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Title:	Evaluation of clinical data
Chapter:	2.7 Clinical investigations, clinical evaluation

Text:	...
Key words:	Clinical data, Evaluation

1. Introduction and purpose

It is the primary purpose of this document to provide guidance to Notified Bodies when reviewing the manufacturers evaluation of clinical data as part of the conformity assessment procedures required by 90/385/EEC (AIMD) [1] and 93/42/EEC (MDD) [2].

This document will also assist manufacturers, by providing guidance on what is expected.

It is not the purpose of this document to define the circumstances under which clinical data are provided and the extent of clinical data needed in relation to a particular medical device.

2. Background

The manufacturer must demonstrate that his intended purpose(s) and claim(s) made in relation to safety and performance are achieved, as referred to in the Directives. As a general rule, such demonstration will require clinical data (see Annex X, 1.1 of MDD).

Evaluation of clinical data as described in Annex X of the MDD and Annex 7 of the AIMD is particularly relevant to assessment of conformity with essential requirements given in MDD, Annex I, I General requirements, sections 1 and 3 and AIMD Annex 1,

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

Reference to Directives:	Article/ Annex:	Reference to standards:
AIMD	Annex 1 (I.1, I.2, I.5), Annex 7	
MDD	Annex I (I.1, I.3, I.6), Annex X	
IVD		

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I General requirements, sections 1 and 2. Attention should also be paid to Annex I, I.6 (MDD) and Annex 1, I.5 (AIMD).

3. Explanation of terms

For the purpose of this document:

- 3.1.** *Clinical data* is data which is relevant to the various aspects of the clinical safety and performance of the device. This may include data from prospective and retrospective clinical investigations of the device concerned as well as market experience of the same or similar devices and medical procedures and information from the scientific literature.
- 3.2.** The *Evaluation of clinical data* is the process by which clinical data from all selected sources (literature, results of clinical investigations and other) is assessed to establish conformity of the device with the pertinent essential requirements of the Directive, and to demonstrate that the device performs as intended by the manufacturer. The outcome of this process is a report which includes a conclusion on the acceptability of risks and side effects when weighed against the intended benefits of the device.

4. Clinical data to be provided by the manufacturer

As a general rule, and in particular in the case of implantable devices and devices in Class III, evidence of the clinical performance and safety of a medical device is provided by means of clinical data, which is supplied by the manufacturer in accordance with Annex X (MDD) or Annex 7 (AIMD). All the conformity assessment procedures leading to "CE" marking address the issue of clinical evaluation by the manufacturer. In the case of Annexes II and III, the Notified Body is involved.

Clinical evaluation is based on the assessment of the risks and the benefits, associated with use of the device, through either

1. A compilation of relevant scientific literature, that is currently available as well as, where appropriate, a written report containing a critical evaluation of this compilation (the "literature route") or
2. The results of all the clinical investigations made (the "clinical investigation route"), or

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3. a combination of 1 and 2 above.

Where the clinical evaluation is based on such a combination of 1 and 2, it should include an overall assessment. It is important that the manufacturer relates the data to the specific device, having regard to the hazards identified (see 4.1).

The manufacturer must decide whether the available data is sufficient to demonstrate conformity with the Directive, having regard to (a) the similarity of the characteristics of the device(s) to which the data relates and the device(s) for which conformity is being assessed, and so the applicability of the findings to the devices being assessed, and (b) the adequacy of the data in addressing the relevant aspects of Directive conformity.

NOTE If the available literature is sufficient to demonstrate conformity with the Directive, there will be ethical considerations associated with performing further clinical investigations (e.g. delay in availability of a given device leading to the loss of benefit of this device).

4.1. Identification of aspects of safety and performance to be addressed through clinical data

The manufacturer is required by the Directive to perform a risk analysis. A risk analysis is important in helping the manufacturer identify known or reasonably foreseeable hazards associated with use of the device, and decide how best to estimate the risks associated with each hazard¹. From the results of the risk analysis, the manufacturer lays out how each risk is addressed and decides on the acceptability of risks when weighed against the intended benefits.

The risk analysis includes technical and clinical aspects relating to the particular device concerned.

