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GUIDELINES ON MEDICAL DEVICES

POST MARKET CLINICAL FOLLOW-UP STUDIES

A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical Devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interest parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts where circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector.

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Preface

This document is intended to be a guide for manufacturers and Notified Bodies on how to carry out Post-Market Clinical Follow-up (PMCF) studies in order to fulfil Post-Market Surveillance (PMS) obligations according to Section 3.1 of Annex II, Section 3 of Annex IV, Section 3 of Annex V, Section 3.1 of Annex VI or Section 4 of Annex VII of the Medical Devices Directive (93/42/EEC) and Section 3.1 of Annex 2, Section 3 of Annex 4, Section 3.1 of Annex 5 of the Active Implantable Medical Devices Directive (90/385/EEC). These Sections refer to requirements of Annex X of Directive 93/42/EEC and Annex 7 of Directive 90/385/EEC, respectively.

Attention is drawn to paragraph 8 of Article 15 of Directive 93/42/EEC which spells out the provisions of Article 15 that are not applicable to clinical investigations conducted using CE-marked devices within their intended use.

Similarly when PMCF studies are conducted using CE marked devices within their intended use, the provisions of section 2.3.5 of Annex X of Directive 93/42/EEC do not apply. However, the provisions of Directive 93/42/EEC concerning information and notification of incidents occurring following placing devices on the market are fully applicable.

1. Introduction

While clinical evidence is an essential element of the premarket conformity assessment process to demonstrate conformity to Essential Requirements, it is important to recognise that there may be limitations to the clinical data available in the pre-market phase. Such limitations may be due to the duration of pre-market clinical investigations, the number of subjects and investigators involved in an investigation, the relative heterogeneity of subjects and investigators and/or the controlled setting of a clinical investigation versus the full range of clinical conditions encountered in general medical practice.

A precondition for placing a product on the market is that conformity to the relevant Essential Requirements, including a favourable benefit/risk ratio, has been demonstrated. The extent of the data that can be gathered in the pre-market phase does not necessarily enable the manufacturer to detect rare complications or problems that only become apparent after wide-spread or long term use of the device. As part of the manufacturer's quality system, an appropriate post-market surveillance plan is key to identifying and investigating residual risks associated with the use of medical devices placed on the market. These residual risks should be investigated and assessed in the post-market phase through systematic Post-Market Clinical Follow-up (PMCF) study(ies).

Clinical data obtained from post-market surveillance and during PMCF studies by the manufacturer are not intended to replace the pre-market data necessary to demonstrate conformity with the provisions of the legislation. However, they are critical to update the clinical evaluation throughout the life-cycle of the medical device and to ensure the long term safety and performance of devices after their placing on the market.

PMCF studies are one of several options available in post-market surveillance and contribute to the risk management process.

2. Scope

The objective of this document is to provide guidance on the appropriate use and conduct of PMCF studies to address issues linked to residual risks. The intention is not to impose new regulatory requirements.

PMCF studies are an important element to be considered in PMCF or PMS plans. The principles for PMCF studies set out in this guidance are not intended to replace PMCF or PMS plans. They are or may be applicable to PMCF studies conducted for other purposes.

This document provides guidance in relation to:

i) the circumstances where a PMCF study is indicated;

ii) the general principles of PMCF studies involving medical devices;

iii) the use of study data (for example to update instructions for use and labelling); and

iv) the role of a notified body for medical devices in the assessment of PMCF plans and of the results obtained from the plans as part of conformity assessment.

This document does not apply to *in vitro* diagnostic devices.

3. References

Council Directive 93/42/EEC of 14 June 1993 concerning medical devices as last amended by Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007.

Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices last amended by Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007.

Interpretative Documents

MEDDEV 2.7.1	Clinical Evaluation: A Guide for Manufacturers and Notified Bodies
MEDDEV 2.7.1, Appendix 1	Evaluation of Clinical Data – A Guide for Manufacturers and Notified Bodies – Appendix 1: Clinical Evaluation of Coronary Stents

GHTF Final Documents:

SG1/N41:2005	Essential Principles of Safety & Performance of Medical Devices
SG1/N44:2008	The Role of Standards in the Assessment of Medical Devices
SG1/N065:2010	Registration of Manufacturers and Other Parties and Listing of Medical Devices
SG2/N47:2005	Review of Current Requirements on Post-Market Surveillance
SG5/N1:2007	Clinical Evidence – Key Definitions and Concepts
SG5/N2:2007	Clinical Evaluation
SG5/N3:2010	Clinical Investigations

International Standards:

EN ISO 14155:2011	Clinical investigation of Medical Devices for human subjects Good clinical practice; Second edition 2011-02-01
EN ISO 14971:2009	Application of risk management to medical devices

Others:

US Department of Health and Human Service, Agency for Healthcare Research and Quality:

Registries for Evaluating Patient Outcomes: a User's Guide (Executive Summary, April 2007).

