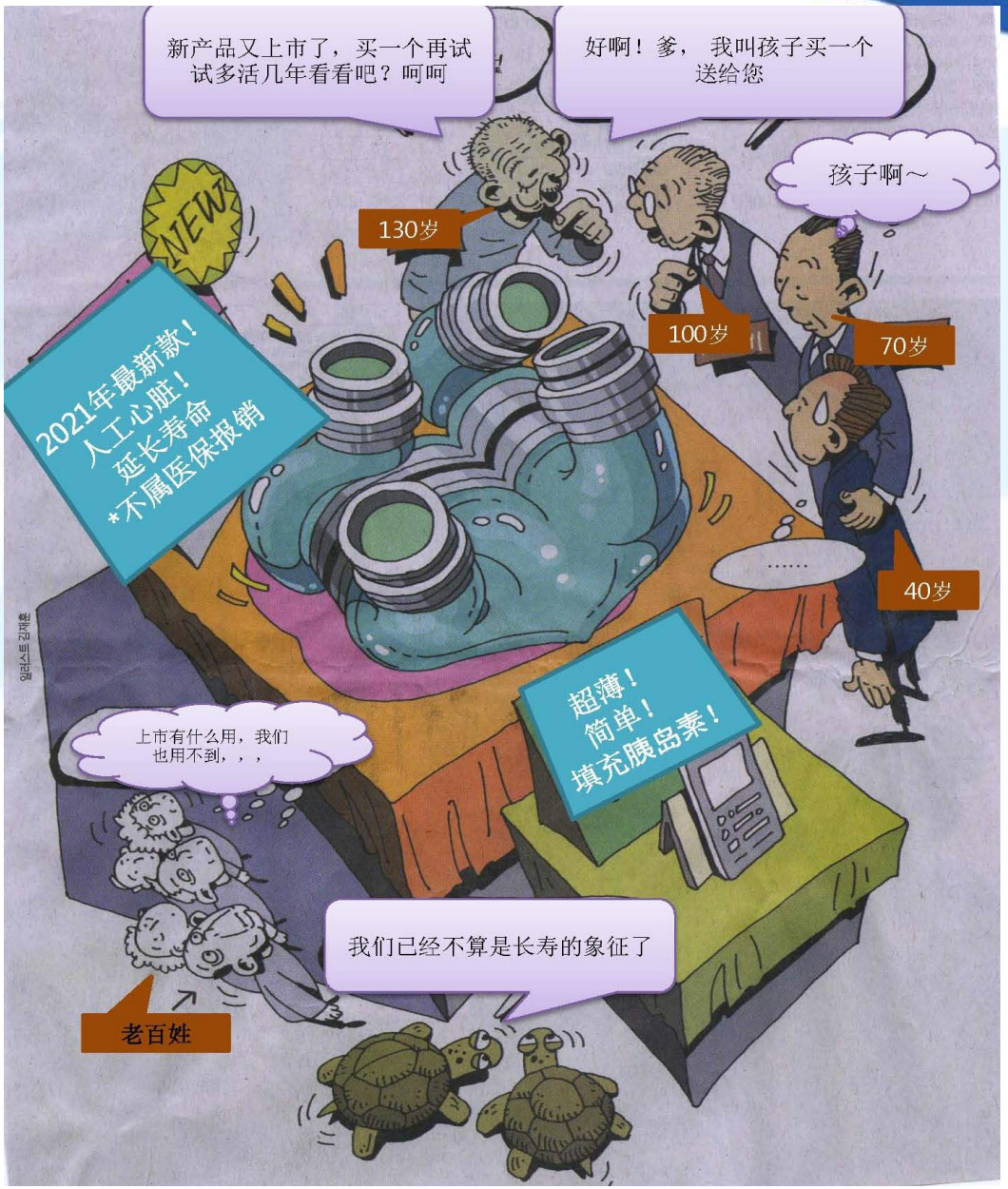
CONFORMITY ASSESSMENT
for
ADVANCED MEDICAL DEVICES

