Developing a Medical Device with ancillary medicinal substance
Important considerations and NB Expectations

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MEDTEC Europe
Agenda

- **Step 1: Define the Regulatory Approval Route for your Product**
  - Classification of Device Drug Combination Products
    - Possible Combinations
    - Considerations & common misconceptions
    - Guidance

- **Step 2: Understand the CE Certification Process**
  - Routes to Conformity
  - CE Certification & CA Consultation Process
  - Documentation Requirements
  - Common gaps in submissions and available guidance

- **Step 3: Post CE Certification Considerations**
  - Strategies for handling change
Step 1: Define the Regulatory approval route for your product

Definitions & Product Classification
What is a medical device?

Any instrument, apparatus, appliance, software, material or other article 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;“
What is a medicinal product?

Article 1 Directive 2001/83/EC as amended by Directive 2004/27/EC defines a medicinal product as:

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.
In case of doubt

Article 2(2) 2001/83/EC Medicines Directive states

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 provisions of this (medicines) Directive shall apply.
Regulatory Options for a Device containing a drug

Product Classification Considerations
Regulatory options for medical devices which combine a medicinal substance

1) Device intended to administer a medicinal product (not integral)
   Regulated as a Medical Device

2) Device and drug which form an integral (but not reusable) product
   Regulated as a Medicinal Product

3) Device incorporating as an integral part a medicinal product where the action of the medicinal substance is ancillary
   Regulated as a Medical Device

3) Device incorporating a medicinal product derived from human blood or plasma where the action of this substance is ancillary
   Regulated as a Medical Device

5) Advanced Therapy Medicinal Product combined with device
   Regulated as a Advanced Therapy Medicinal Product
Device with ancillary medicinal substance

**Classification:**
- Directive 93/42/EEC, Annex IX Rule 13: All devices incorporating, as an *integral* part, a substance which, if used separately, can be considered to be a *medicinal product*, as defined in Article 1 of Directive 2001/83/EC (Pharmaceutical), *and* which is liable to act on the human body with action *ancillary* to that of the devices, are in Class III.

- .... must be a medical device under 93/42/EEC
- drug must act in an *ancillary* way to the device
- “device” cannot be merely a means of delivering a drug

**Examples:** *Wound Care dressings incorporating an antimicrobial agent where purpose of agent is to provide ancillary action on the wound.*
*Heparin-coated catheters, steroid tipped pacing wires, antibiotics incorporated into devices*

Regulated as a Medical Device
Medical device with ancillary human blood derivative

Regulated as a Medical Device

- Applies to a medicinal product constituent or a medicinal product derived from human blood or human plasma which is ancillary to device
- Rule 13 is applicable
- EMA Consultation is Mandatory
- Access to the PMF is required

- For example, surgical sealants containing human serum albumin
Classification Considerations

Why is it important?
## Medical Device Vs. Medicinal Product

<table>
<thead>
<tr>
<th><strong>Medical Device</strong></th>
<th><strong>Medicinal Product</strong></th>
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<tbody>
<tr>
<td>Designed to perform certain functions based on quality, safety and performance</td>
<td>Developed in clinical trial on basis of quality, safety and efficacy</td>
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<tr>
<td>Generally based on mechanical, electrical and/or materials engineering</td>
<td>Based on pharmacology and chemistry, now encompassing biotechnology and genetic engineering</td>
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<td>Generally acts by physical means</td>
<td>Biologically active: effective when absorbed into the human body</td>
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<td>Short product lifecycle and investment recovery period</td>
<td>Extensive product lifecycle and long investment recovery period</td>
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<tr>
<td>Medical Device Industry......</td>
<td>Pharmaceutical Industry.......</td>
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<tr>
<td>Short development times</td>
<td>Process to obtain market access is lengthy</td>
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<td>Speed to market critical</td>
<td>Products protected by long exclusivity periods</td>
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<tr>
<td>High volume, low cost products</td>
<td>Regulatory approval costs</td>
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<tr>
<td>CE Marking costs vary between NBs and Device Class</td>
<td>Same procedure applies to all products</td>
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<td>Level of control matched to the degree of risk in the device based on classification rules</td>
<td>Based on quality, safety, efficacy and risk/benefit</td>
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<tr>
<td>Based on quality, safety, performance/usefulness and risk/benefit</td>
<td>National / MRP / Centralised Procedures</td>
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<tr>
<td>CE mark gives single market provision - automatic mutual recognition across EU &amp; EFTA</td>
<td>Regulatory Approach Precautionary</td>
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<td>Regulatory Approach Proportional</td>
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Common Borderline Case Misconceptions
Classification Considerations & Misconceptions

