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Appendix 1

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GUIDELINES ON MEDICAL DEVICES

EVALUATION OF CLINICAL DATA - A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES -

Appendix 1 : Clinical Evaluation of Coronary Stents

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 were 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.

GUIDELINE ON CLINICAL EVALUATION OF CORONARY STENTS

I. OBJECTIVE AND PURPOSE

This document provides guidance to manufacturers on the clinical evaluation of coronary stents, thus assisting them in their clinical investigation(s) and the subsequent evaluation of all clinical data required under Directive 93/42/EEC concerning medical devices (MDD), as amended. It should further be used by Notified Bodies as part of their Design Dossier review or Type Test certification and any subsequent significant change notifications. It is also aimed at assisting Member States' authorities when verifying that the device meets the essential requirements laid down in Annex I of the MDD during post market surveillance.

This guideline should be read in conjunction with MEDDEV 2.7.1 "Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies" which covers evaluation of clinical data. It describes the main requirements for the clinical evaluation of coronary stents based on current state-of-the-art and on experience drawn from the most recent reviews of clinical studies. It does not attempt to exhaustively cover the clinical evaluation of coronary stents. Furthermore, this guideline is subject to the evolution of the state-of-the-art.

II. BACKGROUND AND LEGAL BASIS

II-1 Background

Cardiac intervention without surgery has profoundly changed the management of cardiac patients, particularly those with coronary artery disease. The first interventional procedure involved percutaneous transluminal coronary angioplasty (PTCA), but was soon considered to be in need of further development in view of relative early re-stenosis and recurrence of symptoms. This led to the development of bare metal stents (BMS), in an attempt to prevent re-stenosis. However, re-stenosis continued to occur in some patients however as BMS are not perfectly suited to address the process of intimal thickening. This results from the cascade of events initiated by the trauma of the intervention in combination with the underlying arterial disease with inflammation, smooth muscle cell migration, proliferation and sometimes thrombus formation occurring.

Currently, the majority of coronary artery dilatation procedures involve the deployment of a stent. This consists of the placing of a mechanical scaffold at the site of the treated segment in order to increase the radial support of the vessel wall. In addition, pressing the stenotic structure (plaque) against the arterial inner wall tends to prevent disruption of plaque and dissected flaps and hence reducing the risk of embolization and further dissection. This aims to restore local perfusion and coronary perfusion reserve. The stent itself will, however, confer new properties into the treated segment of artery and may induce subsequent biological responses, for example intimal hyperplasia which may, to some extent, undermine the initial advantages of stent placement.

Stenting may also lead to mechanical damage of the arterial wall through over-expansion of angioplasty balloons or abrasion of the arterial wall by the stent during deployment. The damage imposed may lead to biomechanical and biochemical actions causing localized inflammation, thrombus formation or arterial inflammation. Redevelopment of arterial obstructions can significantly affect medical outcomes with partial or complete stenosis leading to reduced local or global heart muscle perfusion and potentially infarction.

In an attempt to reduce re-stenosis and as a result of research into the underlying processes, drug eluting stents (DES) were developed.

II-2 Legal basis

Coronary stents fall within the scope of the MDD. In DES, the medicinal substance(s) incorporated in the stent has/have an ancillary action to that of the stent within in the meaning of Article 1.4 of the MDD. In view of the above and pursuant to Article 9 of the MDD, the applicable classification rules for these devices are Annex IX, Chapter III, Section 2.4 (rule 8) and for DES also Annex IX, Chapter III, Section 4.1 (rule 13). Both rules lead to classifying all coronary stents as class III medical devices.

Confirmation of conformity with the requirements concerning the characteristics and performance under normal conditions of use of the device and evaluation of side-effects and of the acceptability of the benefit/risk profile must be based on an evaluation of clinical data¹. In accordance with Annex X, section 1.1, this clinical evaluation must consist of either a critical evaluation of the relevant (both positive and negative) scientific literature currently available supporting the safety, performance, design characteristics and intended purpose of the device (where there is demonstration of equivalence of the device in question to the device to which the data relates, and where the data adequately demonstrate compliance with the relevant essential requirements) or a critical evaluation of the results of all clinical investigations made or a combination of both. The objectives of a clinical investigation must be to verify a positive benefit/risk profile of the device for the indications and limitations of use as specified by the manufacturer.

