

1. Type of Sample: IVD designed for use with specific Instrument as a closed system

2. Condition of Packing: IVD should be packed in properly labeled sealed containers that give the details of the manufacturer and/ or the importer

3. Number of Samples Essential: As specified by the laboratory for testing one Batch by the Laboratory

4. Accessories Required: As required by the laboratory

5. Manufacturer's Normal/ Level I and Pathological/ Level II control Solution for testing one batch of IVD where ever applicable.

6. Documents Required: Documents to be submitted as per check list at **Annexure-1**

10. Storage of Products:

All reagents must be stored as indicated in the instructions for use / labels. Some products may not need refrigeration. If refrigerated storage space is inadequate to store the entire test kit, they may be divided such that labile reagents can be refrigerated separately from the non-labile supplies. Calibrated thermometers or other environmental monitoring devices are placed at each location where reagents and specimens are stored, i.e. ambient, refrigerator and freezer. Temperatures are recorded daily.

11. Performance evaluation testing:

i. Performance specimen reference panel:

Testing laboratory will receive and store samples from collecting sites, perform sample characterization, and test products submitted.

Collection of specimens for performance evaluation panel :-

Specimens are collected as serum or plasma (with appropriate anti-coagulant) from patients suspected or confirmed to have target pathogens or from the blood

bank (mainly for negative specimens). Where clinical information is available, this should be captured.

Newly collected specimens are assigned a unique identification number at the collection site and then assigned with a Lab specimen identification number upon arrival at the testing laboratory. The specimens are processed and aliquoted into working volumes of 250µl and stored at -20^{o}C or -80^{o}C until testing commences. During the testing period, the specimens are stored at 2 to 8 °C and this time period does not exceed one week. After the completion of testing, they are again stored at -20^{o}C or -80^{o}C. The number of freeze/thaw cycles for each specimen should be within the number specified in the manufacturer's Instructions for Use, or where not specified then no more than 5 freeze-thaw cycles. Where a false reaction is identified during evaluation then an unused aliquot should be used for retesting

ii. Characterization of the performance evaluation panel:-

The laboratory performance evaluation panel must be characterized for presence or absence of target analyte by using reference standard / product /method.

iii. Seroconversion panels

A seroconversion panel is a series of specimens, sequentially collected over a period of time, from an individual developing antibody in response to acute infection. The assay under evaluation may also be tested using the commercial seroconversion panel, where ever applicable;

iv. WHO / International reference preparations

Where ever applicable, testing laboratory may evaluate the IVDs using WHO / International reference preparations the assay under evaluation in singular on one lot.

12. Laboratory testing

Each product under evaluation is used strictly in accordance with the instructions for use (IFU) issued by the manufacturer. The IFU submitted must be same as part of the dossier assessment for the product license.

13. Supplies

The manufacturers / Importer of products will provide the products and any equipment necessary for the evaluation free of charge.

14. Recording test results and interpretation of test results:

All test results are recorded on standardized test result worksheets and then entered Report template for a simple/rapid assays for further data analysis as shown in Table 1 below. Visual interpretation of results of subjectively read assays is made independently by operator and two more readers (without the knowledge of the others' sets of results) and entered into the data collection sheets. When the three readers interpret the results differently from each other, the consensus is recorded as that interpretation which occurs two out of three times.

Table 1 - Results legend for data collection sheets for subjectively read assays

Scoring index	RDT results
0	Non-reactive
1	Reactive (Very weak band)
2	Reactive (Medium to Strong Band)
7	Debris/invalid

The following parameters will also be recorded by the concerned analyst

- Results of control and test lines are recorded as negative or positive by each technician.
- Where control line is very weak (+1 on band intensity template), this should be recorded in notes section.
- Marked abnormalities or issues affecting interpretation, such as poor blood clearance, should be recorded in notes section.
- Absent Control Lines: If control line is recorded as absent by either technician ('Invalid test result'), the test is recorded as invalid by that technician. (In such cases, the result is not included in calculation of detection rates during later analysis).

