

EXHIBIT UU-3

Guidance for Industry

Nonclinical Studies for the

Safety Evaluation of

Pharmaceutical Excipients

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)

May 2005
Pharmacology/Toxicology

Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients

Additional copies are available from:

*Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>*

or

*Office of Communication, Training, and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
<http://www.fda.gov/cber/guidelines.htm>*

**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)**

**May 2005
Pharmacology/Toxicology**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	1
III.	SUBMISSION OF SAFETY DATA.....	2
A.	Over-the-Counter Products	3
B.	Generic Products.....	3
C.	New Drug or Biological Product Application.....	3
D.	Requests for Additional Safety Data	4
E.	Exceptions.....	4
IV.	RECOMMENDED STRATEGIES TO SUPPORT MARKETING OF NEW EXCIPIENTS IN DRUG PRODUCTS.....	4
A.	Safety Pharmacology	4
B.	Potential Excipients Intended for Short-Term Use	5
C.	Potential Excipients Intended for Intermediate Use.....	6
D.	Potential Excipients Intended for Long-Term Use	6
E.	Potential Excipients for Use in Pulmonary, Injectable, or Topical Products	7
F.	Photosafety Data	8
V.	SUMMARY	8

Contains Nonbinding Recommendations

**Guidance for Industry¹
Nonclinical Studies for the Safety Evaluation
of Pharmaceutical Excipients**

This guidance represents 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. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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. It is also intended to foster and expedite the development of new excipients, communicate to pharmaceutical and excipient manufacturers current CDER and CBER recommendations on the nonclinical safety data that should be generated to support excipient development, and increase uniformity within CDER and CBER as to expectations for the nonclinical safety evaluation of excipients.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In this guidance, the phrase *new excipients* means any inactive ingredients that are intentionally added to therapeutic and diagnostic products, but that: (1) we believe are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery (e.g., enhance absorption or control 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 excipients include fillers, extenders, diluents,

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.

Contains Nonbinding Recommendations

wetting agents, solvents, emulsifiers, preservatives, flavors, absorption enhancers, sustained-release matrices, and coloring agents. Within the context of this guidance, the term *excipient* applies to macromolecular substances such as albumin, or substances such as amino acids and sugars that are used in drug and biological products. It does not, however, apply to process or product-related impurities (e.g., degradation products, leachates, residual solvents) or extraneous contaminants.

Not all excipients are inert substances; some have been shown to be potential toxicants. The Federal Food, Drug, and Cosmetic Act of 1938 (the Act) was enacted after the tragedy of the elixir of sulfanilamide in 1937 in which an untested excipient was responsible for the death of many children who consumed the pharmaceutical. The Act required manufacturers to perform safety testing of pharmaceuticals and submit new drug applications (NDAs) demonstrating safety before marketing. Since that time, the Agency has become aware that certain other excipients used in commerce can cause serious toxicities in consumers of prescription and over-the-counter (OTC) drug products in the United States and other countries.

This guidance describes the types of toxicity data that the Agency uses in determining whether a potential new excipient is safe for use in human pharmaceuticals. It discusses recommended safety evaluations for excipients proposed for use in OTC and generic drug products, and describes testing strategies for pharmaceuticals proposed for short-term, intermediate, and long-term use. It also describes recommended excipient toxicity testing for pulmonary, injectable, and topical pharmaceuticals.

III. SUBMISSION OF SAFETY DATA

Most, if not all, drug products could not be made without the use of excipients. Tablets, capsules, suspensions, and others all require one or more excipients in their formulations. Excipients may also have functions, for example, in sustained release preparations or in enhancing drug penetration through the skin.

