F36B NR Minimal Requirements for the Content of the Technical files of In Vitro Diagnostic Medical Devices according to the IVDR

0/ ADMINISTRATIVE REQUIREMENTS
Name and address of the Manufacturer (must be consistent on the label, in the instructions for use and in the EU Declaration of conformity).
Name and address of Notified Body
Name and address of EU Authorised Representative
Contract with EU Authorised Representative
Company profile
Certificates
Identification of technical documentation (number, date of issue, revision)
Revision history
Manufacturer´s declarations
1/ IVD MD DESCRIPTION AND SPECIFICATION, INCLUDING VARIANTS AND ACCESSORIES
1.1/ IVD MD description and specification
Name or trade name of in vitro diagnostic medical device (IVD MD) (state name (names) of IVD MD as mentioned on IVD MD label and related documents).
General description of IVD MD
EMDN code
Basic UDI-DI (according to Part C of Annex VI).
Intended purpose of the IVD MD (according to Section 1.1 c) of Annex II). i. what is to be detected and/or measured; ii. its function such as screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic; iii. the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate; iv. whether it is automated or not; v. whether it is qualitative, semi-quantitative or quantitative; vi. the type of specimen(s) required; vii. where applicable, the testing population; viii. the intended user; ix. in addition, for companion diagnostics, the relevant target population and the associated medicinal product(s).
Description of the principle of the assay method or the principles of the operation of the instrument
Rationale for the qualification of the product as an IVD MD
Classification (risk class) of the IVD MD and the justification for the classification rules applied (in accordance with Annex VIII).
Conformity assessment procedure
Description of the components and where appropriate, the description of the reactive ingredients of relevant components (e. g. antibodies, antigens, nucleic acid primers).
Description of the specimen collection and transport materials provided with the IVD MD or description of specifications recommended for use.
For the instrument of automated assays: the description of the appropriate assay characteristics or dedicates assays.
For automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation.
Description of any software to be used with the IVD MD
Description or complete list of the various configurations/variants of the IVD MD that are intended to be made available on the market.
Description of the accessories for a IVD MD, other IVD MDs and other products that are not IVD MDs, which are intended to be used in combination with the IVD MD.

1.2/ Reference to previous and similar generations of the IVD MD
Overview of the previous generation or generations of the IVD MD produced by the manufacturer, where such IVD MDs exist.
Overview of identified or similar IVD MDs available on the Union or international markets, where such IVD MDs exist.
2/ INFORMATION TO BE SUPPLIED BY THE MANUFACTURER
Complete set of the label or labels on the device and on its packaging, such as single unit packaging, sales packaging, transport packaging in the case of specific management conditions, in the languages accepted in the Member States where the IVD MD is envisaged to be sold.
Complete set of the Instructions for use in the languages accepted in the Member States where the IVD MD is envisaged to be sold.
3/ DESIGN AND MANUFACTURING INFORMATION
Description of the critical components of the IVD MD such as antibodies, antigens, enzymes and nucleic acid primers provided or recommended for use with the IVD MD.
For instruments it is a description of major subsystems, analytical technology such as operating principles and control mechanisms, dedicated computer hardware and software.
Overview of the entire system for instruments and software
For software it is a description of the data interpretation methodology, namely the algorithm.
For IVD MDs intended for self-testing or near-patient testing it is a description of the design aspects that make them suitable for self-testing or near-patient testing.
Information to allow the manufacturing processes such as production, assembly, final product testing, and packaging of the finished IVD MD to be understood. More detailed information shall be provided for the audit of the quality management system or other applicable conformity assessment procedures.
Identification of all sites, where manufacturing activities are performed, including suppliers and sub-contractors.
4/ GENERAL SAFETY AND PERFORMANCE REQUIREMENTS
General safety and performance requirements according to Annex I, that are applicable to the IVD MD taking into account its intended purpose, and shall include a justification, validation and verification of the solutions adopted to meet those requirements, including: - justification of (non) applicability of each general requirement; - method or methods used to demonstrate conformity with each applicable general safety and performance requirement; - reference to applied common specifications („CS“), harmonised standards or parts thereof (specific reference to the applied date of issue) or other solutions applied; - reference to controlled documents and records as evidence of demonstrate of conformity with each harmonised standard, CS or other method applied to demonstrate conformity with the general safety and performance requirements. The information referred to under this point shall incorporate a references to the location of such evidence within the full technical documentation.
5/ BENEFIT-RISK ANALYSIS AND RISK MANAGEMENT
The benefit-risk analysis (as referred to in sections 1 and 8 of Annex I) and solutions adopted and the results of the risk management referred to in Section 3 of Annex I.
Manufacturers shall establish, implement, document and maintain a risk management system Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a IVD MD, requiring regular systematic updating. In carrying out risk management manufacturers shall: a) establish and document a risk management plan for each IVD MD; b) identify and analyse the known and foreseeable hazards associated with each IVD MD; c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse; d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4;

e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, the benefit-risk ratio and risk acceptability;
f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of Section 4.

