MDCG 2022-3 Rev. 1 Verification of manufactured class D IVDs by notified bodies

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MDCG 2022-3 revision 1 changes	
2.	Clarification added on applicability of batch testing requirements
4.1.1	Test plan: bullet ‘decision making criteria for success or failure of the batch’ removed
4.1.1	Clarification added: 30 ‘calendar’ days
4.1.2	Test plan: bullet ‘decision making criteria for success or failure of the batch’ removed
4.1.2	Written contract between the notified body and the EURL: bullet ‘decision making criteria for success or failure of the batch’ added
4.1.2	Clarification added: 30 ‘calendar’ days
4.1.2	Paragraph added on agreements between manufacturers and EURLs
5.	Note under Table 1 removed
5.1	First sentence modified
5.3	Note added under Table 3
6.	Clarification added: 30 ‘calendar’ days

1. Introduction

Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR) establishes the requirements for notified bodies involved in the conformity assessment of applicable classes of *in vitro* diagnostic medical devices (IVDs). Manufacturers must demonstrate that the devices conform to relevant requirements based upon objective evidence and analysis.

In accordance with these conformity assessment procedures[1], in addition to quality management system and technical documentation assessments, notified bodies are required to verify product batches of class D IVDs in line with Annexes IX and XI of the IVDR. Therefore, in order to verify the conformity of class D IVDs, manufacturers should forward to notified bodies the reports on tests carried out on each manufactured batch of class D devices[2]. Furthermore, the manufacturer should make available samples of manufactured class D devices or batches of devices to the notified body in accordance with pre-agreed conditions and detailed arrangements. The notified body involved in the conformity assessment of class D IVDs should request one of the EU reference laboratories (EURLs), if designated by the European Commission[3], to carry out batch testing on those devices. The EURL should, in turn, inform the notified body about its findings. Following this verification procedure, manufacturers may place class D IVDs on the market unless the notified body communicates to the manufacturer within an agreed timeframe, but not later than 30 days after reception of the samples, any other decision[4]. In the absence of a designated EURL for a device, the requirements relating to EURLs do not have to be applied.

2. Scope

This document aims to provide guidance to notified bodies to clarify their role and responsibilities in relation to samples of manufactured class D devices or batches of devices in accordance with Annexes IX and XI of the IVDR.

This guidance also describes best practices for notified bodies in performing conformity assessment procedures relating to the verification of manufactured class D IVDs. It also includes guidance on:

- relevant information to be included within the notified body's procedures,

[1] IVDR Article 48
[2] IVDR Annex IX section 4.12 & Annex XI section 5.1
[3] IVDR Article 100
[4] IVDR Annex IX section 4.13 & Annex XI section 5.2

- the content of the required pre-agreed conditions and detailed arrangements[5] between the notified body and the manufacturer,
- guidance on the frequency of samples of devices or batches of devices to be sent to the EURL[6].

It is understood that the IVDR requirements related to testing every product batch, and consequently this guidance document, are relevant for devices for which the concept of batches is applicable. For example, the concept of batches is not applicable for medical device software. Therefore, the corresponding IVDR batch testing requirements and this guidance document are not relevant to class D medical device software.

3. Definitions

3.1. Class D IVDs

The IVDR refers to class D devices in rules 1 and 2 of Annex VIII as follows:
Devices intended to be used for the following purposes are classified as class D:

- detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration;
- detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation;
- determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management.

[IVDR, Article 47(I) & Annex VIII Section 2 Rule 1]
Devices intended to be used for blood grouping, or to determine foeto-maternal blood group incompatibility, or for tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation or cell administration, are classified as class C, except when intended to determine any of the following markers:

- ABO system [A (ABO1), B (ABO2), AB (ABO3)];
- Rhesus system [RH1 (D), RHW1, RH2 (C), RH3 (E), RH4 (c), RH5 (e)];
- Kell system [Kel1 (K)];
- Kidd system [JK1 (Jka), JK2 (Jkb)];
- Duffy system [FY1 (Fya), FY2 (Fyb)]

[IVDR, Annex VIII Section 2 Rule 2]

[5] IVDR Annex IX Section 4.12 & Annex XI Section 5.1
[6] IVDR Annex IX Section 4.12 & Annex XI Section 5.1

Note: Please see MDCG 2020-16[7] (Guidance on Classification Rules for *in vitro* Diagnostic Medical Devices under Regulation (EU) 2017/746) for examples of devices falling in Class D.

