Drug-Device Combination & Borderline Products: Classification and Regulatory Challenges

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Plan

• Outline & Experience
• DDC and Borderlines
• DDC / Borderlines and Classification
• Decision Making on DDC / Borderlines
• DDC / Borderlines Classification Challenges
• DDC / Borderlines Regulatory Challenges
• How to Respond?
Outline & Experience
Outline

New Regulation, Guidance, Initiatives.....

➢ New drug–device combinations / borderlines are becoming increasingly complex
  - How will they be efficiently and effectively reviewed and approved?

➢ How to achieve a consistent approach to combination product development in an inconsistent and changing world?

➢ Experience of industry and regulatory agencies collaboration: (i.e: Combination Products Coalition).

➢ Future Challenges & Opportunities.

....Increased interest in the Topic!
Experience
Regulatory Affairs

➢ Converging and Complementary Technologies

  • Significant number of MAs include a device component
  • Increasingly medical devices include a medicinal components

➢ 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
DDC & Borderlines
Medical Device / Drug

Definitions

**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.

**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, 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
What is DDC / Borderline?

Definitions

Device

Drug

Biologic

Dry Powder Inhaler (DPI)
mAb Single Use Pre-Filled Syringe
# The spectrum of drugs, biologics and devices

## Medical Technology Spectrum

<table>
<thead>
<tr>
<th>IVDs</th>
<th>Medical Devices</th>
<th>Tissue Engineering</th>
<th>Cell Therapy</th>
<th>Gene Therapy</th>
<th>Biotech</th>
<th>Chemicals</th>
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| • reagents  
• processors  
• analysers  
• proteomics  
• companion diagnostics  
• laboratory developed tests | • prosthetics  
• monitors  
• therapeutics  
• life-support  
• drug delivery  
• surgical instruments  
• software | • xenografts  
• allografts  
• autografts | • stem cells  
• somatic cells | • genomics  
• vectors | • bioreactors  
• biotransformation  
• transgenics | • synthetics  
• naturally occurring |

**Advanced Therapy Medicinal Products (ATMPs)**

**Medical Devices** (FDA Center for Devices and Radiological Health)

**Combination Product:**

- Drug + Device
- Drug + Biologic
- Biologic + Device

**Biologics** (FDA Center for Biologics Evaluation & Research / Center for Devices Evaluation & Research)

**Drugs** (FDA Center for Drugs Evaluation & Research)
DDC / Borderlines and Classification
Combination product regulations are a relatively recent, and specific regulations only exist in certain markets.

No specific regulatory submission formats exist for combination products — all markets use existing drug, device or biologic application / submission procedures. Challenges!!!

- Combination products are, therefore, submitted either as drugs and/or devices and/or biologics in line with the national procedures for those product types [Africa / Europe] - multiple applications may be required in some cases.

  * North Africa (Morocco, Algeria, Tunisia, Egypt): If a Device contain an Active pharmaceutical ingredient then, the FP is classified as Drug.

The determination as to which regulations, submission procedure and pathway to market is followed is largely based on Primary Mode of Action (FDA) / Principal Intended Action (EMA) and whether the product forms a single integral unit (not re-usable) or is a co-pack, kit or set.
Decision Making on DDC / Borderline?

Emergent Markets Regulations: Examples

- Chinese Government Circular # 16 (2009) refers to “Combination Products” as products consisting of drugs and medical devices, produced as a single entity.

- Decisions regarding how to regulate other combination products are taken on a case-by-case basis by CFDA.
  - Requirement to be “classified” by the CFDA “Service Center” in conjunction with CMDE and CDE.

- No separate or specific regulatory approval process for Combination Products.
  - Drug or device registration may involve synchronous consultative reviews by both drug and device reviewers.

- There are no regulations for combination products in Brazil.

- Most combination products will be regulated either as a drug or a device, depending on the primary intended action (device only if the primary action is not fulfilled by pharmacological, immunological or metabolic means).

- Constituents of co-packaged and cross-labelled combination products may be regulated as both a drug and a device.