April 2011

长寿的钥匙，人工脏器



Origin:
Chungang Sunday

MEDICAL DEVICE

Definition

- Instrument
- Apparatus
- Implant
- Machine
- Appliance
- Software
- Material
- Other similar or related article

which doesn't achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

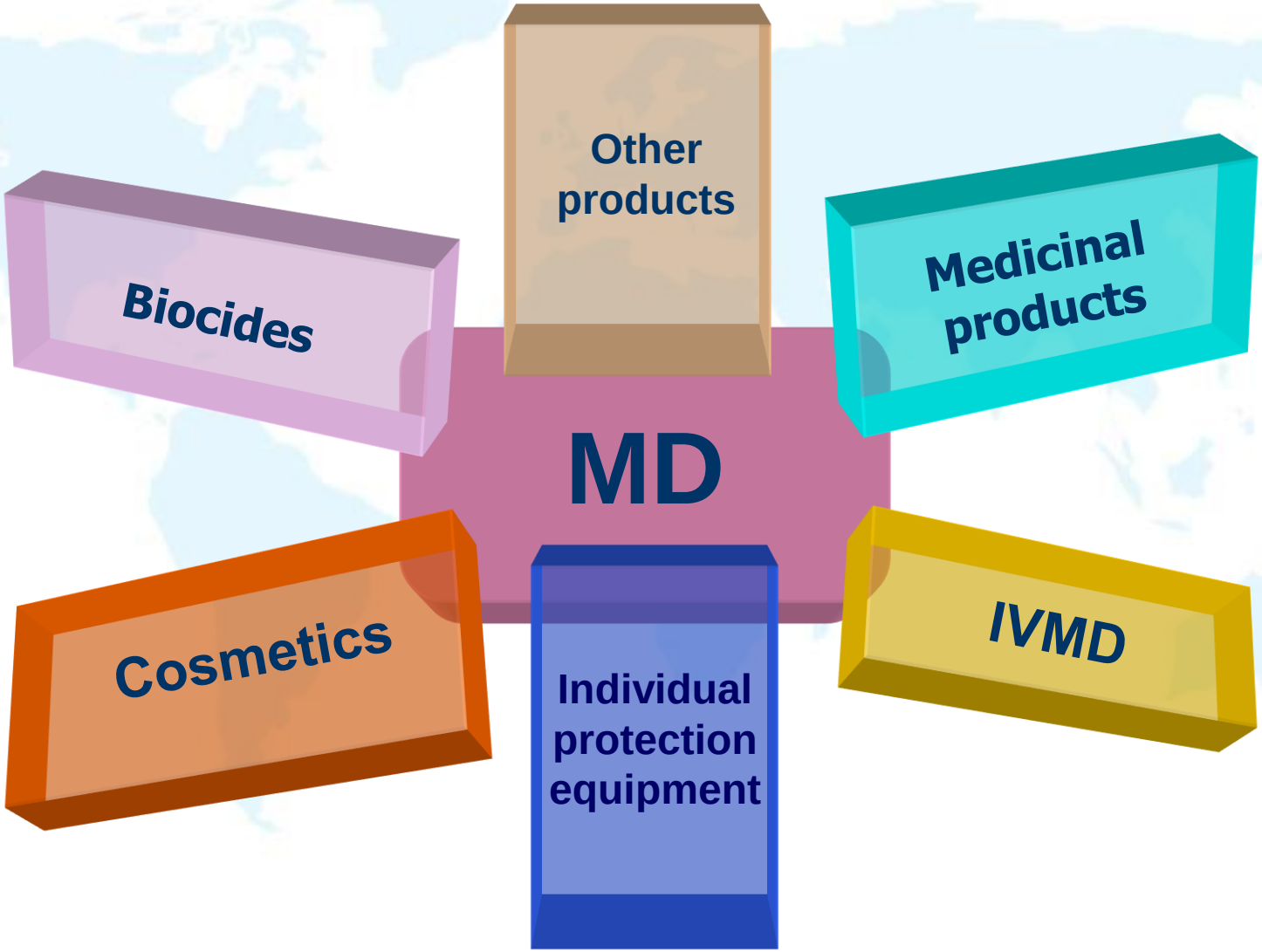
- Diagnosis
- Prevention
- Monitoring
- Treatment
- Alleviation

} disease / injury

- Compensation
- Investigation, replacement, modification, or support of the anatomy or of a physiological process
- Supporting or sustaining life
- Control of conception
- Disinfection of medical devices

MEDICAL DEVICE

Definition



MEDICAL DEVICE

Borderline Issues

Is this product a medical device ?

