

Combination Drugs: Regulatory Guidance and Expectations

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- This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

Objectives

- Review Guidances related to Combination drug development.
- Review the concept of “bridging studies”.
- Examples of combination drug programs in which nonclinical (NC) studies were requested.

Guidance: Nonclinical Safety Evaluation of Drug or Biologic Combinations

- Most pertinent FDA guidance (2006)
 - Does not pertain to oncology, botanical and antiviral products
- EMA
- ICH M3R(2)

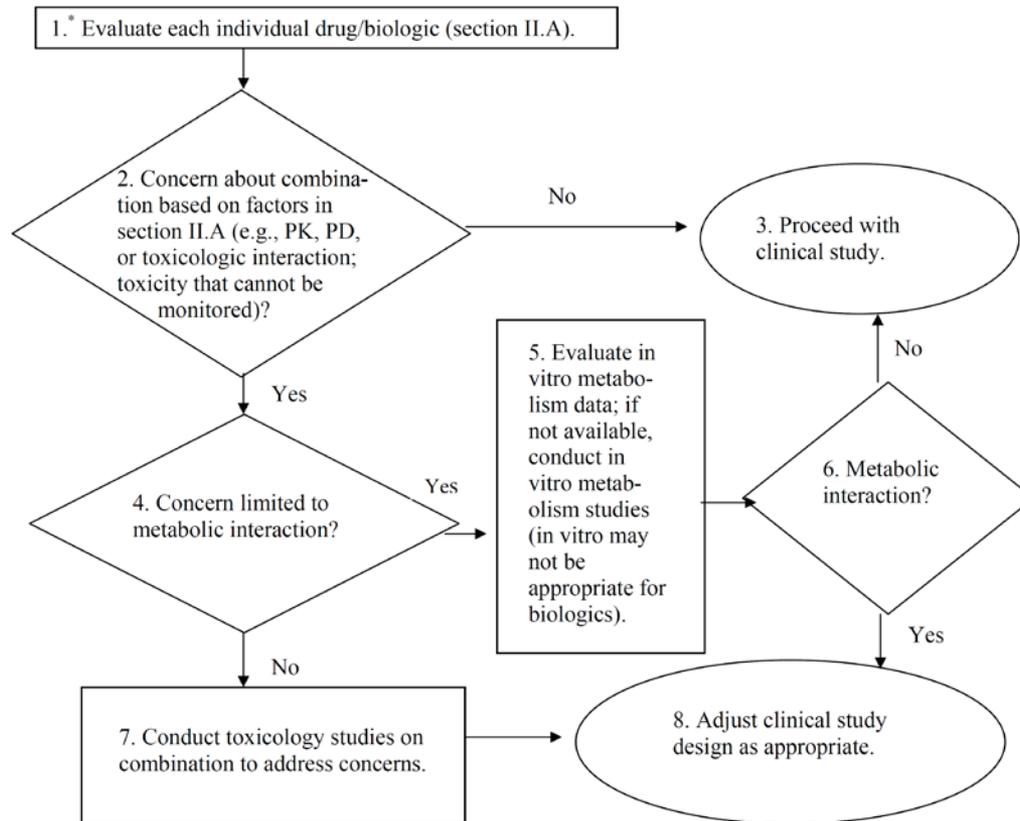
FDA Guidance

- “Nonclinical Safety Evaluation of Drug or Biologic Combinations”
- Three paradigms:
 - 2 or more approved drugs
 - At least 1 New Molecular Entity (NME)
 - Both NME’s

Paradigm 1

2 or more approved drugs
(no NME's)

