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Approach to Combination Products for Non-Alcoholic Steatohepatitis (NASH)

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Conflict of Interest and Disclaimer Statement

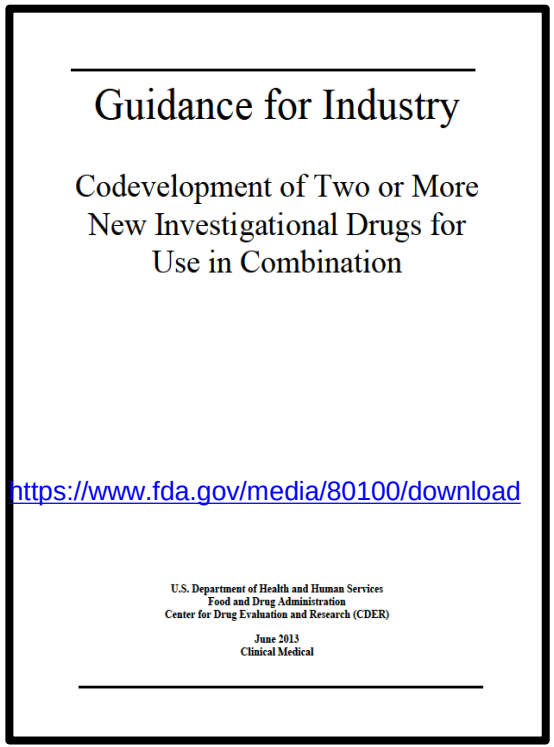
I have no financial disclosures regarding pharmaceutical drug products. I have no conflicts of interest related to my presentation.

Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.

Outline

- Guidances for combination product development
- Possible drug-drug combinations for treatment of NASH
- Fixed Combination Rule 21 CFR 300.50
- Regulatory guidance for combination product development for two non-approved investigational drugs for NASH.
- Non-clinical considerations for developing two non-approved drugs for NASH
- Clinical approach to development of two non-approved drugs for NASH.
- A few words about bi-specific antibody and bi-specific protein development

Guidance Documents Used to Develop This Presentation



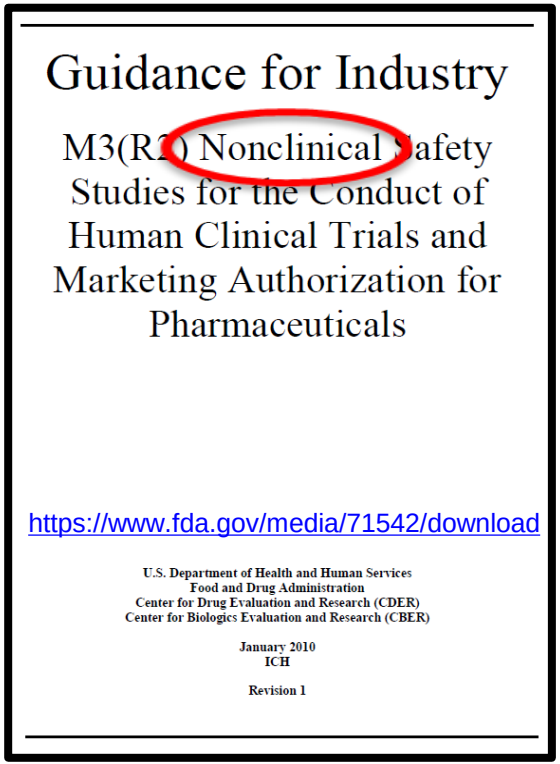
Guidance for Industry

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

https://www.fda.gov/media/80100/download

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2013
Clinical Medical



Guidance for Industry

M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

https://www.fda.gov/media/71542/download

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2010
ICH

Revision 1

https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types

Combination Product Definition Combination Product Types

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Combination products are defined in 21 CFR 3.2(e). The term combination product includes:

1. A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Combination Product Types

What are some examples of combination products?

Examples of single-entity combination products (where the components are physically, chemically or otherwise combined) (21 CFR 3.2(e)(1)):

- Monoclonal antibody combined with a therapeutic drug
- Device coated or impregnated with a drug or biologic
  - Drug-eluting stent, pacing lead with steroid-coated tip, catheter with antimicrobial coating, condom with spermicide, transdermal patch
- Prefilled drug delivery systems (syringes, insulin injector pen, metered dose inhaler)

Examples of co-packaged combination products (the components are packaged together) (21 CFR 3.2(e)(2)):

- Drug or vaccine vial packaged with a delivery device

What are possible combinations in developing drugs to treat NASH?