MD

- **Medical purpose ?**
- **Principal intended action ?**

Combined Products for „Advanced Therapy

Combined products already regulated:

- MD + medicinal products (a)
- MD + non viable animal derivatives (b)
- MD + blood or plasma derivatives (c)

ITC ASIA

Combined Products .....(a)

- Directive 93/42/EEC (MD)
- Directive 2001/83/EEC
- Directive 2004/27/EEC

Combined Products .....(b)

- Directive 93/42/EEC
- Directive 2003/32/EC (BSE/TSE)

Combined Products .....(c)

- Directive 93/42/CEE (MD)
- Directive 2000/70/EEC

Examples of Medical Devices

- bone cement,
- dental filling materials,
- materials for sealing, approximation, or adhesion of tissues (e.g. cyanocrylates, fibrin-based adhesives not of human origin),
- sutures, absorbable sutures,
- soft and hard tissue scaffolds and fillers (e.g. collagen, calcium phosphate, bioglass),
- intrauterine devices,
- blood bags,
- systems intended to preserve and treat blood

Examples of Medicinal Products

- spermicidal preparations,
- gases intended to be used in anaesthesia and inhalation therapy
- topical disinfectants (antiseptics) for use on patients
- artificial tears,
- water for injections

Device or Medicinal Product?

In order to decide which regime (MDD or MPD) applies, the following criteria should be examined:

Step 1: The **intended purpose** of the product taking into account the way the product is presented

Step 2: The method by which the **principal intended action** is achieved. If the primary action is pharmacological, immunological or metabolic the product is pharmacological (*medicinal product*)

The principal intended action of a product may be deduced from:
- the manufacturer's labeling and claims,
- scientific data regarding mechanism of action

Primary Mode of Action

Medical devices may be assisted in their function by pharmacological, immunological or metabolic means, but as soon as these means are not any more ancillary with respect to the principal purpose of a product, the product becomes a medicinal product.

