

Novartis Pharma AG

Comments to

**FDA Draft Guidance for Industry on**

**Nonclinical Studies for Development of Pharmaceutical Excipients**

**(Docket No. 02D-0389)**

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Novartis is a major pharmaceutical company with a significant and increasing market share on the US market. The company welcomes the opportunity to review this draft Guidance. Please find below our comments.

## General Remarks

Novartis Pharma AG welcomes the concept and outline of a Guidance regarding “Nonclinical Studies for Development of Pharmaceutical Excipients”. As part of a global organization, we would be interested in a globally consistent approach towards such requirements, e.g. under auspices of the ICH process. In this context, we are concerned about potential discrepancies of this proposed guideline with existing pharmacopoeias and requirements of other regulatory bodies.

- In some parts of the proposed guidance the term “development” is used in the context of new excipients. Since the guidance focuses on nonclinical safety evaluation, we would prefer to replace the term “development” with the term “safety evaluation”.
- Specific nonclinical safety studies are foreseen for new excipients for injectable formulations. Hence, we would propose to add in the document a section on “Potential excipients for use in injectable products”. In this section, aspects such as the following are recommended for consideration:
  1. At the intended concentration for intravenous administration (bolus and/or infusion) in vitro hemolysis study should be performed to ensure low hemolytic potential.
  2. At the intended concentration for intramuscular or subcutaneous administration, plasma profile of creatinine kinase can provide information on muscle damage.
  3. Appropriate studies may be needed to evaluate protein binding in relation to local tolerability.
- Please use consistent wording regarding specific nonclinical studies, i.e. use either 28-day and 90-day or one month and 3-month toxicology studies.
- In some instances, the terms “ingredient” and “inactive ingredient” are used in the document. It is unclear whether these terms are synonymous to the term “excipient”. If not, the difference has to be defined; if yes, we would prefer a single term to be used.
- The guidance describes the needs for nonclinical studies “for compounds for which adequate prior human exposure has not been documented” (page 6, line 112-113). This implies that nonclinical testing for compounds with documented adequate prior human use would not be necessary. In this context, we would request a clarification regarding the following:
  1. What constitutes documented human use?
  2. Which kind of documentation would be required to support “adequate prior human use”?
  3. Would documented “adequate prior human use” outside of the area of application of this guidance (the United States of America) be sufficient to substitute for nonclinical testing according to this guidance?
- Page 3, lines 128-129; page 4, lines 174-175; page 5, lines 197-198: The term “maximum duration of clinical use” is used in the headings B, C and D. We would suggest to replace

this term to read “nonclinical studies to support clinical use for up to xxx duration of clinical use”. This would be consistent with the approach and wording in the ICH M3 guidance (“Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals”).

## **Specific Comments to Guidance sections**

### **II. Background**

Page 1, lines 39-41: The text excludes certain compounds normally used in biological products to be excipients.

Novartis comment: Amino acids, sugars and albumin are considered excipients that provide stabilization and their use is not limited to biological products. In this context, it is not clear why the term excipient does not apply to amino acids, sugars and macromolecular compounds like albumin. If a different guidance applies for conducting nonclinical studies for these type of compounds, that guidance should be referred to here. However, if there is no other guidance that applies to these compounds, this statement implies that these compounds can be used without nonclinical studies for any route of exposure and this may not be appropriate.

Page 2, line 51: The term “therapeutic substance” should be replaced by “drug and biological products”.

Page 2, lines 54-55: The text stipulates that “an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require”...

Novartis comment: The text implies that prior human use must be under conditions relevant for the proposed use. It is not sufficiently clear what these conditions are. Are such conditions primarily given by the use of the excipient in an approved pharmaceutical preparation in a similar indication and composition and with an identical route of administration or can e.g. data from other routes of administration, but with similar exposure or from the use of the excipient in a different composition (food additive, cosmetic) be used? We would appreciate a clarification of the term “conditions relevant for the proposed use”.

Page 3, lines 98-99: We would appreciate if the Guidance could be more specific regarding potential additional toxicological data if a new excipient shall be used e.g. in pediatric patients.

### **A. Safety pharmacology**

Page 3, lines 122 and 126: We understand that a judgement whether an excipient is “pharmacologically active” or not would be based on its effects in a standard battery of safety pharmacology studies (as defined in the ICH S7 guidance). This judgement would not include other considerations such as e.g. resorption enhancement or other influences on the drug substance. This needs to be clarified.

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## **B. Potential excipients intended for a maximum duration of clinical use of 14 consecutive days or less**

Subtopic 2 (lines 147-152) and subtopic 4 (lines 157-161): Subtopic 2 states that ADME data can generally be either obtained in separate (pharmacokinetic) studies or as toxicokinetic analyses in toxicology studies. However, subtopic 4 implies that the one month repeat dose toxicity studies should include toxicokinetic analyses. This would not facilitate the option to investigate ADME of a new excipient solely based on separate pharmacokinetic studies. We see a lack of consistency here.

## **D. Potential excipients intended for a maximum duration of clinical use of more than 3 months**

Footnote to subtopic 3: We think that not only substantial human experience but also substantial and adequate chronic toxicity data in animals for closely related excipients justify to conduct a 9-month study in nonrodents versus a 12-month study.

Page 6, line 244: It is understood that the various in vitro cell transformation assays, as currently conducted, are not frequently used and their results are of limited value. They do not provide any mechanistical information should a positive result occur. Conversely, while negative results may be supported by sufficient data that the compound under question is not a rodent or human carcinogen, we have reservations against the proposed use of such assays in the weight of evidence approach for carcinogenicity of excipients. Furthermore, the lack of data on cell transformation assay results on a variety of excipients in databases and the open literature may limit its application. Also, there is limited agreement regarding the best suited protocol for such assays. We propose to state that results of cell transformation assays may be used in the weight of evidence for carcinogenic risk but should not be considered a carcinogenicity test. Moreover, some guidance should be provided regarding acceptable test protocols.

## **E. Potential excipients for use in pulmonary or topical products**

Page 6, lines 253-255 and page 7, lines 262-263: The text implies that sensitization testing and assessment for excipients used in pulmonary drug products would be based on guinea pig maximization studies or murine local lymph node assays.

Novartis comment: The recently released FDA Guidance on “Immunotoxicology Evaluation of Investigational New Drugs” recommends to conduct specific tests for respiratory sensitization potential for compounds that are administered by inhalation. We think that this guidance offered in these documents should be consistent..

## **F. Photosafety data**

We note that the FDA Guidance on Photosafety testing is still in draft status.

We would think that it is appropriate to note that new topical excipients would normally be evaluated concomitantly with the drug substance in its formulation in animal studies with topical administration. Normally, this should not invoke the need for stand alone photosafety studies for the new excipient. This should be clearly stated.