

December 23, 2002



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Dockets Management Branch
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**Re: Docket No. 02D-0389, CDER 200078. Draft Guidance for Industry on
Nonclinical Studies for Development of Pharmaceutical Excipients; Availability.
Pages 61910-61911 [FR Doc. 02-24985, Vol. 67, published October 2, 2002]
NAS 0; Not Product Specific
General Correspondence: Other**

Dear Sir or Madam:

Please find enclosed comments from GlaxoSmithKline on the draft Guidance for Industry: Nonclinical Studies for Development of Pharmaceutical Excipients. Specific comments are identified by section number and line number as they appear on the pdf published copy of the guidance.

GlaxoSmithKline appreciates the opportunity to provide comments for consideration during development of this guideline. Although we have recommended some revisions to the draft guidance, we fully support its development and look forward to working with the Agency to finalize a document that provides practical, high quality scientific advice suitable for incorporation into drug development programs. An approach to testing of truly novel excipients which maintains consistency with ICH M3 approaches to testing of new chemical entities, while retaining flexibility for a case-by-case examination of excipients that are somewhat qualified through prior use, is welcomed.

This submission is provided in paper via duplicate copies with an additional copy on diskette (Word 97) and an electronic copy via email according to the instructions provided at <http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm>.

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Please contact me at (919) 483-4483 if you require clarification of any of these comments. Thank you for your consideration.

Sincerely,

A handwritten signature in black ink that reads "Alison Bowers". The signature is written in a cursive style and is underlined with a single horizontal stroke.

Alison Bowers
Director
Regulatory Affairs

**CDER 200078. Draft Guidance for Industry on
Nonclinical Studies for Development of Pharmaceutical
Excipients; Availability.**

**Pages 61910-61911 [FR Doc. 02-24985, Vol. 67, published
October 2, 2002]**

II. Background

Lines 50-52, Page 6 footnote 5: It appears that the excipient testing in animals could be combined with conventional drug toxicity studies with minimal impact on the progression of clinical testing. However, to have appropriate controls to assess excipient toxicity an additional separate untreated or placebo control group may be warranted.

It would be advisable to provide sponsors with the flexibility to *either* include excipient groups along with the active ingredient in repeat dose toxicology, reproductive toxicology and carcinogenicity studies, *or*, to be able to conduct separate studies in cases where the excipient could be used with several different products.

Lines 84, 85 & 98, 99: Special studies e.g. juvenile toxicology are not mentioned *per se* but this section includes a reference to 'use in pediatric patients'. If the guidance is intentionally silent on this matter we suggest that an option be provided to consult with the appropriate Division regarding any requirement to conduct special studies.

III. Recommended Development Strategies to Support Marketing of New Excipients in Drug Products

B. Potential Excipients Intended for Maximum Duration of Clinical Use of 14 Consecutive Days or Less

Lines 136, 137: It should be clarified that a rising, single dose study in a non-rodent will be acceptable in place of an acute study. This is consistent with ICH M3 and the CDER guidance on Single Dose Acute Testing for Pharmaceuticals, which acknowledges that preliminary dose-range finding data for repeat-dose testing of non-rodents may be acceptable.

Line 143: For animal welfare and practical reasons, the maximum feasible dose for repeat dose toxicology studies by the oral administration route should be set at 2g/kg, or 2% dietary inclusion, rather than the proposed 5 g/kg or 5% of diet. The human relevance of toxicity studies conducted in animals that may be rendered physiologically abnormal through gross perturbation of their diet or other means has been repeatedly questioned. The guidance remains silent with respect to other routes of administration e.g. inhalation. A basis for inhaled dosing, e.g. XX multiple of anticipated human dose, would be helpful either via this guidance or via Division-specific consultation.

D. Potential Excipients Intended for a Maximum Duration of Clinical Use of More than 3 Months

Lines 218, 219 & page 5 footnote 4: We suggest that it is made clear that the intent of this guidance is consistent with the approach taken in ICH M3 for duration of repeat dose studies in non-rodents, taking into account previous experience with the class of compound. Thus a 12-month toxicity study rather than a 9-month study in the non-rodent species will not always be the default option. A specific cross-reference to ICH M3 and/or ICH S4A would be helpful.

Lines 224, 227, 233: The carcinogenicity testing options specified in the draft document are:

1. a conventional carcinogenicity study in 2 species
OR
2. a conventional carcinogenicity study in one species **plus** a transgenic mouse study
OR
3. reasoned argument (see below) **plus possibly**, (a) a cell transformation assay or (b) one transgenic mouse carcinogenicity study or (c) a conventional carcinogenicity study in one species.

Lines 230-231: There is no *a priori* scientific reason to regard any of the transgenic mouse models used for alternative carcinogenicity testing as being incapable of responding to non-genotoxic carcinogens. Available evidence indicates the contrary, as the p53 heterozygous mouse develops sarcomas in response to subcutaneous implantation of foreign bodies (identification transponders) or on exposure to non-genotoxic carcinogenins, such as cyclosporin. The phrase "*should be a model sensitive to nongenotoxic carcinogenic events*" is therefore misleading and should be deleted.

Lines 234-241: It is proposed that carcinogenicity studies should be considered on an individual basis, and that if 5 conditions are met, a carcinogenicity test may not be needed. To ensure consistency in the application of the guidance these conditions could be more closely specified. For instance, "*absence of accumulation*", "*limited systemic exposure*" and "*negative histopathology from chronic toxicology studies*" should all be defined.

Lines 243- 244: There does not appear to be a scientific justification for regarding a cell transformation assay as an equivalent to a conventional bioassay. This option should be removed.

Lines 244- 245: On current evidence, a single study in a transgenic mouse cannot be considered to provide the same level of data on the human carcinogenic potential as a 2 year bioassay in a conventional rodent. The scientific rationale for recommending the use of one type of transgenic mouse model rather than another is currently a matter of scientific uncertainty and debate.