- What claims are being made for the product?
- Principle Mode of action?
- Only contains a small amount of ........
  - No concept of “amount” of a medicinal substance in the medical device regulations
  - Inclusion must be justified and scientific data provided to support any claims that they are not liable to act to avoid a Class III, Rule 13 classification
- Drug is not intended to act
  - This does not preclude them from being liable to act on the body
- Countries may have differing opinions
- Important to communicate with Notified Body early in the development process
Classification Watch Outs – Natural Ingredients

– “Natural” Ingredients = Safe and Healthy ????
– Herbals, Chinese and Homeopathic Medicines
  – Clove oil – antiseptic, analgesic and sedative properties
  – Tea Tree Oil – antibacterial & antifungal properties
  – Aristolochia – Used in TCM as a slimming aid - contains toxic and carcinogenic aristolochic acids associated with kidney failure and cancer.
  – Belladonna contained in comfort eye drops
– Perceived gap between Medicinal Product and MDD regulation
– Does the therapeutic benefit outweigh the risk?
Classification Watch Outs – Orally Administered?

- Examples of products administered orally?
  - Simethicone
  - Slimming aids
  - Products for constipation
- Generally considered medicinal products
- Potential secondary pharmacological action through absorption into systemic circulation
- Never intended to be classified as a Medical Device
- No Rule in MDD
Classification Watch Outs – Biotech Products?

- Examples of products produced using Biotechnology
  - Extracellular matrices (ECM) in wound healing
  - Growth Factors – Orthopaedic and wound healing applications
  - Recombinant DNA / Proteins
- Regulation (EC) No 726/2004 requires approval via centralised procedure (EMA)
- Manufacturers perceive biotech derived materials safe
  - Safer alternative to use of animal tissue such as collagen
  - Do not contain tissues / cells of human origin
  - Caution: May utilise animal tissue in manufacture
- Potent compounds – can be difficult to determine principle mode of action
- Seeing a huge increase in applications
What to do if unsure about Classification?
What to do if unsure about Classification?

It’s a critical early decision

Speak with a NB with experience of such Combinations

Early & throughout the development process
Available Guidance on Classification

- Speak to NBs with experience of Device Drug Combinations
- MEDDEV 2.1/3 Rev 3
- MHRA Bulletin No. 17 – Medical devices and Medicinal Products
- MHRA Guidance Note No 8 – A Guide to what is a Medicinal Product
- Manual on borderline and Classification in the Community Regulatory Framework for medical devices
Step 2: Understanding the CE Certification Process
Devices containing and ancillary medicinal product

- Devices containing a ancillary medicinal product = merging of two different worlds

- Primarily developed by Medical Device Manufacturers
  - Development usually conducted by material scientists / engineers
  - May have little / no experience of medicinal product regulation
  - Can be daunting if unfamiliar with expectations

- Seeing more Pharmaceutical Companies exploring the Medical Device route and collaborations with Device Manufacturers

Do not fear the process
Lots of guidance and experience available
Breakdown of Devices containing ancillary medicinal substance by Technology

- Vascular: 24%
- Orthopaedic: 15%
- Active Implantable: 15%
- Woundcare: 21%
- Latex: 10%
- Other: 15%
Commonly used ancillary medicinal substances

