Directives 90/385/EEC and 93/42/EEC

MEDICAL DEVICES

Clinical Evaluation Report
Presentation guide

The elements of the clinical evaluation report are records of the process that the manufacturer applies to the identification, selection, appraisal and critical analysis of clinical data in order to meet the applicable essential requirements of medical devices Directives.

The purpose of this guide, intended to manufacturers of medical devices, is to specify the different elements to be included in the clinical evaluation report, which is part of the design dossier and technical file within the frame of CE marking procedures for medical devices, whatever the class of the medical device is.
I – REFERENCE DOCUMENTS

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Table A: reference documents

NOTE
French transposition laws are available in the Journal Officiel de la République Française (Official gazette of the French Republic).
European Directives are available in the Official Journal of the European Union.
Standards are available at AFNOR www.afnor.org
GHTF (Global Harmonization Task Force) guidelines are available on the following website: www.gh.tf.org
II – Definitions

**Bias:** bias is a systematic deviation of an outcome measure from its true value, leading to either an overestimation or underestimation of a treatment’s effect. It can originate from, for example, the way patients are allocated to treatment, the way treatment outcomes are measured and interpreted, and the way data are recorded and reported. [Adapted from GHTF SG5/N2R8:2007]

**Clinical data:** the safety and/or performance information that is generated from the clinical use of a device. Clinical data are sourced from:

- clinical investigation(s) of the device concerned; or
- clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or
- published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.

[derived from Article 1.2.k MDD and Art. 1.2.k AIMDD]

**Clinical evaluation:** a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer’s Instructions for Use.

Note: In exceptional cases where an instruction for use is not required, the collection, analysis and assessment are conducted taking into account generally recognised modalities of use.

**Clinical evidence:** the clinical data and the clinical evaluation report pertaining to a medical device. [GHTF SG5/N2R8:2007]

**Clinical investigation:** systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device.

Note: ‘clinical trial’ or ‘clinical study’ are synonymous with ‘clinical investigation’. [EN ISO 14155:2011]

**Equivalent device:** a device for which equivalence to the device in question can be demonstrated.

(See the explanation in this guidance document, section IV)

**Feasibility study:** a clinical investigation that is commonly used to capture preliminary information on a medical device (at an early stage of product design) to adequately plan further steps of device development, including needs for design modifications or parameters for a pivotal study. [MEDDEV 2.7/2 revision 2]

**Clinical performance:** behaviour of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s). [EN ISO 14155:2011]

**Clinical safety:** freedom from unacceptable clinical risks, when using the device according to the manufacturer’s Instructions for Use. [MEDDEV 2.7/2 revision 2]
Note: In exceptional cases where an instruction for use is not required, the collection, analysis and assessment are conducted taking into account generally recognised modalities of use.

**Clinical use:** use of a medical device in or on living human subjects.

Note: Includes use of a medical device that does not have direct patient contact.

**Intended purpose:** the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional materials. [MDD Art. 1.2.g, AIMDD Art. 1.2.f]

**PMCF plan:** the documented, proactive, organised methods and procedures set up by the manufacturer to collect clinical data based on the use of a CE-marked device corresponding to a particular design dossier or on the use of a group of medical devices belonging to the same subcategory or generic device group as defined in Directive 93/42/EEC. The objective is to confirm clinical performance and safety throughout the expected lifetime of the medical device, the acceptability of identified risks and to detect emerging risks on the basis of factual evidence. [MEDDEV 2.12/2 rev.2]

**PMCF study:** a study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labelling. [MEDDEV 2.12/2 rev.2]

**Sufficient clinical evidence:** an amount and quality of clinical evidence to guarantee the scientific validity of the conclusions.

**III – Principles of clinical evaluation**

**III.1) What is a clinical evaluation?**

Clinical evaluation is a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to analyse whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer’s instructions for use.

The requirements for clinical evaluation apply to all classes of medical devices. The evaluation should be appropriate to the device under evaluation, its specific properties, and its intended purpose.