It is important to perform risk-benefit assessments on proposed new excipients in drug products and to establish permissible and safe limits for these substances. This requires evaluation of a safety database. With proper planning, however, it is often possible to assess the toxicology of an excipient in a relatively efficient manner. For example, sponsors can develop new excipients concurrently with safety evaluation of new drug and biological products by adding groups of animals that receive the excipient to studies that would have been conducted anyway to develop a drug substance. The Centers recognize that existing human data for some excipients can substitute for certain 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 in this guidance. For example, the Centers will continue to consider factors such as use in previously approved products or GRAS status as a direct food additive. Under some circumstances (e.g., similar route of administration, level of exposure, patient population, and duration of exposure) experience associated with the prior use may adequately qualify an excipient. However, it may be necessary for the safety database associated with that excipient to be brought up to current standards (e.g., submission of additional genetic

Contains Nonbinding Recommendations

toxicology data). The available information that supported the prior use will be considered in light of any proposed new use by the appropriate review division. It is important to note that the inclusion of an excipient in a USP/NF monograph or other non-FDA document is not an indication that the substance has been reviewed by the FDA and found safe for use.

A. Over-the-Counter Products

For products marketed under OTC drug monographs, 21 CFR 330.1(e) requires: “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 comply with these requirements and to have appropriate supporting data in its files. The provisions of § 330.1(e) do not apply to OTC products marketed under NDAs or abbreviated new drug applications (ANDAs). Some excipients used in NDA-approved drug products may not be safe for use in OTC products (e.g., some toxic excipients used in cancer chemotherapeutics).

B. Generic Products

Requirements for submitting safety information on excipients 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 excipients 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 excipients in the final formulations be the same as those in the reference listed drug product, although the applicant must demonstrate that the inactive ingredients do not affect the safety or efficacy of the proposed drug product (21 CFR 314.94(a)(9)(ii)). However, we recommend that the applicant identify and characterize the differences in excipients 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.

C. New Drug or Biological Product Application

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

Contains Nonbinding Recommendations

D. Requests for Additional Safety Data

We may request additional safety data if we determine that the proposed conditions of use are not fully supported by the available data. We may request a pharmacokinetic profile for excipients that are extensively absorbed or biotransformed. When applicable, drug-excipient interaction studies may also be requested. The proposed conditions of use of a new excipient (e.g., use in pediatric patients)² may affect the need for toxicology data. The sponsor is encouraged to contact the appropriate review division for guidance.

E. Exceptions

We recognize that every excipient is unique and that scientifically valid reasons may exist for modifying and deleting certain preclinical studies listed in this guidance for a given combination of excipient and proposed use. For example, it may be justifiable for the safety evaluation of excipients deemed necessary for the delivery of lifesaving therapies to be abbreviated (relative to the evaluation of excipients for use in products for low morbidity indications) or completed post-approval. As another example, excipients that are large polymers that differ from previously characterized excipients only in molecular weight (chain length) can be adequately characterized in an abbreviated manner using less safety data, provided that the new excipient and the previously studied excipient are sufficiently similar with regard to physical state, pharmacokinetics, and levels of unreacted monomers and other impurities. We will consider such excipients on a case-by-case basis. The sponsor is encouraged to contact the appropriate review division to receive specific guidance when necessary.

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

We recommend that all pivotal toxicology studies be performed in accordance with state-of-the-art protocols and good laboratory practice regulations. The following recommendations are primarily intended for excipients for which adequate prior human exposure has not been documented.

A. Safety Pharmacology

We recommend that all potential new excipients be appropriately evaluated for pharmacological activity using a battery of standard tests (see ICH guidance S7A).³ These evaluations can 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 safety evaluation of an excipient, since, if the excipient is found to be pharmacologically active, this information can influence subsequent development. Appropriate regulatory guidance can be given by the responsible review division.

² Concerning use in pediatric patients, see the CDER draft guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance page at <http://www.fda.gov/cder/guidance/index.htm>.

