The Device Side of Combination Products

Technical and Regulatory Challenges in Life Cycle Management

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What are combination products?
Combination Product

Combination products are the combination of two or more regulated entities (e.g. drug/device, biologic/device).

Each entity (constituent part) contributes one or more mode of action to the final product.

Example: Prefilled syringe has at least two modes of action
  - Syringe = subcutaneous injection
  - Medication = pharmaceutical action

A CP is generally approved by a regulator based on its primary mode of action (i.e. the mode that contributes the most important therapeutic effect)
Combination Product Types

There are three types of combination products:

1. Single-entity (e.g. integral)
2. Co-packaged (e.g. kits)
3. Cross-labeled (e.g. virtual)
Combination Product Types

Single-entity (e.g. integral) examples:

- Prefilled drug delivery systems
  - Prefilled syringes
  - Prefilled autoinjectors
  - Prefilled pen injectors
  - Prefilled on-body delivery systems
  - Dry-powder inhalers
  - Metered dose inhalers
  - Prefilled nasal sprayers
  - Transdermal patches
  - Iontophoretic delivery systems
Combination Product Types

Single-entity (e.g. integral) examples (cont.):

• Medicated devices
  – Drug-coated stents
  – Drug-coated catheters
  – Drug-coated pacemaker leads
  – Antimicrobial surgical scrubs
  – Antimicrobial wound dressings
  – Antibiotic-impregnated surgical mesh
  – Antibiotic bone cements
  – Spermicidal condoms
Combination Product Types

Co-packaged (e.g. kits) examples:

• Convenience kits
  – Surgical trays with anesthetic and/or surgical scrub
  – Vial and syringe packs
  – Injector pen with user-loaded prefilled cartridge
  – Liquid medication with dose-dispenser

• Other
  – Collagen sponge with bone morphogenic protein
Combination Product Types

Co-labeled (e.g. virtual) examples:

• Companion diagnostics

• Photodynamic therapy (laser activated drug)

• Contrast agent and diagnostic imaging
Combination Products in Biotechnology

Examples:
- Prefilled syringes
- Prefilled autoinjectors
- Prefilled pen injectors
- Prefilled on-body delivery systems
- Prefilled nasal sprayers
CP Pre-market Guidance

FDA – Guidance: “Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products”

FDA – Draft Guidance: “Glass Syringes for Delivering Drug and Biological Products”

FDA – Draft Guidance: “Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development”

ISO – 11040 series for prefilled syringes

ISO – 11608 series for needle-based injection systems

CP Post-market Guidance

FDA – Draft Guidance: “Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA”
IPAC-RS Product Lifecycle Device Change Management Survey

• 125 respondents provided information on how they would have handled 15 scenarios related to different types of product change

• Considerable variation was seen across the proposed changes in terms of testing conducted and reason for the testing

• There was broad uncertainty about the appropriate regulatory pathway to get approval for the change

• Overall all, there was a lack of consistency in the approaches adopted and a lack of risk management to inform decision making
Why Make Changes During LCM?

- Improve Performance, Safety, and/or Usability
- Improving Manufacturability or Production Yields
- Addition of New Features or Functionality
- Supplier Changes
- Improvement or Discontinuation of Materials or Components
- Complaints/CAPA
Technical Considerations
The development of medical devices and combination products that contain a device constituent is a regulated activity.

- 21 CFR 4 - Current Good Manufacturing Practice Requirements for Combination Products
  - For single-entity CPs containing a biologic and a device both the biologic cGMP and Device QSR regulations apply.
  - Design controls apply to device constituents and device-containing final products.
Device and Combination Product Development

- OUS countries applying device requirements to a single-entity typically require compliance to ISO 13485, “Medical Devices – Quality Management Systems.”
  
  - ISO 13485 includes product realization requirements specifying how to design and develop devices.
Device and CP Life-Cycle Management

• Both FDA Design Controls and ISO 13485 contain requirements for assessing design changes

• 21 CFR 820.30(i) – “Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.”
• ISO 13485:2016 (7.3.9)
  – “The organization shall document procedures to control design and development changes. The organization shall determine the significance of the change to function, performance, usability, safety and applicable regulatory requirements for the medical device and its intended use.”

