Combination Products – Integrating FDA’s Streamlined Approach

FDAnews Inspection Summit
November 6, 2015
This document is intended to facilitate an oral briefing. It is not intended for use as a stand-alone report.
Agenda

- Recent FDA Combo Products Study
- Background Combination Products
- Part 4
- AAMI: Technical Information Report (TIR)
- Case Study
- Inspection Survey
- Recent 483 and WL discussion
Study Reports: Combo Product Reviews

- HHS FDA: Combination Product Review Intercenter Consult Process Study (October 14, 2015)
  - Consistency and clarity of FDA’s communication related to product reviews
- Combination Products Coalition; Recommendations to FDA Centers (May 23, 2014)
Background

- Part 4 Final Rule:
  As set forth in Part 3 (21 CFR Part 3.2(e)), a Combination Product is comprised of any combination of:
  - A drug and a device
  - A device and a biological product
  - A biological product and a drug
  - A drug, a device, and a biological product
Types of Combination products are defined as follows:

(1) Single Entity: A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity

Examples of single-entity products
- Prefilled syringe
- Transdermal patch
- Drug-eluting stents

NOTE: drug packaged as part of container/closure, such as a vial, would not be considered a combo product
(2) **Co-packaged**: Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products

Examples of co-packaged products

- Drug with delivery mechanism, i.e., nebulizer, inhaler, dropper or syringe
- Convenience kits, i.e., first aid kits or surgery kits
(3) **Cross-labeled**: A drug, device, or biological product **packaged separately** that according to its investigational plan or proposed labeling is:

- intended for use only with an approved individually specified drug, device, or biological product **where both are required to achieve the intended use, indication, or effect** and
- where upon approval of the proposed product the labeling of the approved product would **need to be changed**, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose

Examples of cross-labeled products

- Light-emitting devices which specify a certain antibiotic or protein solutions to be used in a medical procedure
- Drug with specific applications for delivery mechanism
The Final Rule

- The new rule *does not* introduce any new regulations, it just *clarifies how existing regulations are expected to be implemented.*

- *No products are grandfathered* – all combination products, regardless of introduction date, are expected to be compliant to the regulations.
So how does the final ruling impact each type of combination product relative to GMPs compliance strategy?
This is where the “challenge” begins

The rule was created to:

- Reduce redundancy
- Clarify how the regulations should be applied
- Provide options to the Industry on how they could approach implementing the Part 4 cGMP requirements – streamline or not
Constituent Parts Establish the GMP Regulations

- The constituent parts* of a combination product retain their regulatory status (as a drug or device, for example) after they are combined.

- Allow the Primary Mode of Action (PMOA) to influence the direction and strategy
  - In particular, compliance with either the cGMP regulations for drugs 21 CFR 210 and 211 or the quality system (QS) regulation for devices 21 CFR 820 will satisfy many, though not all, of the cGMP requirements applicable to both drug and device constituent parts.
  - However, the PMOA does not dictate the Compliance strategy.

*Constituent part is a drug, device, or biological product that is part of a combination product
Cross-Labeled Products

- Part 4 – straight forward approach – each constituent part needs to meet their applicable GMP regulations.
- From the Final Rule: while these are separately manufactured and marketed, they remain separate for the purposes of applying the cGMP regulations.
- No new requirements
Co-Packaged Convenience Kits

**Convenience Kit:** kits that solely include products that are:

1. Marketed independently
2. Labeling – Package label is the same – whether marketed independently or within a kit

The only additional cGMP requirements that would generally apply to such a convenience kit would be those applicable to the assembly, packaging, labeling, any sterilization, or further processing of the kit itself.
HOWEVER, if any products to be included in a kit are repackaged, relabeled, sterilized or otherwise modified for purposes of their inclusion in the kit, the kit is **NOT** a “convenience kit” and all the cGMP requirements applicable on any changes made to the constituent parts would apply.

**KEY:** the implications of additional processing impacts stability and shelf-life requirements and subsequent labeling and could result in misbranded and/or adulterated product
cGMP Compliance Strategy
cGMP Compliance Options

- The final rule offers several approaches to selecting the cGMP operating requirements applicable to a co-packaged or single-entity combination product.