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

a) eliminate or reduce risks as far as possible through safe design and manufacture;
b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and
c) provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users.

Manufacturers shall inform users of any residual risks.

In eliminating or reducing risks related to use error, the manufacturer shall:

a) reduce as far as possible the risks related to the ergonomic features of the IVD MD and the environment in which the IVD MD is intended to be used (design for patient safety), and
b) give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).

The characteristics and performance of IVD MD shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the IVD MD, as indicated by the manufacturer, when the IVD MD is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.

IVD MDs shall be designed, manufactured and packaged in such a way that their characteristics and performance during their intended use are not adversely affected during transport and storage, for example, through fluctuations of temperature and humidity, taking account of the instructions and information provided by the manufacturer.

All known and foreseeable risks, and any undesirable effects shall be minimised and be acceptable when weighed against the evaluated potential benefits to the patients and/or the user arising from the intended performance of the IVD MD during normal conditions of use.

6/ PRODUCT VERIFICATION AND VALIDATION

6.1/ Information on analytical performance of the IVD MD

Specimen type (different specimen types that can be analysed, including their stability such as storage, where applicable specimen transport conditions and, with a view to time-critical analysis methods, information on the timeframe between taking the specimen and its analysis and storage conditions such as duration, temperature limits and freeze/thaw cycles).

Analytical performance characteristics (referred to in Section 9.1 of Annex I and in Section 6.1 of Annex II)

Accuracy of measurement

a) Trueness of measurement

This Section shall provide information on the trueness of the measurement procedure and summarise the data in sufficient detail to allow an assessment of the adequacy of the means selected to establish the trueness. Trueness measures apply to both quantitative and qualitative assays only when a certified reference material or certified reference method is available.

b) Precision of measurement

This Section shall describe repeatability and reproducibility studies.

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

Analytical specificity
This Section shall describe interference and cross reactivity studies performed to determine the analytical specificity in the presence of other substances/agents in the specimen.

Information shall be provided on the evaluation of potentially interfering and cross-reacting substances or agents on the assay, on the tested substance or agent type and its concentration, specimen type, analyte test concentration, and results.

Interferents and cross-reacting substances or 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 such as medicinal products;
b) substances ingested by the patient such as alcohol, foods;
c) substances added during specimen preparation such as preservatives, stabilisers;
d) substances encountered in specific specimen types such as haemoglobin, lipids, bilirubin, proteins;
e) analytes of similar structure such as precursors, metabolites or medical conditions unrelated to the test condition including specimens negative for the assay but positive for a condition that can mimic the test condition.

Metrological traceability of calibrator and control material values.

Measuring range of the assay
This Section shall include information on the measuring range regardless of whether the measuring systems are linear or non-linear, including the limit of detection and describe information on how the range and detection limit were established.

This information shall include a description of specimen type, number of specimens, number of replicates, and specimen preparation including information on the matrix, analyte levels and how levels were established.

In case if it is relevant, a description of any case, where at high analyte concentration results in a lower response than expected (“hook effect”) together with the data on how to mitigate this effect, for example by dilution.

Definition of assay cut-off
This Section shall provide a summary of analytical data with a description of the study design including methods for determining the assay cut-off, such as:

a) the population(s) studied: demographics, selection, inclusion and exclusion criteria, number of individuals included;
b) method or mode of characterisation of specimens; and
c) statistical methods such as Receiver Operator Characteristic (ROC) to generate results and if applicable, define grey-zone/equivocal zone.

The analytical performance report referred to in Annex XIII

Summary of Safety and Performance parameters (SSP) according to Article 29 of IVDR.
For class C and D IVD MDs, other than IVD MDs for performance studies, the manufacturer shall draw up a summary of safety and performance.

- the summary shall be written in such a way that it is understandable to the intended user and, where relevant, to the patient and shall be made publicly available via Eudamed;
- the draft of the summary of safety and performance shall be part of the documentation to be submitted to the notified body involved in the conformity assessment pursuant to Article 48 and shall be validated by that body;
- the manufacturer must indicate on the label or in the instructions for use where the summary is available.

6.2/ Information on clinical performance and clinical evidence. Performance Evaluation Report

The documentation shall contain the performance evaluation report, which includes the reports on the scientific validity, the analytical and the clinical performance, as referred to in Annex XIII, together with an assessment of those reports.

