

March 23, 2005

Division of Dockets Management  
HFA-305  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, Maryland 20852

Re: Docket No. 2005D-0004

Dear Sir or Madam:

Provided herewith are two (2) copies of Alcon's comments regarding FDA's Draft Guidance on "Nonclinical Safety Evaluation of Drug Combinations".

If you have any questions regarding these comments, please contact me via e-mail at [garry.heidel@alconlabs.com](mailto:garry.heidel@alconlabs.com) or via telephone at (817) 551-6813.

Sincerely,

Garry G. Heidel  
Director Regulatory Compliance  
Alcon Research, Ltd.

Attachment

# Nonclinical Safety Evaluations of Drug Combinations

Alcon Research, LTD. Comments

Date: 2005 March 23

Docket Number : 2005D-0004

1	2	(3)	4	5	(6)
FG	Clause No./ section./ (e.g. A.1)	Paragraph/ Figure/Table/ Note (e.g. Figure 1)	Type of comment <sup>2</sup>	Comment (justification for change)	Proposed change
Nonclin Pharmacology		Figure A.	ge	Current statement in diamond (box) 7. of Fig A. is incomplete	In diamond (box) 7. of Figure A. add "pharmacology/" before "toxicology".
Nonclin pharmacology		Figure B.	ge	Current statement in diamond (box) 3. of Fig B. is incomplete	In diamond (box) 3. of Figure B. add "pharmacology/" before "toxicology".
Nonclin pharma - cology		Figure C.	ge	Current statement in diamond (box) 3. of Fig C. is incomplete	In diamond (box) 2. of Figure C. add "and section IV.C" after "section II.A2"
Nonclin pharmacology		Figure C.	ge	Current statement in diamond (box) 7. of Fig C. is incomplete	In diamond (box) 7. of Figure C. add "pharmacology/" before "toxicology".
Toxicology	Part I. Introduction	Page 1 Lines 20/21 and footnote No. 2	te	Delete adjunctive therapy from scope of FDC. The FDC guidance document does not adequately address adjunctive therapy and is ambiguous in this regard. Clinically, hundreds of drugs are used in infinite combinations (label & off label) for treatment of a medical condition and to conduct nonclinical safety studies on all possible combinations would be a monumental task.	Create separate <i>Guidance for Industry</i> given the scope of adjunctive therapy.

1 FG = Functional group

2 Type of comment: ge = general te = technical ed = editorial

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Toxicology	Part I. Introduction	Page 1 footnote No. 3	te		Create separate <i>Guidance for Industry</i> to specifically address Ophthalmic FDCs due to low systemic exposure potential of combination products intended for ophthalmic products.
Toxicology	II. B	Lines 125-126	te	Include option for reporting retrospective data collected for the high dose of each drug evaluated in general toxicity studies to reduce number of study animals and cost.	FDA recommends that combination studies.....several dose levels of the combination and a high dose of each drug alone. <b>The data supporting the toxicity of the high dose of each drug may be reported from retrospective studies conducted in the same sex, age and species.</b>
Toxicology	II. B	Lines 124-125	te	Duration of general toxicity bridging studies conducted before phase I and phase II clinical studies should be based on proposed clinical duration, if toxicity concerns (narrow safety margin, interaction potential) are identified with the FDC.	General toxicity bridging study up to 1 month for subchronic indication and up to 3 months for chronic indication should be considered prior to initiation of phase I or II clinical studies if specific toxicity concerns (narrow safety margin, interaction potential) are identified for the FDC.

**End of Comments**

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