i. Test kit controls

When available, manufacturer-supplied positive and negative test kit controls will be run as indicated in the IFU for all test formats at the commencement of each testing session. Where positive and negative test kit controls are not supplied by the manufacturer, as will be the case for many rapid diagnostic tests, the laboratory will provide an in-house quality weakly reacting control specimen.

ii. Internal control lines for POCTs

Generally, most POCTs contain a control band, line or spot to determine that the test device is operating correctly. Most control bands/lines/spots will become visible with the addition of reagent (i.e. buffer). However, some POC tests will contain a control band/line/spot that becomes visible with addition of specimen. It is imperative that the exact nature of the control band/line/spot is ascertained and recorded in the report. An experiment using distilled water instead of specimen is performed to verify this point, if not explicitly mentioned in the IFU.

iii. Interpretation of results

The interpretation of results for each assay under evaluation is made strictly according to the manufacturers' instructions as described in the IFU. Invalid test results are recorded on the data collection sheets including where the control line does not appear or in any other way the test result is invalid as defined by the IFU.

15. Acceptance criteria /standards

Performance evaluation of the IVDs shall be based upon testing of various applicable parameters, their acceptance criteria and interpretation.

- ✓ As per the rule 7 of MDR 2017, IVDs shall conform to the standards laid down by the Bureau of Indian Standards established under section 3 of the Bureau of Indian Standards Act, 1985 (63 of 1985)

or

- ✓ As may be notified by the Ministry of Health and Family Welfare in the Central Government, from time to time.

or

- ✓ Where no relevant Standard of any IVDs such IVDs shall conform to the standard laid down by the International Organisation for Standardisation (ISO) or the International Electro Technical Commission (IEC), or by any other pharmacopoeial standards or

or

- ✓ In case of the standards which have not been specified above the device shall conform to the validated manufacturer's standards.

List of Currently available Product standards / specifications at **Annexure- 5**

16. Cost effectiveness

Testing fee may be calculated by the testing lab in such a way that they cover the expenses subject to market conditions. Laboratories are advised not operate in a profit-oriented manner and is treated as a public safety and on the government theme of Make in India and Easy of doing business angle.

17. Training and supervision

The following issues are key to minimizing error and maximizing the value of evaluation:

- The HOD will be responsible for training the laboratory technicians in the evaluation protocol and in the performance of each assay undergoing evaluation;
- Only those personnel who have received specific training for this evaluation will be employed in the evaluation;
- Accurate record keeping is crucial to the success of the evaluation and the HOD will be responsible for ensuring that all data required for the evaluation are properly recorded on the data collection sheets, and are accurate and up to date;
- It is important to plan work in advance and follow standard operating procedures as prepared and controlled by the Evaluating Laboratory;
- To reduce the risk of adding an incorrect specimen to a test device/well, before starting the test run, the operator will prepare worksheets and label all tubes, dilution vessels, test devices or plates with the specimen's unique number;
- Because objective, machine-generated, permanent results for simple/rapid diagnostic tests are not feasible, it is essential that the HOD emphasizes to the operator performing the tests the need for accurate recording of results and recordkeeping;
- To minimize the risk of error, it is recommended that the results are read and recorded independently by three trained staff members;
- To allow immediate correction of erroneous recording of results (rather than differences in visual interpretation), the HOD or designee should assess the

results as soon as possible to allow him to return to the original test device to investigate apparently discordant readings;

- For the investigations performed at the Evaluating Laboratory at least one representative result from both positive and negative specimens and all discrepant and/or unexpected results will also be recorded by taking electronic images.
- To minimize the risk of error, results will be directly exported from the platform wherever possible. If this is not the case, results should be entered by one staff member and verified by another.

18. Turnaround Time for testing:

A batch shall be tested within 20 working days from the date of receipt of sample in the laboratory.

19. Retention of samples and Report:

A sample from the IVD lot may be retained by the laboratory as retained sample where ever required. One copy of Test Report will be retained by Sample Receipt and in archives.

20. Administrative Review:

The Reports shall be submitted for Administrative Review to QA department.

21. Disposal of Samples and retention of Reports:

Samples shall be retained under specified condition by the laboratory up to one year after the date of expiry after which they will be disposed as per the procedures of the 'Waste Disposal Committee'. Reports/ documents shall be retained in Archives as per SOP of laboratory.