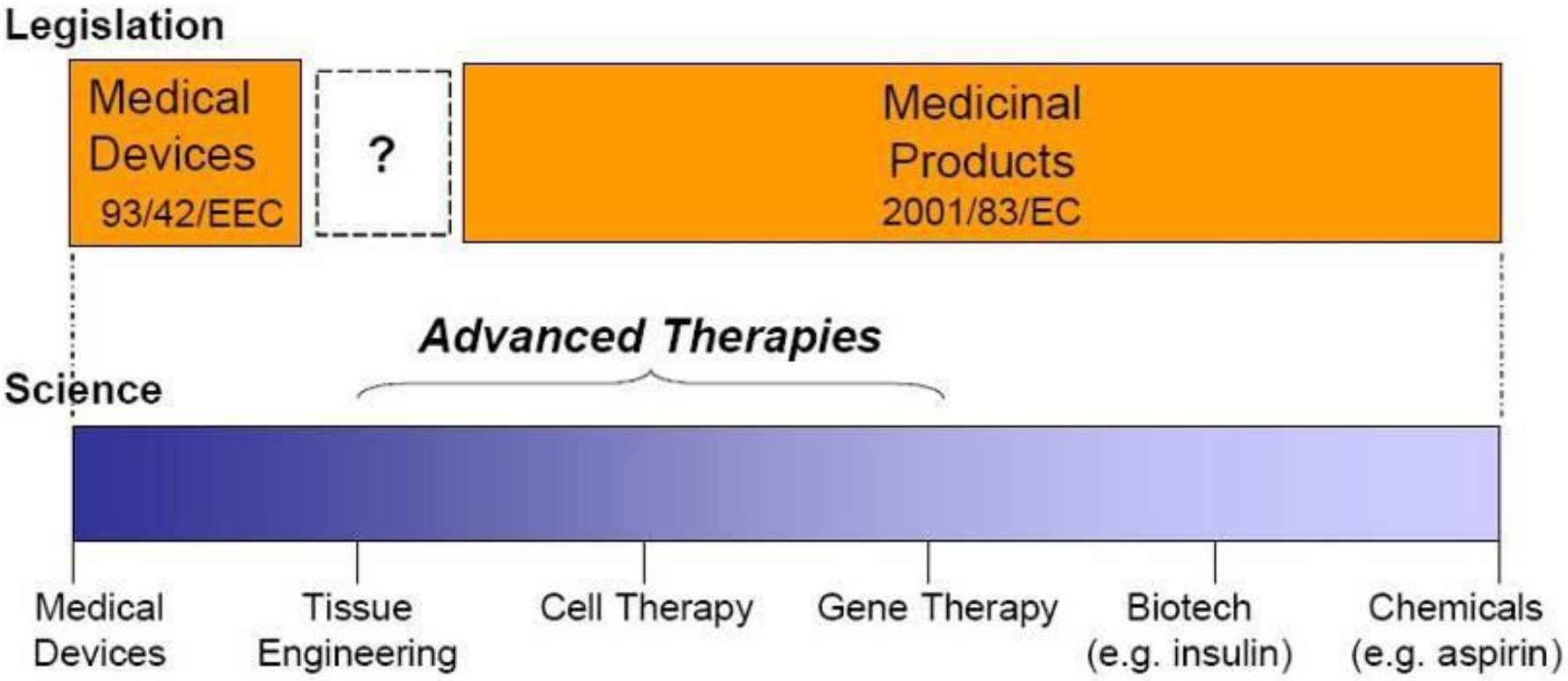
The claims made for a product, in accordance with its method of action may, in this context, represent an important factor for its classification as medical device or medicinal product.

Examples of Combination Products Classified as Medical Devices

- ✓ *catheters coated with heparin or an antibiotic agent,*
- ✓ *bone cements containing antibiotics,*
- ✓ *root canal fillers which incorporate medicinal substances with secondary action,*
- ✓ *blood bags containing anticoagulant or preservation agents,*
- ✓ *soft tissue fillers incorporating local anaesthetics,*
- ✓ *condoms coated with spermicides,*
- ✓ *electrodes with steroid-coated tip,*
- ✓ *wound dressings, surgical or barrier drapes with antimicrobial agent,*
- ✓ *intrauterine contraceptives containing copper or silver,*
- ✓ *drug eluting coronary stents.*

Combined Products .....(c)

- **MD + blood or plasma derivatives ....**
  93/42/EEC Art. 1.4.a …. NB seeks a mandatory scientific opinion from the European Agency for the Evaluation of Medicinal products (EMEA) about quality and safety


Legislation
Medical Devices 93/42/EEC
?
Medicinal Products 2001/83/EC
Advanced Therapies
Science
Medical Devices
Tissue Engineering
Cell Therapy
Gene Therapy
Biotech (e.g. insulin)
Chemicals (e.g. aspirin)

Exemptions from the scope of Reg. 1394/2007… (2)

- Products containing **non-viable human or animal cells/tissues are excluded** from the definition if they do not act by pharmacological, immunological, metabolic means

- **“non-viable cell and tissue products”**
  - No ATP
  - No medicinal product
  - Medical device?
    - Human: excluded from Directive 92/43/EEC *….2004/23/EC(?)*
    - Animal: Yes *….2003/32/EC*

Combined Products

- Any **“advanced”** aspect turns medicinal product or medical device into ATP
- Borderline issues
- Overlapping issues:
  - Evaluation of **device component** by notified body
  - Evaluation as a **medicinal product**

Specific Provisions for MD combined in ATMP

- MD which forms part of an ATMP shall meet the essential requirements laid down in Annex I to 93/42/EEC

- AIMD which forms part of an ATMP shall meet the essential requirements laid down in Annex 1 to 90/385/EC

Specific Provisions for MD combined in ATMP

In addition to the requirements laid down in Art. 6(1) of Reg. (EC) No. 726/2004, **applications** for the authorization of an ATMP containing MDs, bio-materials, scaffolds or matrices **shall include**:

- a description of the **physical characteristics and performance** of the product, and
- a description of the **product design methods**, in accordance with Annex I to Directive 2001/83/EC.