For coronary stents incorporating a medicinal substance, the Notified Body shall refer to a member state designated competent authority for medicinal products or to the European Medicines Agency (EMA) for their scientific opinion. The opinion of the Competent Authority for medicinal products or EMA on the quality and safety of the substance is based on the clinical data from the evaluation of the DES, pharmacological properties of the substance and data on the usage of the substance in other applications in accordance with Annex I, Section 7.4 of the MDD and with the EMA/CHMP/EWP/110540/2007 guideline.

III. RELEVANT DOCUMENTS

- Council Directive 93/42/EEC concerning medical devices, last amended by Directive 2007/47/EC of the European Parliament and of the Council.
- EMA/CHMP/EWP/110540/2007: Guideline on the clinical and non clinical evaluation during the consultation procedure on medicinal substances contained in drug-eluting (medicinal substance-eluting) coronary stents.
- EN 14299:2004 Non active surgical implants – Particular requirements for cardiac and vascular implants – Specific requirements for arterial stents.
- EN 12006-3:1998 Non-active surgical implants – Particular requirements for cardiac and vascular implants – Part 3: Endovascular devices.
- EN ISO 10993 Biological evaluation of medical devices.
- EN ISO 14155-1:2003 Clinical investigation of medical devices for human subjects – Part 1: General requirements.
- EN ISO 14155-2:2003 Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans.
- EN ISO 14630:2005 Non-active surgical implants – General requirements.
- EN ISO 14971:2007 Medical devices – Application of risk management to medical devices.
- GHTF SG5 N2R8:2007 Guidance on clinical evaluation.
- ISO/DIS 25539-2 Cardiovascular implants – Endovascular devices – Part 2: Vascular stents.
- MEDDEV 2.1/3 (2001) Interface with other directive – Medical devices/medicinal products.
- MEDDEV 2.7.1(2003) Evaluation of clinical data: A guide for manufacturers and notified bodies.
- MEDDEV 2.12-2 (2004) Guidelines on post market clinical follow-up.

¹See Annex X, section 6a of the MDD, as amended.

IV. PRECLINICAL ASSESSMENT

Prior to undertaking a clinical investigation of a stent, pre-clinical testing is necessary and should include the following; (conformity to the standards referenced in brackets are considered to fulfil the relevant requirements of Directive 93/42/EEC).

- biocompatibility testing (EN-ISO 10993 series);
- bench testing in line with EN 14299;
- animal studies (EN 14299, EN ISO 14630, EN 12006-3);
- in the case of DES, appropriate testing of the medicinal substance including interaction between the medicinal substance and the device, pharmacodynamics and characterisation of time-release profiles (see EMEA guideline);
- for rare and serious risks associated with the use of coronary stents (such as risk of late thrombosis), specific tests shall be considered (e.g. endothelialization testing, tissue measurements, assessment of any late inflammatory response, etc); in case of DES, see EMEA guideline.

Note: the ISO Standard (ISO 25539-2) on coating durability/stability, analysis of the uniformity of the drug distribution is currently under development.

V. CLINICAL INVESTIGATION

In order to evaluate whether the device is suitable for the purpose(s) and the population(s) for which it is intended, the objectives of a clinical investigation according to Annex X, Section 2.1 of the MDD are:

- to verify that under normal condition of use the performance of the device is in accordance with the manufacturer's claimed intended purpose, and
- to determine any undesirable side effects, under normal condition of use and assess whether they constitute risks when weighed against the intended performance of the device.

Coronary artery disease covers a wide spectrum of different pathological changes in terms of size and/or length of vessel involved, numbers of lesions, sites of lesions, clinical presentation (acute coronary syndrome versus chronic stable angina pectoris). Also, coronary artery disease may be complicated by other co-existent pathologies such as diabetes and/or hypertension. It is therefore important that in evaluating safety and performance of coronary stents these populations and pathologies are reflected in the instructions for use.

