

	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/2.5.5/Rec4
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Title:	Assessment of the sensitivity of In Vitro Diagnostic Medical Devices - guidance on the application of the CTS
Chapter:	2.5.5 Conformity assessment for particular product groups

Text:	„The devices must be designed and manufactured in such a way that they are suitable for the purposes referred to in Article 1(2)(b), as specified by the manufacturer, taking account of the generally acknowledged state of the art. They must achieve the performances, in particular, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer.“
Key words:	Sensitivity, CTS, seroconversion panels

1. Purpose of this Recommendation

The purpose of this Recommendation is to provide guidance to Notified Bodies and manufacturers on the application of the Common Technical Specification (CTS) and use of seroconversion panels to be analysed for screening or confirmatory assays, in assessing the sensitivity of In Vitro Diagnostic (IVD) medical devices.

2. Introduction

The term sensitivity describes the detectability of the target marker by the respective VD medical device. The diagnostic sensitivity of a device is differentiated from its analytical sensitivity.

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

Reference to Directives:	Article/ Annex:	Reference to standards:
AIMD	--	
MDD	--	
IVDD	Annex: I	

Stage	proposed by	Rev.-Nr.	Rev. date	accepted	amended	withdrawn	Page
3	ad hoc group/NBRG	2	06.03.2001	06.03.2001			1/4

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3. Definitions and Explanations

The following definitions of Diagnostic Sensitivity and Analytical Sensitivity are extracted from the references listed in section 8 and are as given in the Common Technical Specifications (CTS).

Diagnostic sensitivity^{1,2,3}

The diagnostic sensitivity is the probability that the device gives a positive result in the presence of the target marker. Diagnostic sensitivity is therefore expressed as the percentage of positive results obtained in a well characterised set of specimens containing the target marker.

Analytical sensitivity^{4,5}

In the context of the assays covered by the Common Technical Specifications (CTS), analytical sensitivity may be expressed as the limit of detection: i.e. the smallest amount of the target marker that can be precisely and continuously distinguished from the background.

Note :

While there is a direct correlation to be expected between diagnostic and analytical sensitivity for devices which detect (pathogen) components like nucleic acids or antigens, there may be no intrinsic correlation between the two parameters for antibody tests. This lack of correlation may be caused by the interindividual variation of the polyclonal humoral immune responses with respect to the epitopes provided by the test antigens.

Explanation of Seroconversion panels

A seroconversion panel consists of serial samples (members) obtained from an individual during the early infection phase. Seroconversion panels are usually obtained from back-up donations of plasma donors who have been freshly infected by the respective pathogen. The serial samples of a seroconversion panel reflect normal disease progression and therefore usually reflect a significant change of the measured parameter, normally from negative to positive. Due to different practices or regulations, which may be based on ethical considerations, the time intervals between the serial samples of a seroconversion panel may vary. For example, with current practices in some countries, the time interval between two plasma donations may be 3 - 4 days.

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4. Assessment of diagnostic sensitivity

The diagnostic sensitivity of a new device is determined during its performance evaluation in direct comparison with (a) comparator device(s) reflecting the generally accepted level of detection. A set of specimens reflecting the target population and containing the target marker should be tested by the new and the comparator device(s), ideally in parallel.

Test results discrepant between the devices are resolved by evaluation of the respective sample in further test systems, by use of an alternative method or marker, by a review of the clinical status and diagnosis of the patient and/or by the testing of follow-up samples. On the basis of these data for many discrepant samples it should be possible to categorise the discrepant results into false positive/true negative or false negative/true positive.

Among the devices specified by Annex II, List A, of the IVD-directive, the blood screening devices (anti-HCV, anti-HIV1/2, HBsAg and anti-HTLV tests) usually provide a high diagnostic sensitivity with all samples of characterised positive populations being correctly classified.

5. Assessment of analytical sensitivity

The analytical sensitivity for a new device is determined during its performance evaluation in direct comparison with (a) comparator device(s) reflecting the generally accepted level of detection at that time. The analytical sensitivity is usually determined by serial dilution of reference materials (where available, recognised national or international standards should be used).

