

Device-Drug Interface: The European Experience

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(for Eucomed)

‘Medical device’ definitions

- any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:
 - diagnosis, prevention, monitoring, treatment or alleviation of disease;
 - diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap;
 - investigation, replacement or modification of the anatomy or of a physiological process;
 - control of conception

and *which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.*

'Medical device' definitions

[under revision]

- *Pharmacological means*

... an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response or which blocks the response of another agent. Although not completely reliable, the presence of a dose-response correlation is indicative of a pharmacological effect.

- *Immunological means*

... an action which involves an action in or on the body by stimulation and/or mobilisation of cells and/or products involved in a specific immune reaction.

- *Metabolic means*

... an action which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in, and available for, normal body function. The fact that a product is itself metabolised does not imply that it achieves its principle intended action by metabolic means.

‘Pharmaceutical’ definitions

- ***Directive 2001/83/EC as amended by Directive 2004/27/EC***
(OJ L 136 pp 34-57)
- ***Medicinal product (Art 1(2)):***
 - (a) Any substance or combination of substances *presented as having properties* for treating or preventing disease in human beings
 - (b) Any substance or combination of substances which may be *used in or* administered to human beings *either* with a view to restoring, correcting or modifying physiological functions *by exerting a pharmacological, immunological or metabolic action, or to* making a medical diagnosis

'Pharmaceutical' definitions

- *Directive 2001/83/EC as amended by Directive 2004/27/EC*
- *Art 2:*
 1. This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process
 2. **In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a 'medicinal product' and within the definition of a product covered by other Community legislation the provision of this Directive shall apply**
 3. Notwithstanding paragraph 1 and Article 3(4), Title IV of this Directive shall apply to medicinal products intended only for export and to intermediate products

'Pharmaceutical' definitions

- ***Substance:***
 - Any matter irrespective of origin which may be:
 - human, *e.g. human blood or blood products;*
 - animal, *e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products, etc;*
 - vegetable, *e.g. micro-organisms, plants, parts of plants, vegetable excretions, extracts, etc;*
 - chemical, *e.g. elements, naturally-occurring chemical materials and chemical products obtained by chemical change or synthesis.*

Information sources?

- Medical devices directives (Article 1 definitions)
- Pharmaceutical directives definitions (Directive 2001/83/EC)
- **MEDDEV 2.1/3 rev 2 July 2001**
http://www.europa.eu.int/comm/enterprise/medical_devices/meddev/2_1_3_07-2001.pdf
(This document is under revision)
- *Medical Devices Bulletin 17* (February 2006)
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=369
- *Guidance for Notified Bodies: Devices which incorporate a medicinal substance* - June 2003
(This document is difficult to find on the MHRA web site; a notice was issued to the effect that it is under revision at one point)
- *EMEA draft guideline: Procedural aspects and dossier requirements for the consultation to the EMEA by a Notified Body on an ancillary medicinal substance used in a medical device (EMEA/CHMP/401993/2005)*
- Trade association documents

Information sources?

- Draft EMEA guideline: 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
- Draft guideline: *Suitability of the graduation of delivery devices for liquid dosage forms*
 - February-August 2005 consultation
 - ‘Question and answer’ on ‘*What are the requirements for the graduation of measuring devices for liquid dosage forms of medicinal products for human use ... in particular in relation to the suitability of the graduation of the measuring device and dosing precision of the related product; and the suitability of the measuring device for the related product*’ rather than a final guideline
 - CHMP Quality Working Party questions and answers
- Draft EMEA guideline: Human cell-based medicinal products

MDEG consideration

- A number of cases have been submitted to the Medical Devices Experts Group to determine the status of products
- Outcome is an advisory position as to whether a product should be a pharmaceutical or a medical device
- Not all member states follow the advice
- Within a member state there may be divergent implementations
- EU guidance document incomplete (but under revision)

Drug-device combinations

- Drug delivery device + drug = Pharmaceutical
 - e.g. prefilled syringe
 - e.g. trans-dermal drug delivery system

Intended for use only as a complete product
- Medical device + drug (secondary action) = Medical device(?)
 - e.g. pacemaker lead impregnated with steroid to prevent local tissue reaction and thus extend life of lead
 - e.g. IV catheter coated internally with heparin to help prevent occlusion

Drug or device?