For BMS, clinical evaluation shall be conducted in line with MEDDEV 2.7.1 and relevant standards (EN ISO 14155-1 and -2 and relevant parts of EN 12006-3, EN 14299 and EN 14630).

In addition to the above-mentioned requirements:

- for DES, the usefulness of the drug shall always be supported by appropriate clinical investigation data;
- for innovative stents², the clinical investigation must be designed appropriately to assess the novel feature(s) of the device (e.g. bio-absorbability, biological coating, etc.).

It is important that generic claims are not made for devices that have been studied in limited patient populations. Specific claims must be backed up by specific clinical data.

² An "innovative stent" is a stent incorporating unique characteristics dissimilar to any currently CE-marked coronary stents, e.g. a stent with a novel active coating, biodegradable stents, requiring novel clinical techniques for placement or incorporating completely new design concepts.

V.1 Clinical investigation design

The design of the clinical investigation must be based on the claims made by the manufacturer and as part of the demonstration of compliance with the essential requirements of the MDD. Controlled randomized studies shall be conducted when necessary to substantiate claims made by the manufacturer.

The demonstration of the benefit-risk profile of the stent system under investigation may require a randomized comparative study design. In such a case the choice of the comparator shall be justified and, in particular, the validity of the comparator should have been established previously by (an) appropriately conducted clinical investigation(s).

V. 2 Definition of population under clinical investigations

It is important for the population being studied that there are well-defined eligibility criteria, taking into account the safety and performance claims and any other future marketing claims. Criteria such as the specific site of the lesion, length of lesion, type of lesion, diameter of vessels, as well as risk factors including but not limited to diabetes, multiple lesions, bifurcated lesions and a post-myocardial infarction situation must be considered.

All patients should be on well-defined medically recommended anti-thrombotic medication unless otherwise justified.

V.3. Number of patients for enrolment.

The number of patients to be enrolled shall be justified on the basis of a sound scientific rationale, through the use of statistical calculation to support the hypotheses.

The design of a study without control group (either prospective or historical) shall be specifically justified. When such a study is designed to measure performance and safety, it shall include a sufficient number of patients completing the study to allow the primary performance and safety end-points specified in the clinical investigation plan to be estimated with a 95% confidence interval.

V.4. Duration of the clinical investigation

Timelines for acceptable evaluation of the performance and safety will depend upon the characteristics of the stent as well as the coronary pathologies and/or medical conditions for which it is intended. Timelines should always be justified. Appropriate endpoints should take into consideration the time-frame of expected complications:

- for a BMS, generally a minimum of 6 months;
- for a DES and other “innovative stents”³, generally a minimum of 12 months. Moreover, a long-term follow-up of patients included in the investigation should be performed and a post market clinical follow-up shall be considered and conducted unless duly justified as mentioned in section VII below.

Longer timeline may be required.

V.5. Analysis

Where angiographic, intra-vascular ultrasound (IVUS) and other imaging endpoints are specified in premarket studies, these should be analysed by an independent core laboratory. If possible a blinded adjudication of clinical events should be utilised.

³ Other relevant EU legislation should be accounted for in designing clinical investigations, e.g. Council Directive 97/43/Euratom on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, when appropriate.

V.6 Performance Endpoints

V.6.1 Device and Procedural Success Endpoints.

These acute endpoints may be divided into Device Success Endpoints and Procedure Success Endpoints. These endpoints should include but are not limited to:

- successful delivery of the stent to the targeted lesion site in the coronary artery;
- appropriate balloon expansion (if applicable);
- appropriate stent deployment;
- successful removal of delivery system after release of the stent;
- safe removal of the device in case of deployment failure.

Device Success includes the above. Procedure Success includes the above with additional criteria related to the clinical outcome of the procedure with the use of both investigational and non-investigational devices.

For example, acute success is classified according to the following definitions:

Clinical device success.

Successful delivery and deployment of the investigational stent(s) at the intended target lesion (this includes successful delivery and deployment of multiple overlapping stents) and successful withdrawal of the stent delivery system with attainment of a final residual stenosis of less than 50% of the target lesion as observed by Quantitative Coronary Angiography (QCA) or by visual estimation if QCA is not available and without use of a device outside the assigned treatment strategy. Standard pre-dilation catheters and post-dilatation catheters (if applicable) may be used.