Conformity to the Essential Requirements can only be assumed when the following items are aligned with each other:

1. the information materials supplied by the manufacturer (the labelling, instructions for use, available promotional materials, including accompanying documents foreseen by the manufacturer),
2. the clinical evaluation (the device description used for the clinical evaluation)
3. the available clinical data (such as results of Clinical Investigations, publications, PMS studies, etc.),
4. the risk management file
5. the usability demonstration

III.2) When clinical evaluation is to be performed?

Clinical evaluation is conducted throughout the life cycle of a medical device, as an ongoing process. Usually, it is first performed during the development of a medical device in order to identify data that need to be generated for market access. Clinical evaluation is mandatory for initial CE-marking and it must be actively updated thereafter. As reminder, it addresses the section 7.3.7 of the ISO 13485 standard, current version.

III.2.a) During device development

Typically, manufacturers carry out clinical evaluations to:

1. define needs regarding clinical safety and clinical performance of the device;
2. in case of possible equivalence to an existing device, evaluate if there are clinical data available and determine equivalence;
3. carry out a gap analysis and define which data still need to be generated with the device under evaluation, whether clinical investigations are necessary and if so, to define the study design.

III.2.b) Clinical evaluation for initial CE-marking

Clinical evaluation is required to be carried out for the conformity assessment process leading to the CE-marking and placing on the market of a medical device. The purpose is to:

1. document that there is sufficient clinical evidence to demonstrate conformity with the Essential Requirements covering clinical performance and clinical safety;
2. identify aspects that need to be addressed systematically during post-market surveillance (PMS), e.g. in post market clinical follow-up studies (PMCF Studies) required under the medical device directives. Typically, these aspects include estimation of residual risks and uncertainties or unanswered questions (such as rare complications, uncertainties regarding long-term performance, safety under wide-spread use).

III.2.c) Updating the CE: frequency and consideration

The manufacturer should define and justify the frequency at which the clinical evaluation needs to be actively updated.

The clinical evaluation is actively updated:

- when the manufacturer receives new information from PMS that has the potential to change the current evaluation;
- if no such information is received, then
  - at least annually if the device carries significant risks or is not yet well established; or
  - every 2 to 5 years if the device is not expected to carry significant risks and is well established, a justification should be provided.
When involvement of notified bodies is required, updates are usually coordinated with the notified body. Typically, they are aligned with the timetable for the renewal of the certificates.

In accordance with the Directives, the clinical evaluation and the clinical evaluation report must be actively updated with data obtained from post-market surveillance.

### III.3) How is Clinical Evaluation performed?

There are discrete stages in performing a clinical evaluation:

- **Stage 0 - Scope of clinical evaluation**:
  - It explains the scope and context of the evaluation, including which products/ models/ sizes/ settings are covered by the clinical evaluation report, the technology on which the medical device is based, the conditions of use and the intended purpose of the device;
  - It documents any claims made about the device's clinical performance or clinical safety.

- **Stage 1 - Identification of pertinent data**:
  - It explains the literature search strategy;
  - It presents the nature and extent of the clinical data and relevant pre-clinical data that have been identified.

- **Stage 2 – Appraisal of pertinent data**:
  - It explains the criteria used by the evaluators for appraising data sets;
  - It summarises the pertinent data sets (methods, results, conclusions of the authors);
  - It evaluates their methodological quality, scientific validity, the relevance for the evaluation, the weighting attributed to the evidence, and any limitations;
  - It presents justifications for rejecting certain data or documents.

- **Stage 3 - Analysis of data**:
  - It explains if and how the referenced information, such as confirmation of compliance with clinical data requirement from applicable harmonised standards and the clinical data, constitute sufficient clinical evidence for demonstration of the clinical performance and clinical safety of the device under evaluation;
  - It explains whether there are adequate data for all aspects of the intended purpose and for all products/ models/ sizes/ settings covered by the clinical evaluation.
  - It describes the benefits and risks of the device (their nature, probability, extent, duration and frequency);
  - It explains the acceptability of the benefit/risk profile according to current knowledge/ the state of the art in the medical fields concerned, with reference to applicable standards and guidance documents, available medical alternatives, and the analysis and conclusions of the evaluators on fulfilment of all Essential Requirements pertaining to clinical properties of the device (MDD ER1, ER3, ER6; AIMDD ER1, ER2, ER5);
  - It analyses if there is consistency between the clinical data, the information materials supplied by the manufacturer, the risk management documentation for the device under evaluation;
  - whether there is consistency between these documents and the current knowledge/ the state of the art;
  - It identifies any gaps and discrepancies;
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- It identifies residual risks and uncertainties or unanswered questions (such as rare complications, uncertainties regarding medium- and long term performance, safety under wide-spread use) that should be further evaluated during PMS, including in PMCF studies.