- Two drugs previously approved for an indication other than NASH.
- One investigational drug paired with a drug that has been previously approved for an indication other than NASH.
- Two new investigational drugs that may or may not have a separate indication for NASH
- There are other ‘combinations’ that do not meet the same regulatory statutes of drug-drug combinations, e.g., bi-specific antibodies, bi-specific protein products.

21 CFR § 300. 50 Fixed Combination Rule

- Under 21 CFR 300.50, also known as the “combination rule”, sponsors must show that each component of a combination makes a “contribution to the claimed effects” and that 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 as defined in the labeling of the drug.”

Co-Development of two or more new drugs

This guidance is intended to assist sponsors in the codevelopment[2] of 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. For purposes of this guidance, these not-previously-developed drugs are referred to as *new investigational drugs*. The guidance provides recommendations and advice on how to address certain scientific and regulatory issues that may arise during codevelopment of two or more new investigational drugs. It is not intended to apply to development of fixed combinations of previously approved drugs or to development of a single new investigational drug to be used in combination with a previously approved drug or drugs. FDA believes the recommendations in this guidance relevant to demonstrating the contribution of the individual new investigational drugs to the effect(s) of the combination are consistent with the requirements of 21 CFR § 300.50, "fixed-combination prescription drugs for humans." This guidance applies only to drugs and biological products regulated by the Center for Drug Evaluation and Research.[3] The guidance is not intended to apply to biological products regulated by the Center for Biologics Evaluation and Research or medical devices.

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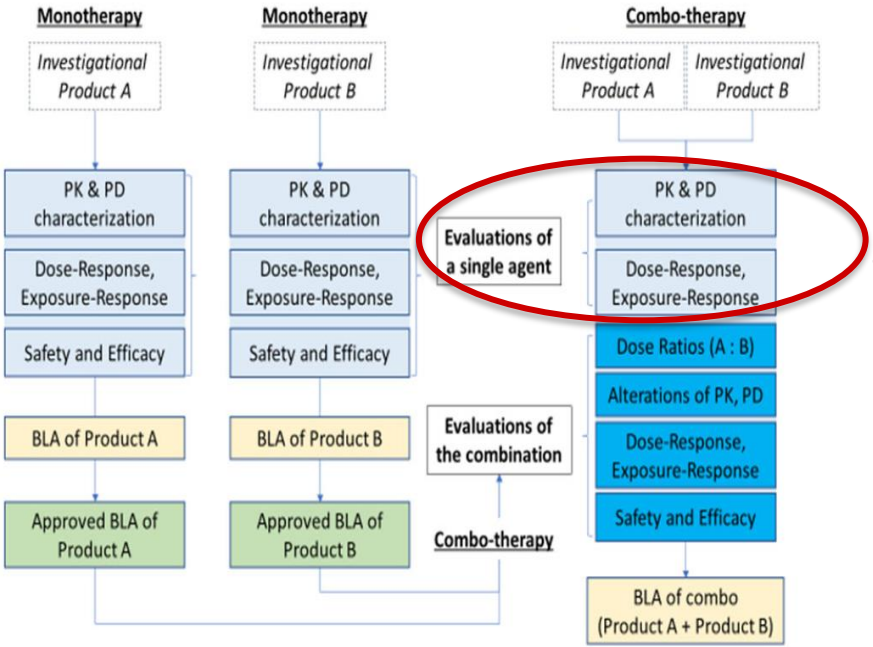
[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] The term *codevelopment* as used in this guidance refers to the concurrent development of two or more new investigational drug products that are intended to be used in combination to treat a disease or condition. A sponsor may elect to codevelop two or more new investigational drug products to be marketed as individual agents intended to be used in combination as a fixed-combination or co-packaged drug.

Non-Clinical Considerations for Combination Drug Development of Two New Investigational Products



(1). The biological rationale can be supported by in vitro or preferably in vivo animal models demonstrating that the combination has substantial activity and provides greater activity, a more durable response, and/or a better toxicity profile than the individual new investigational drugs.

(2). For combinations of two early-stage entities, nonclinical combination toxicity studies are recommended to support clinical trials. *Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*

Source: Zheng S, Prell R, Sheng J, Wang YM, Hamuro L. Changing the Drug Development and Therapeutic Paradigm with Biologic Drug Combinations and Bispecifics: How to Choose Between These Two Approaches? *Clin Transl Sci.* 2022 May 25. doi: 10.1111/cts.13345. Epub ahead of print. PMID: 35611545.
*see ICH M3(R2)

Sponsor Rationale for Co-Development of Two Investigational Agents

1. The combination is intended to treat a serious condition.

2. There is a strong biological rationale for use of the combination, e.g., the agents target complementary parts of the same molecular pathway or steps in the disease pathogenesis.

