Recent and Upcoming Changes and Challenges in the USA

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- Quick History
- Recent Changes
- Older Changes
- Other Onging Activities
- Challenges

Quick History

Quick History

- Quick History
  - Combination Products have been around for over 27 years (since 1990 in the USA)
  - Implementing regulations and guidance followed slowly
  - The Office of Combinations Products (OCP) was created in 2002
  - Significant, and sorely needed regulation and guidance started in earnest just over the last ten years
  - This has accelerated with an explosion in the last two years
  - This has created opportunity
    - To understand FDA's thinking,
    - To use to ensure consistency
    - and to provide input through comment
  - It has also created difficulties
    - Working with difficult, sometimes untenable draft guidance
    - Being forced to comply with new requirements on old projects
    - Trying to keep up

Recent Changes

Recent Changes

- Recent Regulatory Regulation and Guidance (Last Month)
  - **Deciding When to Submit a 510(k) for a Change to an Existing Device – Final Guidance - October 2017**
  - **Deciding When to Submit a 510(k) for a Software Change to an Existing Device – Final Guidance - October 2017**
    - **Hopeful Content! Considers potential for 510(k) as one of two submissions for a Combination Products.**
    - *"This guidance(s) does not specifically address combination products, such as drug/device or biologic/device combinations; however, the general principles and concepts described herein may be helpful to manufacturers in determining whether submission of a 510(k) is required for changes to (software-containing) device constituent parts of combination products."*
  - *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA – Draft Guidance – October 2017*
    - ***Includes changes that involve changes to Devices***
  - *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA – Draft Guidance – October 2017*
    - ***Defines drug-device combination products as Complex Generics, allowing additional formal meetings on NDAs***
  - **Classification of Products as Drugs and Devices & Additional Product Classification Issues – Final Guidance - September 2017**
    - **Not directly combination Product related, but helps understand how FDA classifies drugs and devices**

Recent Changes

- Recent Regulatory Regulation and Guidance (2016-2017)
  - *How to Prepare a Pre-Request for Designation (**Pre-RFD**) – Draft Guidance January 2017*
  - *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA – Draft Guidance January 2017*
  - *Considerations in Demonstrating Interchangeability With a Reference Product – Draft Guidance January 2017*
    - ***Both Contain significant new concept of Threshold Analyses and Non-inferiority (Quantitative) Comparative HF Studies***
  - **Current Good Manufacturing Practice Requirements for Combination Products – Final Guidance - January 2017**
  - **Combination Product Adverse Event Reporting Regulation – Final Rule - December 2016**
  - **eCTD Technical Conformance Guide v1.1 – Final Guidance September 2016**
  - **Safety Considerations for Product Design to Minimize Medication Errors – Final Guidance April 2016**
  - *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development – Draft Guidance February 2016*
  - **Applying Human Factors and Usability Engineering to Medical Devices –Final Guidance - February 2016**

Older Changes

Older Changes

- Older Regulatory Regulation and Guidance – Still creating problems
  - **Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products – Final Guidance - June 2013**
    - **Referenced Constantly**
  - *Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA - Draft Guidance - January 2013*
    - ***Not Much Help, Hopefully will be dropped of significantly changed***
  - *Rheumatoid Arthritis: Developing Drug Products for Treatment – Draft Guidance - May 2013*
    - ***Source of "Real life User Experience" clinical Studies***
  - *Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4 – Draft Guidance - April 2013*
    - ***Still a draft; still a terrible guidance, still always referenced for PFS***

Ongoing and Emerging Issues

Other Onging Activities

- FDA Survey
  - Combination Product Review - Intercenter Consult Process Study, October 14, 2015
    - FDA internal Survey that identified significant areas for improvement

- Series of Blog Posts
  - Blog Post – " The Merging of Medical Products: Enhancing review Posted on October 15, 2015 by Robert M. Califf, M.D. and Jill Hartzler Warner, J.D.
  - Blog Post – "Leaning in' on Combination Products", Posted on March 7, 2016 by Nina L. Hunter, Ph.D., and Rachel E. Sherman, M.D., M.P.H.
  - Blog Post – " Developing a Consensus Voice: The Combination Products Policy Council", Posted on April 6, 2016 by Nina L. Hunter, Ph.D., and Rachel E. Sherman, M.D., M.P.H.
  - Blog Post – " Piloting an Improved Intercenter Consult Process, Posted on August 1, 2016 by Michael Rappel, Ph.D., and Rachel E. Sherman, M.D., M.P.H.
  - Blog Post – " Making Continuous Improvements in the Combination Products Program: The Pre-RFD Process", Posted on August 11, 2016 by Thinh Nguyen and Rachel E. Sherman, M.D., M.P.H.