4. Definitions

Clinical Data[1]:

The safety and/or performance information that is generated from the 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.

Clinical Evaluation[2]:

The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.

Clinical Evidence[2]:

The clinical data and the clinical evaluation report pertaining to a medical device.

Clinical Investigation[2]:

Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety or performance of a medical device.

Device Registry[3]:

An organised system that uses observational study methods to collect defined clinical data under normal conditions of use relating to one or more devices to

[1] Council Directives 90/385/EEC and 93/42/EEC
[2] GHTF document SG5/N1R8: 2007: Clinical Evidence – Key Definitions and Concepts
[3] GHTF document SG5/N4:2010: Post Market Clinical Follow-Up Studies, based on the definition in Agency for Healthcare Research and Quality, "Registries for Evaluating Patient Outcomes: A User's Guide", as modified.

evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical or policy purpose(s).

Note: The term "device registry" as defined in this guidance should not be confused with the concept of device registration and listing. (See GHTF SG1N065)

Post-market clinical follow-up (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.

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.

Residual Risk:

Risk remaining after risk control measures has been taken[4] .

[4] EN ISO 14971

5. Circumstances where a PMCF study is indicated

Following a proper premarket clinical evaluation, the decision to conduct PMCF studies must be based on the identification of possible residual risks and/or unclarity on long term clinical performance that may impact the benefit/risk ratio.

PMCF studies may review issues such as long-term performance and/or safety, the occurrence of clinical events (e.g. delayed hypersensitivity reactions, thrombosis), events specific to defined patient populations, or the performance and/or safety of the device in a more representative population of users and patients.

Circumstances that may justify PMCF studies include, for example:

- innovation, e.g., where the design of the device, the materials, substances, the principles of operation, the technology or the medical indications are novel;
- significant changes to the products or to its intended use for which pre-market clinical evaluation and re-certification has been completed;
- high product related risk e.g. based on design, materials, components, invasiveness, clinical procedures;
- high risk anatomical locations;
- high risk target populations e.g. paediatrics, elderly;
- severity of disease/treatment challenges;
- questions of ability to generalise clinical investigation results;
- unanswered questions of long-term safety and performance;
- results from any previous clinical investigation, including adverse events or from post-market surveillance activities;
- identification of previously unstudied subpopulations which may show different benefit/risk-ratio e.g. hip implants in different ethnic populations;
- continued validation in cases of discrepancy between reasonable premarket follow-up time scales and the expected life of the product;
- risks identified from the literature or other data sources for similar marketed devices;

- interaction with other medical products or treatments;
- verification of safety and performance of device when exposed to a larger and more varied population of clinical users;
- emergence of new information on safety or performance;
- where CE marking was based on equivalence.

PMCF studies may not be required when the medium/long-term safety and clinical performance are already known from previous use of the device or where other appropriate post-market surveillance activities would provide sufficient data to address the risks.

6. Elements of a PMCF study

Post-market clinical follow-up studies are performed on a device within its intended use/purpose(s) according to the instructions for use. It is important to note that PMCF studies must be conducted according to applicable laws and regulations and should involve an appropriate methodology and follow appropriate guidance and standards.

PMCF studies must be outlined as a well designed clinical investigation plan or study plan, and, as appropriate, include:

- clearly stated research question(s), objective(s) and related endpoints;
- scientifically sound design with an appropriate rationale and statistical analysis plan;
- a plan for conduct according to the appropriate standard(s);
- a plan for an analysis of the data and for drawing appropriate conclusion(s).

Objectives of PMCF studies

The objective(s) of the study should be stated clearly and should address the residual risk(s) identified and be formulated to address one or more specific questions relating to the clinical safety or clinical performance of the device. A formal hypothesis should be clearly expressed.