3.2. Batch

A defined amount of material, either starting material, intermediate or finished product which is uniform in its properties and has been produced in one process or series of processes.
[EN 13975:2003]

3.3. Common specifications

A set of technical and/or clinical requirements, other than a standard, that provides a means of complying with the legal obligations applicable to a device, process or system.
[IVDR Article 2 (74)]

3.4. EU Reference Laboratory (EURL)

A European Union reference laboratory designated according to Article 100 of the IVDR.

3.5. Verification

Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled.
[EN ISO 9000:2015]

3.6. Sample

One or more units of product, either components or finished devices, drawn from a batch without regard to the quality of the units
[EN 13975:2003]

3.7. Specimen

Small portion of a body fluid or tissue taken from an individual for examination, study or analysis of one or more quantities or characteristics to determine the character of the whole.

4. Notified Body Procedures

The notified body should have documented procedures for[8]:

[7] https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2020_guidance_classification_ivd-md_en.pdf
[8] IVDR Annex VII

- The verification process
- The establishment of a test plan identifying all relevant and critical parameters which need to be tested for the device, including decision making criteria for success or failure of the batch
- The provision for the reaching of an agreement with the manufacturer concerning when and where the necessary sample or batch testing has to be performed

An agreement on the batch verification arrangements should be in place between the notified body and the manufacturer of the class D IVD. In addition, provided that a EURL is designated for this device, the notified body should also make arrangements with the EURL for the testing of the device.

The notified body should draw up a testing plan for the device to be provided to the EURL (see also section 4.1.2 below). This plan should be based upon the results of the notified body's conformity assessment, the performance verification opinion of an EURL[9], as well as, any other relevant information from the manufacturer and the EURL. The EURL may propose justified changes based on its scientific expertise. The testing plan is then agreed between the notified body and the EURL. It should be included in the agreement between the notified body and the manufacturer, and in the written contract between the notified body and the EURL. It should be noted that EURLs are independent scientific and testing bodies designated by the Commission for the purposes defined in IVDR. Therefore, EURLs should not be considered as subcontractors to notified bodies in the same sense as other testing laboratories.

4.1. Pre-Agreed Conditions and Detailed Arrangements

The performance of a class D IVD will usually have already been verified by a EURL for that device[10]. The verification of manufactured batches will typically be arranged with the same EURL. Nevertheless, a different EURL designated with the applicable scope and equipment may be chosen. In the case of several EURLs available for a certain device, the notified body should decide (following consultation with the manufacturer) which EURL is most appropriate to perform the batch verification. Factors to be considered include, for example, the product range of the manufacturer (due to other class D devices to be tested), sample logistics as well as language or other issues which may affect the choice of EURL.

4.1.1. Agreement between the notified body and the manufacturer

The agreement between the notified body and the manufacturer should include at least the following:

- Test plan, as approved by the EURL
    - Relevant and critical parameters to be tested
    - Samples to be tested

[9] IVDR Articles 48.5 & 100 2(a)
[10] IVDR Articles 48.5 & 100.2(a)

  - Specimens to be tested
  - Other specific materials provided by the manufacturer
  - Testing frequency
  - Test platform and protocol used
  - Reference to any applicable common specifications and relevant standards or other solutions chosen by the manufacturer[11]
  - Reference to the designation scope of the EURL
- The logistics of the provision of samples and other materials (e.g. calibrators and controls) or equipment from the manufacturer to either the notified body and/or the EURL, including the need for any special storage and transport arrangements
- Special arrangements in the case of devices or specimens with exceptionally short shelf-lives or the need for special equipment.
- Provision of batch release quality control (QC) results from the manufacturer to the notified body
- Details of the information to be provided by the manufacturer to the notified body and to the EURL with each batch
- Commitment of the manufacturer to inform the notified body if the manufacturer is to send the samples directly to the EURL
- Commitment of the manufacturer to immediately inform the notified body of any changes that may have an effect on the verification of manufactured batches. This may include changes to manufacturing, raw materials (ingredients, formulation etc), equipment, quality control, transport or storage
- Commitment of the manufacturer to inform the notified body and the EURL of any relevant scientific, technical or clinical information which has come to its knowledge, which may have an impact on the scientific or technical validity of the batch verification testing scheme. This could include, for example, information on emergence of a new variant strain for microbiological assays, or knowledge of new interfering or cross-reacting substances
- Agreement of the manufacturer for the notified body to provide any relevant information to the EURL
- Provision of the results and conclusions of the verification of manufactured batches from the notified body to the manufacturer, including an agreed timeframe (not more than 30 calendar days after reception of the samples)
- Financial conditions, e.g. costs for material storage and logistics
- Contact information for communication between the notified body and the manufacturer

The manufacturer may be actively engaged in the selection of the EURL that will perform the batch testing.