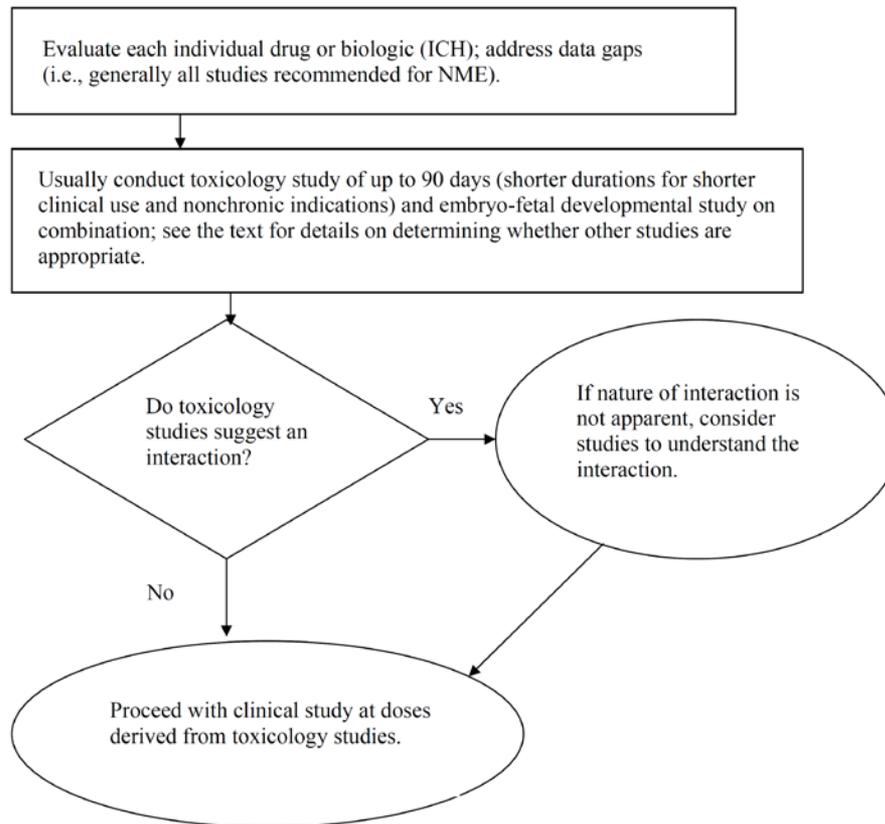
Paradigm 1



Paradigm 2

- At least 1 NME

Paradigm 2



Paradigm 3

- Where 2 NME's are combined
- Evaluate each separately
- Then perform a 90 day general tox study and embryo-fetal study with combo.
- Safety concern?
 - If no, proceed with clinical study derived from tox studies.
 - If yes, is the concern about metabolism? If yes, then conduct clinical PK study.
 - If no metabolic safety concern, might have to conduct general tox study with combo.

EMA: Guideline on the Non-clinical Development of Fixed Combinations of Medicinal Products

1. When developing a fixed combination the non-clinical program will vary depending on the characteristics of the single components, on the existing non-clinical and clinical experience of their individual and concomitant use as well as the intended clinical use.
2. *When there is no experience from use of the combination, even if the individual components are known, bridging studies addressing expected and potential unexpected pharmacodynamic, pharmacokinetic and toxicological interactions are in principle needed.*
3. For any non-clinical combination study, the dose selection should be based on considerations of interspecies differences in pharmacokinetics as well as pharmacodynamics in order to, as close as possible, encompass the clinical situation, both in terms of systemic exposure of animals to the individual components as well as in relation to pharmacodynamic effects while avoiding highdose non-clinical effects that may be irrelevant to human safety assessment.

ICH M3 R(2)

1. For 2 early-stage entities, NC combination toxicity studies are recommended to support clinical trials.
2. Provided complete NC development programs are being conducted on the individual entities and a NC combination toxicity study is warranted to support combination drug trials, the duration of the NC combination toxicity study should be equivalent to the duration of the clinical trial, up to a maximum of 90 days. This study would also support marketing.