Performance evaluation plan (referred to in Section 1.1 of Part A of Annex XIII).
The clinical performance study documents referred to in Section 2 of Part A of Annex XIII shall be included and/or fully referenced in the technical documentation.
6.3/ Stability (excluding specimen stability)
Planning and overview of performed studies related to: - Claimed shelf-life (in accordance with Section 6.3.1. of Annex II); - In-use stability (in accordance with Section 6.3.2. of Annex II); - Shipping stability (in accordance with Section 6.3.3. of Annex II); Testing shall be performed on at least three different lots manufactured under conditions that are essentially equivalent to routine production conditions. The three lots do not need to be consecutive. Accelerated studies or extrapolated data from real time data are acceptable for initial shelf-life claims but shall be followed up with real time stability studies.
6.4/ Software verification and validation:
Evidence of the validation of the software that is used in the finished IVD MD: - summary results of all verification, validation and testing performed in-house and applicable in an actual user environment prior to final release. It shall also address all of the different hardware configurations and, where applicable, operating systems identified in the labelling.
6.5/ Additional information required in specific cases
IVD MDs placed on the market in a sterile or defined microbiological condition: - description of the methods used, including the validation reports, with regard to packaging, sterilisation and maintenance of sterility; - validation report also includes tests for bioburden, pyrogenic tests and if necessary, tests for residues of the sterilization agent.
In the case of IVD MDs containing tissues, cells and substances of animal, human or microbial origin, information on the origin of such material and on the conditions in which it was collected.
In the case of IVD MDs placed on the market with a measuring function, a description of the methods used in order to ensure the accuracy as given in the specifications.
If the IVD MD is to be connected to other equipment in order to operate as intended, a description of the resulting combination including proof that it conforms to the general safety and performance requirements set out in Annex I when connected to any such equipment having regard to the characteristics specified by the manufacturer.
7/ EU DECLARTION OF CONFORMITY
Draft of EU Declaration of conformity in accordance with Annex IV IVDR.
8/ QUALITY MANAGEMENT SYSTEM DOCUMENTATION (Article 10 sec. 8 IVDR)
The Quality Management System shall cover all parts and elements of a manufacturer's organisation dealing with the quality of processes, procedures and IVD MDs. It shall govern the structure, responsibilities, procedures, processes and management resources required to implement the principles and actions necessary to achieve compliance with the provisions the IVDR.
Strategy for regulatory compliance, including compliance with conformity assessment procedures and procedures for management of modifications to the IVD MDs covered by the system.
Identification of applicable general safety and performance requirements and exploration of options to address those requirements.
Management responsibility
Resource management, including selection and control of suppliers and sub-contractors.
Risk management as set out in Section 3 of Annex I.
Performance evaluation, in accordance with Article 56 and Annex XIII, including PMPF.
Product realisation, including planning, design, development, production and service provision.

Verification of the UDI assignments made in accordance with Article 24(3) to all relevant IVD MDs and ensuring consistency and validity of information provided in accordance with Article 26.
Setting-up, implementation and maintenance of a post-market surveillance system, in accordance with Article 78.
Handling communication with competent authorities, notified bodies, other economic operators, customers and/or other stakeholders.
Processes for reporting of serious incidents and field safety corrective actions in the context of vigilance.
Management of corrective and preventive actions and verification of their effectiveness.
Processes for monitoring and measurement of output, data analysis and product improvement.
9/ TECHNICAL DOCUMENTATION ON POST-MARKET SURVEILLANCE (Article 78 IVDR)
Post-market surveillance system of the manufacturer for each IVD MD manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of IVD MD. That system shall be an integral part of the manufacturer's quality management system referred to in Article 10(8).
The post-market surveillance system shall be suited to actively and systematically gathering, recording and analysing relevant data on the quality, performance and safety of IVD MD throughout its entire lifetime, and to drawing the necessary conclusions and to determining, implementing and monitoring any preventive and corrective actions.
Data gathered by the manufacturer's post-market surveillance system shall in particular be used: a) to update the benefit-risk determination and to improve the risk management as referred to in Chapter I of Annex I; b) to update the design and manufacturing information, the instructions for use and the labelling; c) to update the performance evaluation; d) to update the summary of safety and performance referred to in Article 29; e) for the identification of needs for preventive, corrective or field safety corrective action; f) for the identification of options to improve the usability, performance and safety of the IVD MD; g) when relevant, to contribute to the post-market surveillance of other IVD MDs; and h) to detect and report trends in accordance with Article 83. The technical documentation shall be updated accordingly.
If in the course of the post-market surveillance, a need for preventive or corrective action or both is identified, the manufacturer shall implement the appropriate measures and inform the competent authorities concerned and, where applicable, the notified body. Where a serious incident is identified or a field safety corrective action is implemented, it shall be reported in accordance with Article 82.