Strategies in Designing Clinicals for Fixed-Combination Drugs

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Our Objectives Today

• Understand how FDA has applied the Combination Drug Policy in decisions on requirements for pivotal – efficacy &/or safety -- trials for a sampling of combination drugs

• Learn to approach developing clinicals for fixed combinations that focuses on the unique aspects of each formulation; not rote adherence to the factorial model

• Learn how to solve for “X” in 2 * 2 = X
From Regulation to Policy

• **21 CFR 300.50** – a regulation; thus, has the force and effect of law

• But, a FDA regulation need not involve a specific legal requirement. Under 21 CFR 10.90(a):
  – “FDA regulations are promulgated in the Federal Register under § 10.40 or §10.50 and codified in the Code of Federal Regulations. Regulations may contain provisions that will be enforced as legal requirements, or which are intended only as guidelines and recommendations, or both.”

• 21 CFR 300.50, by its express words, is a “policy”
21 CFR 300.50 – Regulation = Policy

• The Food and Drug Administration`s policy in administering the new-drug, antibiotic, and other regulatory provisions of the Federal Food, Drug, and Cosmetic Act regarding fixed combination dosage form prescription drugs for humans is as follows: …
• (a) Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and 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 for the drug. Special cases of this general rule are where a component is added:
  – (1) To enhance the safety or effectiveness of the principal active component; and
  – (2) To minimize the potential for abuse of the principal active component.
OTC Combinations

21 CFR 330.10(a)(4)(iv)

- An OTC drug may combine 2+ safe and effective active ingredients and will be generally recognized as safe and effective ("GRASE")
  - when each active makes a contribution to the claimed effect(s);
  - when combining the actives does not decrease the safety or effectiveness of the individual actives; and
  - when the combination, as used under adequate directions for use and warnings, provides rational concurrent therapy for a significant proportion of the target population
Default Policy – The Factorial Study

• Classic combination study – factorial approach to determine # of arms
  – Not specifically required under 21 CFR 300.50

• However, no where (that I could find) is the factorial approach articulated “in stone”

• If we examine other FDA reference sources, we see flexibility is either overt or clearly inferrable

• And, flexibility is also clear from examining how FDA has applied the Combination Policy
“The making of regulatory judgments on combination drug products is an exercise in logic, requiring knowledge of the law, Food and Drug Administration policy, and the clinical data on the drug….

As in any intellectually alive institution, ideas are tested through free debate in conferences and meetings before important decisions are reached. We attempt to live by policy, and not personal whim, and this is particularly true in an area as sensitive as fixed-combination drug.”


Flexibility in Combination Policy …

• “But the factorial study, the factorial analysis strictly doesn't really address the combination question, because it could be driven by the aspirin alone component and the dipyridamole alone component.…

So, it is the pairwise comparisons, that is, the combination versus A and the combination versus B, that is the most relevant to the combination policy. We have had these conversations for 30 years.”

Dr. Robert Temple, FDA, before the Peripheral and Central Nervous Drugs Advisory Committee, April 28, 1998, Transcript at 160-161. (Emphasis added)
Flexibility in Combination Policy …

• “Generally speaking, the Division has required for fixed dose combination antihypertensive products that the effects of the combination (A + B) be greater than the effects of either one alone (A or B). Moreover, the effects of several doses of A in combination with several doses B be evaluated (often in a factorial trial) so that some description of the use of A+B can be compared with either A or B alone.”

“DR. LIPICKY: Just one more thing to add. I guess I really would like to see, at least in the hypertension area, dose-ranging trials not be called phase II anything. They are phase III. That is the basis of approval. You really have to discard this business of phase I, phase II, phase III. It is where that thing fits in the necessity for getting approved. So, the program in its entirety I think is a different issue, but a dose-ranging trial can be considered phase III, is phase III, and is actually phase III for a combination product. It is the only trial that is required.”