- Antibiotics
- Antimicrobial agents
- Local anaesthetics
- Anti-coagulants
- Steroids
- Anti-proliferative / Anticancer compounds
- Anti-Inflammatory agents
- Human Thrombin
- Human Serum Albumin
CE Certification Process

Routes to Conformity
In accordance with the MDD, the route to conformity available for a Class III, Rule 13 device is either:

- Follow the procedure relating to the EC declaration of conformity set out in Annex II which includes Annex II.3 - Full Quality Assurance (FQA) and Annex II.4 - Design Examination (DE). The same NB must complete both conformity assessments.

or

- Follow the procedure relating to the EC type-examination set out in Annex III (EC Type Examination) coupled with either the procedure relating to the EC verification set out in Annex IV (EC Verification) or the procedure relating to the EC declaration of conformity set out in Annex V (production quality assurance).
Conformity Assessment Routes  Class III Devices

Annex II

- Full Quality Assurance & Design examination certification
- QMS include design & development

Annex III with Annex IV or V

- EC Type Examination with Annex IV (EC Verification) or Annex V (production quality assurance).
- Requires the testing of batches of the devices to allow certification
- Device-drug combinations may not have a supporting harmonised standard to detail the testing required
- Expensive to set-up and validate testing.
CE Certification Process for Device with ancillary medicinal substance

- NB examination of Design Dossier to confirm product conforms to relevant provisions of Directive (ERs)
  - NB will verify that manufacturer has followed his declared procedures and those required by the Directive
  - NB monitors the manufacturer’s system for producing his Declaration of Conformity
- NB must seek opinion on medicinal aspects via Consultation process with a EU Competent Authority or EMA (Annex I, ER 7.4)
What is a Medicinal Consultation?

- Scientific opinion on the quality and safety of the ancillary medicinal substance including the clinical benefit/risk profile of the incorporation of the substance into the device

- NBs do not have the competence internally to make a decision on the quality and safety of the ancillary medicinal substance

- Competent Authorities & EMA have responsibility for the approval and control of medicines
  - Have access to relevant information concerning the risks related to the use of the medicinal substance
Breakdown of Consultation types

- New Consultations
- Supplemental Consultations
- New Drug Substances
- EMA Consultations
Who Conducts the Consultation?

Any Competent Authority or EMA

The consultation is between the Notified Body & Competent Authority

It is at the discretion of the manufacturer to choose the Competent Authority in consultation with its Notified Body

So who do we use and how are they selected? ……
Competent Authorities – Main Players

- **MHRA (UK)**
  - Combined agency for drugs and devices
  - Pragmatic approach
  - Highly regarded across EU

- **MEB (The Netherlands)**
  - Need 2 months’ warning of a submission
  - Structured approach
  - Will give a timetable – but are unlikely to go faster
Competent Authorities – Main Players

- **MPA (Sweden)**
  - Open to discussion
  - Expert in DES area
  - MPA only accept a certain number of new applications per year, but will continue to accept changes to previously approved devices

- **IMB (Ireland)**
  - Recently amended their internal processes
  - Reputation for good scientific staff, limited device experience
  - Now have processes in place
Competent Authorities – Main Players

- The European Medicines Agency (EMA)
  - Administration agency funded by fees plus Commission
  - Manages centralized MAs and European scientific advice
  - NB Consultations on blood products and some chemical molecules – guidance published on EMEA website
  - No Assessors – ‘contracts’ to Member States for assessment
  - Outcome of consultations is seen by all EU CAs
  - Need to give advance notice of submission
  - Expensive but SME can apply for a reduction in fees
Consultation with a Medicines CA

- Used to dealing with very big pharmaceutical companies
- Medical device applications are a tiny part of their work – may be unfamiliar with device regulation
- Length of time for review and approval
  - 210 days, with Clock Stops for questions raised
  - Change of Assessor may occur during consultation
- May have varying interpretations of regulations
Consultation Fees

