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DRAFT

GUIDELINE ON THE DEVELOPMENT OF MEDICINAL SUBSTANCES CONTAINED IN DRUG-ELUTING (MEDICINAL SUBSTANCE-ELUTING) CORONARY STENTS

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GUIDELINE ON THE DEVELOPMENT OF ACTIVE SUBSTANCES CONTAINED IN DRUG-ELUTING CORONARY STENTS

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EXECUTIVE SUMMARY

This Guideline is intended to assist applicants and the Notified Bodies in the consultation procedure to the competent bodies of the member states or the EMEA regarding the assessment of usefulness and safety applied to a medicinal substance, which is of ancillary purpose, in a drug-eluting (medicinal substance-eluting) coronary stent (DES).

1. LEGAL BASIS

It should be read in conjunction with Directive 2001/83/EC as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Guidance document MEDDEV 2. 1/3 rev 2
- Guidelines on a medical devices Evaluation of clinical data: a guide for manufacturers and notified bodies MEDDEV. 2.7.1
- Guidelines on a medical devices Vigilance system MEDDEV 2.12-1 rev 4
- Guidelines on post market clinical follow-up MEDDEV 2.12-2
- Note for Guidance on Clinical Safety Data Management ICH E2
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- Guideline on Risk Management Systems for Medicinal Products for Human Use

2. INTRODUCTION

The benefit of percutaneous coronary intervention is often limited by restenosis. Even with the best medical treatment, including stents, restenosis continues to occur in some patients because stents are not designed to address the process of intimal thickening that results from the cascade of events initiated by arterial injury. The restenosis process involves thrombus formation, inflammation and signal transduction, which mediates smooth-muscle-cell migration and proliferation. The rate of restenosis after stenting varies considerably from ~10% to as much of 40% in certain patient groups. Much research has been conducted to the pathophysiology and treatment of in-stent restenosis. Drug eluting stents (DES) have turned up as a potential solution for restenosis. DES are combination products composed of a medicinal product(s) and medical devices and since the medicinal product(s) has an ancillary function to the device they are in accordance with the Council Directive 93/42/EEC still classified as medical devices. According to the medical device legislation, the Notified Body has to consult one of the competent bodies of the Member States or the EMEA with regards to the quality, safety and usefulness of the medicinal substance incorporated as integral part of the device, taking into account the intended purpose of the device. The aspect of "usefulness" relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the device. It refers to the suitability of the medicinal substance to achieve its intended action and whether the potential inherent risks (aspects of "safety") due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the device. Guidance is needed with regard to the non-clinical and clinical data required for the evaluation of the medicinal substances contained in DES.

The Medical Devices Directive and its corresponding Guidelines state that in the case of implantable devices, active implantable devices and devices of Class III, evidence of the clinical performance and

safety of a medical device is provided by means of clinical data. Clinical data are relevant to the various aspects of the clinical safety and performance of the device and can be based on (1) published and/or unpublished data on market experience of the device; or a similar device for which equivalence to the device in question can be demonstrated; or (2) a prospective clinical investigation(s) of the device concerned; or (3) results from a 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.

Equivalence in this context is defined as:

- Clinically: used for the same clinical condition or purpose; used at the same site in the body; used in similar population (including age, anatomy, physiology); have similar relevant critical performance according to expected clinical effect for specific intended use.
- Technically: used under similar conditions of use; have similar specifications and properties; viscosity, surface characteristics; be of similar design; use similar deployment methods (if relevant); have similar principles of operation.
- Biologically: use of same materials in contact with the same human tissues or body fluids.

3. SCOPE

The scope of the present document is restricted to the development of medicinal substances contained in DES coronary stents.

4. BACKGROUND

Different possibilities can be distinguished depending on the knowledge on the ancillary medicinal substance i.e.:

1. the medicinal substance of the combination is known to the competent authority and already registered in the setting of a DES for a specific indication (see section 7.3) in the Community and the applicant claims:
    a. comparative medicinal substance release characteristics **(A)**:
        i. same stent material with the same polymer material (**A1**)
        ii. same stent material with different polymer material (**A2**)
        iii. different stent material with same polymer material (**A3**)
        iv. different stent material with different polymer material (**A4**)
    b. different medicinal substance release characteristics **(B)**
2. the medicinal product of the combination is known to the competent authority but not registered in the setting of a DES **(C)**;
3. the medicinal product of the combination is a new active substance and therefore not known to the Competent Authority neither as a medicinal product nor in the setting of a DES **(D)**.