– Cardiovascular And Renal Drugs Advisory Committee, October 20, 2000, Transcript, p. 177. (Emphasis added)
Flexibility in Combination Policy …

• “….Special cases of this general rule [the Combination Policy in 21 CFR 300.50] are where a component is added: (1) "To enhance the safety or effectiveness of the principal active component..." This regulation suggests that each of the components of a fixed combination regimen needs to contribute to the overall efficacy of the combination. Although drug combinations for \( H. pylori \) are not "fixed", factorial designs are recommended by the Division to ensure that each component contributes to overall efficacy. Since factorial designs may induce some complexity to \( H. pylori \) study designs, "modified factorial designs" may be considered in certain situations:
   
   – (1) when \( H. pylori \) resistance has been shown to develop in association with antibiotic monotherapy (making monotherapy unethical) and,
   
   – 2) when eradication rates for single agents have been well documented in the literature. It is suggested that sponsors discuss appropriate factorial designs with the Division during protocol development.”

• Points to Consider – Clinical Development and Labeling of Anti-infective Drug Products, March 1995 Addendum -- *Helicobacter pylori*-Associated Peptic Ulcer Disease -- Indication #25
(Emphasis Added)
Flexibility in Combination Policy …

• When evaluating combination vaccines, CBER’s guidance for industry on combination vaccines recommends that clinical trials compare the immune responses elicited by the combination vaccine versus separate injections, and that these trials be conducted to demonstrate non-inferiority of the combination vaccine.


http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3586b1o.pdf
• **CBER will give special consideration to alternative proposals for demonstrating the efficacy of multiple serotype combination vaccines, where determining efficacy of the vaccine against each serotype may be difficult.**
  
  – Studies designed to demonstrate efficacy for such vaccines could be based upon epidemiologic data regarding the disease incidence of each serotype in the target population. Thus, while the primary endpoint may be the aggregate of disease with all serotypes included in the vaccine, the study should be of sufficient size to allow meaningful subgroup analysis of protection against at least some individual serotypes.
  
  – For multiple serotype vaccines where clinical efficacy can not be demonstrated due to an insufficient number of homologous cases, efficacy may sometimes be inferred from immunogenicity data.
    
    • This use of immunogenicity data is strengthened if a serological correlate(s) of protection was identified for the serotypes for which clinical efficacy was demonstrated. Supporting immunogenicity data for such less common serotypes should be comparable to that elicited by heterologous serotypes for which clinical efficacy was demonstrated.
    
    • Functional assays comparing the immune response elicited by the various serotypes may be especially useful in this regard. In all such cases, CBER encourages an early consultation regarding such issues.
Flexibility – Other Indicia

• 505(b)(2) Policy – October 14, 2003 Letter denying Pfizer/Pharmacia petition on 505(b)(2) NDAs

Precisely what additional data will be necessary for approval of a drug will vary from case to case and is generally the subject of discussion between the sponsor and FDA during the drug development process. For example, a 505(b)(2) application for a new dosage form (such as a transdermal patch or a novel drug delivery mechanism) that cannot be approved as a petitioned ANDA — because clinical studies are necessary to demonstrate safety and/or effectiveness — must contain whatever data are necessary to demonstrate that the new dosage form is safe and effective to treat the indications approved for the listed drug. Similarly, approval of a drug product for a new indication with the same strength and dosing regimen as a previously approved drug product will require evidence establishing that the drug is effective for the new indication. But new safety information may not be necessary because the underlying drug has already been shown to be safe at the approved dosing level. Thus, the nature and extent of the reliance on the agency's conclusion of safety and effectiveness for a listed drug are the same for applicants under section 505(b)(2) and 505(j); it is only the amount of additional data necessary to support the approval of the proposed drug product that may differ.
Eloxatin® (oxaliplatin)
Sanofi Synthelabo

• Accel. Approv. (clinical benefit not established) in combination with infusional 5-FU/LV, is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and irinotecan.

