Drug-Device combinations - Understanding the regulatory pathway

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Outline

- Importance?
- Legislation & Definitions
  - Borderline Between Medicines & Devices
  - Types of Combinations
- Cases
- Variations vs Extension applications
- Devices Incorporating an Ancillary Medicinal Substance: Notified Body Consultation
- Scientific Advice
- Current Challenges
Why is the regulatory pathway important?

- Development strategy
- Data package
- Regulatory legislation
- PV activities
- CA/NB
- Cost
- Time to market
- Lifecycle management
Legislation
EU pharmaceutical legislation - Human

Devices Legal Framework

- **Medical Devices**
  Directive 93/42/EC
  - Extended by Directive 2000/70/EC
    (stable derivatives of human blood/plasma)
  - Extended by Directive 2001/104/EC
    (additional categories of blood products)

- **In vitro Diagnostic Devices**
  Directive 98/79/EC

- **Active Implantable Medical Devices**
  Directive 90/385/EC

**Latest technical revision:** Directive 2007/47/EC

**Guidance:** MEDDEV, consensus statements and interpretative documents
26 September 2012 EC adopted:

- A proposal for a Regulation on medical devices (to replace: Directive 90/385/EEC regarding active implantable medical devices and Directive 93/42/EEC regarding medical devices);

Once adopted by the European Parliament and by the Council, will replace the existing three medical devices directives.

Texts of the proposals and other related documents are available on EC website.

Expected adoption in 2014, then gradually come into effect from 2015 to 2019.
Medicinal Product Definition

Article 1 Directive 2001/83/EC

Any **substance** or **combination of substances** presented as having properties for treating or preventing disease in human beings; or

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.
Medical Device Definition

Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for medical purposes for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of 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
Ancillary Medicinal Substance

Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of directive [2001/83/EC] and which is liable to act on the body with ancillary action to that of the device, that device must be assessed and authorised in accordance with this Directive Article 1(4) 93/42/EEC.

Same requirement for devices containing blood products.

[A product] placed on the market in such a way that the device and medicinal product form a single integral product ... exclusively for use in the given combination and which is not reusable ... governed by [2001/83 EC].

The relevant essential requirements in Annex 1 to [93/42/EEC] shall apply as far as safety and performance related features are concerned.
Drug-Device Combinations

- Integral Combinations (at the time of administration to the patient)
  - In combinations which are devices, the medicinal substance must have an ancillary function
  - In combinations which are medicines, the device is generally a delivery device

- Medicinal Product and Medical Device “Kit”
Integral Combinations: Drug or Device?

Primary Intended Purpose achieved by one of the following means:

PHARMACOLOGICAL
METABOLIC
IMMUNOLOGICAL

MEDICINAL PRODUCT 2001/83 EC
Integral Combinations: Drug or Device?

Primary intended purpose achieved by other means:

For example PHYSICAL or simple CHEMICAL

Medical Device 93/42/EEC
Case Study: Primary Intended Purpose

Gentamicin bone cement / spacer devices

Fixation of prosthesis

MEDICAL DEVICE

Gentamicin coated PMMA beads
Deliver antibiotic
Local antibiotic therapy by implantation in infected bone cavities
Klemm, K. Clin Microbiol Infect 2001; 7:28-31

MEDICINAL PRODUCT
Case Study: Haemostat

- FLOSEAL Haemostatic Matrix is a proprietary combination of cross-linked gelatin granules and topical human thrombin.

- Indicated in surgical procedures as an adjunct to haemostasis

- Thrombin Solution mixed into the Gelatin Matrix

- Regulated as a medical device incorporating a medicinal substance having ancillary action

- Received CE Mark approval under the EU MDD.
Case Study: Refillable Insulin Pen

Kit comprising an insulin pen and insulin cartridges

Pen is subjected to the MDD

Insulin cartridge is a medicinal product
NEXPLANON

Subdermal implant for contraception

- Non-biodegradable sub-dermal contraceptive implant
- Implant: a single rod etonogestrel dispersed in a matrix of ethylene vinyl acetate (EVA) co-polymer
- Implant is placed inside a stainless steel needle which is fitted to an applicator
- The loaded applicator is placed in a polyester tray which is subsequently sealed with lidding foil
NEXPLANON
Subdermal implant for contraception

- Implant was assessed as a medicinal product
- Applicator comply with the Annex 1 of the MDD
  - Usability of the device supported by a clinical study
  - Complies with relevant ISO requirements
Delivrie film-coated tablets

Contraception

- Film coated tablets placed in a cartridge that fits the dispenser
- Tablets indicated for continuous use for 120 days followed by a 4 days mandatory break
- Dispenser is CE marked
Delivrie film-coated tablets

Contraception

Number of hours until you should take a pill (hollow tiles)
Reminder sound on

Number of hours since you should have taken a pill (solid tiles)
Reminder sound on
Number of pills to take (1)

Status:
5 hours before your reference time.

Status:
5 hrs past your reference time.

