Regulatory challenges of developing a combination product in a globalised world
An industry perspective

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CASSS CMC Strategy Forum – May 2016
Outline

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

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

• Experience of industry and regulatory agency collaboration: Combination Products Coalition & FDA

• Future Challenges & Opportunities
What is a combination product?

- Device
  - DIPRIFUSOR Syringe Pump

- Drug
  - CRESTOR Tablets

- Biologic
  - SYNAGIS Powder for injection (with solvent) in glass vial

Examples of combination products:
- SYMBICORT TURBUHALER Dry Powder Inhaler (DPI)
- FLUMIST/FLUENZ vaccine in single-use pre-filled intranasal sprayer
Scope & Definitions
The spectrum of drugs, biologics and devices

<table>
<thead>
<tr>
<th>Medical Technology Spectrum</th>
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</thead>
<tbody>
<tr>
<td><strong>IVDs</strong></td>
</tr>
<tr>
<td>• reagents</td>
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<td>• processors</td>
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<td>• analysers</td>
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<td>• proteomics</td>
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<td>• companion diagnostics</td>
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<td>• laboratory developed tests</td>
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<td>• software</td>
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Advanced Therapy Medicinal Products (ATMPs)

COMBINATION PRODUCT:
- Drug + Device
- Drug + Biologic
- Biologic + Device

Medical Devices
(FDA Center for Devices and Radiological Health)

Biologics
(FDA Center for Biologics Evaluation & Research / Center for Drugs Evaluation & Research)

Drugs
(FDA Center for Drugs Evaluation & Research)
Combination Products
How are they regulated?

- **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.

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

- The determination as to which regulations, submission procedure and pathway to market is followed is largely based on **Primary Mode of Action** and whether the product forms a single integral unit (not re-usable) or is a co-pack, kit or set *

* This is the case for most major markets
Drug? Biologic? Device?
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

Medical Purpose ...
diagnosis, treatment, prevention of disease and/or intent to affect / modify bodily function

Drug

Biologic

Device
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
Regulation of Combination Products

**Single Entity**
2 or more components combined, e.g. chemically or physically

**Co-Packaged**
2 or more components packaged together in a market unit

**Cross Labelled**
2+ components sold separately but intended to be used only in combination and require both products to achieve the intended use

- **Drug Eluting Stent**
- **Drug Filled Vial + Empty Syringe**
- **Photoactive Drug + Light Source**
Regulation of Combination Products

Single Entity

Co-Packaged

Cross Labeled

Jurisdiction/Pathway: Drug or Biologic (CDER / CBER)

Jurisdiction/Pathway: Device (CDRH)

Primary mode of action achieved by chemical, biological or metabolic means?

YES

NO

Pre-Filled Syringe

Drug-eluting stent

Office of Combination Products

Product Designation
Regulation of Combination Products

Principal intended action by pharmacological, immunological or metabolic means?

No reference to ‘cross labelled’ or ‘co-packaged’ products – each constituent is considered as an individual product: i.e. medicinal product and medical device
Combination Products, Drugs & Devices

Combination Product Type | Market(s) | Example | Primary Mode of Action | Lead Regulatory Agency | Regulatory Approval Process | Applicable Regulations and/or Reqs
---|---|---|---|---|---|---
Single Entity |  | PRE-FILLED SYRINGE | DRUG | DRUG | DRUG | DRUG and Device
Co-Packaged |  | PRE-FILLED SYRINGE CONSTITUENT | DRUG | DRUG | DRUG | DRUG + Device
 | NEEDLE CONSTITUENT | DEVICE | DEVICE | DEVICE | DEVICE | DEVICE
Co-Packaged |  | PRE-FILLED SYRINGE AND NEEDLE CONSTITUENTS | DRUG | DRUG | DRUG | DRUG and Device
Cross-labeled |  | PRE-FILLED SYRINGE CONSTITUENT SYRINGE PUMP | DRUG | DRUG | DRUG | DRUG + Device

MUST manage DRUG and DEVICE REQUIREMENTS
# Regulation of Combination Products

## Case Study: Faslodex

<table>
<thead>
<tr>
<th>Combination Product Type</th>
<th>Primary Mode of Action</th>
<th>Lead Regulatory Agency</th>
<th>Regulatory Approval Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single entity / integral, not reusable, pre-filled syringe CO-PACKAGED with safety needle</td>
<td>DRUG (CDER)</td>
<td>DRUG (NDA)</td>
<td>DRUG (MAA)</td>
</tr>
<tr>
<td>PRE-FILLED SYRINGE AND NEEDLE CONSTITUENT</td>
<td>DRUG</td>
<td>DRUG</td>
<td>DRUG</td>
</tr>
<tr>
<td>PRE-FILLED SYRINGE CONSTITUENT NEEDLE CONSTITUENT</td>
<td>DEVICE</td>
<td>DEVICE</td>
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Same product → Different regulatory designation and approval pathway

Syringe containing pharmaceutical formulation

Needle supplied with the syringe and attached prior to administration

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Emerging Regulations in Emerging Markets

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.
Emergence and convergence of new medical technologies
Combination Product Development

Working in a pressure cooker

How to manage a single approach that meets non-aligned and evolving requirements?

Industry wants to have consistent approach to combination product development

Increasing complexity of medical technology

Changing regulatory requirements

Timings & Cost

Combination Product Development
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
Industry & Regulatory Agency Collaboration Case Study

What is the CPC?
A group of leading companies in the drug, device and biologics industries, the CPC works to improve the regulatory environment for combination products by developing and advocating policy positions on regulatory issues affecting combination products.

What is the CPC’s mission?
The Coalition’s Mission is to improve the regulatory environment for combination products. To that end, the Coalition focuses on developing and advocating policy positions on issues affecting combination products.

www.combinationproducts.com
Industry & Regulatory Agency Collaboration

Case Study

Examples of recent CPC led initiatives
- Organised workshop with FDA to discuss industry comments on draft guidance to accompany Combination Product Final Rule (21 CFR Part 4)
- Proposal to FDA for more efficient & effective review of Human Factors submissions related to Combination Products
- Published journal articles on key emerging topics such as digital health and the regulation of software & apps

Key Strengths of CPC
- Strong and longstanding relationship with FDA, in particular Office of Combination Products.
- CPC respected by FDA and seen as the ‘go to’ industry group on issues affecting combination products
- Ensures industry’s views are co-ordinated – facilitates debate and discussion when required.
- Allows industry to communicate with FDA with one voice
Industry & Regulatory Agency Collaboration

Future Challenges & Opportunities

- An increasing number and diversity of combination products are in development
  • Expected to grow further over the coming years

- Lack of clarity on how regulatory agencies will review these products
  • Need for effective internal inter-disciplinary collaboration

- A framework needs to be in place to regulate these combination products such that they are safe and effective in the hands of users
  • More dialogue and discussion is required between industry & regulatory agencies to develop this framework

- Consequently more groups and forums focused on the regulatory aspects of combination products are required

  • TOPRA Medical Technology Special Interest Network (SPIN)
    • Becoming more active on combination product topics

  • IPAC-RS Device Working Group
    • Focused on inhalation combination products
“Coming together is a beginning; keeping together is progress; working together is success.”

Henry Ford
Questions?