• Studies – no placebo arm
## Oxaliplatin (Recurrent) (accelerated approval)

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The Policy in Action – Arthrotec®

- Diclofenac sodium/misoprostol Tablets
- Clinicals here
  - D + M vs. D
  - D + M vs. Placebo
  - No arm vs. M alone
- Reason – not discernible – but use of M alone arm may have been viewed as not adding to the knowledge as the key here was in reduction of ulcers with NSAID use
The Policy in Action – Arthrotec® …

• Bioequivalence studies for bridging:

3. Dr. Neuner summarized the following conclusions from her review of Arthrotec efficacy:

A. Study 349 provides support for the efficacy of Arthrotec in the treatment of OA. Arthrotec 50 TID and Arthrotec 75 BID showed efficacy similar to diclofenac 75 BID and all three showed efficacy superior to placebo. This trial supports the use of Arthrotec only for patients using diclofenac 150mg daily.

B. The use of Arthrotec for the treatment of RA is not supported by this application. Study 352 failed to demonstrate that diclofenac 75mg BID, Arthrotec 50 TID and Arthrotec 75 BID showed efficacy superior to placebo. The four remaining RA studies utilized flawed designs.

4. If bioequivalence is established between the Arthrotec formulation proposed for marketing and Voltaren, however, it will be unnecessary to re-prove efficacy with clinical studies, so that reservations described in the preceding paragraph will not be of consequence.
The Policy in Action – OTC Drugs

• Written Standard is similar
• In practice, handling of OTC drugs is more flexible
• **Listerine®** --
  – In vitro antimicrobial activity -- 30-second kill-time studies
  – In vivo activity S-T study of combination vs. a “clinically tested standard” and negative control
• **Excedrin® Migraine** – combination studied against placebo alone – each of the ingredients were rational and in formulation for different reasons
The Policy in (Future) Action -- Botanicals

- Botanical drugs composed of multiple parts of a single plant species, or of parts from different plant species, currently are subject to the combination drug requirements. However, FDA intends to propose revisions to its regulations to allow for the exemption of such botanical drugs from application of the combination drug requirements under certain circumstances.

Reasons for Non-Factorial Approach?

• Eloxatin® -- Accelerated approval scenario – not ethical to have a placebo arm in cancer trial
• Arthrotec® -- study aim not efficacy, but enhanced safety
• Combination vaccines –
  – Lack of subjects for subgroups
• Results can be more difficult to analyze
Waxman-Hatch 3-Year Exclusivity and Combination Products

- **Legal Standard** – sponsor conducted adequate and well-controlled clinical investigations essential to the approval
- **Clinicals** – do not include bioequivalence studies; but can be a study aimed at safety
- **Essential to approval** – that the application could not have been approved without the study
- **Sponsor conducted** – does not include literature references or use of 505(b)(2) alone
ANDA Suitability Petition – An Approach to Avoiding Clinicals?

- Can’t use to create a combination
- Can use to substitute one active for another
  - E.g., Arthrotec® -- might petition to replace the NSAID
- Standard
  - FDA must grant unless clinical investigations are needed to show safety or effectiveness
- Down side – public process
- Up side – cheaper route to market if granted
- Tips
  - Timing – be “formulation ready”
  - Impact on Waxman-Hatch exclusivity if denied
What Do We Take Away From This?

• Focus on your product
  – Are the actives serving different purposes?
    • If so, less need for factorial approach
    • Does one ingredient mitigate a side effect of another (e.g., Arthrotec®)
  – What indication are you seeking? Design your studies to achieve the label claim

• Negotiate your endpoints

• Learn the precedents – others are out there
Additional Resources

- WHO Draft Guidelines For Registration Of Fixed Dose Combination Medicinal Products

- EMA Guideline on Fixed-combination Medicinal Products. 2008 - CPMP/EWP/240/95, Rev. 1
Thanks

To Gail Gillenwater, Ph.D.,
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who shared with me her insights in dealing with combination drugs
Questions?

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