[11] IVDR Article 100 2(a)

4.1.2. Written contract between the notified body and the EURL

The written contract between the notified body and the EURL should include at least the following:

- Test plan, as approved by the EURL
  - Relevant and critical parameters to be tested
  - Samples to be tested
  - Specimens to be tested
  - Test platform and protocol used
  - Other specific materials provided by the manufacturer
  - Testing frequency
  - Reference to any applicable Common Specifications and relevant standards or other solutions chosen by the manufacturer[12]
  - Reference to the designation scope of the EURL
- Decision making criteria for success or failure of the batch
- The logistics of the provision of samples and other materials (e.g. calibrators and controls) or equipment from the manufacturer to either the notified body and/or the EURL, including the need for any special storage and transport arrangements
- Special arrangements in the case of devices or specimens with exceptionally short shelf lives or the need for special equipment
- Details of the information to be provided to the EURL with each batch
- Commitment of the notified body to inform the EURL of any changes that may have an effect on the verification of manufactured batches
- Commitment of the notified body to inform the EURL of any relevant scientific, technical or clinical information which has come to its knowledge, which may have an impact on the scientific or technical validity of the batch verification testing scheme. This could include, for example, information on emergence of a new variant strain for microbiological assays, or knowledge of new interfering or cross-reacting substances
- Provision of the results of the verification of manufactured batches from the EURL to the notified body
- Commitment of the notified body to provide the EURL with all of the necessary information from the conformity assessment, in order for the EURL to plan and perform the batch verification testing
- Estimated timeframe for schedule for testing and reporting of findings from the EURL (maximum 30 calendar days)
- Provision of the EURL's opinion on performance verification by the notified body to the EURL in cases where a different EURL is to perform the batch verification testing of manufactured batches to the one involved in the initial certification
- The findings of previous sample or batch tests performed by this or other EURLs

[12] IVDR Article 100 2(a)

- Testing fees according to the price list of the EURL
- Contact information for communication between the notified body and the EURL

The manufacturer may have agreements directly with an EURL for aspects such as logistics of shipment of instruments and samples or responsibility for the equipment, under the oversight of the notified body.

5. The provision of samples to the EU reference laboratory

The notified body is required to have procedures detailing criteria to determine which products will be made available to the EURL and with which frequency.

The frequency of sending samples of batches to the EURL should be based upon the general principle that the higher impact of device failure, the higher number of batches has to be tested.

When determining the frequency of sending samples of batches to the EURL consideration should be given to the relative risk/impact of the device based on the type of intended use, in accordance with the table below:

Transmissible Agents (in order of decreasing risk)	Blood Grouping (in order of decreasing risk)
- First-line assays falling under the first indent of rule 1 section 2 Annex VIII: "*detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration"* - First-line assays falling under the second indent of rule 1 section 2 Annex VIII: *"detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation"* - Confirmatory and supplemental assays - Devices falling under the third indent of rule 1 section 2 Annex VIII:	- ABO (risk for blood donation recipients) - RH1 (D) (risk of antibody stimulation) - Other blood groups (risk of antibody stimulation),

"determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management."	

Table 1: Relative risk of class D IVDs

5.1. Determining the initial number of samples of manufactured class D devices or batches of devices to be sent to the EURLs

For first-line assays falling under the first indent of rule 1 section 2 Annex VIII every batch has to be tested.