- These options are:
  1. Non-streamlined approach – demonstrate compliance with the specifics of both cGMP regulations applicable to each of the constituent parts included in the combination product
  2. (a) Demonstrate compliance using the streamline approached based on the CFR 210/211 drug cGMPs
  2. (b) Demonstrate compliance using the streamlined approached based on the CFR 820 QSR regulation
## Transition to a Streamlined cGMP Approach

<table>
<thead>
<tr>
<th>CGMP Requirements</th>
<th>Title</th>
<th>If the Operating Manufacturing Control System is Part 820 (QS Regulation)</th>
<th>If the Operating Manufacturing Control System is Part 210/211 (CGMP Regulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>§ 211.84</td>
<td>Testing and approval or rejection of components, drug product containers, and closures</td>
<td>§ 820.20 Management responsibilities</td>
<td></td>
</tr>
<tr>
<td>§ 211.103</td>
<td>Calculation of yield</td>
<td>§ 820.30 Design controls</td>
<td></td>
</tr>
<tr>
<td>§ 211.132</td>
<td>Tamper-evident packaging requirements for over-the-counter (OTC) human drug products</td>
<td>§ 820.50 Purchasing controls</td>
<td></td>
</tr>
<tr>
<td>§ 211.137</td>
<td>Expiration dating</td>
<td>§ 820.100 Corrective and preventative actions</td>
<td></td>
</tr>
<tr>
<td>211.165</td>
<td>Testing and release for distribution</td>
<td>§ 820.170 Installation</td>
<td></td>
</tr>
<tr>
<td>§ 211.166</td>
<td>Stability testing</td>
<td>§ 820.200 Servicing</td>
<td></td>
</tr>
<tr>
<td>§ 211.167</td>
<td>Special testing requirements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>§ 211.170</td>
<td>Reserve samples</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
AAMI Standard

- **AAMI TIR48:2015**
- Quality Management System (QMS) Recommendations on the Application of the US FDA’s CGMP Final Rule on Combination Products
  - Approved August 14, 2015 by the Association for the Advancement of Medical Instrumentation
Inspectional Readiness

Key points to consider in preparation for a successful FDA inspection
FDA Challenges

- There is NO inspection strategy on how the FDA districts will audit combination products

- Having a good relationship with the Center does not necessarily translate to a successful inspection
<table>
<thead>
<tr>
<th>Responder Primarily Manufacturer Of</th>
<th>Regulatory Filing</th>
<th>Product Type</th>
<th>Inspected by FDA?</th>
<th>Describe Investigators</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Combination Products</td>
<td>PMA</td>
<td>CL</td>
<td>Yes</td>
<td>Both skill-sets</td>
<td>FDA 483</td>
</tr>
<tr>
<td>(2) Pharmaceuticals and Biologics</td>
<td>NDA, IND, 510(k), PMA</td>
<td>SE CP (not kits) CP (kits) CL</td>
<td>Yes</td>
<td>Medical Device skill-set</td>
<td>Warning Letter</td>
</tr>
<tr>
<td>(3) Combination Products</td>
<td>BLA</td>
<td>SE</td>
<td>Yes</td>
<td>Pharmaceutical/Biologic skill-set</td>
<td>No observations</td>
</tr>
<tr>
<td>(4) Combination Products</td>
<td>NDA</td>
<td>SE CP (not kits) CP (kits)</td>
<td>Yes</td>
<td>Team of both skill-sets</td>
<td>FDA 483</td>
</tr>
<tr>
<td>(5) Medical Devices</td>
<td>510(k)</td>
<td>CL</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>(6) Pharmaceuticals and Biologics</td>
<td>NDA, BLA</td>
<td>SE</td>
<td>Yes (4/14 PAI)</td>
<td>Team of both skill-sets (CDER Inspector, LA District inspector with medical device background, LA District inspector with pharma/biologics background)</td>
<td>FDA 483</td>
</tr>
<tr>
<td>(7) Medical Devices</td>
<td>510(k)</td>
<td>SE</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>(8) Combination Products</td>
<td>NDA</td>
<td>SE</td>
<td>Yes (2/2014 drug and 12/2014 [assembly and packaging])</td>
<td>Pharma/Biologic skill-set. (More attention on the DP manufacturing and testing; related plant systems; training. No questions related to DHF)</td>
<td>FDA 483</td>
</tr>
<tr>
<td>(9) Pharmaceuticals and Biologics</td>
<td>IND, BLA, PMA</td>
<td>SE CP (not kits) CP (kits) CL</td>
<td>Yes</td>
<td>Pharmaceutical/Biologic skill-set</td>
<td>No observations</td>
</tr>
<tr>
<td>(10) Medical Devices</td>
<td>510(k)</td>
<td>SE</td>
<td>Yes</td>
<td>Medical Device skill-set</td>
<td>No observations</td>
</tr>
</tbody>
</table>
## Survey Results