- Stage 4: Finalise the clinical evaluation report

The clinical evaluation report summarises and draws together the evaluation of all the relevant clinical data documented or referenced in other parts of the technical documentation. The clinical evaluation report and the relevant clinical data constitute the clinical evidence for conformity assessment.

III.4) Who should perform a Clinical Evaluation?

The clinical evaluation should be conducted by a suitably qualified individual or a team.

The manufacturer should take the following aspects into consideration:

1. The manufacturer defines requirements for the evaluators that are in line with the nature of the device under evaluation and its clinical performance and risks.
2. The manufacturer should be able to justify the choice of the evaluators through reference to their qualifications and documented experience, and to present a declaration of interest for each evaluator.

As a general principle, the evaluators should possess knowledge of the following:

1. research methodology (including clinical investigation design and biostatistics);
2. information management (e.g. scientific background or librarianship qualification; experience with relevant databases such as Embase and Medline);
3. regulatory requirements; and
4. medical writing (e.g. post-graduate experience in a relevant science or in medicine; training and experience in medical writing, systematic review and clinical data appraisal).

With respect to the particular device under evaluation, the evaluators should in addition have knowledge of:

1. the device technology and its application;
2. diagnosis and management of the conditions for which the device is intended to be used, knowledge of medical alternatives, treatment standards and technology (e.g. specialist clinical expertise in the relevant medical specialty).

The evaluators should have at least the following training and experience in the relevant field:

1. a degree from higher education in the respective field and 5 years of documented professional experience; or
2. 10 years of documented professional experience if a degree is not a prerequisite for a given task, related to the clinical evaluation.

There may be circumstances where the level of evaluator expertise may be less or different; this should be documented and duly justified. It is understood that the competences can be shared on a team, knowing that the plan and the report need to be signed by all the members of the team.
IV – Equivalence

Clinical, technical and biological characteristics shall be taken into consideration for the demonstration of equivalence:

- **Clinical:**
  - used for the same clinical condition (including when applicable similar severity and stage of disease, same medical indication), and
  - used for the same intended purpose, and
  - used at the same site in the body, and
  - used in a similar population (this may relate to age, gender, anatomy, physiology, possibly other aspects), and
  - not foreseen to deliver significantly different performances (in the relevant critical performances such as the expected clinical effect, the specific intended purpose, the duration of use, etc.).

- **Technical:**
  - be of similar design, and
  - used under the same conditions of use, and
  - have similar specifications and properties (e.g. physicochemical properties such as type and intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, surface texture, porosity, particle size, nanotechnology, specific mass, atomic inclusions such as nitrocarburising, oxidability), and
  - use similar deployment methods (if relevant), and
  - have similar principles of operation and critical performance requirements.

- **Biological:** Use the same materials or substances in contact with the same human tissues or body fluids.

Exceptions can be foreseen for devices in contact with intact skin and minor components of devices; in these cases risk analysis results may allow the use of similar materials taking into account the role and nature of the similar material. Different aspects of equivalence and compliance to different Essential Requirements can be affected by materials. Evaluators should consider biological safety (e.g. in compliance to ISO 10993) as well as other aspects necessary for a comprehensive demonstration of equivalence. A justification explaining the situation should be provided for any difference.

