EUROPEAN CO-ORDINATION NB-MED NOTIFIED BODIES	**Co-ordination of Notified Bodies Medical Devices (NB-MED) on Council Directives 90/385/EEC, 93/42/EEC and 98/79/EC**	**Recommendation** **NB-MED/2.5.4/Rec2**

Title:	**Verification of Manufactured Products for the IVD Directive**
Chapter:	**2.5.4** Conformity assessment procedures; **Verification of manufactured products**

Text:	**Annex IV-6 and Annex VII-5: "In the case of devices covered by Annex II, List A, the manufacturer shall forward to the notified body without delay after the conclusion of the controls and tests the relevant reports on the tests carried out on the manufactured devices or each batch of devices. Furthermore, the manufacturer shall make the samples of manufactured devices or batches of devices available to the notified body in accordance with pre-agreed conditions and modalities."**
Key words:	**conformity assessment, verification of manufactured products, witness testing**

Purpose of Recommendation

The aim of this Recommendation is to define modalities for the verification of manufactured products as required by Annex IV (6) and VII (5) of the IVD Directive.

Annex IV (6) and VII (5) of the IVD Directive do not define how the verification of manufactured products should be performed. According to article 5 (3) this should be addressed in the Common Technical Specification (CTS), however this has not been included in the initial draft of the CTS. This necessitates the agreement of some general principles, which Notified Bodies, industry and their regulators can use as terms of reference in order to achieve a common understanding of regulatory compliance.

This recommendation will address the following:

- Who should perform the verification of manufactured products?
- In what circumstances is physical testing required?

A rationale and history sheet is available; please contact Technical Secretariat.

Reference to Directive:	**Article/ Annex:**	**Reference to standards:**
AIMD		
MDD		
IVD	Article:9; Annex: II, IV-6; VII-5	

Stage	Proposed by	Rev.-Nr.	Rev. date	accepted	amended	withdrawn	Page
3	NBRG/IVD-TF	3	11.04.2000	06.06.2000			1/6

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- How frequently should products be verified?
- What tests should be performed?
- What is the definition of a batch?

Introduction

This document proposes modalities for the verification of manufactured product, based on the risk of the device. This document acknowledges that those Annex II, list A devices which pose the highest risk[1] require the maximum level of control to ensure consistency of the product, but accepts that an increased level of flexibility can be exercised for devices posing a lower risk. The verification of manufactured products and especially physical testing of the devices by or on behalf of the Notified Body is the highest level of control. This is part of the conformity assessment process and additional to the manufacturer's quality control procedures. This should be performed by the Notified Body following the review of the conformity assessment procedures such as the design dossier review.

This document does not aim to be prescriptive as more than one possible solution can achieve the desired goal. The aim of this paper is to set out criteria that may help to establish the appropriate control procedure that the Notified Body will implement.

Who should perform the verification of manufactured products?

The Notified Body should conduct the verification of manufactured products. In all cases the NB reviews the QC release data generated by the manufacturer and gives his approval for the release of the products or batch(es) of products in question. In addition the mechanism for the physical verification of manufactured products could be achieved by one or more of the following:

1. The NB tests samples of the batch of products to be verified.
2. The NB provides specific material to the manufacturer, who then tests the samples of the batch to be verified using the specific material according to agreed procedures,
3. The NB witnesses the testing of the samples of the batch according to agreed procedures at the manufacturers premises.

[1] For the purpose of this document, "risk" means the likely frequency with which a hazard will occur and the severity of that hazard. An example of a hazard would be misclassification by a serological screening assays, which could have a severe impact on a multiple recipients of blood products.

When is physical testing by the Notified Body required?

According to the principles already outlined, those devices that pose the highest risk require the maximum level of control to ensure that the device is manufactured consistently according to the approved design. The matrix list below is based on commonly agreed estimations of the relative risk of IVD medical devices, taking account of their intended use.

This document anticipates that the Annex II, list A screening assays pose the greatest risk. The failure of screening assays has the greatest potential to harm the largest number of people as these are used in testing of blood donations.

The greatest risk posed for blood grouping assays is determination of ABO group. Failure to determine the correct ABO type of either the donor or the recipient poses the greatest risk since most individuals have pre-existing antibodies to the antigens they lack. The remaining Annex II list A blood grouping tests can be divided into 2 categories: tests for the D antigen and tests for the remaining antigens C, c, E, e and K. The D antigen is the most antigenic of these and therefore poses the greatest risk of antibody stimulation.

The remaining devices in Annex II List A are ranked as follows in order of decreasing risk;
- confirmation assay for screening devices,
- diagnostic devices,
- confirmation assays for diagnostic devices.

Confirmation assays for screening devices are used to confirm the result of the initial screening assay. They therefore have an impact on the safety of the screening process and are thus of a higher risk that the diagnostic assays and their confirmatory devices.

Having established the relative risk of these devices it is important to determine the frequency of testing. The highest risk devices require the maximum level of verification. This means that for the screening assays, each batch is to be physically tested, as agreed with the Notified Body. IVDs grouped in the remaining risk categories should initially be tested each time as prescribed by the Notified Body. However, with a demonstrated history of appropriate performance the Notified Body could agree to the frequency of testing being reduced. The point at which this can occur should be agreed between the manufacturer and the Notified Body. The point at which the Notified Body will agree to reduce the frequency of testing, will depend on several factors, including the established consistency of the device, confidence in the manufacturers QC release system, etc. This point could be different for each

device, and may vary if particular characteristics of the device make it more prone to variation, for example, where the performance of blood typing reagents may be dependant on certain formulation characteristics (such as pH) and may vary accordingly.

