FDA Regulatory Considerations for Codevelopment of Two or More New investigational Drugs for Use in Combination in NASH

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Disclosure Statement

• No conflicts of interest
• Nothing to disclose
• This talk reflects the views of the author and should not be construed to represent FDA’s views or policies
• A pediatric hematologist-oncologist by training; a regulatory expert in liver disease by design
Greetings from the FDA and DGIEP
Overview

• Definitions and Rationale
• Regulatory Framework for Drug Combinations
• Lessons Learned in other disease areas
  – Oncology Experience
  – Antiviral Experience
Focus of Presentation

• Two or more new drugs that have not been previously developed for any indication to be used in combination to treat a disease or condition

• Not intended to apply to development of fixed combinations of previously approved drugs or to development of a single new investigational drug

• Not intended to apply to development of combination products comprised of two or more different types of medical products (e.g., drug and device, drug and biological product, or all three together). (See 21 CFR Part 3)
• Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects

• The dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy

• Often factorial studies are needed to show the contribution of each component of a fixed-combination drug
Why Combinations?

- Multiple therapeutic targets to provide greater effectiveness than either ingredient alone
  - Either by having a greater effect for a single indication or by treating more than one indication
- Minimize adverse events
  - Having one active ingredient enhance the safety or effectiveness of another active ingredient
- Minimize development of resistance (more durable response)
- Patient convenience
- Facilitate compliance with a prescribed regimen
- Minimize the potential for abuse of an active ingredient

- Regulatory Concerns and Challenges:
  - Information on how each ingredient in a combination contributes to the effect of the combination is a fact “material” to the consequences that may result from customary use of that product
  - It is within FDA's authority to require testing as is necessary to establish the safety and effectiveness of ingredients used in combination
Qualifying Criteria

• Strong biological rationale for use of the combination

• A full nonclinical characterization of the activity of both the combination and individual new investigational drugs or short-term clinical study on established biomarker

• A compelling reason why the new investigational drugs cannot be developed independently
Stepwise Approach

• Determine whether co-development is an appropriate development plan
• Nonclinical codevelopment
  ➢ Demonstrate the biological rationale for the combination
  ➢ Nonclinical safety characterization (ICH M3, R2, S9)
• Clinical codevelopment
  ➢ Early human studies (Phase I): safety of individual drug, safety and dosing of combination
  ➢ Clinical Pharmacology: PK, bioavailability of each drug separately
  ➢ Proof of concept studies (Phase II): contribution of each drug in the combination and combination itself
    ❑ Dose finding prior to phase III: important to refine the combination dose or doses and select dose(s) for phase 3 trials
    ❑ Test multiple doses of both drugs for optimal combination- if one is more active than the other, multiple doses of more active drug
    ❑ Study multiple doses of drug to find which one is more toxic
  ➢ Phase III studies
    ❑ Design will be determined case-by-case based on effects of combination and individual drugs, the feasibility of monotherapy and SOC
### Scenario 1: each drug has activity, can be administered separately
- AB v. A v. B v. SOC or PBO
- AB+SOC v. A+SOC v. B+SOC v. PBO+SOC*

### Scenario 2: each drug cannot be administered separately
- AB v. SOC
- AB+SOC v. PBO+SOC*

### Scenario 3: one active and other inactive, can be administered separately
- A v. AB v. SOC
- AB+SOC v. A+SOC v. PBO+SOC*

*If SOC known effective therapy.
REGULATORY CONSIDERATIONS
Proposed Revisions to the Current Rule

• Existing regulations in subpart B of part 300 (21 CFR part 300) on prescription fixed-combination drugs being revised

• New provisions applicable to prescription and nonprescription fixed-combination and co-packaged drugs

• Harmonize requirements for prescription and OTC products and make them consistent with FDA’s long-standing policy

Proposed Revisions to the Current Rule (2)

- Specific evidentiary requirements must be met for approval
  - Ensures therapeutic purpose of all active ingredients, even those that might not be considered active ingredients in other contexts, is claimed
  - Amount and type of data and information needed may vary depending on a number of factors, including the therapeutic intent of the combination
  - Scientific justification for the testing and data that might be needed must be provided

- Sufficient evidence must be provided to demonstrate that product meets the requirements of § 300.53(a), including demonstrating:
  - The contribution of each active ingredient to the effect(s) of the combination
  - That combining the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients
Exceptions to the Rule

• For products which it would be infeasible or medically unreasonable or unethical to meet the requirements of the proposed rule:
  – Proposed § 300.60 would give FDA the authority to grant a waiver of some or all of the requirements of the proposed rule at the request of an applicant or interested person or on its own initiative

• Products such as whole blood, individual or pooled transfusible blood components (e.g., pooled platelets), pooled plasma products, and plasma derivatives from human or animal sources (e.g., immune globulins) would not be regarded as fixed-combination drugs
When Are Factorial Studies Needed?