Consistency of detection limits for the known pathogen geno- and subtypes is determined by serial dilution of samples with known amounts of geno-/subtypes. The performance evaluation has to reflect the prevalence situation in the target population and assessment is made on the basis of the generally accepted levels of detection at that time.

6. Performance Evaluation using seroconversion panels

Detection of samples as soon as possible after infection is an important feature and a major field for device improvement. During the early phases of infection, pathogen components are present and low-titre and low-avidity antibodies are initially

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generated. The presence of these constantly increases with time and may decrease again at later stages of the infection. For example, in the case of blood donation screening assays, the earliest possible detection of infection is very important to prevent transmission to blood donation recipients. To verify the suitability of a device for screening purposes, performance evaluation on seroconversion panels must be carried out.

After assessing the performance of the new device in several seroconversion panels, the overall performance of a new device is compared to the comparator device(s). This, together with the diagnostic sensitivity, is the principal basis for assessing the suitability of a new device for screening purposes.

7. Genotype / subtype sensitivity

Regarding the consistent detection of the known pathogen geno- and subtypes, comparative testing of true-positive and geno-/subtyped samples will provide information about potential assay-specific lack of sensitivity in relation to geno-/subtypes. The comparative test results in combination with the prevalence situation of the target populations are the basis of the assessment as to whether the device reflects the generally accepted levels of detection at that time.

8. References

1. NCCLS (Dec. 1994) – Specifications for Immunological Testing for Infectious Diseases; Approved Guideline – code I/LA18-A
2. Galen S., Gambino S.R. (1975) – Beyond normality: the predictive value and efficiency of medical diagnosis – John Wiley & Sons, New York.
3. Armitage P., Berry G. (1994) – Statistical Methods in Medical Research, Third edition – Blackwell Scientific Publications, London.
4. EN 12286: 1998 – In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Presentation of reference measurement procedures.
5. Ekins R., Edwards P. (1997) – On the meaning of sensitivity – Clin. Chem.; 43: 1824-31.

	Co-ordination of Notified Bodies Medical Devices (NB-MED) on Council Directives 90/385/EEC, 93/42/EEC and 98/79/EC	<u>Rationale and history sheet</u> to NB-MED/2.5.5/Rec4
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Rev. 1: Meeting of NBRG IVD Taskforce, Frankfurt, 25th July 2000:
Originally raised as Inquiry 60 and presented to group along with a "principles" document from MN, explaining sensitivity and use of seroconversion panels. It was agreed that MN's document will be further developed and presented to the next IVD-TF meeting.

Meeting of NBRG IVD Taskforce, Brussels, 6th November 2000:
Presented to meeting as document NBRG 220. Agreed after discussion that this should be a Recommendation, as it is the best available format for such a document with existing status and document control. Further developed and passed to NBRG meeting next day.

Meeting of NBR Group, Brussels, November 9th 2000:
Draft document was presented to the meeting (without rev. no.). NBRG agreed that the document, as discussed and revised during the meeting, should be presented for formal adoption at the March 2001 NB-MED Plenary meeting.
Confirmed at stage 2
Revision 1

Rev. 2: Notified Body Meeting, Brussels, March 6 & 7, 2001:
Mr. Virefléau presented the tabled new draft NB-MED Recommendation (see EOTC–letter M1 Mail 03 VII) which based on based on the earlier Inquiry 60 („Seroconversion panels to be analysed for screening (Table 1) or confirmatory assays (Table 4)“, see NBM/55/00); the "IVD task force" has met on July 25, 2000 in Frankfurt and on November 6, 2000 in Brussels. Mr. Andrews/LRQA – convenor of the IVD task force – emphasised that all comments reached the task force were considered and that there is really need for this NB-MED Recommendation.
Mr. Andrews asked to delete within chapter 1 "Purpose of this Recommendation" the words "Competent Authorities"; new text: "The purpose of this Recommendation is to provide guidance to Notified Bodies, ~~Competent Authorities~~ and manufacturers on the application of the Common Technical Specification (CTS) ...".
The revised document, with its "Rationale and history" sheet will be disseminated to all member of NB-MED a.s.a.p. with the request to fit the document in the current booklet of NB-MED recommendations.
Confirmed at stage 3
Revision 2

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