For assuming equivalence:

- equivalence can only be based on a single device;
- all three characteristics (clinical, technical, biological) need to be fulfilled;
- similar means that no clinically significant difference in the performance and safety of the device would be triggered by the differences between the device under evaluation and the device presumed to be equivalent;
- the differences between the device under evaluation and the device presumed to be equivalent need to be identified, fully disclosed, and evaluated; explanations should be given why the differences are not expected to significantly affect the clinical performance and clinical safety of the device under evaluation;
- the manufacturer should investigate if the medical device presumed to be equivalent has been manufactured via a special treatment (e.g. a surface modification, a process that modifies material characteristics); if this is the case, the treatment could cause differences in respect to technical and biological characteristics; this should be taken into account for the demonstration of equivalence and documented in the CER;
- if measurements are possible, clinically relevant specifications and properties should be measured both in the device under evaluation and the device presumed to be equivalent, and presented in comparative tabulations;
• comparative drawings or pictures should be included in order to compare shapes and sizes of elements that are in contact with the body;
• the manufacturer is expected to:
  o include the supporting non-clinical information (e.g. pre-clinical study reports) in the technical documentation of the device, and
  o in the clinical evaluation report, summarise the information and cite its location in the technical documentation;
• for the evaluation of the technical characteristics, devices that achieve the same therapeutic result by different means cannot be considered equivalent;
• for the evaluation of the biological characteristics:
  o when a detailed chemical characterisation of materials in contact with the body is needed, ISO 10993-18 Annex C can be used to show toxicological equivalence but this is just a part of the evaluation of the biological criteria;
  o sourcing and manufacturing procedures may adversely affect impurity profiles; analytical methods chosen to characterise medical devices should appropriately take into consideration knowledge concerning expected impurity profiles (tests may have to be repeated when production methods or sourcing are changed);
  o it may be necessary to show from histopathological studies that the same host response is achieved in vivo in the intended application and the intended duration of contact;
  o for animal tests, differences between species may limit the predictive value of the test; the choice of the test and its predictive value should be justified;
  o abrasion, if relevant, and host response to particles may also need to be considered.
• the only clinical data that are considered as relevant are the data obtained when the equivalent device is a CE-marked medical device used in accordance with its intended purpose as documented in the IFU.

Note: Exceptions can be considered. When the equivalent device is not a CE-marked device, information concerning the regulatory status of the equivalent device and a justification for the use of its data should be included in the clinical evaluation report. The justification should explain if the clinical data is transferrable to the European population, and an analysis of any gaps to good clinical practices (such as ISO 14155) and relevant harmonised standards.
### V – Clinical Evaluation Report

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<th>Table of contents</th>
<th>Example of contents</th>
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| **1. Scope of the clinical evaluation** | 1. Identification of devices covered by this clinical evaluation report, products, models, sizes, software versions, accessories, their proprietary names, code names assigned during device development.  
2. Concise physical and chemical description, including materials. Whether the device incorporated medicinal substances (already on the market or new), tissues, or blood products. Mechanical and physicochemical characteristics; others (such as sterile vs. non-sterile, radioactivity etc.); picture or drawing of the device.  
3. Technologies used, whether the device is based on a new technology, a new clinical application of an existing technology, or the result of incremental change of an existing technology. Description of innovative aspects of the device.  
5. Exact description of the intended purpose as described in the device's IFU (In exceptional cases where an instruction for use is not required, describe the generally recognised modalities of use), with exact medical indications (if applicable) and contraindications; claims made in available promotional materials. Name of disease or condition, clinical form, stage, severity, symptoms or aspects to be treated/managed/diagnosed, target patient population, target user group. Intended application of the device, single use/reusable, invasive/non-invasive, implantable, duration of use or contact with the body, maximum number of repeat applications. Identification of organs, tissues or body fluids contacted by the device. Precautions.  
6. Claims on clinical performance and clinical safety foreseen by the manufacturer.  
7. Whether the device is already CE marked, whether it is on the market, since when, in what regions, history of the device, including date of past modifications with reasons and description, sales volumes.  
8. Changes since the last report, whether the device has been modified, identification of new products, models, sizes, software, accessories, new intended purposes, new claims, new events related to the device with an impact on clinical evaluation. Identification of the sections of the clinical evaluation report that are concerned with the new information and have been modified.  
9. Other aspects if relevant. |
| **2. Clinical background, current knowledge, state of the art** | 1. Identification of medical fields concerned/ relevant medical conditions.  
2. Brief summary and justification of the literature search strategy |
applied for retrieval of information on current knowledge/ the state of the art, including sources used, search questions, search terms, selection criteria applied to the output of the search, quality control measures, results, number and type of literature found to be pertinent. Appraisal criteria used.