¹ The loss/absence of the performance of a given device as claimed by the manufacturer and which could result in the loss of benefit of a treatment may be considered a hazard.

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It should distinguish between aspects associated with

- (i) the medical procedure for which the device is intended,

For example, the risks versus benefits associated with extracorporeal lithotripsy as compared with conventional (surgical and not surgical) methods of kidney stone removal.

- (ii) the technical solutions adopted,

For example the risks versus benefits associated with different technologies of extracorporeal lithotripsy such as those involving generating shock-waves with electric sparks (electrohydraulic method), with an electromagnetic generator or a piezoelectric system.

- (iii) aspects specific to the design and use of the particular device concerned.

For example the risks versus benefits associated with the shockwave coupling method, size of the focal zone, the stone localisation and targeting system (X-ray, ultrasound) and the trigger method

This distinction should be used to identify the type and specificity of clinical data needed. Where the available data is not sufficient to address the identified clinical hazards relating to one or more of the above aspects, a clinical investigation will be needed (see also section 4.3.1). The objectives of the clinical investigation should focus on those aspects not sufficiently addressed by the available data.

4.2. Literature route

If the manufacturer's clinical evaluation to be submitted to the Notified Body takes the form of a review of the relevant scientific literature, the following requirements should be fulfilled:

4.2.1. Compilation of the relevant literature

- a) The compilation should be related to the hazards identified in the clinical part of the risk analysis (see 4.1.), and support the arguments set out in the report.
- b) Published literature should be taken from recognized scientific publications including unfavourable as well as favourable data.

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Factors which may influence the scientific validity of the published literature include:

- i) whether or not the author's conclusions are substantiated by the available data;
 - ii) the extent to which the published literature is the outcome of a study, following scientific principles for example, in having demonstrable and appropriate endpoints, inclusion and exclusion criteria and an appropriate and validated number of patients submitted.
 - iii) whether or not the literature still reflects the “generally acknowledged” state of the art;
 - iv) the relevance of the author's background and expertise in relation to the particular device and/or medical procedure involved; and
 - v) lack of impartiality.
- c) Other scientific data, such as the documented results of the manufacturers bench testing, including *in vitro* testing and animal studies, and an assessment of compliance with relevant technical standards, may be necessary to
- (i) alone, or in combination with other data, demonstrate compliance with relevant essential requirements of the Directives;
 - (ii) establish the extent of similarity between device(s) and medical procedure(s) covered by the scientific literature and the characteristics of the device being assessed.
- d) For well-established or simple devices, documented expert opinions with rationale from duly qualified medical practitioner(s) or other expert(s) suitably qualified in the area concerned can also be used to demonstrate safety and performance. In selecting such expert(s), the manufacturer should give due regard to their background and expertise in relation to the area concerned and any conflict of interest which may compromise impartiality. Such an expert opinion should be signed and dated by the author.

4.2.2. Written report

- a) A written report containing a critical evaluation is required, unless a justification for its absence is given, e.g. if the particular device itself is the subject of the publication and the critical evaluation of risks and intended benefits is already adequately covered by the publication.
- b) The report should be written by a person suitably qualified in the relevant field and knowledgeable in the state-of-the-art.

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- c) The report should be based on the scientific literature considered, and should be accompanied by a listing and copy of the publications quoted.
- d) The report should be related directly to the device under certification.
- e) The report should discuss all the referenced scientific literature and should address unfavourable as well as favourable data
- f) The report should contain a short description of the medical device and its intended functions, a description of the intended purpose and the application of the device as well as the indications and contraindications for its use.
- g) The report should clearly establish the extent to which the literature relates to the specific characteristics and features of the device being assessed. This should take due account of the extent of similarity between the device(s) covered by the literature and the device now being assessed, and therefore relevance in the areas of, for example, design, technology, principles of operation, critical performance characteristics, specified conditions for use etc.
- h) The report should demonstrate that those aspects of use of the device, including performance, addressed in the clinical part of the risk analysis are met as claimed by the manufacturer, and that the device fulfils its intended purpose as a medical device.
- i) The identified hazards, the associated risks and the appropriate safety measures for patients, medical staff and third parties should be covered in the report, for example by reference to the manufacturer's risk analysis.
- j) A risk/benefit assessment, which justifies the acceptability of each remaining risk when weighed against the intended benefits from use of the device, should be included.
- k) The report should contain appropriate cross-references to the attached publications.
- l) Market experience of the same or similar devices can form part of the report.
- m) Results of laboratory testing, biocompatibility and compliance with technical standards, or reference to these results, if available, can additionally be used in the report to demonstrate compliance with certain essential requirements and the relevance of the scientific literature that is referred to.