ANNEXE 1

CHECK LIST OF DOCUMENTS

Documents required to be submitted along with batch of sample for Quality Control evaluation-

1. Forwarding letter from the Importer / manufacturer / Authorized official(s) of CDSCO/ Zonal, Sub zonal and Port offices etc.
2. Product Inserts
3. Quality Control Protocols specific for the product.
4. Batch specific Certificate of Analysis and Quality Control Test Results.
5. Batch Release Certificate from the country of origin of product.
6. Copy of Import License/ test license/ manufacturing license issued by the concerned licensing authority

ANNEXE 2

Name and address of the laboratory

(name of Section / department)

E-mail :---------- Website: ----------

SAMPLE RECEIPT

Dated the _____

Name & Ref. No. of Forwarding Authority:_____

_____

_____

Date & Time of Receipt _____

Lab Ref. No: _____

(Office use only) (Office use only)

ENCLOSURE DETAILS	AVAILABLE OR NOT AVAILABLE	MANUFACTURER/ IMPORTER /SUPPLIER DETAILS
1. PRODUCT INFORMATION (AVAILABLE/NOT AVAILABLE) 2. TECHNICAL DOSSIER (AVAILABLE/NOT AVAILABLE) **3. PRODUCT PROTOCOL** (AVAILABLE/NOT AVAILABLE) 4. copy of the manufacturing or Import or Test license under which the sample is imported or manufactured *		

*__Applicable for sample received from manufacturer or Importer or Port office of CDSCO__

PRODUCT DETAILS	***OTHER DETAILS***
4. INDIGENOUS PRODUCT **5. IMPORTED PRODUCT** **6. IMPORTED BULK** **7. LEGAL SAMPLE** **8. FIELD SAMPLE**	9. SEAL CONDITION (WHETHER INTACT OR NOT) 10. COLD CHAIN REQUIRED: **(YES / NO)** **11. WHETHER COLD CHAIN MAINTAINED:** **(YES / NO) [ICE PACK/DRY ICE/OTHERS]**

TESTING FEE DETAIL

S.NO	DD NO.	***DATE***	***AMOUNT***	***BANK DETAIL***

SAMPLE(S) DETAIL

S. NO.	BRIEF DETAILS OF SAMPLES/PRODUCTS	LOT / BATCH NO.	QUANTITY REQUIRED	QUANTITY RECEIVED (Number of Kits/Number of Tests)	DATE OF	
					MFG.	EXPIRY
1.						

Name & Signature of Authorized
Officials receiving the Sample(s)

Received on behalf of the Manufacturer/Supplier
(Name & Signature of authorized person with date)

- E-mail of Authorized person to whom reports will be sent:- _____
- Phone No. / Mobile No. _____

ANNEXE 3

Name and address of the laboratory

(name of Section / department)

E-mail :---------- Website: ----------

Dated the _____

TO

_____
_____
_____
_____
_____
_____

Reference No.

PLEASE FURNISH THE FOLLOWING DOCUMENTS:

Any further information, if required, shall be asked for subsequently.

1.

2.

Signature of Officer in-charge

ADDERESS FOR CORRESPONDENCE:

Name and Designation of the Head of the laboratory

Address of the laboratory

Phone:

FAX:------- E-mail---------- Website : ----------

For all correspondences please quote LAB file reference number

NOTE:

1. TESTING OF SAMPLES WILL BE DEFERRED IF PROTOCOL OR OTHER DOCUMENTS NOT RECEIVED OR INCOMPLETE DOCUMENTS RECEIVED OR CLARIFICATIONS PENDING.
2. DESPATCH OF FINAL TEST REPORTS WILL BE WITHHELD IF TESTING CHARGES NOT RECEIVED.

LAB WORKING HOURS: ------- A.M. –---------- P.M.