Assessment Procedure …Art. 9 of ATMP 1394/2007

- **Final evaluation** of the ATM Product by EMEA
- The application shall include evidences of MD conformity to **essential requirements** referred in Art. 6
- The application shall include (where applicable) results of MD/AIMD part **assessment by NB**
- EMEA **shall recognize** those results (may request for more information)
- If the application does not include NB assessment conclusions related to MD/AIMD, EMEA **shall seek an opinion** on device conformity to NB identified by a manufacturer, **unless** CAT for medical devices decides that involvement of NB is not required.

Classification

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.

Ref: MEDDEV 2.7.1 Appendix I “II-2 Legal basic” pg 3

Reference

- **MEDDEV 2.7.1 Appendix 1**
  EUROPEAN COMMISSION
  Guideline
  Clinical Evaluation of Coronary Stents

- **EMEA/CHMP/EWP/110540/2007**
  European Medicines Agency
  COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

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

Drug regulatory Bodies

- **State Institute for Drug Control (SUKL)**

  http://www.sukl.cz/

- **European Agency for the Evaluation of Medicinal Products (EMEA)**

  http://www.ema.europa.eu/

Evaluation of Medicinal Substance

For coronary stents incorporating a medicinal substance, the **Notified Body** shall refer to

- A member state designated competent authority for medicinal products

or

- European Medicines Agency (EMEA) for their scientific opinion.

Ref: MEDDEV 2.7.1 Appendix I "II-2 Legal basic" pg 3

EMEA Certificate

Step 1. Application by manufacturer

Step 2. Assessment by EMEA

Step 3. Issue of EMEA certificate

Consultation of Medicinal Substance

The opinion of the Competent Authority for medicinal products or EMEA on the quality and safety of the substance is based on

- 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
- EMEA/CHMP/EWP/110540/2007 guideline.

Ref: MEDDEV 2.7.1 Appendix I "II-2 Legal basic" pg 3

The Consultation Process

- is initiated by the Notified Body (application to a CA)
- is carried out by a Competent Authorithy
  - normally the CA that once approved the drug
  - all documentation to be supplied by the NB
- is not formally an application for a drug approval but should address the same issues
  - it is often a new drug delivery technique
  - local compared to systemic drug administration
  - local tolerance
  - new pharmacokinetics
  - new drug delivery time-frame
  - toxicity studies
- the NB decides (certificate or not) based on the CA's opinion

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 fulfill 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 characterization 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. tissue measurements, assessment of any late inflammatory response, etc); in case of DES, see EMEA guideline.**

Ref: MEDDEV 2.7.1 Appendix I "IV Preclinical Assessment" pg 4

Evaluation of Clinical data supporting CE marking

ITC ASIA

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,

to identify relevant gaps in the literature which should be addressed by a specifically designed clinical investigation.

Ref: MEDDEV 2.7.1 Appendix I “VI EVALUATION OF CLINICAL DATA SUPPORTING CE MARKING” pg 8

Evaluation of Clinical data supporting CE marking

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- 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:

- 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;

- 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;

- Biological equivalence: use of the same materials in contact with the same human tissues or body fluids;

- Relevant gaps in the literature which should be addressed by a specifically designed clinical investigation.
- A Post Market Clinical Follow up (PMCF) is important for coronary stents in order to evaluate long term safety and performance

Ref: MEDDEV 2.7.1 Appendix I “VI EVALUATION OF CLINICAL DATA SUPPORTING CE MARKING” pg 8

Categorizations of Medicinal Substance

The medicinal substance of the combination is already used in a CE marked DES with the same indication (see section 7.3) and the Manufacturer claims:

Comparable medicinal substance release characteristics (A):

i. Same stent material with the same surface coating and drug carrier system (A1);

ii. Same stent material with a different surface coating and drug carrier system (A2);

iii. Different stent material with same surface coating and drug carrier system (A3);

iv. Different stent material with different surface coating and drug carrier system (A4).