3. Applicable standards and guidance documents.

4. Description, natural course and consequences of the medical conditions concerned. Whether there are different clinical forms, stages and severities of the conditions. Frequency in the general population, by age group, gender, ethnicity, familial predispositions, genetic aspects.

5. Description of available therapeutic/ management/ diagnostic options, historical context and developments, summary of advantages and disadvantages of the different options, benefit/ risk profiles and limitations in relation to the different clinical forms, stages, and severities of the medical conditions and in relation to different target populations. Description of the benefits and risks (nature, extent, probability, duration, frequency), acceptability of undesirable side-effects and other risks (including the nature, severity, probability and duration of acceptable harm).

6. Hazards due to substances and technologies that could be relevant to the device under evaluation. The mechanisms of harm, clinical aspects of minimisation and management of side effects and other risks.

7. Types of users. Diverging opinions of professionals as to the use of the different medical options. Unmet medical needs.

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<th>3. Device under evaluation</th>
<th>3.1. Type of evaluation</th>
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<td>Whether the clinical evaluation is based on</td>
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<td>- scientific literature currently available, and/or</td>
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<td>- clinical investigations made</td>
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<td>- clinical data generated from risk management activities and the PMS programmes or</td>
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<td>- whether demonstration of conformity with essential requirements based on clinical data is not deemed appropriate.</td>
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If clinical data is not deemed appropriate, adequate justification for any such exclusion has to be given:

- The justification must be based on the output of the risk management process.
- The device/body interaction, the intended used and claims of the manufacturer have to be specifically considered.
- Adequacy of demonstration of conformity with the Essential Requirements based on performance evaluation, bench testing and pre-clinical evaluation in the absence of clinical data has to be duly substantiated.
- A clinical evaluation is still required and the above information and evidence-based justification should be presented in the clinical
3.2. Clinical data from literature

Brief summary and justification of the literature search strategy applied for retrieval of clinical data, including objectives, sources used, search questions, search terms, selection criteria applied to the output of the search, quality control measures, results, number and type of literature found to be pertinent.

3.3. Demonstration of equivalence (only when equivalence is claimed)

1. Identification of the equivalent device and its manufacturer. Exact name, models, sizes, software versions, accessories, etc. Name of the manufacturer. Relationship to the device under evaluation (predecessor/ successor, others). If the device is not CE-marked, justification for the use of the data, based on the other regulatory status.

2. Comparison of clinical, biological and technical characteristics (see Appendix A1 for details). Justification of equivalence, description of relevant clinical, biological and technical characteristics that affect clinical properties of the device, differences between the intended purpose of the device under evaluation and the equivalent device (indications, contraindications, precautions, target patient groups, target users, mode of application, duration of use/ number of re-applications, others), type of device-body interaction. Choice, justification and validity of parameters and models for non-clinical determination of characteristics.

3. Identification of pre-clinical studies carried out and literature used, concise summaries of studies and literature (methods, results, conclusions of the authors), evaluation of the methodological quality of the study or document, the scientific validity of the information.

4. Comparative tabulations for the device under evaluation versus the equivalent device showing parameters relevant to the evaluation of the three characteristics. Comparative drawings or pictures of the device and the equivalent device showing the elements in contact with the body.

5. Identification of differences, evaluation if differences are expected or not to influence the clinical performance and clinical safety of the device, reasons for assumptions made.

6. Conclusions concerning equivalence. Whether the comparison carried out covers all products/ models/ sizes/ settings/ accessories and the entire intended purpose of the device under evaluation, or only certain products/ models/ sizes/ settings/ accessories, or selected aspects of the intended purpose, which ones.

7. Conclusions whether equivalence is demonstrated or not; it it is demonstrated, confirmation that the differences are not expected to affect the clinical performance and clinical safety of the device under evaluation; description of any limitations and gaps.

