FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Regulatory Considerations for

Codevelopment of Two or More New investigational Drugs for Use in Combination in

NASH

Stephanie O. Omokaro, MD
Division of Gastroenterology & Inborn Errors Products (DGIEP)
U.S. Food and Drug Administration (FDA)
Center for Drug Evaluation and Research

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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)

21 CFR 300.50

Fixed Combination Prescription Drugs for Humans

- 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

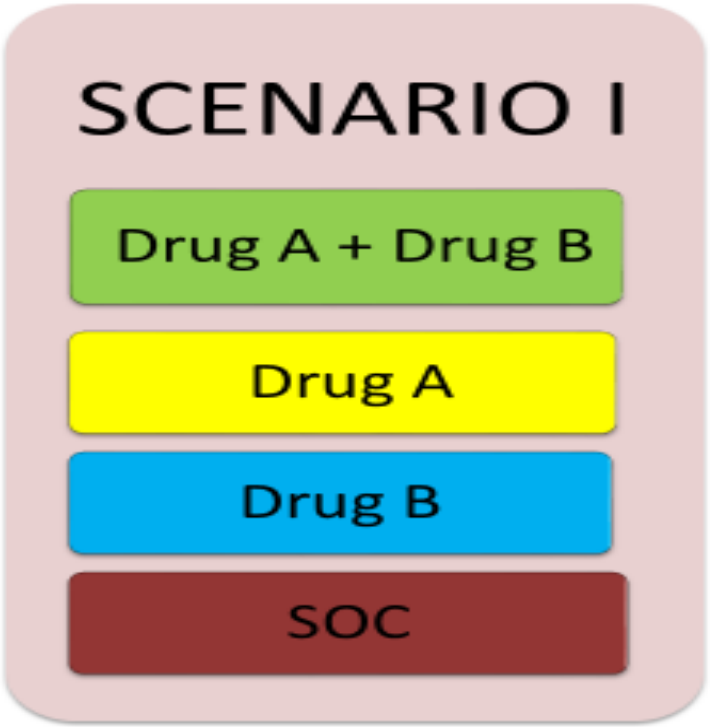
- Regulatory Concerns and Challenges:
  - Information on how each ingredient in a combination contributes to the effect of the combination is a fact "material" to the consequences that may result from customary use of that product
  - It is within FDA's authority to require testing as is necessary to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

