European Regulation of Drug-Device Combinations and the Borderline: Can South Africa learn from international Best Practice?

Elizabeth Baker Group Manager MHRA

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Our Experience

- Converging and Complementary Technologies
  - Significant number of MAAs include a device component
  - Increasingly medical devices include a medicinal component

Why? Life-cycle Management Strategies
  - Innovative drive to improve public health

- Device components in medicines are increasingly complex
- Increased ADRs related to inappropriate use of device component or medication errors; device component can be pivotal in determining risk:benefit and effectiveness in use
- Increasing demand for scientific and regulatory advice on combination and ‘companion’ products

Increasing regulatory engagement
Medicines/Device borderline is blurring
Regulatory gaps are emerging
STEP 1 ATTACHING THE NEEDLE

- To switch on the RebiSmart® device press the "Start" button for a few seconds.
- Press and hold the "ON" button until the welcome screen appears.
- When the information screen appears, press "Start".

STEP 2 INJECTING
Medicines-Device Combinations and Classification

- **The importance of classification**
  - In Europe two sets of legislation and regulatory systems that operate differently
  - A product is EITHER a medicinal product OR a medical device
  - Combinations of medicines and devices are common but there is no ‘combination product’ classification

- **Borderline relies on Principle Mode of Action in the claims made** (Pharmacological, Immunological, Metabolic)

- For combination products the two sets of legislation work together but do not duplicate requirements

- For medical devices NBs* work alongside Competent Authorities (*Notified Bodies)

  These principles are not changing with new Regulations
# Medicines & Devices
## Same principles - Different Implementation

**Medical Devices**
- Single market provision, automatic mutual recognition without national measures.
- Procedures set out in MDD based on quality, safety, performance/usefulness and risk/benefit.
- Compliance with Essential Requirements underpinned by European and International standards.
- Notified Bodies verify that manufacturers and devices meet requirements. “Co-regulation” with the Competent Authority.
- Conformity procedures apply controls and oversight matched to the degree of risk inherent in the device.

**Medicines**
- Single market but all individual MS can/do participate in approval process.
- Procedures set out in MPD based on quality, safety, efficacy and risk/benefit.
- Compliance with prescriptive data requirements underpinned by guidelines.
- Competent Authority assesses and authorises each individual product.
- Same procedure applies to all products but proportionate data requirements.
- IP Protection for new molecules and in certain other circumstances.

**Different Manufacturing Site Clinical Trial and Vigilance Requirements**
Definitions

Medical device
Any instrument, apparatus, appliance, software, material or other article .... alone or in combination, (including software ____), intended by the manufacturer .... for:
diagnosis, prevention, monitoring, treatment or alleviation of disease,
..................handicap,
investigation, replacement, modification of the anatomy or 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.

Medicinal product
Any substance or combination of substances presented ..... for treating or preventing disease in human beings;
Or

Any substance or combination of substances ... 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.
PMMA Bone Cement with Antibiotic
PMMA Beads Impregnated with Antibiotic for soft Tissue Infection
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
- Competent Authority Enquiries (Helsinki Procedure)

Art. 2(2) Directive 2001/83

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

Case C-109/12 Lyocentre: CA in a MS can challenge a CE mark
Medicinal Product or a Medical Device?
Depends on mode of action of the PRODUCT in the indication

Primary Intended Purpose achieved by one of the following means:

- PHARMACOLOGICAL
- METABOLIC
- IMMUNOLOGICAL
- (and All ATMPs)
- (and All in vivo diagnostics))

Deliver/Localise

Medicinal Product

Drug/Device Combination

Primary intended purpose achieved by other means:

For example PHYSICAL
- SIMPLE
- CHEMICAL
- MECHANICAL
- DIGITAL

Medical Device
Or Active Implantable Medical Device

Ancillary Drug

Device/Drug Combination
For Combination Products
Legislation meshes together

Devices
Legislation

Medicines
Legislation
Device with integral ancillary medicinal substance

- Bone cements/spacers with gentamicin
- Wound dressings with antimicrobials
- Catheters/stents/grafts coated with heparin
- Drug-eluting stents with anti-proliferatives

![Bone cement with gentamicin](image1)

![Elastoplast](image2)

![Heparin coated catheter](image3)
Notified Body Consultation

For the medicinal substances the notified body shall,

• having verified the usefulness of the substance as part of the medical device - taking account of the intended purpose of the device,

• seek a scientific opinion from an EU medicines authority or the European Medicines Agency (EMA) on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device.

When issuing its opinion, the competent authority or the EMA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body.