These different possibilities of the DES raise important questions about the data needed for adequate evaluation in vivo and in vitro of the medicinal substances contained in DES in order to establish safety and usefulness. The combination of DES creates the potential for local as well as systemic effects not seen previously with bare metal stents (BMS). The combination exhibit properties that are obviously uncharacteristic for medical devices just as the evaluation of the drug component cannot solely be based on conventional methods used to evaluate drugs, because DES are primarily designed for local drug elution. Although it is recognised that the total amount of medicinal product incorporated in the DES is substantially lower than used systemically in clinical applications, local safety aspects are a major point of concern and should be taken into account in the (non-)clinical evaluation programme. It has to be recognised that on the technical side, device expertise is qualitatively different from expertise with the medicinal product. The risk-benefit balance of medicinal substances in the context of a DES is linked with the chosen stent platform and medicinal substance carrier and will have an impact on the overall evaluation of the device to be performed by

the Notified Bodies Evaluation of the safety and usefulness of the medicinal substances in the context of a DES in coronary stenting is complicated by the fact that they are linked with each other in terms of major adverse cardiac events (MACE).

5. BENCH TESTING

In all cases (**A, B, C, D**), the applicant is expected to perform a series of bench tests on the integrity of the device component of the investigational product. The sponsor must demonstrate that the drug and device neither chemically nor physically interact adversely with each other. In addition, it is important for the applicant to elucidate how application of the drug and drug-carrier to the device may affect its fatigue and corrosion properties, coating integrity, durability, and any other relevant product-specific components.

6. NON-CLINICAL TESTING

6.1 Biocompatibility testing of the device

The applicant must perform biocompatibility testing of the BMS to support the initiation of a human clinical study as is described in the Essential Requirements. Applicants should document and discuss the extent of biocompatibility testing **(A, B, C, D)**. Testing for blood-contacting implants typically includes findings of cytotoxicity, and haemocompatibility.

6.2 Nonclinical testing requirements for the drug-eluting stent

6.2.1 Pharmacodynamics (proof of concept)

There is no known reliable animal species to serve as a model for human atherosclerotic disease. No animal model has been successful in replicating the magnitude of clinical benefit observed in humans with DES and there is poor correlation between animal and human effectiveness parameters and study results. This applies to **A, B, C, D**.

6.2.2 Non-clinical pharmacokinetic testing

Drug-eluting coronary stents create major challenges in their in vivo **(B, C, D)** pharmacokinetic characterization. The devices are designed to distribute drug locally, with the intent to maximize bioavailability within local vascular tissue. The development of a suitable in vivo local pharmacokinetic testing model is complicated by the lack of an animal model equivalent to human atherosclerotic disease (see 6.2.1). DES pharmacokinetic testing consists of local, regional, and systemic assessments. Furthermore, factors such as stent geometry, homogeneity of stent strut apposition to the vessel wall, and drug hydrophobicity should be taken into account because of major differences in drug distribution, even within the same stent. In vitro PK studies of drug properties, such as rates of dissolution, have also been required for drug-eluting stent approval **(B, C, D)**. In vivo pharmacokinetic studies are very important to quantify the duration of drug exposure **(B, C, D)**. Drug concentrations should be measured at the local (tissue), regional (organ), and systemic levels in animals **(B, C, D)**. In the case of very small drug doses, time-release profiles usually suffice to demonstrate safety for human trials **(B, C, D)**. The profiles are typically collected in an appropriate animal model and reflect besides tissue drug levels also the quantity of drug remaining on the device. These critical laboratory and animal studies can also serve as the basis for an in vivo–in vitro correlation.

6.2.3 Testing multiple overlapping stents

The impact of stent design and luminally protruding struts should be evaluated within the context of imperfect implantation and implanting multiple overlapping stents. Both may alter flow, thereby creating areas of separation, recirculation, and stagnation where drug can pool with minimal dilution

from flow, and substantial drug deposition could occur from these pools of blood-solubilized drug **(A, B, C, D).**

6.2.4 Preclinical toxicity studies

Because prediction of efficacy is not reliable from current animal models, animal testing is primarily limited to the evaluation of safety. The proposed clinical drug dose and release characteristics should be justified by nonclinical data **(B, C, D)** (see above). Preclinical dose range finding studies are strongly recommended, showing effects across ranges from sub-therapeutic to toxic levels **(B, C, D)**. A multiple dose study should be performed in an animal model to establish safety margins, and toxicity in choosing a dose for clinical trials **(B, C, D)**. The dosing studies will establish an efficacy margin between the sub-therapeutic dose and the therapeutic dose, and a safety margin between the therapeutic dose and the toxic dose.