<table>
<thead>
<tr>
<th>Responder Primarily Manufacturer Of:</th>
<th>Regulatory Filing</th>
<th>Product Type</th>
<th>Inspected by FDA?</th>
<th>Describe Investigators</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>(5) Medical Devices</td>
<td>510(k)</td>
<td>CL</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>(7) Medical Devices</td>
<td>510(k)</td>
<td>SE</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>(10) Medical Devices</td>
<td>510(k)</td>
<td>SE</td>
<td>Yes</td>
<td>Medical Device skill-set</td>
<td>No observations</td>
</tr>
<tr>
<td>(1) Combination Products</td>
<td>PMA</td>
<td>CL</td>
<td>Yes</td>
<td>Both skill-sets</td>
<td>FDA 483</td>
</tr>
<tr>
<td>(4) Combination Products</td>
<td>NDA</td>
<td>SE</td>
<td>Yes</td>
<td>Team of both skill-sets</td>
<td>FDA 483</td>
</tr>
<tr>
<td>(8) Combination Products</td>
<td>NDA</td>
<td>SE</td>
<td>Yes (2/2014 drug and 12/2014 [assembly and packaging])</td>
<td>Pharma/Biologic skill-set. (More attention on the DP manufacturing and testing; related plant systems; training. No questions related to DHF)</td>
<td>FDA 483</td>
</tr>
<tr>
<td>Pharmaceuticals and Biologics</td>
<td>NDA, BLA</td>
<td>SE</td>
<td>Yes (4/14 PAI)</td>
<td>Team of both skill-sets (CDER Inspector, LA District inspector with medical device background, LA District inspector with pharma/biologics background)</td>
<td>FDA 483</td>
</tr>
<tr>
<td>(3) Combination Products</td>
<td>BLA</td>
<td>SE</td>
<td>Yes</td>
<td>Pharmaceutical/Biologic skill-set</td>
<td>No observations</td>
</tr>
<tr>
<td>Pharmaceuticals and Biologics</td>
<td>IND, BLA, PMA</td>
<td>SE</td>
<td>Yes</td>
<td>Pharmaceutical/Biologic skill-set</td>
<td>No observations</td>
</tr>
<tr>
<td>(9) Pharmaceuticals and Biologics</td>
<td>IND, BLA, PMA</td>
<td>SE</td>
<td>Yes</td>
<td>Pharmaceutical/Biologic skill-set</td>
<td>No observations</td>
</tr>
<tr>
<td>Pharmaceuticals and Biologics</td>
<td>NDA, IND, 510(k), PMA</td>
<td>SE</td>
<td>Yes</td>
<td>Medical Device skill-set</td>
<td>Warning Letter</td>
</tr>
</tbody>
</table>
Opening presentation or inspection management should include the following:

- **Product Portfolio** – identify those that are considered Combination Products. Note which processes are under what quality system, if appropriate.
- **SOPs** should clearly identify how the organization is addressing the Part 4 requirements.
- **Organizational structure** – be able to show how the personnel and technical competency are being addressed. Ex. You have a Director position that oversees the combination products Quality – ensure that the Job Description is clear on the background as well as technical experience required.
- **Training Plan**: current on-the-job as well as overall company training on combination products – Part 4 requirements.
During the Inspection