3. A full non-clinical characterization of the activity of both the combination and the individual new investigational drug(s), or a short-term clinical study on an established biomarker, suggests that the combination may provide a significant therapeutic advance and is superior to the individual agents alone.

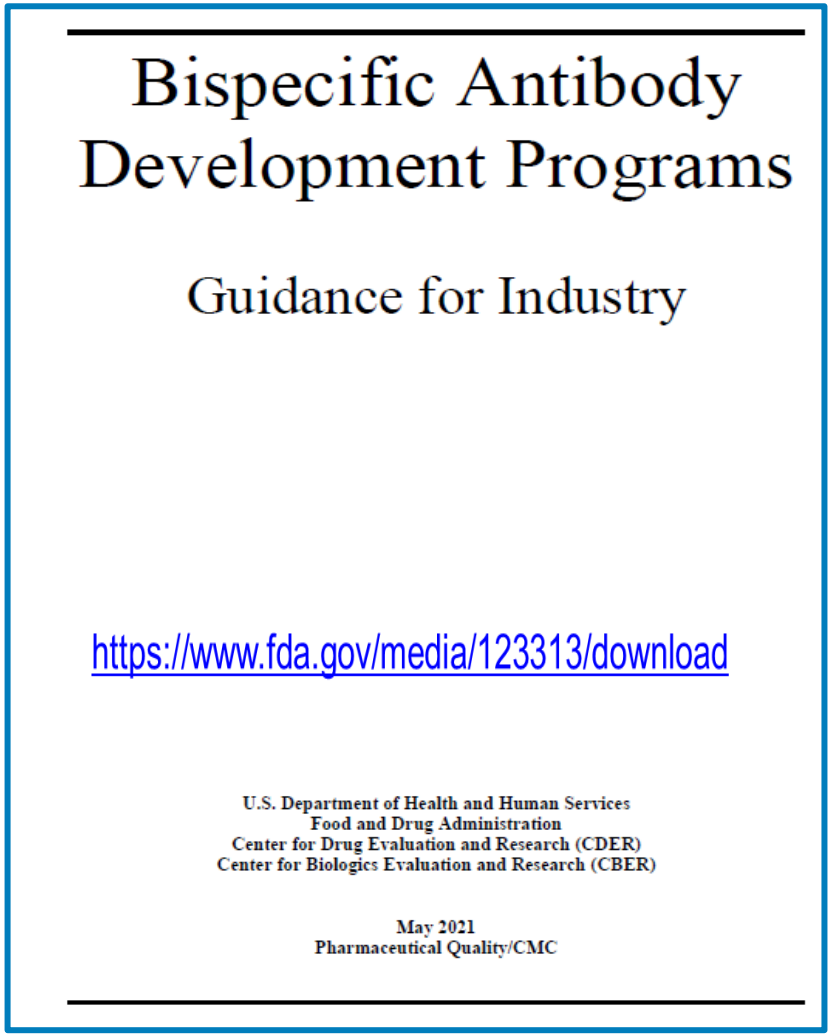
4. Provides a compelling reason why the new investigational agents cannot be developed independently (i.e., why monotherapy for the disease leads to very limited activity but potential for greater activity when used in combination).

Clinical Development (Phase 2)

- Demonstrate the contribution of each individual new investigational drug in the combination to the extent possible and needed (to the extent not sufficiently established by existing data).
- Provide evidence of the effectiveness of the combination.
- Optimize the dose or doses of the combination to carry forward for phase 3 trials.
- A factorial study designed to assess the effects attributable to each drug in the combination is generally the preferred design to support combination use.

Clinical Development (Phase 3)

Phase 3 trial design can be developed on a case-by-case determination with the Agency based on what has been previously demonstrated for the new investigational products.


Bispecific Antibody Development Programs
Guidance for Industry
https://www.fda.gov/media/123313/download
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Pharmaceutical Quality/CMC

Development of Bi-specific Antibodies or Bi-specific Proteins

1. Antibodies bridging two target cells, i.e., designed to bring immune effector cells in close contact with tumor associated antigens to facilitate cell killing. Proteins that bind two or more complementary receptors.

2. Antibodies or proteins engaging two different targets to mimic function of endogenous protein(s) and in some cases binds the same target to enhance efficacy.

3. FDA's regulation on fixed-combination prescription drugs for humans (21 CFR 300.50) ***does not*** apply to the development of these products, which are considered single molecules.

4. The agency anticipates "..scientific rationale, …mechanisms of action, increased safety and/or efficacy as compared to similar monospecific products to support bispecific antibody development can be derived from data that will depend on a particular situation and could potentially be derived from clinical or animal studies or *in vitro* assays. FDA encourages sponsors to consult with FDA if they wish to use a non-animal testing method".


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