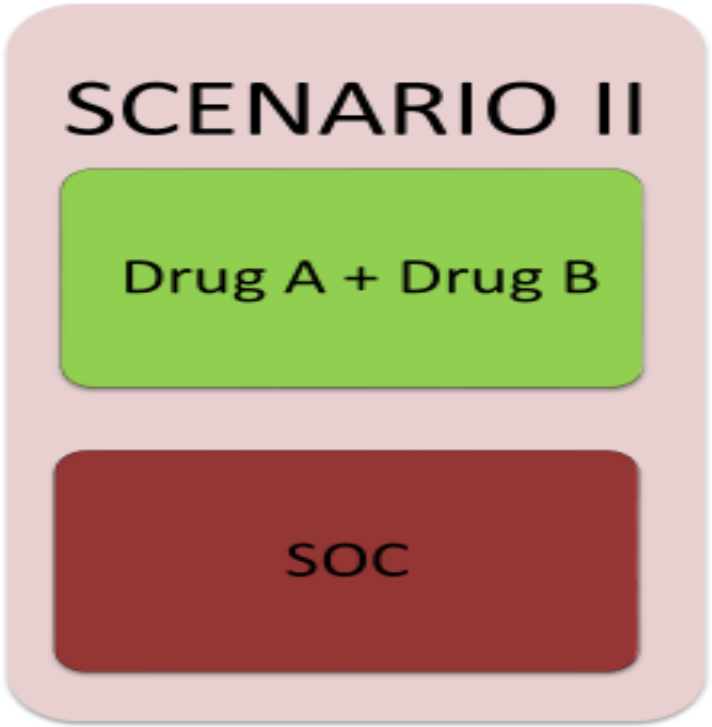
Qualifying Criteria

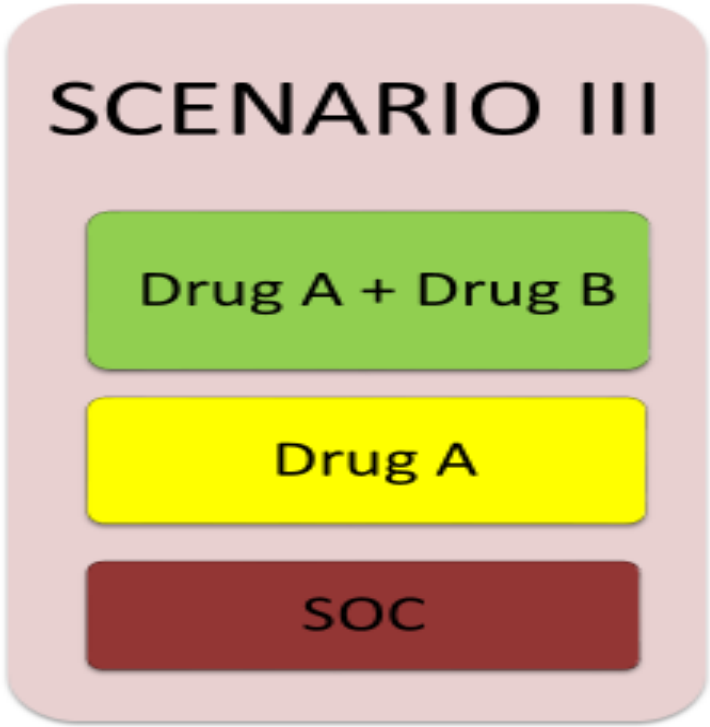
- Strong biological rationale for use of the combination
- A full nonclinical characterization of the activity of both the combination and individual new investigational drugs or short-term clinical study on established biomarker
- A compelling reason why the new investigational drugs cannot be developed 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

https://www.federalregister.gov/articles/2015/12/23/2015-32246/fixed-combination-andco-packaged-drugs-applications-for-approval-and-combinations-of-active

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 transfusable 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

Oncology Experience

- 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

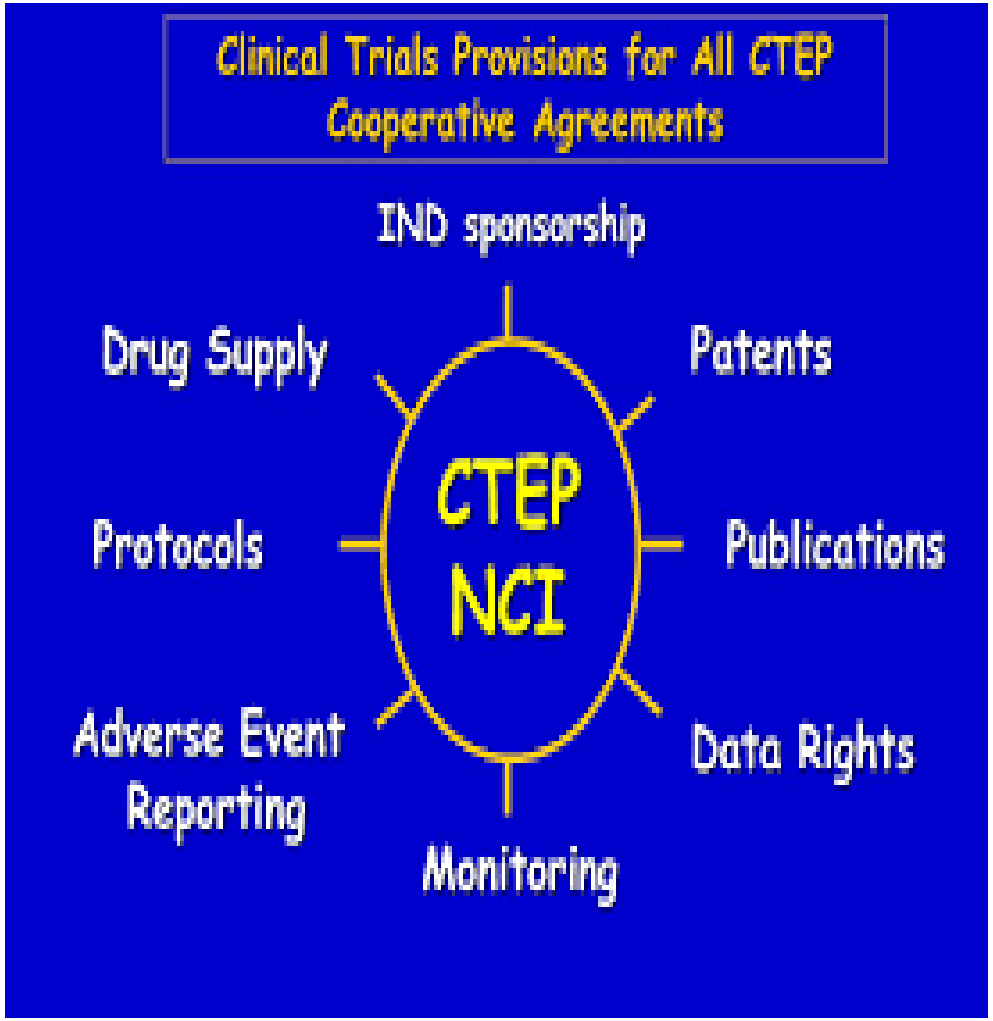
*The Cancer Therapy Evaluation Program (*CTEP*) coordinates the clinical therapeutics development program of the Division of Cancer Treatment and Diagnosis, *National Cancer Institute (NCI)*