Identification of clinical data generated and held by the manufacturer:
### 3.4. Clinical data generated and held by the manufacturer

- All pre market clinical investigations
- All clinical data generated from risk management activities and the PMS programmes which the manufacturer has implemented in Europe and in other countries.

### 3.5. Summary and appraisal of clinical data

Summaries of clinical data generated and held by the manufacturer and of scientific literature found to be pertinent. Including brief summary of the studies or references (methods, results, conclusion of the authors), evaluation of their methodological quality, scientific validity of contents, relevance to the clinical evaluation, weighting attributed to the data, contents used (performance data, safety data, both) reasons for rejecting a study or document, reasons for rejecting some of its contents.

(See annex A6 of MEDDEV 2.7.1 document).

### 3.6. Analysis of the clinical data

#### 3.6.1. Requirement on safety (MDD ER1 / AIMDD ER1)

Summary of conformity assessment with requirement on safety (MDD ER1 / AIMDD ER1).

Analysis whether there are special design features that pose special safety concerns (e.g. presence of medicinal, human or animal components) that were identified in the device risk management documentation and that required evaluation from a clinical perspective, and whether these have been adequately addressed.

Whether the risks identified in the risk management documentation and literature have been adequately addressed.

Whether all the hazards and other clinically relevant information (e.g. clinical precautions for reduction of risks, clinical management of risks) have been identified appropriately.

Whether the safety characteristics and intended purpose of the device requires training of the end-user or other precautions, if users foreseen are adequate, if training requirements and other precautions are described in the IFU.

Whether there is full consistency between current knowledge/the state of the art, the available clinical data, the information materials supplied by the manufacturer, and the risk management documentation for the device.

#### 3.6.2. Requirement on acceptable benefit/risk profile (MDD ER1 / AIMDD ER1)

Summary of conformity assessment with requirement on acceptable benefit/risk profile (MDD ER1 / AIMDD ER1).

Summary of the total experience with the device, including estimated numbers and characteristics of patients exposed to the device in clinical investigations, PMCF, from other user experience, and in the market; duration of follow-up. Nature, extent/severity, probability/frequency, duration of benefits to the patients and of undesirable side-effects and other risks. For each aspect of the intended purpose, whether the benefit/risk profile including its uncertainties or unanswered questions is compatible with a high level of protection of health and safety, corresponding justifications.
3.6.3. Requirement on performance (MDD ER3 / AIMDD ER2)

Summary of conformity assessment with requirement on performance (MDD ER3 / AIMDD ER2). Description of clinical performance. For each intended performance, extent to which evaluation of benefits is possible based on available data, limitations of the data, description of gaps, uncertainties or unanswered questions, and assumptions. Whether available data allows adequate evaluation of performance, limitations of the data, gaps, uncertainties or unanswered questions. Whether there is sufficient clinical evidence for every intended performance.

3.6.4. Requirement on acceptability of side-effects (MDD ER6 / AIMDD ER5)

Summary of conformity assessment with requirement on acceptability of undesirable side-effects (MDD ER6 / AIMDD ER5). Whether the data available is of sufficient amount and quality for the detection of undesirable side-effects and their frequency, limitations of the data, description of gaps, uncertainties or unanswered questions, and assumptions. Whether the undesirable side-effects are acceptable and corresponding justifications.

4. Conclusions

Clear statement concerning compliance to Essential requirements. Acceptability of the benefit/risk profile according to current knowledge/the state of the art in the medical fields concerned and according to available medical alternatives. Suitability of the device, including its IFU, for the intended users and usability aspects; discrepancies. If there is consistency between the clinical data, the information materials supplied by the manufacturer, the risk management documentation for the device under evaluation; discrepancies.

5. Post market surveillance

Description of residual risks and uncertainties or unanswered questions, whether these are acceptable for CE-marking, how these should be followed during PMS (uncertainties regarding medium- and long term performance, safety under wide-spread use, residual risks such as undesirable side-effects and complications occurring at rates below detection possibilities of currently available clinical data, others). Whether these are already being addressed in ongoing PMS activities, e.g. in currently ongoing PMCF studies. Whether new or additional PMS activities, including PMCF studies, should be foreseen.

6. Date of the next clinical evaluation

Suggested date, justification of the date.