Clinical procedural success.

Successful delivery and deployment of the investigational stent(s) at the intended target lesion (this includes successful delivery and deployment of multiple overlapping stents, if applicable) and successful withdrawal of the stent delivery system with attainment of a final residual stenosis of less than 50% of the target lesion as observed by QCA or by visual estimation if QCA is not available and/or using any adjunctive device without the occurrence of ischemia-driven major adverse cardiac event (ID-MACE) during the hospital stay to a maximum of first seven days post index procedure.

In case of multiple lesions treatment, all treated lesions must meet the clinical procedural success.

V.6.2 Clinical Endpoints.

These should include but are not limited to:

- death (cardiac, non cardiac);
- myocardial infarction (MI);
- target lesion revascularisation (TLR, edges included, i.e. +/- 5 mm);
- target vessel revascularization (TVR);
- non target vessel revascularization (Non-TVR);
- pre-defined composite endpoints of the above-mentioned events;
- clinical events related to stent thrombosis.

The Academic Research Consortium Publication⁴ recommends using composite endpoints which include target vessel failure/major adverse cardiac events (TVF/ MACE), a composite endpoint which may vary from investigation to investigation; its components should therefore be specified. The manuscript differentiates between two types of composite end-points depending on the development stage of a device:

- Device-oriented composite, in hierarchical order:
 - cardiac death;
 - myocardial infarction (not clearly attributable to a non-target vessel);
 - target lesion revascularisation.
- Patient-orientated composite, in hierarchical order:
 - all-cause of mortality;
 - any MI (includes non-target vessel territory);
 - any repeat revascularization (includes all target and non-target vessel).

V.6.3 Angiographic and intra-vascular ultrasound (IVUS) endpoints.

Should include but are not limited to:

- rate of binary in-stent and in-segment re-stenosis where re-stenosis is defined by coronary angiography as stenosis of greater than 50% of the luminal diameter;
- late loss: in-stent and in-segment luminal loss (defined as the difference between the Minimal Luminal Diameter [MLD], immediately after the procedure and the MLD at the defined follow-up time);
- intra-vascular ultrasound (if performed): in-stent % volume obstruction, in-stent neo-intimal hyperplasia volume (mm³).

V.7. Safety Endpoints

V.7.1 Peri-procedural safety endpoints.

In terms of procedures and deployment, these include:

- vessel dissection;
- distal embolisation;
- peri-procedural myocardial infarction's (MI's).

V.7.2 Post procedural or follow-up safety endpoints.

V.7.2.1 Clinical safety endpoints:

- see paragraph V.6.2

V.7.2.2 Long term follow-up angiographic and/or IVUS safety endpoints:

- persistent dissection;
- coronary aneurysm;
- presence of thrombus;
- if using Intra-vascular ultrasound (IVUS, initial or acquired): stent mal-apposition.

V.7.2.3 Clinical event related to antiplatelet therapy:

- major bleeding complications

⁴ Reference: Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. Donald E. Cutlip, Stephan Windecker, Roxana Mehran, Ashley Boam, David J. Cohen, Gerrit-Anne van Es, P. Gabriel Steg, Marie-angèle Morel, Laura Mauri, Pascal Vranckx, Eugene McFadden, Alexandra Lansky, Martial Hamon, Mitchell W. Krucoff, Patrick W. Serruys and on behalf of the Academic Research Consortium *Circulation* 2007;115:2344-2351.

Note: relevant medication administered to the patient, e.g. dosage, duration and discontinuation of antiplatelet therapy must be taken into account when determining all endpoints.

VI. EVALUATION OF CLINICAL DATA SUPPORTING CE MARKING

Evaluation of clinical data to support CE marking should be carried out in line with the methodology laid out in the MDD and the relevant guidance (see section III).

Prior to CE marking, a literature review in accordance with MEDDEV 2.7.1 is necessary. Scientific literature in this area is highly targeted and specific. It would be expected that a critical evaluation of literature with an appropriate summary performed by a suitably qualified person is performed. The literature summary should include explanations dealing with both negative as well as positive publications.