Design of PMCF studies

PMCF studies should be designed to address the objective(s) of the study. The design may vary based on the objective(s), study hypothesis research question and endpoints and should be scientifically sound to allow for valid conclusions to be drawn.

PMCF studies can follow several methodologies, for example:

- the extended follow-up of patients enrolled in premarket investigations;
- a new clinical investigation;
- a review of data derived from a device registry; or
- a review of relevant retrospective data from patients previously exposed to the device.

PMCF studies should have a plan describing the design and methodologies appropriate for addressing the stated objectives. The clinical investigation plan/study plan should identify and where needed justify at a minimum:

- the study population (corresponding to the CE-mark scope);
- inclusion/exclusion criteria;
- rational and justification of the chosen study design including use of controls/control groups (where relevant; randomised or not);
- the selection of sites and investigators;
- study objectives and related study endpoints and statistical considerations;
- the number of subjects involved;
- the duration of patient follow-up;
- the data to be collected;
- the analysis plan including any interim reporting where appropriate to ensure continuous risk management based on clinical data; and
- procedures/criteria for early study termination;
- ethical considerations;
- methods of quality control of data where appropriate.

The points above may not all apply to a retrospective data review.

Implementation of the PMCF study, analysis of data and conclusion(s)

The study should:

- be executed with adequate control measures to assure compliance with the clinical investigation or study plan;
- include data analysis with conclusions drawn according to the analysis plan by someone with appropriate expertise; and
- have a final report with conclusions relating back to original objective(s) and hypothesis/hypotheses.

7. The use of study data

The data and conclusions derived from the PMCF study are used to provide clinical evidence for the clinical evaluation process. This may result in the need to reassess whether the device continues to comply with the Essential Requirements. Such assessment may result in corrective or preventive actions, for example changes to the labelling/instructions for use, changes to manufacturing processes, changes to the device design, or public health notifications.

8 The role of the notified body in PMCF

When auditing the quality system of the manufacturer in the framework of one of the conformity assessment annexes of Directive 90/385/EEC or of Directive 93/42/EEC, the Notified Body (NB) shall review the appropriateness of the manufacturer's general post-market surveillance procedures and plans, including plans for PMCF, as relevant.

The Notified Body shall verify that PMCF as part of the overall clinical evaluation is conducted by or on behalf of the manufacturer by appropriately competent assessors (as per section 10.3 of MEDDEV 2.7/1).

The NB shall verify that clinical investigations conducted as part of PMCF plans are conducted in accordance with the relevant provisions of Annex X (as per Article 15.8 of 93/42/EEC), related guidance and relevant standards.

The NB shall as part of its assessment of a specific medical device[5]:

- verify that the manufacturer has appropriately considered the need for PMCF as part of post market surveillance based on the residual risks including those identified from the results of the clinical evaluation and from the characteristics of the medical device in accordance with section 5 of the guidance;
- verify that PMCF is conducted when clinical evaluation was based exclusively on clinical data from equivalent devices for initial conformity

[5] in accordance with Annex II.4, Annex II.7, Annex III, Annex V.6 and Annex VI.6 of Directive 93/42/EEC and Annex II.4, Annex II.7, Annex III and Annex V.6 of Directive 90/385/EEC

assessment and that PMCF addresses the residual risks identified for the equivalent devices;

- assess the appropriateness of any justification presented by a manufacturer for not conducting a specific PMCF plan as part of post market surveillance and seek appropriate remedy where the justification is not valid;
- assess the appropriateness of the proposed PMCF plan in demonstrating the manufacturer's stated objectives and addressing the residual risks and issues of long term clinical performance and safety identified for the specific device;
- verify that data gathered by the manufacturer from PMCF, whether favourable or unfavourable, is being used to actively update the clinical evaluation (as well as the risk management system);
- consider whether, based on the specific device assessment, data obtained from PMCF should be transmitted to the NB between scheduled assessment activities (e.g. surveillance audit, recertification assessment);
- consider an appropriate period for certification of the product in order to set a particular time point at which PMCF data will be assessed by the NB or specific conditions relating to certification for subsequent follow up. (This decision may be based on the residual risks, the characteristics presented in section 5 and the clinical evaluation presented at the time of initial assessment. Conditions the NB may consider could include the need for the manufacturer to submit interim reports between certification reviews, of the clinical data generated from the PMCF and post-market surveillance system).