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

• 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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