• Generally the preferred design to support use of a combination
• Combinations, in which the effect of each active ingredient is directed at the same sign or symptom of a disease or condition (e.g., similar mechanisms of action):
  – Need to demonstrate that the combination has a larger treatment effect than one or more of the active ingredients alone
• Combinations in which one active ingredient is intended to:
  – Provide a direct effect that either potentiates or makes another active ingredient more tolerable
  – Minimize an adverse reaction associated with another active ingredient
  – The trial would have to establish enhanced safety or effectiveness of the combination versus the disease-active ingredient alone

• A factorial study is unlikely to be needed to demonstrate the contribution of each active ingredient in a combination where the active ingredients are directed at different signs or symptoms of a disease or condition or at different diseases/conditions:
  – Evidence that demonstrates that the active ingredients are effective individually and do not interfere with one another (e.g., pharmacokinetic data) may be adequate
  – Each component expected to have its usual, independent effect on a particular symptom/disease, and would not be expected to affect the other symptoms/diseases
Factorial Studies of Limited Utility

- Practical constraints on the use of a factorial design as the number of active ingredients in a combination increases

- The greater number of components in a combination, the greater number of comparisons needed to demonstrate each claimed effect

- At some point, a factorial study design may become infeasible

- Overall power of a factorial study equals ~ the power of the individual comparisons raised to the $n^{th}$ power where $n$ is the total number of comparisons
  - Each individual comparison in a factorial study should be sufficiently powered so that the overall power is at least 80 percent
Barriers to CoDevelopment

• Demonstration of individual contribution

• Less information about clinical safety and effectiveness and dose-response of the individual new investigational drugs

• Lack of flexibility in adjusting the dosage of each active ingredient to an individual patient's needs

• Possibility of overexposure, or unnecessary exposure to a particular active ingredient
LESSONS LEARNED

Oncology Experience - Food for Thought
• Combinations of targeted agents a high priority
  – Resistance to initially effective single agents often develops quite rapidly in many adult tumors
  – More than 100 combination trials initiated since 2000
  – Facilitated by the Intellectual Property (IP) language in CTEP*-industry agreements

• Molecular-targeted effects:
  – Mechanism of Action/Proof of Principle
  – Biomarker assessment and evaluation, assay development and qualification

*The Cancer Therapy Evaluation Program (CTEP) coordinates the clinical therapeutics development program of the Division of Cancer Treatment and Diagnosis, National Cancer Institute (NCI)
Why does CTEP/NCI do combinations of novel agents?

- Molecularly targeted combination studies are the future of personalized medicine
- Combination strategies are critical to improving therapeutic outcomes
  - Rational combination of agents
  - Properly selected patient population
- Trials designed to maximize inhibition of a critical target or target multiple cellular pathways in cells
  - Tumor cell eradication
- NCI uniquely positioned to perform novel agent combination trials by overcoming regulatory, intellectual property, and risk aversion hurdles because of its extensive collaborations with industry and academia
- CTEP’s Regulatory Affairs Branch (RAB) is focused on:
  - Developing partnerships with industry and academics that allow for co-development of novel therapeutics and on assuring that CTEP meets all its regulatory responsibilities with the FDA regarding INDs
  - Facilitating interactions between the FDA, NCI, and Industry
  - Coordinates FDA-NCI Monthly Meeting with the FDA Oncology Director and staff
    - Discuss issues of common interest related to oncology drugs and their approval, with the ultimate goal of streamlining drug development
CTEP Activities

- Preparation and submission of Investigational New Drug Applications (INDs)
- Review of protocols/protocol amendments
- Liaison with FDA, intramural and extramural investigators, pharmaceutical companies
- Preparation of agreements (CTAs and CRADAs) for clinical development of agents
- Coordination of company interactions with NCI and investigators
- Preparation of MTAs for basic research with investigational agents in clinical trials

https://ctep.cancer.gov/about/default.htm
Antiretroviral Experience
Historical Perspective

Treatment Timeline

- Mono-therapy
- Combo NRTI intro
- PIs and NNRTIs use (HAART)
- New classes – entry, INI

Timeline:
- 1983: AZT, ddI, ddC, d4T, 3TC, SQV
- 1987: RTV, IDV, NVP
- 1991: EFV
- 1992: APV, LPV/R, TDF
- 1994: T-20, FTC, ATV, F-APV
- 1995: TPV
- 1996: DRV, MVC
- 1997: FTC, TDF
- 1998: ETV, RAL
- 1999: FTC, TDF
- 2000: FTC, TDF, EFV
- 2001: FTC, TDF
- 2002: FTC, RPV, TDF
Antiretroviral Combination Experience

• Biologic rationale to target different metabolic pathways or different steps in the replication cycle of the pathogen

• All currently available combinations approved on basis of bioequivalence of the combination to individual component drugs taken together, after approval of all individual drugs

• Existing data from approved drugs used to demonstrate the contribution of the individual active ingredients including clinical data on use of the individual ingredients in a combination, in clinical pharmacologic data, and in nonclinical data

• New clinical data would ordinarily be needed only to demonstrate that the bioavailability of the fixed-combination drug is comparable to that of the active ingredients administered individually
Conclusions

• Fixed-drug combinations of new investigational products present a challenge because individual components are not well-characterized

• Development is inherently more complex and requires studies to characterize not only the combination, but also the individual agents to the extent necessary and feasible

• Early engagement with FDA is critical:
  – Consult on the appropriateness before initiation of clinical development of a combination and as needed throughout development process
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