Guidance for Industry

Nonclinical Studies for Development of Pharmaceutical Excipients

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Robert E. Osterberg at 301-594-5476, or (CBER) Martin Green at 301-827-5349.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This document provides guidance concerning development of safety profiles to support use of new excipients as components of drug or biological products. It is intended for use by reviewers within both the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) and by interested individuals in industry. This guidance is intended to foster and expedite the development of new excipients, communicate to industry current CDER and CBER thoughts pertaining to the safety data that should be generated to support excipient development, and to increase uniformity within CDER and CBER as to expectations for the nonclinical development of excipients.

II. BACKGROUND

In this guidance, the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration. Examples of ingredients include fillers, extenders, diluents, wetting agents, solvents, emulsifiers, preservatives, flavors, absorption enhancers, sustained-release matrices, and coloring agents. Within the context of this guidance, the term excipient does not apply to macromolecular compounds like albumin, or compounds like amino acids and sugars that are used in biological products, nor does it apply to process or

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

product-related impurities (e.g. degradation products, leachates, residual solvents), or extraneous contaminants.

Excipients are potential toxicants. It is important to perform risk-benefit assessments on proposed new excipients in drug products and to establish permissible and safe limits for these compounds. Safety data should be submitted to support use of new excipients. As a result, there is a perception that development of new excipients is resource intensive. With proper planning, however, it is often possible to assess the toxicology of an excipient in a relatively efficient manner. For example, sponsors may be able to develop new excipients concurrently with development of new therapeutic substances by adding groups of animals that receive the excipient to studies that would have been conducted anyway to develop a drug substance. We recognize that existing human data for some excipients can substitute for nonclinical safety data, and an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies outlined below. For example, we will continue to consider factors such as use in previously approved products or GRAS status as a food additive. Under some circumstances (e.g., similar route of administration, level of exposure, patient population, and duration of exposure) other factors can adequately qualify an excipient, although it may be important for the safety database associated with that excipient to be brought up to current standards (e.g., submission of additional genetic toxicology data). The applicable information that supported the prior use will be considered in light of any proposed new use.

For products marketed under OTC drug monographs, 21 CFR 330.1(e) sets the criteria for inactive ingredients: "The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. Color additives may be used only in accordance with section 721 of the act and subchapter A of this chapter." It is the manufacturer's responsibility to meet these criteria and to have appropriate supporting data in its files. The provisions of section 330.1(e) do not apply to OTC products marketed under new drug applications (NDAs) or abbreviated new drug applications (ANDAs).

Requirements for submitting safety information on inactive ingredients in ANDAs for generic products are stated in 21 CFR 314.94 (a)(9). Under this regulation, drug products intended for parenteral, ophthalmic, or otic use should contain the same inactive ingredients in the same concentrations as the reference listed drug product, with the exception of buffers, antioxidants, and preservatives, provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product. For other routes of administration (e.g., topical dermal, oral), there is no requirement that the inactive ingredients in the final formulations be the same as those in the reference listed drug product. However, the applicant is required to identify and characterize the differences in inactive ingredients and provide information demonstrating that the differences do not affect the safety of the proposed drug product. Consideration should be given to the prior indication and patient population for which use of the excipient was previously deemed safe. Alternatively, new or additional information to support the proposed new use should be referenced.

A new or inadequately qualified inactive ingredient proposed for use in any product to be marketed pursuant to an NDA, BLA, or ANDA should be supported by adequate data, which may be placed in the application directly or in a drug master file (DMF). This guidance describes what nonclinical data should be submitted to verify that a proposed excipient is safe in the amounts administered if relevant prior human use cannot be adequately documented.

We may request additional safety data if we determine that the proposed conditions of use are not fully supported by the available data. A pharmacokinetic profile could be requested for excipients that are extensively absorbed or biotransformed. Where applicable, drug-excipient interaction studies might also be requested. The proposed conditions of use of a new excipient (e.g., use in pediatric patients) may affect the need for toxicology data.

