Part 15 Public Hearing
FDA Regulation of Combination Products
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PERSONAL EXPERIENCE

- Inhalation device [510(k)]
- Passive transdermal patches [ANDA]
- Medicated tooth paste [IND]
- Iontophoretic drug delivery systems [RFD, IND, *510(k)–NDA*]
- Prefillable syringes [DMF]
- Pens, liquid- and liquid-dry [RFD, 510(k), MAF]
- Autoinjector [RFD, 510(k)]
- Nasal delivery syringe [BMF]
- Diluent syringes [RFD, 510(k)]
- Flush syringes [510(k)]
- Disposable syringes, needles [*510(k)*]
- Surgical kits [*NDA, 510(k)*]
- Surgical scrubs [NDA]
- Infusion Pumps [510(k)]
- *Jet and powder injectors* [*510(k)*]
- *Inhalation delivery systems* [*510(k)-NDA*]

DOWNSTREAM ISSUES

- User Fees
  - PDUFA, MDUFMA
- Quality Systems:
  - 21CFR 210, 211, 820
- Manufacturing/Design Changes:
  - 21CFR 314.70, 601.12, 807.81 814.39
- Adverse Events/Experiences:
  - 21CFR 314.80, 600.8, 803
- Toxicology/Biocompatibility:
  - 21CFR 312.23, ISO-10993-
- Orphan Drug/Humanitarian Device:
  - 21CFR316, 814.100
- Applications:
  - 21CFR 312, 314, 600, 807.81 812, 814

1. What guiding principles should be used when revising the existing Inter-center Agreements?

- Guidance level documents, subject to comment period
- Consistent format, clear language and content; examples
- Distinguish between combination products (Combination Products Office) and products of unclear designation (Product Jurisdiction Office)
- For a combination product do not say, “it’s a drug” or “it’s a device”, or “it’s regulated as a …” ;these statements pertain to a product of unclear designation.
- Address only jurisdiction and application of investigational exemptions and pre-market regulatory authorities; address “downstream issues” in separate guidance(s)
- Describe and diagram designation and dispute resolution processes
- Reaffirm that reviews are consultative and not collaborative
- Virtual Combination Products are created only when brand names are specified and labeling is mutually conforming

2. What factors should be considered in determining primary mode of action?

- Primary Jurisdiction established according to primary mode of action
  - In special cases where the effects are synergistic or mechanism is unclear also consider :
    - Risk
    - Toxic or adverse mode of action
    - Intended use
    - Center capability to assess safety and effectiveness
- Must have foundation in FD&CA, fit drug or device definitions
- Describe/diagram determination/dispute resolution processes in Inter-center Agreement rewrites

3. Is one pre-market review (notification) mechanism more suitable than another?

- Is it appropriate to regulate combination products under 510(k)?
  - Can there be “substantial equivalence” for a combination product?
  - Should a consistent level of regulatory approval be applied to all components [i.e., 510(k) is not pre-market approval]?
- Consider a new (unique) application (CPAA) for combination products? This would require legislation.

4. What criteria should be used in determining if single or multiple applications are necessary? Should the need to use a mixed regulatory approach influence this?

5., 6. What principles should be followed in determining the quality system and adverse event reporting requirements for a combination product?

- Each Guidance should include descriptions/diagrams of determination/dispute resolution processes.
- Guidance should be predictable and consistent on application formatting (e.g., single application, imbedded pull-out, linked or stand-alone).
- For quality systems, design control may be useful for managing combination products; perhaps design reviews throughout development and post-marketing should be required for <u>all</u> combination products, as it will help to identify and manage interactions between the components.
- For adverse events:
  - Reports should be sent to both Centers indicating the report is for a combination product
  - FDA must sort out duplicate reporting

7. Other comments?

- Virtual Combination Products are created only when brand names are specified and labeling is mutually conforming
- Certain combination product examples cited in the CDER-CDRH Inter-center Agreement (which are not composed of finished medical devices) should be reconsidered; if these pharmaceutical dosage forms are combination products then capsules, ointments, implants, depots, and suppositories would also be combination products.
  - passive transdermal patches
  - drug eluting disks