NCI/CTEP Approach

- 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

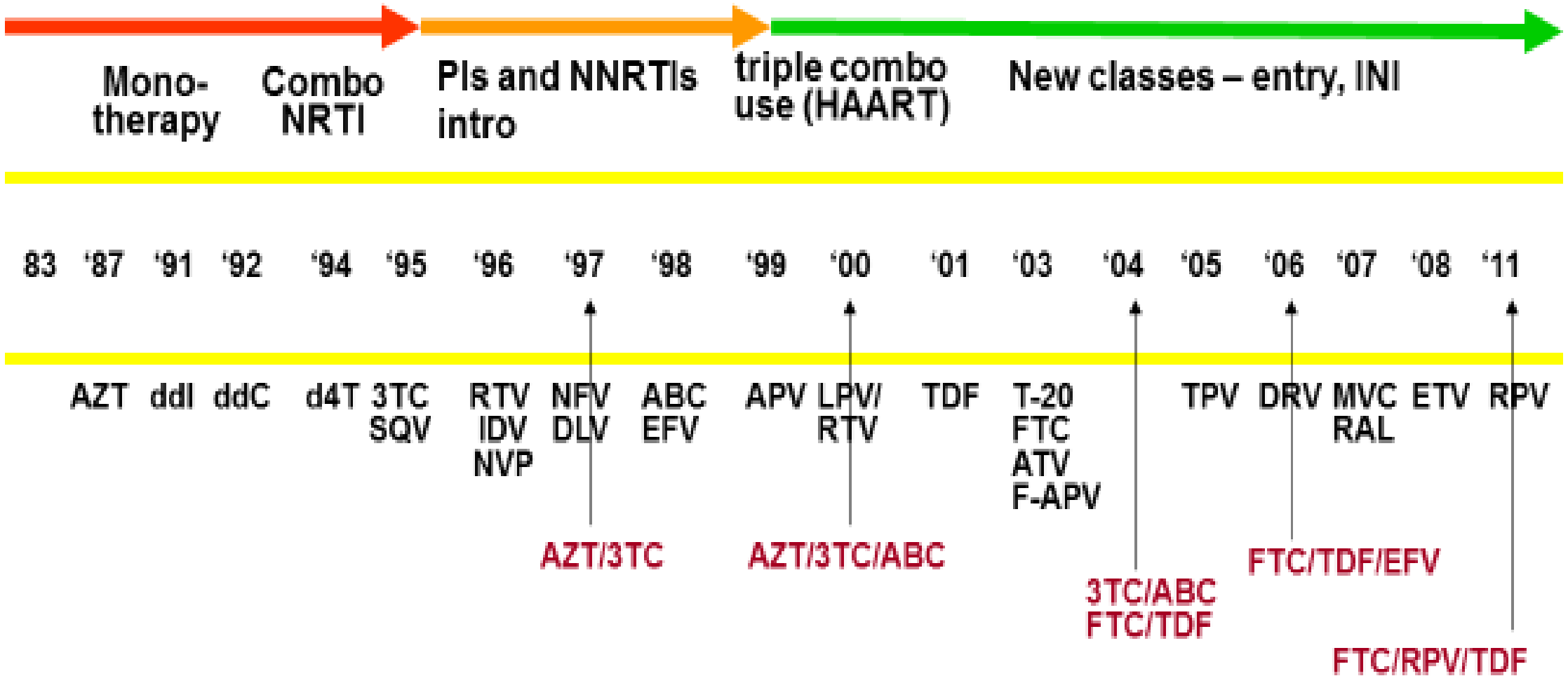


https://ctep.cancer.gov/about/default.htm

Antiretroviral Experience

Historical Perspective

Treatment Timeline



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
  - https://www.federalregister.gov/articles/2015/12/23/2015-32246/fixed-combination-andco-packaged-drugs-applications-for-approval-and-combinations-of-active

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THANK YOU


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