The table below summarises the possible options for each risk group.

Note: In all cases the NB reviews the QC release data generated by the manufacturer and gives his approval for the release of the products or batch(es) of products in question.

Table 1: Modalities of verification procedures for virology devices according to the relative risk of the devices

Products in order of decreasing risk	**Frequency**	**Scope to adjust frequency**
Screening assays: serological & NAT i.e. reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.	every batch	No scope to adjust frequency with history
Confirmation assays for screening assays i.e. reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.	Initially every batch	Limited scope to adjust frequency with history
Diagnostic markers and respective confirmation assays of diagnosis assays i.e. reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.	Initially every batch	Wider scope to adjust frequency with history

Table 2: Modalities of verification procedures for blood typing devices according to the relative risk of the devices

Products in order of decreasing risk	**Frequency**	**Scope to adjust frequency**
Reagents and reagent products for determining the following blood group groups: A, B, O and D	Initially every batch	Limited scope to adjust frequency with history
Reagents and reagent products for determining the following blood group antigens: C, c, E, e and K.	Initially every batch	Wider scope to adjust frequency with history
Related calibrators and control materials for reagents and reagent products for determining the following blood group groups for: A, B, O, D, C, c, E, e and K.	Initially every batch Note: As red cells have a short shelf life, it may only be practicable to release them on the basis of the manufacturer's QC data	Wider scope to adjust frequency with history

What tests should be performed?

Regardless of the mechanism of verification adopted, the same decision making criteria should be applied by the Notified Body.

1. Annex II, list A Virology Devices
   The Notified Body must verify that the batch to be released identifies the key marker sub types and shows suitable performance around the cut off or decision making point. This should be achieved by testing a series of dilutions around the cut off point.

2. Annex II, list A Blood grouping devices
   For the determination of blood group antigens, red cells expressing suitable/appropriate antigens should be tested, according to agreed procedure.

What is a "batch"?

The term "batch" as used in the previous paragraphs is defined in the relevant draft CEN standards, e.g. prEN XXX "Sampling procedures used for acceptance testing of in vitro diagnostic medical devices", November 1999 (document CEN/TC 140/WG 2 N 149) as follows:

"batch (lot): 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."

Note: In multiple lot assays, the manufacturer and Notified Body should control the matching of individual reagent lots.

Rev. 3: Notified Body Meeting, Brussels, November, 2 & 3, 1999:
The NBRG was asked to elaborate new NB-MED Recommendations in light of the IVD-directive if needed.

A small task force on NBRG-IVDD was established and met several times (on 03.12.99 at PEI and on 24.01.2000 at LRQA). First draft documents were elaborated (see also minutes NBRG/166/00 and NBRG/167/00).

Meeting of NBR Group, Brussels, March 2, 2000:
The work results of the small task force (elaborate new NB-MED Recommendations in light of IVDD) were presented to that NBRG-meeting.
The tabled revised working document (without revision no.) on "Verification of Manufactured Product for the IVD Directive" was discussed and some comments for improvement were made. It was agreed that further development will be made by the task force group.

Meeting of NBR Group, Brussels, April 10 &11, 2000:
A new draft document was presented as NBRG/190/00 to that meeting (rev 2). NBRG reworked the document within an intensive discussion. It was decided to fit the document in the *recommendations nomenclature system* under chapter 2.5.4 *Conformity assessment procedures; verifiocation of manufactured products*. Therefore the recommendation gets the number **NB-MED/2.5.4/Rec2**.
NBRG agreed that the document, as discussed and - during the meeting - revised, should be presented for formal adoption at the June NB-MED Plenary meeting **but could find application/knowledge in the meanwhile**.
Revision no: 3
stage 2

Notified Body Meeting, Brussels, June 6 & 7, 2000:
The document (NBM/61/00) was approved by the NB-MED plenary as "best compromise". The following was discussed: *With regard to the question whether also other Competent Authorities than UK-CA are involved in commenting and discussing the new draft Recommendation it was answered that the German Accreditation Body ZLG was involved; comments which were made by ZLG are considered in the tabled document. Mr. R. asked for clarification with regard to reference laboratory (chapter "Who should perform the verification of manufactured products?") whether this is a part of a Notified Body or whether this is totally separated from the Notified Body. Dr. D. answered that this depends of the competence/expertise of the Notified Body (working with a sub-contractor or - in case of own expertise - doing by itself). Dr. H. summarised that the Notified Body is responsible for the sufficient competence for the tasks. With regard to option 2 of batch verification ("The NB provides specific material to the manufacturer, who then tests the samples of the batch to be verified using the*

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specific material according to agreed procedures") Dr. N. raised the potential problem that this could be seen by the Competent Authority as an extended quality control performed by the manufacturer, because this is done by the manufacturer in his premises; in case of adoption of this draft Recommendation the Notified Bodies have to be aware of this potential problem. Some Competent Authorities understand "verification of manufactured products" as a task which has to be performed by the Notified Body either by "wet (?) testing" by the Notified Body (= option 1) or by "witness testing" (=option 3).
Confirmed at stage 3.
Revision no: 3