For other devices, the number of batches to be initially tested should be determined by the notified body. The notified body will take into account the batch-testing regime defined by the manufacturer and the views expressed in the scientific opinion of the EURL, and, where applicable, the views expressed by the experts consulted pursuant to Article 48(6) following tables 2-3 below. This number should also be pre-agreed with the EURL. The number may be determined using a risk-based approach based upon a risk analysis developed by the manufacturer and verified by the notified body. This analysis may take the following parameters into account (*not an exhaustive list*):

- Number of batches produced per year
- Batch release data from previous lots
- Design and technology of the device
- Any changes that may have an effect on the verification of manufactured batches. This may include changes to manufacturing, equipment, quality control, transport or storage
- Devices with short expiry date (e.g. for blood group tests)
- Batch size

Within a batch, the number of samples to be tested also has to be defined and pre-agreed with the aforementioned three parties.

5.2. Re-assessment of the testing frequency

With a demonstrated history of appropriate performance the notified body, in collaboration with the EURL, could agree to the frequency of testing being reduced. Therefore, the notified body should regularly review the manufacturer's risk analysis, the conclusions of which may lead to a modification of the testing frequency. Any adaptations to the testing frequency should be appropriately documented and justified by the notified body taking at least the following into account:

- Batch release data from the manufacturer and EURL
- Manufacturers' quality control release system
- Information related to production process changes
- Post market surveillance data

- The risk and the impact of device failure
- Availability of common specifications
- Technical characteristics of the product
- Stability of the devices
- Shelf life of the devices

In cases of control failure or substantial product modification, the initial testing frequency should be applied again.

5.3. Testing frequency:

The testing frequency for each group of class D IVDs should be determined using the following possible options:

Transmissible agents		
	Initial testing	**Adjusting the frequency**
First-line assays falling under the first indent of rule 1 section 2 Annex VIII	Every batch	No possibility of adjusting testing frequency
First-line assays falling under the second indent of rule 1 section 2 Annex VIII	5 to 10 batches depending of the relative risk of the device	At least 1 out of 5 batches randomly chosen by NB (calculated on the basis of the number of lots produced the previous year) AND At least 1 batch/year
Confirmatory and supplementary assays		
Devices falling under the third indent of rule 1 section 2 Annex VIII		

Table 2: Frequency of testing class D IVDs for transmissible agents

Blood grouping		
	Initial testing	**Adjusting possibility**
ABO determination	5 to 10 batches (depending of the number of batches produced per year)	At least 1/5 batches randomly chosen by NB (calculated on the basis of the number of lots produced the previous year) AND At least 1 batch/year
RH1 (D)		
Other blood groups	Initially one batch (subsequent batches released on basis of quality control data of manufacturer)	At least 1/5 batches randomly chosen by NB (calculated on the basis of the number of lots produced the previous year) AND At least 1 batch/year *(Testing frequency of less than 1/5 may be appropriate for red blood cells if justified and agreed between the NB and EURL.)*
Red blood cell reagents *(due to very short shelf-life of red blood cells, batches can be released by manufacturer based upon their quality control results before EURL results)*		

Table 3: Frequency of testing class D IVDs for blood grouping

Note: Calibrators and controls placed on the market separately should follow the testing frequency of the corresponding device(s)/reagent(s). Device/reagent-specific controls placed on the market separately and intended for use with IVDs falling in the first indent of rule 1 in Annex VIII of the IVDR may follow the adjustable testing frequency set out in the second line of Table 2.

6. Notified body verification of batches of Class D IVDs

Notified bodies are responsible for conducting the verification of batches of manufactured class D IVDs[13] that is performed following review of the manufacturer's QC release data and the findings from the EURL.

In relation to the review of the manufacturer's QC test reports from each batch[14], the minimum aspects to be checked by the notified body are as follows:

- Verification based on relevant raw data (Data output plus indicating valid/invalid/passed/not passed)
- In case of blind testing, verification that the results provided by manufacturer are in accordance with expected results
- The decision making criteria for success or failure of the batch

The notified body should clearly document the outcome of its assessment of the manufacturer's data and EURL's findings.

The notified body and the manufacturer will have agreed a timeframe (of not later than 30 calendar days after reception of the samples[15]) for the communication of the decision of the notified body or any condition imposed by the notified body. Following this verification procedure, manufacturers may place class D IVDs on the market unless the notified body communicates to the manufacturer within this agreed timeframe of any other decision[16].

[13] IVDR Article 48 & Annex VII section 4.5.3
[14] IVDR Annex IX section 4.12 & Annex XI section 5.1
[15] IVDR Annex IX section 4.13 & Annex XI section 5.2
[16] IVDR Annex IX section 4.12 & Annex XI section 5.2