[MDD Essential Requirement ER 7.4]
Notified Body Consultation

Consultation with a Medicines Authority required by conformity assessment procedures

Any appropriately designated Notified Body with

Any Competent Authority in

Any Member State

Including EMA where appropriate

[ EMA compulsory for blood product derivatives and other mandatory scope substances, optional for other centrally authorised molecules ]
Data Requirements

Consultation covers
quality
safety
‘usefulness’

European Guidance sets out data requirements based on Pharmaceutical Directives
Discretion in amount of data on each aspect
Original or published data as appropriate
Medicines with a Device Component
Device Aspects of Medicinal Products

A product placed on the market where the device and medicinal product
- form a single integral product
- are exclusively for use in the given combination and not reusable

Is governed by pharmaceutical directives (2001/83/EC) so application data requirements are subject to that directive

Dossier content and procedure choices - as for any other medicinal product

The relevant essential requirements in Annex 1 to devices directive (93/42/EEC) apply as far as safety and performance related features of the device are concerned.
- Application of relevant standards
- CE marking (where appropriate)
Frequent Issues raised in dossiers for Drug-Device combinations

Quality related issues such as
- physicochemical Interactions between the drug and device
- Stability of the product
- Accuracy of dosage
- Sterilisation

Final device not used in the clinical studies so bridging needed
Usability of device is not demonstrated
Usability study not in target patient population
Training for patients and healthcare professionals not considered
Inappropriate usage not forseen
Risk management plans do not consider device aspects
During Assessment of DDC products focus on:

Presentation of a medicinal product with or as part of medical device may introduce risk of medication error:

• Complexity of using the device
• Number of steps for reconstitution of a product
• Difficulty reading labels/markers and administering correct dose
• Non-equivalence of devices (training, continuity of supply, learned, “generics” & biosimilars)
• Issues with leaving device in-situ for wrong period of time or applying more than one device
• Who/where is the user/patient/carer (⚠️ ‘off the shelf’ devices)
• CE Certification – what does it cover?

➢ Draft Guidance: Good practice guide on risk minimisation and prevention of medication errors includes advice in relation to delivery devices

If there is a potential risk of medication error, this should be captured in the Risk Management Plan
Drug and Device ‘Kits’ including ‘cross-labelled’ products

Challenges for Classification

Borderline between medicines and devices relies on determining primary mode of action but:

- Cases arise where primary & ancillary action cannot be attributed/agreed
  - Scaffolds incorporating growth promoters
  - Topical products with physical and pharmacological actions
  - Increased knowledge of actions of established materials e.g. hyaluronic acid (HA)
  - MDD permits biological actions; is this different from PMI? What about chemical action?

- New Technologies
- ‘Point of Care’ preparation
- Definitions (in guidance) of pharmacological, metabolic and immunological (PMI) are out of date
- Definition of diagnosis is open to interpretation and diagnosis permitted in both medicinal product and medical device definitions
Current Issues and Challenges for Regulation:

• Off-label Use of Medicinal Products in non-integral combinations, *Medical Devices*’ intended to:
  – Enhance availability and/or efficacy of medicinal products
  – Administer a medicinal product otherwise than in accordance with its MA
  – Create a new use for a medicinal product
  – Medicines to enhance the performance of a medical device

• Point of Care Products

• Data Requirements for combinations
  – Life Cycle Management
  – Requirements for the device at clinical trials stage
  – Extent of Human Factors and Usability Testing
  – ‘Equivalence’ of Devices (generics/biosimilars)

• Substance based devices
Public Consultations

EMA Working Parties proposal for a guideline on dossier requirements for medicinal products with a device component (Closed 16th May 2017)

MHRA has consulted on draft document on Human Factors and Usability Engineering (closed & currently being updated after comments)
HMA & CAMD Borderline and Combination Products Working Group

Advise HMA & CAMD on issues relating to the MP/MD borderline and regulation of so-called “combination products”

• To reach common understandings between Member States in relation to interpretation of legislation relevant to the borderline. To provide a forum to discuss the classification of products to aid in decision-making
• To agree common understandings and best practices around assessment and regulation of so-called “combination products”
• To identify gaps in legislation relevant to these products and propose guidance to ensure consistent regulatory decision making and protection of public health,
• (achieved by working through established European networks where possible)

(Excerpts from mandate agreed October 2016)
Revision to EU Medical Device Legislation

(Final Text published in OJ)

Medical Device Directive

Active Implantable Device Directive

In Vitro Diagnostic Device Directive

Medical Device Regulation 2017/745

In Vitro Diagnostic Device Regulation 2017/746

3 year transition

5 year transition

Some Specific Changes Affecting Combination Products regulated as Medical Devices

- Concept of Ancillary Medicinal Substance (Class III Rule 13)
- Consultation with medicines competent authority for Ancillary Medicinal Substances

- Device Labelling and IFU
- Clinical Trials

- Additional Oversight

- Non-viable Cells & Tissues

- Special Classification rule 19 on nanomaterials
- Clinical Data

- Concept remains but no qualifier of ‘liable to act’. (Class III Rule 14)
- Procedure remains; opinion within 210 days as now but 60 days for subsequent amendments.
- NB must implement CA opinion
- CA must update NBs of safety issues
- Must include information on ancillary medicinal product & interactions with other devices or medicinal products
- Device authority must ensure appropriate expertise available
- NB must submit assessment of Class III implantable devices to EC
- Ancillary concept introduced; consultation with Cells and Tissue Authority

- Increased emphasis on clinical data for all devices especially Class III
- Approval based on equivalence exceptional
Specific Changes Affecting Combination Products Regulated as Medicinal Products

- Medicinal Products with integral device component
- Device risk classification rules
- Medicinal Products supplied or used with a medical device
  - Inhalation classification rule 20
  - Declare degree of accuracy for measuring devices and limitations of use in IFU

- Article 117 Amends 2001/83
  Device must meet ERs as now but requirement to provide an opinion from a NB (unless Class I)
- Some new & changed rules for devices result in up-classification;
- Device will have to comply with new MDR including classification, labelling and conformity assessment procedures
Might Changes Affect the Borderline?