Ref: EMEA/CHMP/EWP/110540/2007 “4. BACKGROUND” pg 4

Categorizations of Medicinal Substance

The medicinal substance of the combination is already used in a CE marked DES with the same indication (see section 7.3) and the Manufacturer claims:
different medicinal substance release characteristics (B)

The medicinal substance of the combination is known to the competent authority as an active pharmaceutical ingredient or formulated medicinal product in an authorized medicinal product but not as a component of a (previously) CE marked DES (C)

The medicinal substance of the combination is a new active substance and therefore not known to a Competent Authority neither as an active pharmaceutical ingredient or formulated medicinal product in an authorized medicinal product nor as a component of a CE marked DES (D).

Ref: EMEA/CHMP/EWP/110540/2007 “4. BACKGROUND” pg 4

Clinical Evaluation of Coronary Stents

❖ 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.

- the duration of the study for a minimum of 3 years

Labels and Instructions for Use

- Demonstration of compliance with MDD Annex I Clause 13, EN 980, EN 1041
- Sample of labels (shipping labels, sterile package labels) - Instructions for use - patient information
- Instructions for Use

Manufacturing

- Description of the manufacturing process
- Multiple facilities, critical suppliers, contract sterilizer, etc.: quality assurance certificates issued by an accredited third party inspection body for each facility
- Flow charts including inspection and preventive monitoring steps
- Manufacturing conditions
- Labeling control
- Traceability
- Product and environmental bio-burden, particles

Package Qualification and Shelf life

- Physical package qualification
- Performance of the product after real time and/or accelerated aging
- Shelf life: Maintenance of sterility and performance over the shelf-life of a product

Sterilization

- Ethylene Oxide: EN 556-1; EN 556-2; EN 866; EN ISO 11138; EN 550; ISO 11135; EN ISO 11737; EN ISO 10993-7
- Moist Heat: EN 556, ISO 11138-3, EN 554, ISO 17665-1, ISO 11737
- Irradiation: EN 556-1, EN 556-2, EN ISO 11137, EN 552, EN ISO 11737

- Brief description of the installation qualification and validation summary (method shall assure at least a SAL of 10-6).

- Process Validation Report with physical performance qualification and microbiological performance qualification

Evaluation of Quality System

- EN ISO 13485: 2003
- On site audit
- Although Design Dossier compliance with directive, but if quality system is not fulfill requirement then they can not pass conformity assessment.

Evaluation of Design Dossier

- Introduction
- Essential Requirements Checklist
- Risk Analysis
- Drawings, Design -, Product – Specifications
- Chemical, Physical and Biological Tests
  - In Vitro Testing - Preclinical Studies
  - In Vivo Testing - Preclinical Studies
  - Biocompatibility Tests
  - Bio-stability Tests
  - Microbiological Safety, Animal Origin Tissue
- Clinical Data
- Labels and Instructions for Use
- Manufacturing
- Package Qualification and Shelf life
- Sterilization
- Declaration of Conformity

Chemical, Physical and Biological Tests

- **Microbiological Safety, Animal Origin tissue**
- **Geographical origin and boarding of animals: Species, Country, Herd, Feeding, Age**
- **Origin of material used/nature of starting tissue:**
- **Specified risk material: organ, tissue, body fluid**
- **For TSE-relevant species: If available certificate of suitability of starting materials with respect to TSE issued by EDQM**
- **Veterinary controls**
- **Certificate demonstrating conformance with veterinary inspection criteria indicating that the raw material was fit for human consumption.**
- **Certificate documenting that the applied techniques for stunning and slaughtering were suitable to avoid cross contamination with specified risk material.(References: EN ISO 22442-2)**

Thank you.

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