- Show “objective evidence” on where you have implemented the Part 4 requirements
- If SOPs are not updated, then show redline copies
- Training plans that include combination products
- On-the-job training, if necessary
- New hires and job descriptions
- Auditing practices – need to ensure that you are covering both 21 CFR 210 & 211 as well as 21 CFR 820 (are your auditors competent or is it outsourced?)
Part 4 Implementation Challenges

Organizations have struggled in their approach to addressing the regulations as seen below:

- During the past 2 years, some companies have had a “knee jerk” reaction to the Part 4 regulations
  - Lets do it ALL at once, instead of a systematic approach – what makes sense based on the direction the company is headed
  - Head in the sand – “we have always done it this way, why change, it is TOO much $$$” – we will wait for a regulatory action to change”
  - We aren’t a combo product so these requirements don’t apply to us (repackagers)
**ISSUE:** FDA is alerting health care professionals not to administer to patients compounded or repackaged drugs that have been stored in 3 milliliter (ml) and 5ml syringes manufactured by Becton-Dickinson (BD) unless there is no suitable alternative available. Preliminary information indicates that drugs stored in these syringes may lose potency over a period of time due to a possible interaction with the rubber stopper in the syringe.

**BACKGROUND:** FDA has cleared these syringes as medical devices for general purpose fluid aspiration and injection only. These syringes were not cleared for use as a closed container storage system for drug products, and the suitability of these syringes for that purpose has not been established. This issue may extend to other general use syringes made by other manufacturers that were not cleared for the purpose of closed-container storage usage.
Transition to Streamlined Approach

- Step back and look at the Big Picture
- Breathe – don’t do anything until you …
  - Think about where you are at and where you want to be
  - Develop your Compliance Strategy by creating a Quality Plan
  - Then execute according to the plan
Conclusion and Summary

- cGMP Compliance Roadmap – streamline or not
  - Product type and positioning (PMOA)
  - Regulatory approach (cGMP compliance focus, what are your strength(s) and experience?)
  - Product complexity and risk profile
  - Strategic planning (supply chain, product pipeline)
  - Relationship with Agency – work with them throughout the process – NO SURPRISES!

FINALLY – make whatever you decide, work for you
Regulatory Enforcement

- 2014 - Warning Letter on Combo Products
Observations

#1 Design Control: The firm failed to establish (i.e., define, document, and implement) and maintain design validation procedures to ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions, as required by 21 CFR 820.30(g).

#2 Design Control: The firm failed to establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation, as required by 21 CFR 820.30(i).
Observations (continued)

#3 Purchasing Control: The firm failed to establish and maintain the requirements that must be met by suppliers, contractors, and consultants. The firm failed to evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements, and document the evaluation, as required by 21 CFR 820.50(a).
Procedures for acceptance activities have not been adequately established

- Documented investigation of unexpected or out of specification (OOS) tests results conducted on site in accordance with approved procedure, Investigation of OOS Test Results, are not always fully documented in a timely manner to ensure appropriate actions are executed, identified and documented...

- Reserve drug product samples are not appropriately identified and retained and stored under conditions consistent with product labeling
Laboratory controls do not include the establishment of scientifically sound and appropriate standards and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity.

Specifically, there is a failure to perform growth promotion testing of media received for use in drug manufacturing operations.
Procedures to control the labeling of HCT/Ps were not established

- Firm’s HCT/P labeling procedures do not include requirements to ensure that:
  1) HCT/Ps are labeled in accordance with all applicable Good Tissue Practices labeling requirements; and
  2) review of the labels for accuracy, legibility, and integrity....
Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

There is no written testing program designed to assess the stability characteristics of drug products.

Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined…

Actual yield and percentages of theoretical yield are not determined at the conclusion of each appropriate phase of processing the drug product.
Rework and reevaluation activities have not been documented in device history record

- Your firm’s Online Cartridge Recovery System (CRS) procedure…does not include provisions for documenting the inspection of integrated cartridges during manufacturing operations for the…Prefilled Insulin Delivery Devices…
Drug product containers or closures are reactive, additive, and absorptive so as to alter the safety, identity, strength, quality, and purity of the drug beyond the official or established requirements.
The results of design validation, including method(s), were not adequately documented in design history. Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been adequately established.