(ALL WORKING DAYS FROM MONDAY TO FRIDAY)

ANNEXE 4

(Laboratory letterhead)

F.No :

Dated:

CERTIFICATE OF ANALYSIS

Name of the product (Brand /generic):	
Name and address of the legal manufacturer:	
Name and address of the actual manufacturing site	
Name and address of the Importer:	
Name of supplier: Manufacturer/Importer/Port office of CDSCO/State licensing Authority	
Lot No / Batch No.:	
Product Reference No/ Catalogue No	
Type of Assay:	
Kit components:	
Manufacturing Date:	
Expiry Date:	
Pack size(Number of test per kit)	
Intended Use	
Number of Tests Received:	
Regulatory Approval: Import license / Manufacturing license/Test license License Number: Issue date: Valid Up to:	
Reference standard / product:	
Instrument Details:	
Controls: Negative control Low positive control (L) High Positive Control (H)	
Samples /Panel used Negative Low Positive sample (Bacteria/viral load) Medium Positive sample (Bacteria/viral load) High Positive sample (Bacteria/viral load)	**Number**
Test performed: **Negative Samples /Panel** 1	**Results obtained**

2 3….. **Low Positive sample (Bacteria/viral load)** 1 2 3…… **Medium Positive sample (Bacteria/viral load)** 1 2 3…… **High Positive sample (Bacteria/viral load)** 1 2 3	

Calculation:

Clinical sensitivity:

$$\text{Sensitivity (\%)} = \frac{\text{True Positives}}{\text{True Positives + False Negatives}} \times 100$$

Clinical specificity:

$$\text{Specificity (\%)} = \frac{\text{True Negatives}}{\text{True Negatives + False Positives}} \times 100$$

Positive predictive value (PPV) :

$$\text{PPV} = \frac{\text{(prevalence) (sensitivity)}}{\text{(prevalence) (sensitivity) + (prevalence) (1- sensitivity)}}$$

Negative predictive value (NPV):

$$\text{NPV} = \frac{\text{(1 - prevalence) (specificity)}}{\text{(1 - prevalence) (specificity) + (prevalence) (1- specificity)}}$$

(1 - prevalence) (specificity) + (prevalence) (1- sensitivity)

Accuracy = (True Negatives + True Positives)

(True Negatives + True Positives + False Negatives + False Positives)

Results:

S.No	Testing parameter	Criteria / specification	Result obtained	Remark

Conclusion:

Signature of the Analyst
Name:
Designation:
Date:

Signature of the Lab. Head
Name:
Designation:
Date:

ANNEXE 5

List of Currently available Product standards / specifications:

Product	Technology	Specification/criteria	Reference
Anti-HIV-1/2 and / or HIV-1 p24Ag	ELISA/CLIA/ELFA/ECLIA/CMIA/MEIA, RAPID	Sensitivity 100% Specificity ≥ 98%	CDSCO/NIB Experts committee Recommendation F.No.29/Misc/4/2016-DC(65) dated 13/06/2017
HIV	Molecular Diagnostic kit	Sensitivity 100% Specificity 100% #Accuracy: Variation between the test and assigned value should be within ± 0.5 log for at least 80% of samples tested.	CDSCO/NIB Experts committee Recommendation F.No.29/Misc/4/2016-DC(65) dated 21/02/2019
HBsAg	ELISA/CLIA/ELFA/ECLIA/CMIA/MEIA, RAPID	Sensitivity 100% Specificity ≥ 98%	CDSCO/NIB Experts committee Recommendation F.No.29/Misc/4/2016-DC(65) dated 13/06/2017
HBV	Molecular Diagnostic kit	Sensitivity 100% Specificity 100% #Accuracy: Variation between the test and assigned value should be within ± 0.5 log for at least 80% of samples tested.#	CDSCO/NIB Experts committee Recommendation F.No.29/Misc/4/2016-DC(65) dated 21/02/2019
Anti-HCV	ELISA	Sensitivity 100% Specificity ≥ 98%	CDSCO/NIB Experts committee Recommendation F.No.29/Misc/4/2016-DC(65) dated 13/06/2017
	RAPID	Sensitivity ≥99% Specificity ≥ 98%	
HCV	Molecular Diagnostic kit	Sensitivity 100% Specificity 100% #Accuracy: Variation between the test and assigned value should be within ± 0.5 log for at least 80% of	CDSCO/NIB Experts committee Recommendation F.No.29/Misc/4/2016-DC(65) dated 21/02/2019

