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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE DEVELOPMENT OF A CHMP GUIDELINE ON THE EVALUATION OF NON-CLINICAL AND CLINICAL DATA ON THE MEDICINAL SUBSTANCES CONTAINED IN DRUG-ELUTING (MEDICINAL SUBSTANCE-ELUTING) CORONARY STENTS WITHIN THE FRAMEWORK OF A CONSULTATION PROCEDURE FOR COMBINATION PRODUCTS.

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1. INTRODUCTION

Reduction of restenosis is the main advantage of stenting compared with conventional percutaneous transluminal coronary angioplasty. Stents are medical devices which reduce the restenosis rate to 15-20%. However, restenosis continued 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. Intimal hyperplasia is the mechanism of stent restenosis. The restenosis process involves thrombus formation, inflammation and signal transduction, which mediates smooth-muscle-cell migration and proliferation. The rate of restenosis after stenting depends to a large extent on the lesion being studied, in a simple lesion it is ~10%, in a more complex lesion 15-20% and in a diabetic or small reference vessel, 40%. Several patient and lesion-related predictors of stent restenosis have been defined from angiographic studies. Angiographic restenosis is associated with increased morbidity, mortality and health care costs. Much research has been conducted to the pathophysiology and treatment of in-stent restenosis. medicinal substance-eluting stents, also called coated stents or medicated stents, have turned up as a potential solution for restenosis. Polymer-based elution of both sirolimus and paclitaxel from stent platforms have shown to reduce the neointimal proliferative response to stent-vessel injury and, thus, reduced the occurrence and cost of restenosis. In April 2002, CYPHER™, a sirolimus-eluting stent of Cordis Inc received CE conformity marking in Europe and in January 2003 the TAXUS medical device, a Paclitaxel-eluting stent of Boston Scientific received CE conformity marking in Europe for treatment of de novo coronary artery lesions in native coronary arteries. The introduction of medicinal substance-eluting stents has dramatically impacted the market size and growth rates for coronary stents worldwide. A lot of new companies are currently entering the field of medicinal substance-eluting stents. They are using, besides sirolimus or paclitaxel, new combinations of medicinal substance(s) (chemically synthesised or of biological origin) and stents with the purpose of optimizing safety and usefulness of the stents and in this context, the medicinal substance's Competent authorities are requested to provide an opinion on the quality, safety and usefulness of the medicinal product concerned.

Note: These medicinal substance-eluting stents are combination' products composed of medicinal product and medical devices where the medicinal product has an ancillary function to the device, are classified in the Community as medical devices in accordance with Council Directive 93/42/EEC concerning medical devices and in line with the MEDDEV 2.1/3 rev 2 guidelines relating to the application of: The Council Directive 90/385/EEC on active implantable medical devices and the Council Directive 93/42/EEC on medical devices. The authorisation of such combinations falls ultimately under the remit of the relevant Notified Bodies.

PROBLEM STATEMENT

According to the medical device legislation, the Notified Body shall 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. By definition, 'usefulness' relates to the rationale for using the medicinal substance in relation to the specific 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 medicinal substance-eluting stents. Differences have been noted in the amount of non-clinical and clinical data, where in some case manufacturers support their application dossier on a pharmacological basis, while in other cases application dossiers are supported with large, multi-centered, randomized controlled clinical studies.

Within the framework of assessment of such combination products, different possibilities could be distinguished depending on the knowledge on the ancillary medicinal substance i.e.:

1. the medicinal substance of the combination known to the competent authority and already registered in the setting of a medicinal substance-eluting stent device in the Community and

- a/the applicant claims comparative medicinal substance release characteristics;

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- b/different medicinal substance release characteristics are from a design perspective to be expected;

2. the medicinal product of the combination is known to the competent authority but not registered in the setting of a medicinal substance-eluting stent device;
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 as a medicinal substance-eluting stent device .

These different possibilities of the medicinal substance-eluting stents raise important questions about the data needed for adequate in/vivo, in vitro evaluation of the medicinal substances contained in medicinal substance-eluting stents and the optimal design to establish safety and usefulness of the medicinal substances contained in medicinal substance-eluting stents. Although it is recognised that the total amount of medicinal product incorporated in the medicinal substance/eluting stent 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 (pre)clinical evaluation program. It has to be recognised that on the technical side, device expertise is qualitatively different from expertise with the medicinal product. However, the evaluation of the safety and usefulness of the medicinal substances in the context of a medicinal substance-eluting stent are interlinked 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.

2. DISCUSSION (ON THE PROBLEM STATEMENT)

The evaluation of medicinal substance-eluting stents introduces additional considerations for preclinical and clinical testing, and for manufacturing. Aspects of manufacturing, mechanical performance & testing regimens, chemistry, animal experimentation, pharmacology and safety and efficacy evaluation ask for an integrated assessment. The quality aspects are outside the scope of this document.

The expected non-clinical and clinical data will be discussed in the guideline to be developed. Furthermore, taken into account that the clinical studies are performed in highly selected patient groups but the devices after launching, are commonly used outside the main study selection criteria, recommendations for post marketing surveillance should also be considered. Regulatory harmonization regarding requested information about safety and usefulness of the medicinal substances contained in medicinal substance-eluting stents is needed to achieve optimal care for all patients.

3. RECOMMENDATION

The CHMP Efficacy Working Party and the Safety Working Party recommend to draft a guidance document detailing what data are required to be included in the dossier of a medicinal substance-eluting stent for an adequate assessment of the safety and usefulness of a medicinal product used as an ancillary medicinal substance in a medical device in the context of a Notified body consultation procedure and of the post-marketing programs to be recommended. Recommendations will also be given regarding presentation and interpretation of results.

4. PROPOSED TIMETABLE

It is anticipated that a draft CHMP Guideline may be available 12 months after adoption of the Concept Paper to be later released for 3 – 6 months for external consultation and subsequently finalised within 6 months.

5. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline has involved the EWP, SWP and PhVWP.

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6. IMPACT ASSESSMENT (ANTICIPATED)

The development of this Guideline is anticipated to standardise and facilitate the Competent Authorities for medicinal substances` review of dossiers regarding evaluation of the medicinal substances contained in medicinal substance-eluting stents.

7. INTERESTED PARTIES

European Society for Cardiology; Notified Bodies, Competent Authorities for Medical Devices, Medical Device Industry Trade Associations.

This document will be developed in close cooperation with DG Enterprise (Medical Devices/ Pharmaceuticals)

8. REFERENCES TO LEGISLATION, LITERATURE, GUIDELINES ETC

- Council Directive 93/42/EEC of 14 June 1993 concerning medical devices

- Meddev 2. 1/3 rev2:
  Demarcation between: - Directive 90/385/EEC on active implantable medical devices
  - Directive 93/42/EEC on medical devices
  And Directive 65/65/EEC relating to medicinal products
  And related Directives

- Guideline on post-market clinical follow-up
http://europa.eu.int/comm/enterprise/medical_devices/meddev/2_12-2_05-2004.pdf

- Evaluation of clinical data: a guide for manufacturers and Notified Bodies.
http://europa.eu.int/comm/enterprise/medical_devices/meddev/2_7.pdf

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