7. Dates and signatures

Date of the clinical evaluation report. Statement that the evaluators agree with the contents of the report. Dates, names and signatures of the evaluators. Final release by the manufacturer. Date, name and signature.

8. Qualification of the responsible evaluators

CV to be provided

9. References

Information on declarations of interests to be provided
VI – Documents to provide to LNE / G-MED for assessment

1. Clinical Evaluation Plan
2. Clinical Evaluation Report
3. All data used to support Clinical Evaluation
4. Evidence of CE marking of equivalent device(s) or other valid regulatory status
5. Information material
6. Evaluator’s qualification
7. Evaluator’s conflict of interest declaration
ANNEX 1

Contents of the evaluation file on the usefulness of the drug substance with an ancillary function compared to that of the medical device

**Purpose:** to justify the usefulness of the pharmacologically active substance incorporated as an ancillary to the medical device taking into account the intended use chosen by the manufacturer.

**File contents:** The evaluation report of usefulness must be dated and signed, and must specify the identification and qualification of the evaluator. Moreover, it must contain the following elements:

- Confirmation of the status of the product
- Description of the combined product (physical description, components, features, technology applied…), of the performances claimed, of instructions, target populations, conditions of use including precautions and restrictions of use.
- Description of the pharmacologically active substance added
- Justification of the medical device / medicine combination
- Role of the active substance and its capability to be active in the combination
- Capability of the substance to demonstrate its action on the site treated
- Performances claimed for the pharmacologically active substance as well as the presence of side effects or a device/medicine interaction
- Performances claimed for the medical device
- Instruction manual, labelling and description of the packaging
- Clinical pharmacokinetics data:
  - nature of the exposure (local or systemic)
  - maximum exposure rate and duration of exposure
  - useful dose targeted of the substance on the site treated
  - studies performed concerning the maximum acceptable rate taking into account potential risks and individual variability
  - data on the release of the substance of the medical device: tissue/plasma release, in time and space
- Preclinical data demonstrating the performances of the drug substance
- Results of tests on animals (relevance of the chosen model, combined device test versus device only test)
- Clinical data specific to the use of the drug substance (bibliographical data or clinical investigation or a combination of both)
- Description of the benefits / risks report linked with the potential risks relating to the presence of the drug substance:
  - Risks linked to the nature of the drug (new therapeutic effect, unconventional route of administration, new assay, stability, interaction with the medicine device, difficulty of manufacturing, …)
  - Risks linked with the action mode of the drug (local or metabolic risks, risks linked to the diffusion of the substance at a distance from the treated site, …)
  - Risks linked with deleterious effects expected or not of the drug substance (local or afar side effects, risks at medium or long term, drug interactions, …)
- Final conclusion on the need to incorporate the drug substance.
# ANNEX 2

## Degrees of novelty for a medical device

<table>
<thead>
<tr>
<th>Degree of novelty</th>
<th>Type of novelty</th>
<th>Innovation where the dominant is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Major innovation</td>
<td>Technological and Clinical</td>
</tr>
<tr>
<td>4</td>
<td>Incremental</td>
<td>Technological or Clinical</td>
</tr>
<tr>
<td>3</td>
<td>Substantial</td>
<td>Technological and Clinical</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Technological or Clinical</td>
</tr>
<tr>
<td>1</td>
<td>Lacking or minor novelty</td>
<td>Known technology or Inchanged clinical impact</td>
</tr>
</tbody>
</table>

**Breaking technology**: Device that disrupts technologies in healthcare and could replace it definitely.

**Incremental technology**: Device including a technological breakthrough in comparison to another device.

**Strong clinical impact**: Device which presents a major interest for healthcare especially by improving very statistically the clinical practice, and/or the patient’s condition, and/or providing a new diagnostic strategy in a clinical field.

**Moderate clinical impact**: Device which presents a new interest for healthcare especially by improving the clinical practice, and/or the patient’s condition, and/or providing a diagnostic alternative.

**Lacking or minor novelty**: Device with no or negligible modification compared to a similar device already on the market (like aesthetic modification).

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1 For IVD devices, a new biological test/dosage (of one or several markers) is an incremental technology