



April 25, 2005

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-0004: Comments on the Draft Guidance for Industry: Nonclinical Safety Evaluation of Drug Combinations.

Dear Sir or Madam:

Hoffmann-La Roche, Inc. (Roche) is pleased to have an opportunity to provide comments on the draft Guidance for Industry – Nonclinical Safety Evaluation of Drug Combinations (January 2005). The following comments are provided for consideration to enhance the clarity and application of this Guidance.

General Comments and Questions:

1. The Guidance should give a more explicit definition on its applicability. In particular, under the current definition of 'adjunctive therapy', essentially all potential therapeutic regimens using a combination of several drugs would require combination toxicology studies. This raises the possibility for an exorbitant number of preclinical experiments to support for example, drugs in the metabolic disease area.

The Guidance states on p. 1 that "Adjunctive therapy products may or may not be labeled for concomitant use." However, the Guidance does not adequately incorporate the possibility that adjunctive therapy products may not be labeled for concomitant use. For example, see p. 5, line 174: "Combination developmental toxicity studies need not be conducted if one of the drug products is already known to have significant risk for developmental toxicity, because that risk will already be included in the product labeling for the combination." As noted above, it is possible that an adjunctive product has no combination labeling.

Although co-packaged products and fixed-dose combination products are owned by one sponsor or by partnership, adjunctive therapies may not be owned by the Sponsor, which raises several other practical and legal issues. For example, on Page 2, Section II, 1st paragraph, the last two sentences state that a different duration of use may require that additional work be conducted. This is understandable if the combination products are owned by one sponsor or by partnership but for adjunctive therapies where the sponsor

does not own both drugs, who will perform the nonclinical studies? The company that is owner of the drug or the company that is proposing the combination? Based on the example provided, what if the owner company does not want to extend the acute use drug's duration? Are they still required to perform additional studies or does the sponsor perform studies on drugs that they do not own? Obvious issues that could arise include proprietary rights, intellectual property, confidential information, risks, cost, and tort liabilities.

2. The Guidance should be more explicit on the circumstances and timing of when the combination toxicity studies should be considered in the overall development program. For example, are the studies expected to support defined experimental clinical trials (e.g., a Phase II study to investigate the additive or synergistic effects of two antidiabetic agents that are anticipated to be used in combination, although not specifically labeled for this use), or when there is a reasonable expectation that a drug will be commonly used in practice in combination with other drugs, or both? In the case of the latter situation (i.e., anticipated but not explicitly defined or labeled combination use), are the studies expected at the time of NDA submission, or earlier?
3. If there is no concern for an interactive effect based on the scientific safety considerations mentioned in section IIA, it would be expected that no combination toxicology studies would be required for any of the combinations mentioned in the Guidance. Further comment on the scientific basis and justification of this Guidance, including some examples of studies that added clear value to the safety assessment, would help clarify the intent of the Guidance.

On a scientific basis, the testing expectations or requirements would be expected to be similar for all 3 drug combinations (MD-MD, MD-NME, NME-NME), so it is unclear why the Guidance is divided into 3 areas.

4. The Guidance should clarify whether it is intended to apply to macromolecules (i.e., biologicals) in case they may be co-administered with a small molecule in the clinic, and the specific requirements for such combination studies.
5. All sections entitled "Reproductive and Developmental Toxicity" should be changed to "Developmental Toxicity" because no mention of any reproductive toxicity requirements is found in any of these sections.
6. Adding combination toxicology studies to a development program will increase the time to market. Does the possibility exist for an extension of patent life?
7. The recommendations or considerations on applicability to carcinogenicity studies needs to be clarified. For example, the sentence on p. 5, line 177: "For chronic indications, a carcinogenicity study on the drug combination generally will only be indicated if preneoplastic lesions were observed at a new organ or tissue site in nonclinical studies." Should this be specified as "in nonclinical studies of the combination"? By

"new", does this refer to sites beyond the composite of each component of the combination alone? What is the duration of the "nonclinical studies"?

8. Please define "bridging study of up to 90 days" (see, e.g., p. 6, lines 202 and 234). Does this imply that the data from such studies would be reviewed and a recommendation rendered regarding the need for further studies?
9. Will guidance be forthcoming on the criteria that should be considered for dose selection for each compound and in combination for the combination toxicity studies?

Specific comments:

p. 1, footnote 2: For reasons mentioned previously, it is recommended that adjunctive therapy should not be grouped together with the other "combinations" in this Guidance except when the sponsor owns both products. As an aside, the adjunctive therapy example provided in footnote 2 is for an oncology treatment which will be handled in a different guidance.

p. 4, line 145-147: Could the Agency confirm that preclinical testing of the combination would not be necessary if Phase 1 studies of the combination did not identify serious adverse effects near the dose levels selected for further Phase 2 or 3 studies?

p. 5, line 192: It could be made clearer in this sentence that only testing of the NME itself is suggested and not the MD-NME combination.

p. 6, lines 201-206: This approach is fundamentally different from the MD-MD scenario where combination toxicity studies have only to be conducted under certain circumstances. "If neither individual drug product has serious toxicity at exposures well above the proposed clinical exposure or if there is substantial clinical experience with the combination, FDA may recommend that additional nonclinical studies do not need to be conducted before testing in humans or during Phase 1 (Boxes 2 to 3)." The rationale should be the same regardless of whether one or all of the drugs are NMEs.

p. 6, lines 208-214: What information could be gained from such a study? How would such data be interpreted given that human exposures cannot be achieved, i.e. no safety margins will be achieved?

p. 6, lines 218-221: Can the Agency confirm that no further combination studies should be necessary if neither the NME or marketed drugs show embryofetal developmental toxicity at exposure levels exceeding human exposures - unless DDI is expected which would increase human exposure levels for one of the drugs beyond those tested in animals, in which case additional studies would be necessary.

p. 6, lines 226: "For example..." Could the Agency please provide these examples?

p. 7, line 265: What dose the Agency mean with "exposure ratios that are relevant to the intended clinical use", i.e. several fold above the human exposure, MTD, etc.?

We appreciate the opportunity to present these comments and questions concerning this guidance. If you have any specific questions about the content of this response, please contact the undersigned.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'A. Braen', with a long horizontal flourish extending to the right.

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