Definition

Scope - Human Tissues

Substance Based Devices

Question on how this will affect company strategy on the borderline

(Consensus & guidance needed)

Some changes but these should not affect medicines/device borderline

Scope will include non-viable human tissues

New Classification Rule 21

Some claim device regulation of:

- Osmotic Laxatives
- Antacids
- Locally acting ‘binding agents’ e.g. for phosphates, acetaldehyde
- Alginate Rafts
- Simeticone
- Cough Remedies

BUT not yet agreed
Where to go for Advice

- Regulatory and Scientific Advice available from EMA or National Authorities (for medicines and devices)
- Procedure for MHRA Scientific Advice
  - Briefing document submitted
  - Including written questions
  - A discussion meeting is held
  - Written advice issued (after panel review)
- Fee is charged
- Procedure outlined on MHRA website
- Can be used at any stage of development
- Regulatory advice is free of charge
MHRA Innovation Office

Introduced in March 2013 with the following objectives:

- Facilitate understanding of issues & regulatory requirements to bring innovative products & 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 or researchers developing innovative technologies or products
- Provide regulatory support to such groups in their interaction with the regulatory environment

Engagement with EMA ITF (Innovation Task Force)
Part of a growing EU Innovation Network with other EU national Innovation Offices
Nature of Queries to MHRA Innovation Office (350 to date)

- Medicine: 46%
- ATMP/Biols: 25%
- Device: 17%
- Borderline/DDC: 12%
Case Studies

Examples on:
MHRA Innovation Office webpage
Social media: #InnovationInHealth
Thank You

My contact details
elizabeth.baker@mhra.gov.uk
+44 (0)203 080 6467

UK Guidance:
www.gov.uk/mhra
REFERENCE SLIDES
Advanced Therapy Medicinal Products  
Article 2 Regulation 1394/2007 on ATMPs

(a) ‘Advanced therapy medicinal product’ … for human use:
   - a gene therapy medicinal product*
   - a somatic cell therapy medicinal product *
   - a tissue engineered product as defined in point (b).

(b) ‘Tissue engineered product’ means a product that:
   - contains or consists of engineered cells or tissues, and
   - is presented .......... with a view to regenerating, repairing or replacing a human tissue.

Products exclusively of non-viable cells and/or tissues, .......... and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

* as defined in Part IV of Annex I to Directive 2001/83/EC,
Mandatory scope of EMA

Annex I to Regulation (EC) N° 726/2004:

- Medicinal products developed by means of one of the following biotechnological processes:
  - recombinant DNA technology,
  - controlled expression of genes coding for biologically active proteins [...],
  - hybridoma and monoclonal antibody methods.

- Advanced therapy medicinal products as defined in Article 2 of Regulation (EC) No 1394/2007

- New medicinal products containing a new active substance for which the therapeutic indication is the treatment of any of the following diseases:
  - AIDS, cancer, neurodegenerative disorder,
  - diabetes, auto-immune diseases and other immune dysfunctions,
  - viral diseases.
'medical device’ means any instrument, apparatus, appliance, software, implant, reagent, material or other article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific medical purposes of:

• diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
• diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability,
• investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
• control or support of conception,
• providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations

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

(Products intended specifically to clean, disinfect or sterilise medical devices and devices to control conception are also considered medical devices)
New Classification Rule on Substance Based Devices
administered via body orifice or to skin (MDR Classification Rule 21)

Class III:
- if substance or metabolites systemically absorbed to achieve intended action [***] or
- If intended action is in the stomach or lower GI tract and substance or metabolites are systemically absorbed

Class Iia:
- if applied to skin, nasal or oral cavity as far as pharynx for local action

Class Iib otherwise

Likely to result in up classification of existing products of this type
Clinical evidence needed

Note: See next slide [***]
Substance Based Devices - requirements

- The products shall comply with annex 1 of 2001/83 for ADME, local tolerance, toxicity, interaction with other devices and medicinal products or other substances and potential for adverse reactions.

- Consultation of NB with medicines authority for those products whose substance or metabolites are systemically absorbed to achieve intended action [Previous slide ***]

- CA Opinion to be issued in 150 days and NB to give ‘due consideration to it’

- Labelling must include qualitative composition and quantitative details of constituents achieving intended action

- IFU must include interactions, C/Is, A/Es, risks of overdose