- Not all complaints are handled or investigated uniformly. Complaints involving adverse events are not reviewed and evaluated according to the Complaints Management procedure, but by the Medical Devices Vigilance procedure which does not include the following requirements of the Complaints Management Procedure…
Combination Product Pathways

So let’s walk through a case study and what areas need to be addressed if you are going to use the streamline approach.
Drug PMOA: Case Study

- Metered Dose Inhaler Delivering Chemotherapy for Lung Cancer
  - Chemotherapy is PMOA; Inhaler is not only the primary packaging (container/closure), but also the delivery mechanism
  - Device is critical to safe and effective drug delivery

NOTE: Decisions should be made early on the drug delivery system, to avoid negatively impacting timing of the filing as well as FDA approval.
If pursuing the streamlined approach based on CFR 210 & 211

- Biggest Challenge tends to be Design Control – Formal process for device development; regulated under 21 CFR 820.30
  - Design/Development Planning, Design Inputs, Design Outputs, Design Review, Design Verification/Validation, Design Transfer, Design Changes
  - NOTE: Design controls start during the device development and goes into **clinical trials and continues until end of life**. The documentation is captured in Design History File (DHF)

- For the other 21 CFR 820 Requirements: Management Controls, Supplier Controls, and CAPA, there are similarities between Drug and Device, but nuances need to be well understood.
Design Control

- Design and Development Plan: Road Map
  - Establishing the goal of your device: what is your device supposed to do, what needs to get done to make it, and who is involved in its development?

- Design Inputs
  - Requirements for its use with API (intended use)
  - User requirements
  - Human Factors

- Design Verification and Validation
  - How do you know your device meets specifications and user requirements?
Design Control

- **Device Validation**
  - Critical to have inputs/outputs as soon as possible so V&V can proceed timely
    - The device is a key part of the system and pivotal clinical studies should include intended to-market device
    - Confirm device is suitable to be used by intended user (Human Factors is a critical issue for CDRH)
    - Confirm device is appropriate for drug, drug delivery
      - PK/PD may be significantly influenced by the device
  
- **Regulatory Submission**
  - Device is container/closure (as well as the delivery mechanism) within the CTD
Purchasing Controls

- Suppliers and Components/Services must be approved together and linked together
  - For example: Acme Syringe may supply the syringe for one type of drug, but not for another type of drug
- Purchasing Controls apply to R&D activities for supplier and component selection during the Design Output activity
  - Suppliers and components must be approved prior to Design Transfer
Using Product Risk in Selection and Control Suppliers

- Risk is be used to support the extent of required controls
  - More stringent controls may be required for parts identified as essential for the proper functioning of the device in design output (820.30(d)) during Design Controls
    - Critical for functionality of device
      - Related back to Design FMEA
    - Complexity to manufacture
      - Related back to Process FMEA
Are the CAPA requirements for drugs and devices very different? Is there a gap?

- No, a CAPA is CAPA regardless of industry. However, the difference is the approach the pharmaceutical companies take verses medical device companies. Medical device companies open a CAPA based on severity of an event or triggering of a trend versus pharmaceutical companies, who consider most quality events as CAPAs, not just the serious ones. This is why pharmaceutical companies need to comply with 21 CFR 820.100 requirements when meeting the Part 4 requirements. CAPA should be your apex, not the catch all for your Quality program.

- For example, if you find there's a non-conformance in a process and it is a one-time event, then you wouldn’t open a CAPA, but you would make sure you address the correction and then track it to insure that you have no repeat events. However, if you start seeing a trend, or even several similar occurrence, then you might want to consider opening a CAPA.
Management Controls

- Several challenges that have been seen:
  - Feedback is that Senior Management does not understand Combination Products and how they apply – key is to establish a robust Management Review Program.
  - Personnel – qualified individuals who understand both 21 CFR 211 and 21 CFR 820 requirements
  - Auditing – individuals who are conducting both internal Quality Processes as well as Suppliers
  - Training Program – needs to include the combination products job-specific requirements
Questions?

Thank You

Elaine Messa
emessa@nsf.org
202-257-5848