Regulatory Concepts for Dual Indication Combination Products

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Overview

- **Multipurpose Prevention Technologies (MPTs) defined as products integrating HIV prevention, contraception, and prevention of other sexually transmitted infections**

- **Presentation Outline**
  - **Regulatory terminology and MPTs**
  - **Regulatory perspectives**
    - **For co-developed products**
    - **For dual-indication products**
  - **Coordinating review within FDA**

Regulatory Terminology

- **Combination Product**
  - Includes product consisting of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product [21 CFR 3.2(e)]

- **Fixed-dose combination (FDC)**
  - Combination product with fixed drug doses for convenient administration
    - FDC consisting of two or more marketed drugs
    - FDC consisting of two or more unmarketed/investigational drugs which are being co-developed simultaneously

Regulatory Terminology

- **Dual Indication Product**
  - Product developed for the treatment or prevention of two diseases or medical conditions

- **Examples of Dual Indication Product**
  - **A single active agent with two indications**
    - Oral tenofovir approved HIV treatment and Hepatitis B treatment
  - **Combination of two active agents each individually effective for a separate indication**
    - Juvisync, a fixed-dose combination of sitagliptin and simvastatin
      - Approved for treatment of type 2 diabetes and hypercholesterolemia
      - Individual drugs were separately approved previously

Where do MPTs fall within this terminology?

- **MPTs are multi-indication products**
  - Dual indication if MPT prevents two conditions
- **MPT product could be either a combination product or a single agent**
  - Combination of two active agents: e.g., one microbicide drug plus one contraceptive drug

    or
  - Single active agent: e.g., one active drug with both microbicide and contraceptive effects

MPTs: Dual Indication Products

Combination Product

Two active agents are combined, each agent effective for an indication

Single Active

One agent effective for two indications

MPTs: Dual Indication Products

Combination Product
Two active agents are combined, each agent effective for a separate indication

- Both Agents are Investigational (Co-developed Product)
- Both Agents are Marketed
- Only One Agent is Marketed

Single Active
One agent effective for two indications

Regulatory Considerations for Co-developed Products

- **Available FDA guidances**
  - Co-development of Two or More Unmarketed Investigational Drugs for Use in Combination
  - Nonclinical Safety Evaluation of Drug or Biologic Combinations

- **Information necessary to justify the proposed combination**
  - Rationale supporting the proposed combination and dose
  - Animal toxicity data for separate drugs
  - Drug-drug interaction data, if applicable

Regulatory Considerations for Co-developed Products

- **Contribution of efficacy for each investigational agent should be demonstrated**

- **Some clinical safety considerations**
  - **For two or more unmarketed investigational agents**
    - Clinical safety of individual drugs usually characterized separately in phase 1
  - **If one component in combination is already approved**
    - Existing safety data for the approved component may be considered sufficient provided the same drug dose, formulation, delivery method is being developed in the combination product

Dual Indication Combinations: General Considerations

- **It is expected the development program will be designed to meet the current regulatory requirements for each indication**

- **Advice/input from different Divisions/Centers within FDA will often be necessary, each providing regulatory expertise for the specific indication**
  - E.g., for a microbicide-contraceptive combination, FDA experts in HIV and contraceptive fields will provide input

Dual Indication Combinations: Critical Considerations

- **Whether individual components are investigational or approved for the respective indication**
- **If investigational, is either drug approved as another formulation for the intended indication**
- **If both components already approved, will bioequivalence be sufficient to support efficacy**
  - Will depend on route of administration

Considerations for Microbicide plus HC Combination(1)

- **For example: Intravaginal ring impregnated with two drugs, a microbicide and a hormonal contraceptive (HC)**
  - Are the microbicide and HC approved individually as vaginal ring formulations?
  - If not, then are either approved for use as another vaginal formulation?
  - Is the vaginal ring (delivery device) previously approved as part of another marketed product?

Considerations for Microbicide plus HC Combination(2)

- **Other interactions between microbicide and HC**
  - Local cervicovaginal changes in mucosa, pH, flora which may affect drug absorption and safety profile
- **Are target systemic levels of contraceptive drug achieved?**
- **Chemistry and manufacturing issues e.g., ensuring appropriate drug release rates over time**
- **Evaluation of condom compatibility**

Coordinating Review within FDA

- **Depending on constituent parts, different FDA Centers are responsible for review**
  - Drugs (e.g., microbicides): Center for Drug Evaluation and Research
  - Biologic products (e.g., vaccine): Center for Biologics Evaluation and Research
  - Devices (e.g., condoms): Center for Devices and Radiological Health
- **Combinations may involve cross-Center review (e.g., drug/device or drug/biologic etc.)**
  - FDA Office of Combination Products assigns review jurisdiction
  - Guidance for In: How to Write a Request for Designation

Coordinating Review within FDA

- **For dual indication products, there is no primary or secondary indication designation**
- **For a single agent dual indication product, separate investigational new drug (IND) applications are encouraged for each development indication**
- **Developers are strongly encouraged to consult FDA early**
  - **Consultation can be requested in the pre-IND stage**

Conclusion

- **The FDA recognizes the public health significance of multipurpose prevention products for women**
- **The regulatory pathway for MPTs will be unique and product-specific**
- **The FDA encourages discussion for early in the development program**

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