Challenges in Development of Combination Products for HIV Cure

FDA perspective
HIV Forum 1/25/2018
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FDA Center Assignment of a Combination Product*

- Three relevant FDA centers: CDER, CBER, & CDRH
- Office of Combination Products (OCP) assigns products based on:
  - Primary mode of action (PMOA) OR
  - When PMOA cannot be determined, an algorithm based on consistency and center expertise to evaluate safety and efficacy
- Cross-center consultations are frequent

*21 CFR 3.2 (e)
Co-development Two or More Unapproved Investigational Drugs for Use in Combination

Should ordinarily be reserved for situations that meet all of the following:

- Serious disease or condition
- Compelling biological rationale
- Agents cannot be developed individually
- Data suggesting that the combination may provide a significant therapeutic advance over available therapy and may be superior to the individual agents

CDER Guidance for Industry, June 2013
Phase 1: Early Human Studies of Two or More Unapproved Investigational Drugs for Use in Combination

- The safety and PK profile of each individual new investigational drug should be characterized in phase 1 studies.
- If there is a useful measure (e.g., biomarker) of pharmacologic activity, it will be important to determine dose-response for that measure.
- If testing in healthy volunteers is not possible, the safety profile of the individual drugs should be evaluated in patients with the disease of interest.
- These safety data will guide decisions in later studies about starting doses, dose escalation increments, and final dose selection.

CDER Guidance for Industry, June 2013
### Phase 2: Proof of Concept Studies of Two or More Unapproved Investigational Drugs for Use in Combination

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<tr>
<th>Scenario</th>
<th>Circumstances</th>
<th>Design</th>
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| 1        | • Each drug alone has activity  
          • Each drug can be administered individually | AB vs A vs B vs SOC* or placebo  
               (Standard factorial design) |
| 2        | • One drug is active  
          • One drug is inactive  
               (eg. PK enhancer) | AB vs A vs SOC or AB+SOC* vs A+SOC vs placebo + SOC* |
| 3        | • Components of the combination cannot be administered individually | AB vs SOC* |

*In the case of HIV Cure Studies, there is no SOC*  
CDER Guidance for Industry, June 2013
Development of combinations of approved investigational products for HIV Cure

• No specific FDA guidance
• Pre- and post-approval data (e.g., safety, DDI, etc.) helpful in establishing risk
• Design of proof of concept studies similar to those for unapproved drugs

CDER Guidance for Industry, June 2013
References & Resources

Office of Combination Products (CDER, CBER, and CDRH)
  • combination@fda.gov
  • Classification of Products as Drugs and Devices and Additional Product Classification Issues (Final Guidance), September 2017
  • How to Prepare a Pre-Request for Designation (Draft Guidance), January 2017
  • Current Good Manufacturing Practice Requirements for Combination Products (Final Guidance), January 2017

Center for Drug Evaluation and Research (CDER)
  • Codevelopment of Two or More New Investigational Drugs for Use in Combination (Final Guidance), June 2013
  • CDER Office of Antimicrobial Products Pre-IND Consultation Program website
  • CDERProductJurisdiction@FDA.HHS.GOV

Center for Biologics Evaluation and Research (CDER)
  • CBERProductJurisdiction@FDA.HHS.GOV
Organization of FDA
(Simplified for HIV Cure Forum)