		samples tested.#	
Syphilis	ELISA, RAPID	Sensitivity ≥ 85% Specificity ≥ 93%	CDSCO/NIB Experts committee Recommendation F.No.29/Misc/4/2013-DC(52) dated 14/02/2014
Blood Glucose Test Strips	Test Strips	Conform to IS/ISO 15197:2013	IS/ISO 15197:2013
Malaria Antigen Detection of Pf / Pv (Plasmodium falciparum / Plasmodium vivax)	RAPID	1. For the detection of Pf / Pv in all transmission settings the panel detection score (PDS) should be at least 75% at 200 parasite/µL. 2. False positive rate should be less than 10% 3. The invalid rate should be less than 5%	WHO Recommendation -Good practices for selecting and procuring rapid diagnostic tests for malaria 2012

 # Applicable for Quantitative Molecular Diagnostic Kits

Specifications for Anti-A (Monoclonal) Blood grouping reagent as per Transfusion Medicine Technical Manual (2003), IP 2010

S.No.	Test(s) Conducted	Test RBC	Specification
1.	Titre	A1 A2 A2B	≥ 1:256 ≥ 1:128 ≥ 1:64
2.	Avidity (Sec) /Intensity	A1 A2 A2B	3-4 Sec/3+ 5-6 Sec/2+ to 3+ 5-6 Sec/3+ to 4+
3.	Specificity	A1 A2 A2B B O	Positive Positive Positive Negative Negative
4.	Rouleaux	B O	Absent Absent
5.	Haemolysis	A1 A2 A2B B	Absent Absent Absent Absent

		O	Absent
6.	Prozone	A1 A2 A2B	Absent Absent Absent
7.	Physical Appearance and Colour	Clear and Blue Colored liquid	

Specifications for Anti-B (Monoclonal) Blood grouping reagent as per Transfusion Medicine Technical Manual (2003), IP 2010

S.No.	Test(s) Conducted	Test RBC	Specification
1.	Titre	B A1B	≥ 1:256 ≥ 1:128
2.	Avidity (Sec) /Intensity	B A1B	3-4 Sec/4+ 5-6 Sec/2+ to 3+
3.	Specificity	B A1B A1 O	Positive Positive Negative Negative
4.	Rouleaux	A1 O	Absent Absent
5.	Haemolysis	B A1B A1 O	Absent Absent Absent Absent
6.	Prozone	B A1B	Absent Absent
7.	Physical Appearance and Colour	Clear and Yellow colored liquid	

Specifications for QC Tests on Anti-AB (Monoclonal) Blood grouping reagent as per Transfusion Medicine Technical Manual (2003), IP 2010

S.No.	Test(s) Conducted	Test RBC	Specification
1.	Titre	A1 A2 B	≥ 1:256 ≥ 1:128 ≥ 1:256
2.	Avidity (Sec) /Intensity	A1 A2 B	3-4 Sec/4+ 5-6 Sec/ 3+ 3-4 Sec/4+
3.	Specificity	A1	Positive

		B A2 Ax O	Positive Positive Positive Negative
4.	Rouleaux	O	Absent
5.	Haemolysis	A1 B A2 Ax O	Absent Absent Absent Absent Absent
6.	Prozone	A1 B A2	Absent Absent Absent
7.	Physical Appearance and Color	Clear and Colorless/Cherry Red colored liquid	

Specifications for QC Tests on Anti-D (IgM) Monoclonal Blood grouping reagent as per Transfusion Medicine Technical Manual (2003), IP 2010

S.No.	Test(s) Conducted	Test RBC	Immediate Spin	37oC at 30”
1.	Titre	O+ve(R1r) Or O+ve (R1R2)	1:64 – 128 1:64 – 128	1:128 – 256 1:128 – 256
2.	Avidity (Sec) /Intensity	O+ve(R1r) Or O+ve (R1R2)	5-10 Sec/3+ 5-10 Sec/3+	
3.	Specificity	O+ve(R1r) or O+ve (R1R2) O neg • rr or • r’r or • r”r	Positive Positive Negative	
4.	Rouleaux	O neg • rr or • r’r or • r”r	Absent	
5.	Haemolysis	O+ve(R1r) or O+ve (R1R2) O neg	Absent Absent Absent	