- ANVISA determines the designation and regulatory pathway / requirements for combination products on an ad-hoc, case-by-case basis.

12 | Maghreb Pharma Expo 2018/ Algiers DDC
Decision Making on DDC / Borderlines
Decision Making on DDC / Borderline?

The Complexity of Product Designation

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.

“In cases of doubt” medicines definition takes precedence

But product must meet medicines and device definition for this to apply.
Decision Making on DDC / Borderline?

The Complexity of Product Designation

Primary Mode of Action (PMOA):
- physical mechanical
- chemical metabolized (biological)

Principal Intended Action (and PMOA):
- physical mechanical
- pharmacological immunological metabolic

Diagnosis, treatment, prevention of disease and/or intent to affect / modify bodily function
Decision Making on DDC / Borderline?

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

Heparin coated catheter
Decision Making on DDC / Borderline?

PMMA bone cement with antibiotic

Fixation of prosthesis

MEDICAL DEVICE

Antibiotic impregnated-PMMA chain

Deliver antibiotic

MEDICINAL PRODUCT
Decision Making on DDC / Borderline?

Primary Mode of Action
Not as straightforward as it may seem...

Drug Eluting Stent

Primary Mode of Action
• Stent maintains patency of artery

Secondary Action
• Drug reduces inflammation and restenosis of artery

Drug Eluting Disc

Primary Mode of Action
• Chemotherapy for brain tumor

Secondary Action
• Localised drug delivery
DDC / Borderlines Classification Challenges
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) = Human Factors

Syringe containing pharmaceutical formulation

Needle supplied with the syringe and attached prior to administration
Medicines with integral administration devices

Currently minimal requirements: **Regulated under 2001/83/EC**

**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.

Medicinal product, but...

DDC / Borderline Classification Challenges

<table>
<thead>
<tr>
<th>Combination Product Type</th>
<th>Market(s)</th>
<th>Example</th>
<th>Primary Mode of Action</th>
<th>Lead Regulatory Agency</th>
<th>Regulatory Approval Process</th>
<th>Applicable Regulations and/or Reqs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Entity</td>
<td>Pre-filled Syringe</td>
<td>PRE-FILLED SYRINGE</td>
<td>DRUG</td>
<td>DRUG</td>
<td>DRUG</td>
<td>DRUG and Device</td>
</tr>
<tr>
<td>Co-Packaged</td>
<td>Pre-filled Syringe constituent</td>
<td>PRE-FILLED SYRINGE CONSTITUENT</td>
<td>DRUG</td>
<td>DRUG</td>
<td>DRUG</td>
<td>DRUG</td>
</tr>
<tr>
<td>Co-Packaged</td>
<td>Needle constituent</td>
<td>NEEDLE CONSTITUENT</td>
<td>DEVICE</td>
<td>DEVICE</td>
<td>DEVICE</td>
<td>DEVICE [Device]</td>
</tr>
<tr>
<td>Cross-labeled</td>
<td>Pre-filled Syringe and needle constituent</td>
<td>PRE-FILLED SYRINGE AND NEEDLE CONSTITUENTS</td>
<td>DRUG</td>
<td>DRUG</td>
<td>DRUG</td>
<td>DRUG</td>
</tr>
<tr>
<td></td>
<td>Syringe pump</td>
<td>SYRINGE PUMP</td>
<td>DEVICE</td>
<td>DEVICE</td>
<td>DEVICE</td>
<td>DEVICE [Device]</td>
</tr>
</tbody>
</table>

MUST manage DRUG and DEVICE REQUIREMENTS

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DDC / Borderlines Regulatory Challenges
DDC / Borderlines Regulatory Challenges

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.
DDC / Borderlines Regulatory Challenges

Frequent Issues raised in dossiers for Drug-Device Combinations

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
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
How to Respond?
How To Respond?

- **Proactive** regulatory surveillance is vital

- Ensure close **internal collaboration** between Regulatory Affairs, Quality Assurance and Product Development

- **Engagement with regulators** to develop policy and future regulations
“Coming together is a beginning; keeping together is progress; working together is success.”

Henry Ford

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