ICH M3 R(2)

3. Two late-stage products without adequate clinical experience administered together: NC studies not needed for short-duration clinical studies (i.e., phase 2 study), but NC studies are needed for long-term clinical studies of the combination as well as for marketing

4. NC combination studies should be of equivalent duration of the clinical trial up to a maximum duration of 90 days in 1 relevant species. This study would also support marketing.

ICH M3 R(2)

5. In combinations where there is one early-stage entity with clinical experience combined with a late-stage entity (that has little toxicological concern), NC toxicity studies are not recommended to support proof of concept studies up to 1 month duration.

6. The clinical study of the combination should not be longer than the clinical experience of the individual entities. Later stage or longer duration clinical combination studies should be supported by a NC combination toxicity study.

Bridging studies

- Explanation
- Examples (2)
- Triple combo
- Heterodimerization example

Bridging Explanation

- Generally, the FDA recommends that sponsors conduct nonclinical toxicity studies before clinical studies are initiated if: (1) the drug products have similar target organ toxicity or PD activity; and (2) either drug product causes serious or nonmonitorable toxicity in animals or humans at exposures near the clinical exposure; or (3) any other reason exists for serious clinical concern. For assessment of general toxicity, a **bridging study** may be appropriate, provided the duration is sufficient to elicit the toxicity of concern. For example, a general toxicity bridging study of 3 months' duration could be considered for a chronic indication

Bridging example 1

- Triple combination
- All 3 drugs had been approved
- Two were approved by a different division
- Decision to ask for a 3 month bridging study and an embryo-fetal developmental toxicity study in one appropriate species. These will be needed to support the phase 3 clinical trial.

Bridging study 1, ctd.

- Rationale: Although all 3 drugs had been approved, there were concerns regarding potentiated toxicity of one of the components and potential DDI's. Also, the combination would be given chronically for this indication. Not all of the components were approved for chronic administration.

Bridging example 2

- Receptor heterodimerization
- Both drugs were approved, but there was a unique interaction between the receptors to which both drugs bound.
- Stimulation of 1 of the receptors could activate the other receptor.

Bridging example 2, ctd.

- This possibility could lead to a potentiation of the PD and toxic effect when both drugs administered simultaneously.
- Chronic indication, so 3 month general toxicology study and embryofetal development study (1 species) were requested.

Non-traditional Combinations

- Diastereomers
- Device/drug?
- Biologics
- Botanicals

Diastereomers-Labetalol

- Has 2 chiral carbons
- Exists as 4 stereoisomers
- Two inactive (S,S) and (R,S)
- Two active:
 - (S,R) potent alpha-1 blocker
 - (R,R) blocks alpha-1 and beta-1,2 receptors

Labetalol, ctd.

- Approved as all 4 stereoisomers together
- In retrospect, review of the 2 active stereoisomers have revealed different toxicities.
- Diastereomers are different NME's

Drug/Device

- How would an approved device be handled in OND when combined with a drug?
- Previous experience with CV drug-eluting stents (stents with tacrolimus, etc.) to reduce restenosis.

Drug/device

- What about other combinations of drugs with inert material?
- If one center deems it inert, there is no guarantee that another center will not request NC studies to assess combination toxicity.

Botanicals

- Many botanicals are based on Traditional Chinese Medicine (TCM) where combinations are the norm.
- In most cases, since herbs are almost always given in combination with other herbs, testing the herbs individually is not generally performed.
- New botanical guidance published Dec. 2016:
Botanical Drug Development: Guidance for Industry

Drug A/Drug B

- One of the drugs was an NME
- In one program, chronic toxicology studies and repro toxicology studies were performed with the NME alone and with the combination.

Continued

- Impact of combining the drugs was unclear.
- The effect of Drug A on reproductive toxicology is well established. No carcinogenic effects were observed with Drug B alone.

Summary

- Even with Guidances and years of experience, no two combination applications are the same.
- The amazing array of potential combinations make the regulatory approval process more complex than it appears on the surface.

Conclusion

- With any program, it is imperative to contact the appropriate division for guidance.

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