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- n) Statements concerning the field of use of the device and its indications, contraindications, effects and side effects should be consistent with the instructions for use.
- o) The report should give a concluding opinion with rationale.
- p) The report should be signed and dated by the author.

4.3. Clinical investigations route

4.3.1. Need for clinical investigations

When reviewing the manufacturer's evaluation of clinical data and whether or not a clinical investigation is needed as part of this, due regard should be paid to NB-MED/2.7/R1 [5].

4.3.2. Conduct of clinical investigations

Where the results of clinical investigations form part of the clinical data, the clinical investigations should comply with the relevant sections of Annex X MDD or Annex 7 AIMD. Compliance with the EN 540 [3] carries the presumption that the design and conduct and monitoring of the clinical investigation conforms with the requirements of these Annexes. Whilst not carrying such a presumption of conformity, other equivalent standards may be used.²[4]

4.3.3. The results and final report of the clinical investigation

The documentation on a clinical investigation should include:

1. The identification of the medical device which is the subject of the clinical investigation, consisting of short description of the device. This description should be sufficient to address all the aspects relevant to the clinical investigation. It should include in particular:
 - normal use, intended purpose, indications, contraindications
 - performance as claimed by the manufacturer
2. A clear definition of the objectives of the clinical investigation

² Where justified, the Notified Body may require further information to assess the manufacturers clinical investigation data.

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3. Methodology

- enrolment of subjects, including inclusion and exclusion criteria, rate of enrolment, numbers and grouping
- study start and completion dates
- medical procedures involved
- appropriate, objective endpoints which, if achieved, demonstrate the required safety and performances
- parameters assessed, with frequency and methods of assessment and data acquisition
- statistical methods

4. Results and conclusion

- details of any deviations from the agreed Clinical Investigation Plan, with the reasons and any resulting amendments to the Clinical Investigation Plan for the remainder of the Clinical Investigation, together with the implications for interpretation of results.

NOTE In the case of multi-centre investigations, it should be made clear whether deviations and any subsequent amendments and/or additional or different treatment of results apply to all or only particular centres

- critical evaluation of all the data collected during the clinical investigation
- appraisal of clinical relevance
- demonstration that the objectives of the clinical investigation have been met in the context of the overall assessment of the device's safety and performance.

5. Date and signature of the responsible investigator.

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5. The role of the Notified Body

With regard to the evaluation of clinical data the Notified Body has different roles depending on the conformity assessment procedure followed.

As part of the design/type examination under Annexes II.4 or III, the Notified Body assesses the clinical data assembled by the manufacturer and the manufacturer's evaluation and the validity of the conclusions drawn. (see 5.1)

As part of quality system approval under Annex II.3, the Notified Body assesses the manufacturer's procedure for clinical data evaluation. This may include a review of examples of such evaluations. (see 5.2)

5.1. Examination of a design dossier (Annex II.4) or of a type examination dossier (Annex III)

The Notified Body (NB) examines the documentation submitted according to the preceding sections. In order to do so, the NB should possess enough knowledge and experience in clinical evaluation as stated in section 6 of this document.

5.1.1. Decision making

In reviewing the evaluation of clinical data submitted by the manufacturer, the Notified Body decides whether or not the manufacturer has adequately:

- a) described and verified the intended characteristics and performances related to clinical aspects.
- b) performed a risk analysis and estimated the undesirable side effects.
- c) concluded on the basis of documented justification that the risks are acceptable when weighed against the intended benefits.