Experience suggests that the coronary arteries in domestic crossbred swine and iliac arteries of rabbits are suitable in that their size, access, and injury response are similar to human vessels A key safety concern is stent thrombosis. Animal models, provide useful information regarding stent thrombosis risk in clinical trials. The porcine model can be used to determine stent safety from both thrombosis and neointimal stimulation perspectives. Adverse vascular effects showing poor healing, vessel toxicity, absent endothelization, or neointimal stimulation should be of major concern. The applicant should provide nonclinical safety evidence on the results from both acute and chronic studies. Stent efficacy should be assessed by an absent thrombosis and by neointimal reduction. Data obtained at an early time point (3 or 7 days) should help determine subacute thrombosis risk. Other time points used should be at 28 days to observe neointimal hyperplasia, and at least one late time point to examine long term effects. The late time point (3 or 6 months) depends on when “healing” and drug release are both complete. Three-month follow-up is generally acceptable if no adverse effects are noted at this time. However, it is to be recognised that given the inability to extrapolate animal outcome to clinical outcome data in humans, there is currently no consensus on the duration of animal testing before testing in humans. Although it is generally agreed that the early post implantation period (from 1 week to 1 month of follow-up) is useful for gaining preliminary evidence about the tendency for acute stent thrombosis as well as the neointimal tissue formation with respect to the 6-month human condition, the total length of required follow-up should be discussed by the applicant by means of the biological and release characteristics of the product and animal data. E.g. later time points are important given the impact of peri-stent late remodeling as an additional cause of peri-stent effects that would impact the clinical outcome. This applies to **A2-4, B, C, D.** All animals experiencing death or other untoward clinical events should be examined. Such deaths typically occur in the first 24 hours after implant, but may occur later if healing is impaired. Sudden death later than 24 hours should be vigorously investigated for cause, as the drug might have interfered with healing.

Simple visual description of the histopathology is discouraged as the sole evaluation. A more rigorous (semi) quantitative and defined scale for arteriography and histopathology evaluation (inflammation, vascular healing, endothelization) should be presented as well. Full protocols, gross photographs, histologic photomicrographs, and detailed pathology reports should be made available.

When a drug is bound directly to a stent, the stent without drug can be satisfactory control. Polymer coatings by their nature typically induce inflammatory response and fibrinoid deposits. When polymer of carrier is present, additional controls to evaluate the carrier alone, without the drug, must be included. It is key that early inflammatory reactions meet safety criteria for later time points as well.

Only one stent should be implanted per artery except when issues of stent overlap or multiple stent dosing are considered. While avoiding overlap during initial evaluation, purposeful overlap should be performed in later studies. The intended distance of overlap should be discussed by the applicant.

6.2.5 Clinical testing of the active substance if not an approved medicinal product

Additional animal toxicity and human Phase I studies are to be expected if the drug component is not approved **(C, D)**. An additional requirement would be an initial human testing in healthy volunteers

intended to determine the no observed adverse effect level. The testing typically needs to evaluate study questions that are specific to the DES device.

7. CLINICAL DATA

7.1 Clinical pharmacokinetic testing

It is recognised that generating human PK data can be difficult for combination products because they often use very small drug doses. The applicant may need to develop highly sensitive analytical methods to collect fitting PK data or to demonstrate that such studies are impractical **(B, C, D)**. Human toxicity Phase I studies are to be expected to determine the no observed adverse effect level (NOEL) if the drug component is not approved **(D)**.

7.2 Clinical surrogate measures and exploratory testing

Improvement of angiographic and/or intravascular ultrasound biomarkers of luminal stenosis provides important information **(A2-4, B, C, D)**. The dose-related benefit and adverse effects should be characterised in randomised,controlled studies **(B, C, D)**. The aim of dose-response studies is to define the most effective dose for confirmatory trials.

7.3 Confirmatory clinical trials

The clinical evaluation of drug-eluting stents is primarily aimed to demonstrate safety and usefulness; and the study design should fulfil both.