Mandatory phase (days 1-24)
Flexible phase (days 25-120)
Sayana Press
Contraception

- Uniject® injection system
- Usability of the device demonstrated in clinical study
- Medicinal product
Medicines with a device component

- **Primary purpose** is to release the active substance
- **Subject to regulation under 2001/83/EC but device component needs to be taken into account**
Development Considerations

• Increasing sophistication and complexity:

Packaging materials
Compatibility (extractables/leachables)
Quality maintained through processing (e.g. sterilisation)
Product stability
Accuracy of dosing
Performance (temperatures, drop tests etc.)
Patient friendly
Tamper-proof/evident
Devices

‘Straightforward’

- Drug-eluting stents with anti-proliferatives
- Catheters impregnated with antibacterials
- Bone cements/spacers with gentamicin
- Wound dressings with silver
- Catheters/stents/grafts coated with heparin
Devices

Borderline/More complex

- Drug-eluting balloons
- Wound healing products in liquid/gel presentation
- Chlorhexidine coated surgical gloves
- IVF media with gentamicin
- Solutions for donated organ transport with allopurinol/adenosine
- Claims for chemical action rather than pharmacological, immunological or metabolic
- Use of products derived from biotechnology e.g. monoclonal antibodies, recombinant proteins claimed not to be medicinal products
Medicines presented with Separate Administration Devices
Administration Devices must be CE marked - is the CE mark enough?

- Not necessarily

- Take into account the product in question
  - Physical/Chemical Compatibility
  - Accuracy of Dosage
  - Ease of use (population)

- Examples of problems:
  - Spacer Devices
  - 5ml Spoons
  - Nebuliser
Proposals for the future: Amendment of Annex 1 to 2001/83/EC

New Regulation on medical devices currently under negotiation proposes amending Annex 1 of 2001/83/EC to require:

- Where a product is [a medicine] the 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, where for the conformity assessment of the device, if used separately, [would involve] a notified body the [applicant is required] 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.

- Unless the authority is advised by its experts for medical devices that involvement of a notified body is not required
Decision Making on the Borderline

Based on Evidence about the product and the claims made

- Mechanism of action – scientific evidence
- All characteristics of the product taken into account
- Case by Case decision
- Product literature and promotional material

Art. 2(2) Directive 2001/83 EC

- “In cases of doubt” medicines definition takes precedence
- But product must meet medicines and device definition for this to apply.
Variations versus Extension Applications

Guideline on the Categorisation of Extension Applications (EA) Versus Variations Applications (V) October 2003

Changes requiring an extension application: Changes to strength, pharmaceutical form and route of administration
Example: **Parenterals:**
- Solution for injection: vial to PFS.....EA
- Powder + Solvent vial to PFS....EA
**Inhalation:** Powder from hard capsules to disc....EA

Inclusion of medical devices:
Addition, replacement or deletion of measuring or administration devices not being an integrated part of the primary packaging are variations.

Addition or replacement of spacer devices for metered dose inhalers is a Type II variation, unless the device is an integral part of the medicinal product and the change results in a change to the strength, pharmaceutical form or route of administration for which an EA should be submitted.
Devices Incorporating An Ancillary Medicinal Substance: Notified Body Consultation

- NB needs to verify usefulness of the medicinal substance
- Quality, safety, usefulness must be verified by analogy with methods specified in Annex 1 of 2001/83/EC

- **Consultation with EU Medicines CA**
  - Notified Body and manufacturer choose CA
  - consultation on drug substance aspects

- **OR**

- **Consultation with EMA**
  - mandatory - human blood derivatives and medicinal products derived from biotechnology
  - voluntary - drug substance authorised via centralised procedure
MHRA Consultation Procedure

- MHRA Guidance Note 31 explains the information required by the Agency for the Consultation and the format in which it should be supplied.
- Data in CTD format

- **Handled in a similar way to MAA:**
  - Validation, fee confirmation, invoicing, allocation
  - Monitoring of progress by Service co-ordinator
  - 90 / 120 day target assessment times
  - Quality, Non-clinical and Clinical Assessment
  - Request for further information

- **Outcome is different:**
  - MHRA Decision Notification report to the Notified Body:
    - ‘Based upon the data provided, MHRA are able/unable to verify the quality, safety and usefulness (clinical benefit/risk) of the ancillary drug substance as incorporated into the device’
  - NB conveys final decision to EMA/CA
MHRA Consultation Procedure

The indications and claims made in the Instructions for Use (IFU) leaflet and should reflect the scope of the clinical data presented.

If there is any change in the design or manufacture of the device which could have an effect on the quality, safety or usefulness of the drug substance in the device or in respect of amended or additional data, a new consultation form should be completed with a new reference number (Supplementary Consultation).

Changes to the qualitative or quantitative composition relating to the active substance(s), or indications for use etc. would normally be subject to a new, full consultation.
Current Challenges

- Possible regulatory 'gap' in the use of **biological substances** in devices?
  - Delivery device with monoclonal antibody coating
  - Matrix with recombinant growth factor
  - Matrix comprising recombinant proteins
MHRA Scientific Advice

MHRA offers Scientific Advice to applicants
• Briefing document
• Written questions
• A discussion meeting
• Written advice
• Fee is charged
• Procedure outlined on MHRA website
• Can be used at any stage of development

Also:
Borderline section offers advice on the status of a product in cases of doubt.

• In making a decision, the MHRA considers each individual product on its merits and any information which may have a bearing on the product's status.

• On-line request form
CHMP Scientific Advice

Provides pan European advice which is agreed by CHMP
Written advice given (possible attendance at pre-submission meeting)
Sometimes quite long procedure
Quite a ‘Formal’ procedure
Fees are higher than national advice
MHRA/NIBSC merger

1 April 2013

http://www.mhra.gov.uk
Thank you for listening.

Any questions?