The assessment carried out by the Notified Body will typically cover the following aspects of the manufacturer's clinical data evaluation:

- 1. The listing and characterisation of the clinical performance of the device intended by the manufacturer and the expected benefits for the patient
- 2. The use of the list of identified hazards to be addressed through evaluation of clinical data as described in paragraph 4.1. of this document

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3. The adequate estimation of the associated risks for each identified hazard by:
 - a) characterising the severity of the hazard
 - b) estimating and characterising the probability of occurrence of the harm (or health impairment or loss of benefit of the treatment) (document with rationale)
4. The decision on the acceptability of risks in relation to each identified hazard, based on the combination of 1, 3a, and 3b using the ALARP³ philosophy [6,7], and characterisation of the corresponding risk/benefit ratio as:
 - **unacceptable** or
 - **broadly acceptable** or
 - **acceptable under specified conditions**⁴ (see ISO/IEC Guide 51 [9])

5.1.2. The report of the Notified Body

The Notified Body writes a report on its assessment of the submitted clinical documentation. The report may be a separate report or part of the Notified Body's overall report. In the latter case the clinical part should be clearly identified.

The Notified Body's report should include:

- Identification of the manufacturer
- Identification of the medical device
- Basis of evaluation (which Directive and which Annex(es))
- Submitted documents
- Description of the device
- Assessment of clinical safety and performance
- Conclusion. The NB should justify and document each step of the decision making process referred in 5.1.1. One single "unacceptable risk/benefit ratio" leads to a negative conclusion.⁵

³ ALARP means "As Low As Reasonably Practicable"

⁴ The assessment of a risk/benefit ratio as "acceptable under specified conditions" implies the determination of those specified conditions under which it can be accepted. At the stage of assessment, the expected benefit to the patient, as well as the risk, has to take account of the generally acknowledged state of the art.

⁵ In some cases, the combination of the conditions specified in order to characterise different Risk/benefit ratios as acceptable may be contradictory or impracticable, and so also leads to a negative conclusion.

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- the names of all NB internal assessors and external experts involved in the assessment of the manufacturers documentation, together with details of the aspects assessed by each
- Date and signature of the responsible assessor

5.2. Evaluation as part of quality system related procedures (Annex II.3)

5.2.1. Review of the procedures

When the manufacturer selects this procedure, the Notified Body should, as part of the review of the manufacturer's quality system, assess the establishment, maintenance and application of the manufacturer's procedures for the documented evaluation of clinical data. This should cover:

- a) the responsibility for the evaluation of the clinical data by a suitably qualified person;
- b) the identification of clinical data, both unpublished (for example contained in the manufacturers files e.g. the complaints history) and published.
- c) the relevance of the clinical data identified as demonstrating compliance with particular requirements of the Directive or cited in particular aspects of the risk analysis⁶.
- d) assuring that clinical investigations are performed in compliance with the applicable regulations and the clinical investigation plan, with a suitable justification for any deviations
- e) identification and evaluation of undesirable side-effects.

This latter point involves identification of known or reasonably foreseeable hazards, qualification of their severity and of their probability of occurrence. It is part of the manufacturer's documented risk analysis based on both favourable and unfavourable data identified as relevant in order to give a balanced view.

5.2.2. Review of samples

⁶ The record of this may take the form of relevant entries in the "ER Checklist" or the risk analysis document within the manufacturer's technical documentation (check with "Explanation of terms")

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The Notified Body, when reviewing samples of the manufacturer's clinical data evaluation, should pay special attention to the following:

- (a) whether or not the data is relevant to the device or medical procedure involved;
- (b) where the manufacturer, in the selected sample, has chosen the "literature route" (see 4.2.), whether the criteria defined in 4.2. have been applied;
- (c) where the manufacturer, in the selected sample, has selected the "clinical investigations route" (see 4.3.), whether the criteria defined in 4.3. have been applied.

When performing the assessment on samples of a manufacturer's risk/benefit assessment, the Notified Body will follow the steps indicated in 5.1.1., 1-4.

6. Notified Body Specific Procedures and Expertise

Notified Bodies should establish and implement internal policies and procedures for the assessment of clinical data in order to:

- a) Ensure that suitable resources, especially relevant knowledge and competence necessary for such evaluation, are available within the Notified Body and/or by contracting external experts.