- Each CA has their own pricing structure
- Fees are based on level of review required
  - Categories are
    - Known medicinal substance from a known source
    - Known medicinal substance from a new source / New indication
    - New Active Substances
CE Certification Process

- **Notified Body Activities**
  - NB must verify the usefulness of the substance as part of the medical device and taking into account the intended purpose of the device
  - Design Dossier examined by NB in parallel with CA Consultation
  - NB will audit the Manufacturers QMS for the device
  - NB is the point contact between Manufacturer and CA

- **Competent Authority Activities**
  - CA will assess data on the quality & safety information of the ancillary medicinal substance including the clinical benefit/risk profile of the incorporation of the substance into the device
  - CA issues a opinion to NB – Positive or Negative

- Can be many rounds of questions and clock stops for both reviews
- NB will not issue CE certificate until all elements are closed
- NB must not go against EMA opinion
Certification and CE Mark

If all is satisfactory
NB issues EC Design Exam Cert and EC FQA Cert & informs CA of its decision.

Manufacturer generates Declaration of Conformity and applies CE mark.

Don’t Forget PMS & Vigilance.
CE Certification Process

Documentation Requirements
General data requirements for medical device with ancillary medicinal substance

- **Design Dossier**
  - Data to show evidence of conformity with Essential Requirements
  - STED Format and contains:
    - General Information, product descriptions, drawings
    - Classification Determination
    - Essential Requirements checklist
    - Risk Analysis
    - Clinical Evaluation
    - Design Controls
    - Labelling and IFU
    - Product Specifications
    - Safety & Performance Data
    - Manufacturing description, validation
    - Sterilization description, validation
    - Packaging description, validation
    - Conclusions
    - Declaration of Conformity

- **Consultation Dossier**
  - Stand alone dossier of information on the Quality, Safety and Usefulness of the ancillary medicinal substance
  - Provided by the Manufacturer to NB as part of the Design Examination application
  - Should include relevant aspects of the finished device, not just the drug substance
  - Content as described in MEDDEV 2.1/3 rev 3
  - CTD is the preferred Format and while its use is not mandatory it facilitates the review
    - **Module 3 - Quality**
      - 3.2.S Drug substance
    - **Module 4 - Non Clinical**
    - **Module 5 - Clinical**
## 3.2.S. Drug Substance Quality

### Content
- General Information
- Manufacturer
  - Manufacturing Process & process controls & Validation
  - Control of materials
- Characterisation
  - Impurities
  - Elucidation of structure
- Control of Drug Substance
  - Analytical procedures and their Validation
  - Batch Analyses
  - Justification of Specifications
- Stability
  - Container Closure system
  - Performance and stability over shelf life
  - Potential degradation of drug substance
  - Real time stability studies

- Information provided in submission dossier or Active Substance Master File (ASMF) or EDQM Certificate of Suitability (CEP)
- European Pharmacopeia monograph
  - Requirements apply as a minimum
- Good Manufacturing Practise Certification

## 3.2.P. Device Product Quality

### Content
- Quantitative Composition
- Manufacture
  - Method of incorporation and critical in-process control
  - Validation, reproducibility, uniformity of drug distribution
  - Packaging Validation
- Control of Intermediate and Final Device
  - Product specification
  - Limits on drug
  - Performance characteristic, release
  - Analytical method validation
  - Packaging system
- Stability
  - Performance and stability over shelf life
  - Potential degradation of drug substance
  - Real time stability studies
Pre-Clinical / CTD Module 4

- **Toxicity**
  - Reference to the known toxicological profile of the medicinal substance and/or results of toxicity tests (ISO 10993 series of standards).