The objective of the literature review is:

- to identify all data generated from clinical investigations or studies of the device in question and/or of equivalent devices;
- to demonstrate, where applicable, equivalence with a similar device already on the market where equivalence in this context is defined in MEDDEV 2.7/1, i.e.:
 - a) clinical equivalence:
when used for the same clinical condition or purpose, at the same site in the body, in a similar population (including age, anatomy, physiology) and have similar relevant critical performance according to expected clinical effect for specific intended purpose;
 - b) technical equivalence:
used under similar conditions of use, have similar specifications and properties (e.g. tensile strength, viscosity, surface characteristics), be of similar design, use similar deployment methods (if relevant), and have similar principles of operation;
 - c) biological equivalence:
use of the same materials in contact with the same human tissues or body fluids;
- to identify relevant gaps in the literature which should be addressed by a specifically designed clinical investigation.

The intended purpose of the device, including clinical indications, contra-indications, and claims shall be based on the result of the evaluation of all available clinical data i.e. all claims must be supported by clinical data.

Side effects and adverse effects observed during clinical investigation as well as those identified by the risk management process) shall be reflected in the information supplied with the device.

A Post Market Clinical Follow up (PMCF) is important for coronary stents in order to evaluate long term safety and performance (pursuant to Annex X, section 1.1c of the MDD and MEDDEV 2.12-2).

VII. POST-MARKET CLINICAL FOLLOW-UP (PMCF)

An appropriate post-market clinical follow-up programme in accordance with MEDDEV 2.12/2 shall be performed for all DES and innovative stents and for all BMS unless duly justified.

Such a programme must be planned and can take the form of a clinical investigation (where the CE marked device is used according to its intended use) and/or registry “All comer” registries, to include those cases treated off-label, should be conducted to better provide clinical safety and performance data in "real world" clinical practice. Any data gathered from real world usage by manufacturers should be used to feedback directly into device labelling.

A clinical investigation or a registry should include:

- a clearly stated objective;
- a scientifically sound design with an appropriate rationale and statistical analysis plan designed appropriately to address the objectives of the study and scientifically sound to allow for valid conclusions to be drawn;
- a study plan which should justify the patient population (to include a representative population with risk factors such as diabetes and hypertension), the selection of sites and investigators, the endpoints and statistical considerations, the number of subjects involved (to ensure capture of the true incidence of late complications), the duration of the study for a minimum of 3 years (taking into account the lifespan of the device and the time of occurrence of late complications), the data to be collected, the analysis planning including any interim reporting, and the procedures for early study termination.

VIII. MODIFICATIONS TO STENT OR INDICATIONS FOR USE

When subsequent modifications of claims or design iterations occur to an already marketed coronary stent it is essential to evaluate, based on a risk analysis, the impact of the modifications. The results of this evaluation will determine the need for any new or additional pre-clinical testing or clinical investigation.

Each claim modification should be approved by the Notified Body. The Notified Body should be provided with documentary supporting evidence enabling them to adequately evaluate and risk assess the manufacturer's desired modification to the product labelling. Particular attention is required with regards to planned extension to the current indications. Claim modifications may also include highlighting the particular suitability (or not) of selected patients cohorts, lesion and arterial morphology, implantation technique e.g. direct stenting.

Each modification influencing the specified drug characteristics and/or drug delivery characteristics requires a consultation by the Notified Body of the relevant Member State-designated Competent Authority for medicinal products or of the EMEA.

For example, in case of modification of a DES the modification may concern:

- the bare stent and the delivery system: here it is necessary to validate with current standards and to provide specific information in the instructions for use when the modification concerns the surface treatment of the stent;
- the carrier: where there is no influence on the kinetics of the medicinal substance, the same standard of validation as for a BMS or a BMS with treated surface may be applied;
- the medicinal substance, the medicinal substance kinetics or a change in the characteristics of the carrier which influences the kinetics of the medicinal substance: a new evaluation of the benefit/risk profile by a comparative clinical investigation and a PMCF is required.