Such expertise should be sufficient to identify and estimate the risks and benefits associated with the use of the medical devices. The evaluation team should be able to evaluate a risk analysis and the risk management strategy performed by the manufacturer. The evaluation team should understand the device technology as well as the medical procedure [8].

Such an evaluation may require input from a qualified medical practitioner (for example physician, dentist, nurse), as appropriate for the particular device, who has clinical experience.

When examining the results of clinical investigations, the evaluation team should have knowledge in planning, conduct and interpretation of clinical investigations. All evaluators should be trained and qualified.

Particular attention should be drawn to training of external experts with regard to the conformity assessment procedure. The Notified Body should be responsible

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for reviewing the opinion of these experts, taking account of their level of knowledge of the provisions of the Directives.

- b) review the evaluation of clinical data provided by the manufacturer.
- c) document the opinion with rationale of all experts involved.
- d) ensure that any external experts involved are impartial and independent from any parties involved, having due regard to any conflict of interest which may compromise impartiality (see also MedDev 2.10/2 [11]) .
- e) document the result of their assessment. This is achieved through a specific report which may be part of, or may be referenced in the overall design / type examination report.
- f) preserve confidentiality of the information and data received from the manufacturer, especially within the terms for contracting external experts.

7. References

1. Council Directive 90/385/EEC of 20 June 1990 concerning active implantable medical devices
2. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices
3. EN 540: Clinical investigation of medical devices for human subjects, 1993
4. ISO 14155 Clinical investigation of medical devices
5. Guidance on when a clinical investigation is needed for CE marking, NB-MED/2.7/Rec1
6. Task force on CE marking of existing products, NBM/026/95 rev 2.
7. EN 60601-1-4 : Medical electrical equipment Part 1: General requirements for safety, 4. Collateral Standard: Programmable electrical medical systems
8. Committee draft ISO/CD 14971, Medical Devices - Risk Management Dated 1998-05-21.

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9. MedDev 1/94 Rev 10: Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers.
10. ISO/IEC Guide 51 Guideline for the inclusion of safety aspects in Standards
11. MedDev 2.10/2 Rev 01.03.99: Designation and monitoring of Notified Bodies within the framework of EC Directives on medical devices.

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Rev. 1 Notified Body Meeting, Brussels, November 3 & 4, 1998:
The NB-MED task force on „Evaluation of clinical data“ presented the current status of the work (see document NBM/172/98).

Revision no: 1

The general structure of this work was accepted on occasion of the last meetings of NB-MED. The document does not deal with clinical investigation but with evaluation of clinical data. Also the key-terms of "clinical data" and "evaluation of clinical data" are explained. Further work will be done also by merging the tabled document with the NB-MED Recommendations NB-MED/2.7/Rec1 *Guidance on clinicals*. Also it was tried for reaching consistency to follow the ALARP philosophy as applied by ISO/TC 210 on *Risk management* in accordance with the ISO/IEC guidance 51. In the current work alternative medicines and miracle products were left out of consideration because it was not so easy to make a guidance; also this is more a task for the member states.

The **members of NB-MED** were asked to send their comments within one month to the Technical Secretariat especially to *literature route/ quality of the scientific data* and to *decision making process*. Next meeting of the task force will be held in January 1999. Further development will be made finally within the NBRG.

Rev. 2 A new draft document NB-MED Recommendation 2.7/Rec3 „Evaluation of clinical data“ was delivered to NBRG for further discussion on its meeting on 01./02.02.99.

Revision no: 2
stage 1.

Rev. 3: NBRG meeting, Dublin, February 1 & 2, 1999:
Previous changes to the document were confirmed, and a few further changes were made to improve clarity, at the 01-02 February 1999, Dublin meeting of the NBRG. It was also decided to send the draft document, with its "Rationale and history" sheet to all member of NB-MED for commenting before presenting it for approval in the Plenary meeting in March 1999.

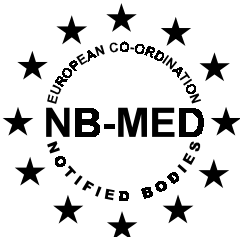
Revision no: 3
stage 1.