Questions to ask yourself ...

- What is the **manufacturer's intended purpose** for the product, taking into account the way in which it is presented?
- What is the **mechanism** by which the product achieves its principal intended action?
 - Medical devices typically achieve this through *physical means*
 - Pharmaceutical products typically achieve this through *pharmacological means, immunological means, or through metabolism*
 - *Impact of new pharmaceutical directive scope?*

Examples of drug/device classification

- **Table – MHRA examples** – *separate document, for information*

Note: The revision of the Medical Device Directive introduces an Article 7 committee procedure for determination of status of borderline products and resolution of classification issues

Consultation process: Devices incorporating drugs

- Notified bodies
 - Obligation to consult with *a* pharmaceutical competent authority where the medicinal substance is liable to *act on the body*
 - *For products with stable human blood derivatives consultation with the EMEA*
- Pharmaceutical competent authority
 - To verify the safety, quality and usefulness of the medicinal substance by analogy with the methods specified in Directive 75/318/EEC
 - related to the intended action of the device
 - justification for drug inclusion with respect to benefit gained
 - may make available relevant pharmacovigilance data
 - The revision of the MDD refers to the pharma CA role as the assessment of safety and quality; usefulness is to be assessed by the NB

Consultation process: Devices incorporating drugs

- EMEA guidance on format and content of dossier to be submitted
 - Stable blood derivatives
 - Other substances
- CTD format
- Taking into account MEDDEV

Devices incorporating drugs - information required

- General information on medical device
- Qualitative and quantitative particulars on medicinal substance
- Overall method of manufacture and specific information on incorporation of medicinal substance
- Control of starting material
 - Pharmacopoeial specifications
 - Additional information for new active substances

Devices incorporating drugs - information required

- Control tests at intermediate stages of manufacture especially re incorporation of medicinal substance
- Control tests on final product re medicinal substance
- Stability information
- Toxicity and bio-compatibility information
 - EN ISO 10993/EN 30993 standards
 - known toxicological profile of medicinal substance
 - new studies

Devices incorporating drugs - information required

- Reproductive function data (unless known)
- Embryo/foetal toxicity, perinatal toxicity (unless known)
- Mutagenic/genotoxic potential (unless known)
- Carcinogenic potential (if needed)
 - Available information
 - Results of genotoxicity testing
 - Chemical structure
 - Duration and level of potential exposure

Devices incorporating drugs - information required

- Pharmacodynamics relevant to use in the medical device
- Pharmacokinetics
 - Local and systemic exposure - maximum level, duration of exposure
 - Maximum plasma level?
 - Patient variability
- Local tolerance
 - EN ISO 10993/EN 30993
 - Literature

Devices incorporating drugs - information required

- Clinical documentation
 - Drug incorporation = usually → **Class III medical device** (Annex IX)
 - Clinical safety of the device as a whole
 - EN ISO 14155 for clinical studies (Annex X)
- Labelling and information provided with the medical device
- *Notice to Applicants-type format* *?CTD format*
- *Pharmaceutical Expert Report useful* *?CTD format*

Drugs with Devices

- Consultation
 - Pharmaceutical competent authority with device competent authority or Notified Body
 - ? Details

Experience

- A number of dossiers have been submitted since 1995 ...
- At least one positive approval from EMEA (published on web site)
- MHRA - around 180 submissions, 82 positive Opinions, 32 negative Opinions (no information published on web site)
 - Processing time around 240 days in 2007
- BfArM – around 80 submissions

Experience

- Comments received from those who have used the system:
 - Ability to choose the CA for consultation welcomed
 - No clear time lines may be provided from the CA
 - FDA processing faster and with a different focus for the same product; in-house processing of all aspects seems to be advantageous
 - Requests for supplementary information common
 - Applications made to a number of different authorities by different manufacturers/NBs
 - Some Agencies more flexible about format than others
 - Lack of direct contact between manufacturer and CA a disadvantage – the NB is usually required to reflect the manufacturer's position
 - CAs appear to give priority to pharmaceutical product licence applications – can result in delays for device-drug assessments

Thank you for your attention