Regulatory Challenges of Drug Device Combination Products in the EU

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Disclaimer

• These are my personal views and not necessarily those of MHRA as an organisation.
Outline

• **Background**
  – Medical devices regulation

• **Challenges for combination products**
  – Classification
  – Dossier information
  – Convergence

• **Current initiatives in EU**
Background
My background

Medical devices incorporating ancillary medicinal substances

Medical Device Directive 93/42/EC:
The quality, safety and usefulness of the substance must be verified by analogy with Annex I to Directive 2001/83/EC.

- Drug-eluting stent
- Heparin coated catheter
- Wound dressings containing silver

- Class III high risk devices under rule 13 of MDD
- Notified Bodies consult Medicines CA or EMA
Medical Devices industry

- Major employer in Europe
- Total sales amount to €100 billion.
- 25,000 companies, 95% are Small and Medium-sized Enterprises (SMEs).

Single market provision

Controls proportional to risk

Co-regulation Device CAs and Notified Bodies

*Internal Market, Industry, Entrepreneurship and SMEs
Role of Device Competent Authority

Notified Bodies
- Initial Designation
- Ongoing Surveillance

Pre Market
- Clinical Investigation
- Review of TSE Summary Reports

Post Market
- Vigilance

Throughout
- Enforcement
What is a Notified Body?

- Third party test and/or certification bodies designated by their national Competent Authorities
- Undertake conformity assessment procedures for specific range(s) of products
- Currently approx. 60 ..
- ‘PIP’ breast implant scandal

“Action Plan for Immediate Actions ”.
Devices Legal Framework-Revision

26 September 2012:

- **Proposed Regulation on medical devices**
  Replaces:
  - Dir. 90/385/EEC active implantable medical devices and
  - Dir. 93/42/EEC medical devices;
- **Proposed Regulation on *in vitro* diagnostic medical devices**
  Replaces
  - Dir. 98/79/EC *in vitro* diagnostic medical devices

Adoption late 2016?
Transition period 3-5 years?
Delays indicate complexity of negotiations
Classification
Definitions

- Unlike US no ‘combination product’ classification (except cATMPs)

**Medicinal product** or **Medical device**

**Medicinal product**

Any substance or combination of substances
- having properties for treating or preventing disease in human beings; or
- used in or administered to human beings …
- by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

**Medical device**

Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination…,

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
Integral DDC products are regulated by **EITHER** the Medical Device Directive (MDD) or the Medicinal Products Directive

- **Primary Intended Purpose:**
  - Pharmacological
  - Metabolic
  - Immunological

- **Integral delivery device**

- **MEDICINAL PRODUCT**
  - 2001/83 EC

- **Primary intended purpose achieved by other means:**
  - e.g. physical or simple chemical

- **MEDICAL DEVICE**
  - 93/42/EEC

- **Ancillary Substance**
Primary intended purpose

PMMA bone cement with antibiotic

Fixation of prosthesis

MEDICAL DEVICE

Antibiotic impregnated-PMMA chain

Deliver antibiotic

MEDICINAL PRODUCT
EU Guidance


EUROPEAN COMMISSION
DG ENTERPRISE and INDUSTRY
Directorate F, Unit F3 “Cosmetics and medical devices”

MEDICAL DEVICES: Guidance document
- Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

GUIDELINES RELATING TO THE APPLICATION OF:

MEDDEV 2.1/3 rev 3

Foreword
The present Guideline is part of a set of Guidelines relating to questions of application of EC Directives on medical devices. This guideline is not legally binding, since only the European Court of Justice can give an authoritative interpretation of Community law. It has been elaborated by an expert group including experts from Member States. Competent authorities provide useful guidance which should assist common experts from Competent Authorities, it is anticipated that:

MANUAL ON BORDERLINE AND CLASSIFICATION IN THE COMMUNITY REGULATORY FRAMEWORK FOR MEDICAL DEVICES

Version 1.17 (09-2015)

Please note: The views expressed in this manual are not legally binding; only the European Court of Justice can give an authoritative interpretation of Community law.

Moreover, this manual shall only serve as guidance by-case application of Community-legislation in Member States. It is for the national competent authorities and national courts to assess on a case-by-case basis.

The content of this manual and all updates are the result of the ongoing working group on borderline and classification. This group is chaired by the European Medicines Agency and composed of representatives of all Member States and other stakeholders.