  – “The review of design and development changes shall include evaluation of the effect of the changes on constituent parts and product in process or already delivered, inputs or outputs of risk management and product realization processes.”
In their recent draft guidance on the Part 4 rule, FDA has reaffirmed the application of design change management to combination products.

FDA Draft Guidance “Current Good Manufacturing Practice Requirements for Combination Products” states: “The manufacturer of a co-packaged or single-entity combination product should ensure appropriate consideration of any implications for the safety or effectiveness of its combination product that might arise from changes to it, including to any constituent part of it.” (pg 15)
Change Examples - Autoinjector

- Container Closure
  - Cartridge/Syringe Barrel
  - Septum/Plunger
  - Silicone

- Fluid Path
  - Needle (material, diameter, length)
  - Hub/Connector
  - Glue

- Delivery Mechanism
  - Spring (force, travel)
  - Syringe siliconization (break loose/glide force)
  - Needle shield (safety function)

- User Interface
  - Outer Shell (grip, color)
  - Notification (visual, audible)
  - Instructions for Use (text, images)

- User Population or Environment
General Principles for Evaluating Changes

1. Use a risk-based approach to evaluate the potential impact of the change
   • To form, fit, and function
   • To cause any new hazards
   • To existing risks
   • To safety and/or essential performance
   • To materials, design, process, user interface and/or intended use
General Principles for Evaluating Changes

2. Determine if the changes can be assessed by verification testing (e.g., functionality, biocompatibility, stability, drug product compatibility), or if validation testing (e.g., human factors/usability, simulated use studies, process validation) will be required.

3. If verification and/or validation testing shows a change to essential performance, and/or safety and efficacy, additional clinical studies will likely be needed to support the changed product.
Regulatory Submission of Product Changes

- Globally, there are no post-market submission requirements specific to combination products.

- Post-market changes are submitted in accordance with the relevant marketing application (e.g. the NDA/BLA in the US).

- Current regulations and guidance related to submission of post-market changes only address changes related to their relevant constituent.
  - Example: NDA CMC change guidance addresses changes to primary container, but not to injection functionality.
Challenges in Determining Change Submission

• Current product specific regulation and guidance provides control, and supporting examples, for the products that are their focus.

• The change submission type is usually determined using a risk-based metric (e.g. major, moderate, minor change for an NDA).

• However, these are based off risk to the constituent of interest – Example: 21 CFR 314.70 – “A supplement must be submitted for any change … that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.”
Challenges in Determining Change Submission

• 21 CFR 314.70 (vi) – “Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.”

• This can be taken to mean almost any change to a delivery system may be a supplement
Challenges in Determining Change Submission

- FDA Draft Guidance – “Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA”

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**Table 1: Type of NDA/BLA Submission for a Change in a Device Constituent Part of a Combination Product Approved under an NDA/BLA**

<table>
<thead>
<tr>
<th>If the Device Constituent Part Were a Stand-Alone Device Approved under a PMA and the Change Would Have Required the Following Submission</th>
<th>Then Submit Information on the Device Change Using This Type of NDA/BLA Submission for the Combination Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMA Original</td>
<td>NDA/BLA Original</td>
</tr>
<tr>
<td>PMA Panel-Track Supplement (New indication/population, without any other change to the constituent parts, supported by new preclinical data and the original preclinical data)</td>
<td>Prior Approval Supplement (Efficacy)</td>
</tr>
<tr>
<td>PMA 180-day Supplement - Design change and labeling change supported by new preclinical and/or limited confirmatory clinical data</td>
<td>Prior Approval Supplement (Efficacy)</td>
</tr>
<tr>
<td>PMA 180-day Supplement - Manufacturing site change</td>
<td>Prior Approval Supplement (Manufacturing)</td>
</tr>
<tr>
<td>PMA 180-day Supplement - Labeling change including nomenclature</td>
<td>(With or without labeling changes)</td>
</tr>
<tr>
<td>(And with a change from the next column)</td>
<td>Manufacturing site change not requiring any clinical data</td>
</tr>
<tr>
<td>PMA Real-Time Supplement (Design or labeling change that does not require clinical data and for which the data provided fall within only one scientific discipline, e.g., electrical engineering, microbiology, or sterilization)</td>
<td>Prior Approval Supplement (Labeling)</td>
</tr>
<tr>
<td></td>
<td>PMA Real-Time Supplement (Design or labeling change that does not require clinical data and for which the data provided fall within only one scientific discipline, e.g., electrical engineering, microbiology, or sterilization)</td>
</tr>
<tr>
<td>PMA Periodic Report</td>
<td>Annual Report</td>
</tr>
</tbody>
</table>