Rev. 4: NB-MED task force on "Evaluation of clinical data" meeting, Brussels, April 07 1999

The document was amended to address the comments made by the UK Medical Devices Agency in relation to Rev 3. The changes include revision of the definition of "Clinical data". The document now clarifies the role of pre-clinical data, for example, in establishing the extent of similarity between device(s) and medical procedures(s) covered by the scientific literature and the characteristics of the device being assessed. Changes also make clear the need to decide whether

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the available data is sufficient to demonstrate conformity with the Directive and the identified clinical hazards.

In relation to the published literature, the document now makes clear that the factors influencing its validity include the extent to which it is the outcome of a study following scientific principles. The document also now states that the report on the compilation of the scientific literature should clearly establish the extent to which the literature relates to the specific characteristics and features of the device being assessed (i.e. its relevance).

Rev. 5: NBRG meeting, Copenhagen, May 10 & 11, 1999:

The comments made by the UK MDA and Swedish MOH were considered. All changes made by the NB-MED Clinical Task Force were considered, and a few further changes were made.

It was agreed that the document, as revised, should be presented for adoption at the June 8-9, 1999 NB-MED Plenary meeting

Revision no: 5
stage 2.

Notified Body Meeting, Brussels, June 8. & 9. 1999:

Dr. Holland presented the results of the meeting of the NBRG on 10./11.05.99 (NBM/86/99 and the rationale & history sheet). The older document on "Clinical evidence" (No 2.7/Rec2, stage 1, see overview-document NBM/77/99) should be deleted because the subject on *clinical evidence* was already defined by the NB-MED Recommendation NB-MED/2.7/Rec1 *Guidance on clinicals* and has got further clarification by the presented draft NB-MED Recommendation NB-MED/2.7/Rec3 *Evaluation of clinical data*. Mr. Virefléau/G-Med mentioned that also the UK MDA comments - tabled as NBM/57/99 - were to be considered. He proposed - based on an older decision - to merge NB-MED/2.7/Rec1 "Guidance on clinicals" and NB-MED/2.7/Rec3 "Evaluation of clinical data". Also he gave further explanation to the wording "prospective" and "retrospective clinical investigations". Further he explained with reference to paragraph 3.2 the meaning of "and other selected sources"; these could be all kinds of clinical data from experience on human beings including retrospective data. Prof. Leitgeb mentioned that he misses a clause that miracle products are not accepted; with reference to paragraph 5.1.1 the decision making process is primarily based on a risk analysis and so low risk miracle products might be accepted. Mr. Virefléau mentioned that within the work of the task force it was very difficult to establish the risk benefit ratio for miracle products; therefore it was decided within a prior NB-MED plenary meeting to drop the aspect of miracle products. Prof. Leitgeb answered that in this case a note should be added that this Recommendation does not apply to miracle products. He proposed to add a sentence like "a device could be rejected even at zero risk if the clinical function is not sufficiently proven". Dr. Rader/TÜV PS explained that in deed there is no special clause for miracle products but there are medical devices where the performance and the function can be substantiated by clinical data and there are some devices where this can not be done; normally the second case - that no clinical data is available that supports the medical device and its performance and function and the claim

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of the manufacturer - should cover also the answer/decision to CE-mark miracle products or not. Mr. Virefléau reminded to the problem of “placebo-effect”; it is very difficult - as discussed in prior meetings - to decide that a miracle product has no benefit at all. It has to take account the possibility of the placebo-effect exactly in the same way as there is a placebo-effect for pharmaceuticals; the benefit can not be estimated.

The NB-MED adopted the revised draft Recommendation document as presented (without any other changes).

The document will be incorporated now in the booklet of NB-MED Recommendations and shall be presented also to the Medical Devices Experts Group (only) for information but not for getting a stage 4 document. In a first step all involved parties should make their experience by application of this Recommendation. Further it was decided that the discussed merging of the both documents (NB-MED/2.7/Rec1 and NB-MED/2.7/Rec3) should also depend of further experience will be made; within about one to two years this should be discussed once again.

Confirmed at stage 3

revision no: 5



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