Guidance on legislation
Borderlines between medical devices and medicinal products

June 2013

Reflection paper on classification of advanced therapy medicinal products

Draft agreed by CAT........June 2014
Adoption by CAT for release for consultation........25 June 2014
Start of public consultation........June 2014
End of consultation (Deadline for comments)........31 October 2014
Draft agreed by CAT........13 May 2015
Adoption by CAT........22 May 2015

Keywords: ATMP classification, Gene therapy, Somatic cell therapy, Tissue engineered Products, Combined ATMPs
Information on device to be provided in an MAA?
Medicines with non-integral administration devices

Separate administration devices must be CE marked - is evidence of the CE mark sufficient?

Not necessarily!

Take into account the overall product
- Physical/Chemical Compatibility
- Accuracy of Dosage
- Ease of use (population)
Medicines with integral device component

Regulated under 2001/83/EC but device component needs to be considered.
Medicinal products with medical device component

Currently minimal requirements:

Annex I (3.2)

12. Where applicable and if needed, a CE marking which is required by Community legislation on medical devices shall be provided.
93/42/EEC:

Article 1 (3):

- If the device and the medicinal product
  - form a single integral product which is …
  - not reusable,

Medicinal product, but…
Essential Requirement 1:
- reduce the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and
- consider the technical knowledge, experience, education and training, .... medical and physical conditions of intended users (design for lay, professional, disabled or other users).

Essential Requirement 13: Information supplied by the manufacturer
- 13.1. Each device must be accompanied by the information needed to use it safely and properly, taking account of the training and knowledge of the potential users.....

Human Factors / usability engineering in EU
Proposed new Medical Device Regulation to amend the MPD?

Article 91
Amendments to Directive 2001/83/EC

In Annex I of Directive 2001/83/EC, point 12 of Section 3.2. is replaced by the following:

‘(12) Where a product is governed by this Directive in accordance with the second subparagraph of Article 1(4) or the second subparagraph of Article 1(5) of Regulation (EU) […] on medical devices[1], the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements of Annex I of that Regulation contained in the manufacturer’s EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.

If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) […][1], the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements of Annex I of that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question, unless the authority is advised by its experts for medical devices that involvement of a notified body is not required.

How will this work in practice?
Feedback….Commission Report on ATMPs
March 2014

• for the device part, the Agency is to rely on the assessment of the notified bodies (if available).
• separate assessment of the medical device and the medicinal product is widely perceived as an excessive burden when the device is not marketed separately.
• stakeholders have difficulties to understand the interaction between the Agency and the notified bodies in practice.
Convergence
Current challenges

- Definitions:
  - Pharmacological, Immunological and Metabolic actions
  - Simple ‘chemical’ action?
  - In vivo diagnostics (what is diagnosis?)

- Principal mode of action of new biomaterials

- Appropriate regulation of medical devices which
  - Enhance availability and/or efficacy of medicinal products
  - Administer a medicinal product ‘off label’
  - Create a new use for a medicinal product

- Needle safety systems – passive/active

- Human Factors requirements

- New technologies and software

Increasing convergence
EU Advice on combinations

- **Regulatory and Scientific Advice** available from EMA or National Authorities
  - Can be used at any stage of development – earlier the better!

- **Innovation office / EMA Innovation Task Force (ITF)**
  - Facilitate understanding of issues and regulatory requirements to bring innovative products and processes to market:
    - ATMPs, stratified medicines, nanomedicines, advanced manufacturing techniques, novel drug/device combinations. Applicable to medicines and devices.
    - Encourage (very) early dialogue with companies/researchers developing innovative technologies and products

- **Committee for Advanced Therapies (CAT)**
MHRA Innovation Office
Case Study

Case Study material courtesy of Dr Stephen Liggett, Prof Ryan Donnelly, QUB
Challenges

- No commercially available microneedle drug product in any jurisdiction
- Limited use of the intradermal route for drug administration
- The use of Gantrez®, a main component of the hydrogel microneedle system under investigation, has been restricted to dental products
Feedback

- “The gap in the availability of accessible guidance and example products was filled by the engagement with the MHRA through the Innovation Office”

- [https://www.gov.uk/government/groups/mhra-innovation-office#case-studies](https://www.gov.uk/government/groups/mhra-innovation-office#case-studies)
Current EU initiatives 

- **Highlighting** the regulatory challenges for manufacturers, competent authorities and notified bodies

- **Reflecting** on collaborative ways forward, taking into account the different regulatory regimes, FDA guidances

- **Participating** in working parties for medicines and medical devices,
  - QWP, BWP, EU Innovation Office Network, EC Borderline and Classification Working Group, ISO Change management WG

  proportionate, appropriate, risk based regulation of drug-device combination products and those falling close to the borderline
Summary

• Challenges for borderline and combination products recognised
• Current positive initiatives in EU

Communication
Thank You

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