We recognize that every compound is unique and that scientifically valid reasons may exist for modifying and deleting certain of the studies listed below for a given combination of excipient and proposed use. For example, it may be justifiable for the development of excipients deemed necessary for the delivery of life saving therapies to be abbreviated (relative to development of excipients for use in products for low morbidity indications) or completed postapproval. As another example, excipients that are large polymers that differ from previously characterized compounds only in molecular weight (chain length) may be adequate using less safety data, provided that the new compound and the previously studied compound are sufficiently similar with regard to physical state, pharmacokinetics, and levels of unreacted monomers and other impurities. We will consider such exciptients on a case-by-case basis. All pivotal toxicology studies should be performed in accordance with state-of-the-art protocols and good laboratory practice regulations. The recommendations given below are primarily intended for compounds for which adequate prior human exposure has not been documented.

III. RECOMMENDED DEVELOPMENT STRATEGIES TO SUPPORT MARKETING OF NEW EXCIPIENTS IN DRUG PRODUCTS

A. Safety Pharmacology

It is recommended that all potential new excipients be appropriately evaluated for pharmacological activity using a battery of standard tests (see ICH S7 guidance). These evaluations may be performed during the course of toxicology studies or as independent *safety pharmacology* studies. It is useful for these data to be obtained at an early point during the development of an excipient, since, if the excipient is found to be pharmacologically active, this information may influence subsequent development.

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

It is recommended that the safety development of potential new excipients that are intended for use in products that are limited by labeling to clinical use of 14 or fewer

consecutive days per treatment episode and are infrequently used include at least the following:

1. Acute toxicology studies should be performed in both a rodent species and a mammalian nonrodent species by the route(s) of administration intended for clinical use (see CDER guidance for industry, *Single Dose Acute Toxicity Testing for Pharmaceuticals*). It is not necessary to determine the LD_{50} of an excipient.[2] It may be appropriate to omit acute toxicology studies from the development of a new excipient under certain circumstances. For example, if repeat-dose toxicology studies are performed in which the *high* dose is the maximum feasible dose (MFD,[3] e.g., 5 g/kg or 5% of the diet) and little or no toxicity is observed at the MFD, it can be assumed that the acute toxicity has been adequately evaluated.

2. It is highly recommended that the absorption, distribution, metabolism, and excretion of the excipient be studied following administration by the clinically relevant route(s) to the same species that are used in the nonclinical safety studies (see the ICH S3A and S3B guidances). These data may be obtained in separate (pharmacokinetic) studies or as toxicokinetic analyses associated with toxicology studies.

3. Excipients should be evaluated in the standard battery of genetic toxicology studies discussed in the ICH S2B guidance.

4. One-month repeat dose toxicology studies should be performed in both a rodent species and a mammalian nonrodent species by the route(s) of administration intended for clinical use. The studies should use state-of-the-art protocols and include complete clinical pathology, histopathology, and toxicokinetic analysis.

5. The reproductive toxicology of the excipient should be evaluated as discussed in the ICH S5A and S5B guidances, including: (1) assessment of potential to affect fertility or early embryonic development to implantation, (2) teratology in both a rodent species and a mammalian nonrodent species, and (3) effects on prenatal and postnatal development, including maternal function. It is suggested that the most efficient way to address these different developmental landmarks is use of a *single-study* rodent assay (as defined in the ICH S5A guidance) to assess all phases of reproductive toxicity, in conjunction with a teratology study in a nonrodent species provided that the available data predict the excipient has minimal toxicity.

C. Potential Excipients Intended for a Maximum Duration of Clinical Use of More than 14 days but Less than or Equal to 90 Consecutive Days.

[2] 53 FR 39650 (October 11, 1988)
[3] Maximum feasible dose

It is recommended that the nonclinical development of potential new excipients that are intended for use in drug products that are labeled for clinical use of more than 14 days but less than or equal to 90 consecutive days per treatment episode include at least the following:

1. All studies from sections A and B in this guidance, with the exception of the 1-month toxicology studies. Note: If toxicity or significant biological activity is observed in short-term studies, one-month toxicology studies may be useful for establishing dosages to be used in 3-month studies.

2. Three-month repeat dose toxicology studies should be performed in both a rodent species and a mammalian nonrodent species by the appropriate route(s) of administration. The studies should use state-of-the-art protocols and include complete clinical pathology, histopathology, and toxicokinetic analysis.

3. Other studies may be called for (e.g., studies involving parenteral administration). Whether more data should be gathered is usually driven by questions raised in the already completed studies.

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

It is recommended that the safety development of potential new excipients that are intended for use in drug products labeled for clinical use of more than 3 months in a given patient (either as a single treatment episode or as a result of multiple courses of therapy to treat a chronic or recurrent condition) include at least the following:

1. All studies from sections A, B, and C of this guidance. Note that 28-day and 90-day toxicology studies are not essential, but may provide useful dosage selection data.