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- PMA Real-Time Supplement
- Prior Approval Supplement (Manufacturing or Labeling)
- Prior Approval Supplement (Efficacy)
- Prior Approval Supplement (Manufacturing)
- Prior Approval Supplement (Labeling)
- 30-day Notice (Manufacturing process or method change only)
- 30-day Changes Being Effected
- Changes Being Effected
- PMA Periodic Report
- Annual Report
Challenges in Determining Change Submission

• FDA Draft Guidance – “Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA”

  – “if a change is made to any constituent part of the combination product that would have required a postmarket submission to FDA if the constituent part were a stand-alone product, then a postmarket submission is required for the combination product.”

• Table demonstrates expected changes for device constituents that would have been PMA products, but what about constituents that would have been 510(k) or exempt devices?
Challenges in Determining Change Submission

• Example: If a prefilled syringe manufacturer considered their device constituent equivalent to a disposable injection needle under 21 CFR 878.4800 (product code GAA), which is a Class I exempt product, there would theoretically not be a requirement to submit under this guidance.

• However, 21 CFR 314.70 would indicate that a change to the syringe would in fact be required.

• The current expectation is that a submission would be required despite the potentially confusing guidance.
There are three primary ways to deal with changes under the current paradigm.

1) Submit your change under the metric and guidance for the approved application (e.g. mostly supplements for an NDA/BLA)

2) Evaluate your change under equivalent regulation and guidance for the device constituent and submit as the most equivalent drug/biologic submission
   - This relies on the regulator to force an upclassification of the change submission if they believe the sponsor chose in appropriately
   - This is also less predictable with regard to review timelines
3) In the US, a sponsor can submit a comparability protocol to propose tests and criteria to demonstrate absence of adverse effects from specified types of change (21 CFR 314.70(e)).

- This potentially reduces the submission for the change (e.g. a change normally needing a supplement may be a CBE instead)

- The protocol must be reviewed by the FDA in the initial application or subsequent supplement and get their approval

- The protocol may be rejected or negotiation may delay approval
Current Efforts
Current Effort

• The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) Device Working Group created a proposed framework for addressing design changes and their associated regulatory submissions – “Management of Design Changes through the Product Lifecycle”

• Contains useful considerations for the evaluation of device constituent changes

• However, it considered them under the drug paradigm (i.e. ICH Q8, Q9, Q10), not under the device paradigm (21 CFR 820.30 and ISO 13485)
Current Effort

• Finalization of FDA’s Draft Guidance on postapproval modification of combination products
  – Release is rumored to be by end of 2016 and magnitude of changes unknown

• Active work by industry groups to improve clarity in regulation and guidance
  – Example: The Combination Product Coalition is working on proposed revisions to regulation and guidance to improve lifecycle management of combinations
The International Standards Organization (ISO) has started the development of a new standard related to lifecycle management of combination products:

- ISO 20069 “Device change management of combination products for administration of medicinal products”

- Purpose: Provide direction on how to manage change to the device constituent of combination products intended to delivery medicinal products
Summary

• Technical evaluation of a device constituent change is a regulated activity that should follow the relevant device regulations and standards.

• Evaluation of the change should be risk-based with particular focus on potential impact to the safety and/or performance of the product and effect on the user/patient.

• Submission of the change is largely dependent on the approval pathway, but the exact submission type for a particular change type is still not well defined.

• Efforts to improve the lifecycle management of device changes to a combination product are ongoing.