		• rr or • r'r or • r"r	
6.	Prozone	O+ve(R1r) Or O+ve (R1R2)	Absent Absent
7.	Physical Appearance and Colour	Clear and Colorless liquid	

Specification for QC Tests on Anti-D (IgM + IgG) Monoclonal Blood grouping reagent as per Transfusion Medicine Technical Manual (2003), IP 2010

S.No.	Test(s) Conducted	Test RBC	Immediate Spin	37oC
1.	Titre	O+ve(R1r) Or O+ve (R1R2)	1:32 – 64 1:32 – 64	1:128 – 256 1:128 – 256
2.	Avidity (Sec) /Intensity	O+ve(R1r) Or O+ve (R1R2)	10-20 Sec/3+ 10-20 Sec/3+	
3.	Specificity	O+ve(R1r) or O+ve (R1R2) O neg • rr or • r'r or • r"r	Positive Positive Negative	
4.	Rouleaux	O neg • rr or • r'r or • r"r	Absent	
5.	Haemolysis	O+ve(R1r) or O+ve (R1R2) O neg • rr or • r'r or • r"r	Absent Absent Absent	
6.	Prozone	O+ve(R1r) Or O+ve (R1R2)	Absent Absent	

7.	Physical Appearance and Colour	Clear and Colorless liquid

Specifications for QC Tests on Anti-AB (Monoclonal) Blood grouping reagent as per Transfusion Medicine Technical Manual (2003), IP 2010

S.No.	Test(s) Conducted	Test RBC	Specification 37°C for 30"
1.	Titre	O+ve(R1r) and O+ve (R0 r)	≥ 1:256 ≥ 1:128 ≥ 1:256
2.	Specificity	O+ve(R1r) and O+ve (R0r) O neg rr or r'r or r''r	Positive Positive Negative
3.	Rouleaux	O neg rr or r'r or r''r	Absent
4.	Haemolysis	O+ve(R1r) and O+ve (R0r) O neg rr or r'r or r''r	Absent Absent Absent
5.	Physical Appearance and Color	Clear and Straw Colored liquid	

Specifications for QC Tests on Anti-A_1 (Lectin) Blood grouping reagent as per NIB data and experts recommendations

S.No.	Test(s) Conducted	Test RBC	Specification

1.	Titre	A1(2) A1B (2)	≥ 1:8 (1+) ≥ 1:4(+)
2.	Intensity	A1(2)	2-3 + (within 2")
3.	Specificity	A1(2) A1B(2) A2(2) A2B(2) B(2) O(2)	Positive Positive Negative Negative Negative Negative
4.	Rouleaux	A2(2) A2B(2) B(2) O(2)	Absent Absent Absent Absent
5.	Haemolysis	A1(2) A1B(2) A2(2) A2B(2) B(2) O(2)	Absent Absent Absent Absent Absent Absent
6.	Prozone	A1(2) A1B (2)	Absent Absent
7.	Physical Appearance	Clear	

Specifications for QC Tests on Anti- H (Lectin) Blood grouping reagent as per NIB data and experts recommendations

S.No.	Test(s) Conducted	Test RBC	Specification
1.	Titre	O(2) A_2 (2) A_1 (2)	≥ 1:8 (1+) ≥ 1:4(+) ≥ 1:1 – 1:2 (1+)
2.	Avidity (sec) / Intensity	O(2) A2 (2) A1 (2)	Strong 2 + to 4 + (within 3") 2+ (within 3") <2+ (within 3")
3.	Specificity	O(2) A2 (2) A1 (2) Oh(2)	Positive Positive Weak Positive Negative
4.	Rouleaux	Oh(2)	Absent
5.	Haemolysis	O(2) A2 (2) A1 (2)	Absent Absent Absent

		Oh(2)	Absent
6.	Prozone	O(2) A2 (2)	Absent Absent
7.	Physical Appearance and Colour	Clear	