2. A 6-month repeat-dose toxicology study should be performed in a rodent species by the appropriate route(s). The study should use state-of-the-art protocols and include complete clinical pathology, histopathology, and toxicokinetic analysis. Studies involving excipients of low toxicity should, in general, use the MFD as the upper limit for testing.

3. A chronic toxicology study should be performed in a mammalian nonrodent species by the appropriate route(s). If toxicity and pharmacologic effect were absent in state-of-the-art subchronic studies, a 6-month study may be sufficient. When toxicity is detected in shorter duration studies, or in rodents, the chronic study in nonrodents should be extended to 1 year.[4]

[4] A 9 month study may be adequate in cases in which substantial human experience exists with closely related excipients or when long-term clinical testing will provide a substantial portion of the safety database.

4. If appropriate (see ICH S1A guidance), one of the following approaches should be used to evaluate carcinogenic potential:

    a. Two-year carcinogenicity bioassays in two appropriate species by the relevant route(s).[5]

    b. A two-year carcinogenicity study in one rodent species plus an *alternative* study (e.g., appropriate use of neonatal or transgenic animals) in a different rodent species. The usual choice for that alternative, absent evidence of genotoxicity, should be a model sensitive to nongenotoxic carcinogenic events.

    c. Submission of documentation providing scientific justification that carcinogenicity data are not necessary. For example, based on negative genetic toxicology data (see ICH S2B guidance for recommended assays), limited systemic exposure, absence of accumulation based on nonclinical and clinical pharmacokinetic data, negative histopathology data from chronic toxicology studies performed at the MFD (absence of preneoplastic lesions and other toxicologic effects), and knowledge of other compounds in the same class, it may be reasonable to forego carcinogenicity testing. Decisions concerning the adequacy of this approach would be made on a case-by-case basis, using a weight-of-evidence approach. In other cases, adequately performed cell transformation assays or one 2-year bioassay in the rat or one transgenic assay, if negative, may be sufficient to contribute to the weight of evidence assessment to address the carcinogenic potential of the excipient. It is strongly encouraged that application of the above approach be undertaken in consultation with appropriate CDER or CBER staff.

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

It is recommended that the safety development of potential new excipients that are intended for use in topical (dermal, intranasal, intraoral, ophthalmic, rectal, or vaginal) or pulmonary drug products include the following[6]:

1. All studies from sections A, B, C, or D, as appropriate, using the appropriate route of administration. Studies that include the to-be-marketed formulation of

[5] When possible, it may be most cost-effective for excipients to be evaluated for carcinogenicity through inclusion in bioassays that are conducted in support of active ingredients. In such cases, it may be appropriate for the carcinogenicity assessment of an excipient to be limited to administration of a single dosage of the excipient per species (addition of a single *arm* to each bioassay), provided that the dosage was either the maximum tolerated dose (MTD) or the MFD.

[6] For cases in which a new excipient is being developed in relation to a specific product, sponsors are encouraged to consult with the appropriate division to determine if additional guidance is available.

the drug product are preferred, if this information is available at the time of excipient development.

2. Sensitization study (e.g., guinea pig maximization study or murine local lymph node assay).

3. Excipients intended for topical use may require support from toxicology studies by both the intended clinical route and by the oral or parenteral route if clinical pharmacokinetic studies conducted under conditions of maximum exposure show patients would experience systemic exposure to the excipient or its metabolite, particularly if limited systemic exposure were observed in nonclinical studies conducted by the clinical route of administration. The developer of a potential new excipient is invited to contact the appropriate center to discuss whether or not this is appropriate for a specific compound.

4. For topical dermal products and ophthalmic products, it may be appropriate to conduct an ocular irritation study.

F. Photosafety data.

It is recommended that excipients be evaluated for photosafety as described in the CDER guidance for industry entitled *Photosafety Testing*.

IV. SUMMARY

In summary, acknowledging the need to develop new excipients, CDER and CBER have proposed a flexible approach that attempts to consider both the type of use the excipient will have in approved products and the biological activity and physical properties of the molecular entity. It is recognized that during the course of data evaluation, the reasons for additional data or the potential to eliminate some studies may become apparent. In such cases, consultation with appropriate center staff is recommended to avoid development delays