The usual standard of evidence for a DES is the randomised, controlled clinical trial. A historical control is rarely acceptable for a novel stent. Actively controlled studies where patients are treated with a commercially available are expected. Randomised controlled trials utilising either a superiority or non-inferiority design and evaluating commonly used clinical endpoints will give the most reliable form of evidence **(B, C, D)**. However, as currently available DES have been associated with late stent thrombosis, the interpretability of non-inferiority approaches may prove difficult in case questions remain about long term safety.

When the medicinal substance of the combination is known to the competent authority and already registered in the setting of a DES and the applicant claims comparative medicinal substance release characteristics **(A2-4)** the use of clinical surrogate measures in the setting of a non-inferiority study against an approved DES may be acceptable, provided that long-term safety concerns can be clearly ruled out for the claimed target population.

The suitable target population will depend on the type of approach chosen by the applicant. Currently, the approved indication for DES is in general limited to patients with symptomatic ischemic heart disease with discrete, de novo lesions in native vessels with reference vessel diameters of 2.5 to 3.5 mm of up to 30 mm in length. However, a broader target population might be pursued provided that the long-term safety is properly studied. In each individual case, the type of comparator and the statistical approach (superiority vs. non-inferiority) should be properly discussed. A non-inferiority design with an already approved DES would only be acceptable if patients are included according to current guidelines. In all cases, background therapy should be standardised according to available recommendations. Specific evidence for generalisability for usefulness and safety of the DES across more complex lesions or patients cohorts (i.e. small vessels, long lesions, lesions at bifurcations, multi vessel disease, diabetes, coronary grafts) will be requested **(A, B, C, D)**.

Study endpoints

Angiographic biomarkers (in-stent/in-lesion minimal lumen diameter, percent diameter stenosis, in-stent/in-lesion late lumen loss), and intravascular ultrasound biomarkers (neointima volume) provide valuable information concerning the usefulness of the antiproliferative agent being studied. They can be used as primary endpoints in the setting of a DES in which the applicant claims comparative medicinal substance release characteristics with an already commercially available DES

(A2-4). In case of the same polymer as a reference DES, in vitro testing alone might be an acceptable option **(A1)**. However, a significant improvement of an angiographic/intravascular ultrasound parameter does not necessarily translate into a better clinical outcome. Conclusions regarding possible improvements of clinical outcome could be difficult since the study will be underpowered.

In terms of study endpoints for other settings of coronary drug-eluting stents **(B, C, D)**, clinically meaningful endpoints are strongly recommended. Ischemia-driven revascularisation of the target lesion, cardiac death and myocardial infarction, should be used as primary endpoint. It is recommended to analyse in addition the single components and clinically relevant groups of components separately, to show consistent results.

Specific consideration should be given to the potential interference/contribution of concomitant therapy on study endpoints.

Duration of follow-up

Timepoints for acceptable pathological evaluation will depend upon the specifics of DES (i.e., polymer and medicinal substance characteristics, elution kinetics, etc). An important question that has to be answered (e.g. by means of extrapolatation of animal data) is whether or not DES implantation merely delays the growth of neointimal tissue, perhaps to a timepoint (far) beyond the currently used 6-month evaluation period. In this context, 6 months is an appropriate endpoint, but additional angiographic evaluation at 12 to 24 months could provide additional information on the longitudinal healing response **(A, B, C, D)**.

Pivotal clinical studies providing data on primary endpoints should last at least one year with careful follow-up (see below).

7.4 Cinical safety evaluation

All potential adverse events should be collected and analysed using a pre-planned methodology. Identified adverse events should be carefully monitored and should be characterised in relation to the DES, patient and lesion characteristics, time course, and other relevant variables **(A, B, C, D)**. Specific consideration should be given to the potential interference/contribution of concomitant therapy. The most important aspects of safety are both short- and long-term rate of major cardiac events (MACE), in particular those related to early and late stent thrombosis. As for other medicinal products, adverse events need to be fully documented by body system. Any sub-population at increased risk of adverse events should be identified. Appropriate ways of observing safety for trials in such vulnerable patient populations are warranted.

Post-marketing surveillance considerations

The information gathered in the post-marketing period is very important. A long-term (e.g., 5-year) post-approval clinical follow-up is strongly recommended. This should be part of the risk-management plan (RMP). Post-approval follow-up could involve patients already enrolled and treated in the pivotal study(ies) but also new patients in the post-approval setting **(A, B, C, D)**. Long-term surveillance could be done via registry data.

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