Onging and Emerging Issues

- Combination Products Council
  - Combination Products Council Established – April 2016
    - Provides a senior-level forum to establish combination product policy across the FDA and ensures that policy is implemented in a consistent manner throughout the Agency.
  - Council Mission
    - Modernize the inter-center consultation process and related aspects of combination product and cross-labeled product review;
    - Promote development of innovative, safe, and effective combination products and cross-labeled products; and
    - Promote alignment in addressing challenging medical product classification issues.
  - Chaired by the Deputy Commissioner for Medical Products and Tobacco (OMPT) or his/her designee, includes representatives from
    - CDER, CBER, CDRH, OCP and Office of Special Medical Programs
- The role and operation of this council and its impact on OCP and Combination Products is still unknown

Onging and Emerging Issues

- 21st Century Cures Act - January 2016
  - Contains section entitled “Combination Products Innovation”, TITLE III—DEVELOPMENT; Subtitle D—Patient Access to Therapies and Information; Sec. 3038
  - Was originally primarily focused on determinations of PMOA based on “Chemical Action” which resulted in mostly designations as a drug.

Onging and Emerging Issues

- 21st Century Cures Act - January 2016
- Contains some elements that may impact Drug Delivery Combination Products
  - Requires OCP to serve a more formal role in coordinating reviews and meetings, making sure the right people are involved.
  - Provides the sponsor the opportunity to request a 75 day meeting with the designated lead center to establish clarity and certainty for the sponsor
    - (I) address the standards and requirements for market approval or clearance of the combination product;
    - (II) address other issues relevant to such combination product, such as requirements related to postmarket modification of such combination product and good manufacturing practices applicable to such combination product; and
    - (III) identify elements under subclauses (I) and (II) that may be more appropriate for discussion and agreement with the Secretary at a later date given that scientific or other information is not available, or agreement is otherwise not feasible regarding such elements, at the time a request for such meeting is made

Onging and Emerging Issues

21st Century Cures Act - January 2016

Most promising elements:

- Confirms that it's generally ***ok to submit separate applications*** for separate (Co-Packaged/Cross Labeled) constituent parts
- Calls for new guidance on development and review process improvements and on variations from the cGMP streamlined approach
- Requires FDA accept (take into account) the prior finding of safety and effectiveness or substantial equivalence of a constituent part and, using a risk-based approach, ***only address any incremental risks and benefits posed by the combination product***

Onging and Emerging Issues

- **Public Meeting on Devices Referencing Drugs (DRDs)**
  - Devices Proposed for a ***New Use with an Approved, Marketed Drug***, when the ***sponsor for the approved drug does not wish to pursue or collaborate*** on the new use, and will not be labeled for the new use
  - Therefore, these are ***NOT considered Combination Products***
  - DRDs may be proposed to:
    - (1) enhance the safety or effectiveness of the marketed drug for its already approved indication;
    - (2) be used with the approved drug for an indication for which the drug is not approved; or
    - (3) provide some other benefit, such as increasing user comfort or convenience. Such new uses have generally also involved a change in how the drug is used or administered, such as a change in dose, route, or rate of administration. DRDs may be proposed:
      - (1) to enhance the safety or effectiveness of the marketed drug for its already approved indication;
      - (2) for use with the approved drug for an indication for which the drug is not approved; or
      - (3) to provide some other benefit, such as increasing user comfort or convenience.
    - Such new uses have generally also involved a change in how the drug is used or administered, such as a change in dose, route, or rate of administration.

- Only Proposes Possibility approval through ***PMA Pathway***

Onging and Emerging Issues

- Device Changes
  - Old Guidance not of Value
  - ICH Q12; ISO 20069 – Both in Draft
- Clincal Bridging
  - RA Clincal Guidance still used to require some clincal data
  - FDA/RAPS/CPC Meeting at the end of the month
- Combination Product Connected Health
  - Wide open, still not defined differnces if part of a Combination Product
- Cross Labeling
  - One or Two Submisions
  - One-Way Labeling
  - First time through Combinations, more drugs/devices later
  - Required Cooperation

Summary

Summary

- Guidance and Regulation on Combination Products was off to a slow start
  - Started to pick up around 10 years ago
- Some of the guidance provided are still Draft and have significant issues provided in Industry Comments have not been addressed
  - Actions do not always reflect old drafts, but some are unfortunatly still used
- There have been significant regualtions and guidance promulgated in the last two years
  - Some are problememmatic
  - It is dififcult to keep up and dificult to adjust into ongoing projects
- Several intiatives portend additional and significant changes
  - Too early to tell
- Still best to take objective, rational, common sense approach with strong scientific justification
  - And hope somone is listening!