- **Pharmacokinetics**
  - Pattern of local and systemic exposure to the medicinal substance including maximum level and duration
  - Relationship to in-vitro control tests
  - Possible systemic exposure may be a safety concern, maximum peak plasma concentration should be established, taking consideration of Individual variability for new active substances release from the device and subsequent distribution and elimination

- **Local tolerance**
  - Of particular relevance since route of exposure to the substance may be different from its conventional application.
  - ISO 10993 standards and/or data from literature
Clinical documentation

- Clinical data will be provided to the notified body to address the safety of the device in its entirety

- Usefulness of the medicinal substance in the device should be addressed by clinical data or in other sections of the dossier
CE Certification Process for devices with ancillary medicinal substance

Common Issues and Gaps
Common Issues and Gaps

- Unrealistic Project Plans
  - Used to fast CE Certification process
  - 210 Day procedure following validation of submission
  - Clock stops for questions
  - **Solution:** Work with NB who has experience of process and discuss plans early on
  - **Solution:** Set realistic expectations internally - allow 9 – 12 months for CE Certification

- Quality of Medicinal Dossier Submission
  - Technical File / Design Dossier STED Format
  - No consideration given to the ancillary medicinal substance
  - **Solution:** Use extensive medicinal product guidance
  - **Solution:** Use Common Technical Format (CTD) will provide detail on CA expectations
Medicinal Substance Supply

- Manufacturer may not consider regulatory requirements when selecting a supplier
- Medical device manufacturers usually only require small quantities on an annual basis
- Issues obtaining necessary information and access to information
- Does the medicinal substance manufacturer have a European DMF or Certificate of Suitability
- For Human Blood Derivatives – Can the Device Manufacturer obtain access to PMF
- **Solution:** Make medicinal substance sourcing a early and critical decision
Common Issues and Gaps

- **Technical Gaps**
  - No controls on the medicinal substance to assure quality in the device is maintained
  - No data available on the incorporation of the medicinal substance within the device
  - No consideration given to medicinal substance in process validation studies
  - No data available on potential impurities formed during processing
  - No consideration of medicinal substance in stability evaluation
  - No data on local tolerance in area indicated for use
  - Limited/no clinical evaluation available
  - Risk/benefit profile not evident
  - **Solution:** Use medicinal product guidance – ICH / EMA / CA Guidance
Step 3: Post CE Certification Considerations

Changes and impact on original CA Consultation
Changes made post CE Certification

- Change is an expected and natural occurrence during the lifetime of a device
  - Addition of new manufacturing sites
  - Improvements to manufacturing processes
  - Shelf life Extension
  - Alternate suppliers
  - Design Improvements – Device family extension

- Guidance on requirements of such changes
  - Essential Requirement 7.4, paragraph 4
Changes made post CE Certification

Essential Requirement 7.4, Paragraph 4

– Where changes are made to an ancillary substance in particular related to its manufacturing process, NB shall be informed of the changes and shall consult the relevant medicines competent authority (i.e. the one involved in the initial consultation), in order to confirm that the quality and safety of the ancillary substance are maintained.

– Competent Authority shall ensure that the changes have no negative impact on the established benefit/risk profile of the addition of the substance to the medical device.
Impact of changes & review required

- Significant changes relating to the medicinal substance or indications
  - New Consultation
- Minor change which could impact on the quality, safety or usefulness of the medicinal substance
  - Supplemental consultation
  - Timeline for review much shorter than initial consultation
  - Supplemental conducted with CA who performed the original consultation
  - Documentation needs to be provided to justify and support changes proposed
  - Comparative data pre and post change
- The Manufacturer is the expert on the finished device and best placed to determine impact of changes
- Case by case basis but useful to discuss requirements with NB
Summary of Key Considerations
Summary of Key Points

– Classification of devices is on a case by case basis but a critical early step in development

– Be cautious of using traditional herbal and homeopathic ingredients in your device

– Have realistic expectations for the timescales involved

– Applications for devices containing ancillary medicinal substances continue to show good growth

– Lots of guidance is available

– Don’t forget to consider the impact changes may have post CE Certification

– Talk to your Notified Body at early stages and over the lifetime of your device development
Questions ?
Thank You

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