³ ICH guidance for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals*

Contains Nonbinding Recommendations

B. Potential Excipients Intended for Short-Term Use

We recommend that the safety evaluation 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 performed in both a rodent species and a mammalian nonrodent species by the route 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 LD₅₀ of an excipient.⁴ It may be appropriate to omit acute toxicology studies from the safety evaluation of a new excipient under certain circumstances. For example, if repeat-dose toxicology studies are performed in which the *high* dose is the limit dose (e.g., 2 g/kg or 2 percent of the diet) and little or no toxicity is observed at that dose, it can be assumed that the acute toxicity has been adequately evaluated. In some cases, a dose-escalation study is considered an acceptable alternative to a single-dose design (see ICH guidance M3).⁵
2. It is recommended that the absorption, distribution, metabolism, and excretion of the excipient be studied following administration by the clinically relevant routes to the same species that are used in the nonclinical safety studies (see ICH guidelines S3A and S3B).⁶
3. It is recommended that excipients be evaluated in the standard battery of genetic toxicology studies discussed in ICH guidance S2B.⁷
4. It is recommended that 1-month repeat-dose toxicology studies be performed in both a rodent species and a mammalian nonrodent species by the route of administration intended for clinical use. It is important that the studies include complete clinical pathology, histopathology, and toxicokinetic analysis.
5. It is recommended that the reproductive toxicology of the excipient be evaluated as discussed in ICH guidelines S5A and S5B,⁸ including: (1) assessment of potential to affect fertility or early embryonic development to implantation; (2) teratology in both a

⁴ 53 FR 39650 (October 11, 1988)

⁵ ICH guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* (<http://www.fda.gov/cder/guidance/index.htm>)

⁶ ICH guidelines for industry *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies* and *S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies* (<http://www.fda.gov/cder/guidance/index.htm>)

⁷ ICH guidance for industry *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals* (<http://www.fda.gov/cder/guidance/index.htm>)

⁸ ICH guidelines for industry *S5A Detection of Toxicity to Reproduction for Medicinal Products* and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility* (<http://www.fda.gov/cder/guidance/index.htm>)

Contains Nonbinding Recommendations

rodent species and a mammalian nonrodent species; and (3) effects on prenatal and postnatal development, including maternal function. The most efficient way to address these different developmental landmarks is use of a *single-study* rodent assay (as defined in ICH guidance S5A) 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 Intermediate Use

We recommend that the nonclinical safety evaluation of potential new excipients that are intended for use in drug products that are labeled for clinical use of more than 2 weeks but less than or equal to 3 months per treatment episode include at least the following:

1. All studies from Section IV.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, 1-month toxicology studies may be useful for establishing dosages to be used in 3-month studies.
2. We recommend that 3-month repeat-dose toxicology studies be performed in both a rodent species and a mammalian nonrodent species by the appropriate route of administration. It is important that the studies include complete clinical pathology, histopathology, and toxicokinetic analysis.
3. We may ask for additional studies (e.g., studies involving parenteral administration). This request is usually driven by questions raised in the completed studies.

D. Potential Excipients Intended for Long-Term Use

We recommend that the safety evaluation 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 Section IV.A., B., and C. of this guidance. Note that 1-month and 3-month toxicology studies are not essential, but may provide useful dosage selection data.
2. We recommend that a 6-month repeat-dose toxicology study be performed in a rodent species by the appropriate route. It is important that the study include complete clinical pathology, histopathology, and toxicokinetic analysis. We recommend that studies that involve excipients of low toxicity in general use the limit dose as the highest dose for testing.
3. It is important that a chronic toxicology study be performed in a mammalian nonrodent species by the appropriate route. 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, a chronic study in nonrodents of 9 to 12

Contains Nonbinding Recommendations

months may be appropriate. The sponsor is encouraged to contact the appropriate review division for guidance.

4. If appropriate (see ICH guideline S1A),⁹ one of the following approaches may be used to evaluate carcinogenic potential:
 - a. Two-year carcinogenicity bioassays in two appropriate species by the relevant routes.¹⁰
 - b. A 2-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. We encourage discussion with the appropriate review division of the usual choice for that alternative assay.
 - c. Submission of documentation providing scientific justification that carcinogenicity data are not necessary. For example, based on negative genetic toxicology data (see ICH guidance S2B 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 maximum feasible dose (MFD) (absence of preneoplastic lesions and other toxicologic effects), and knowledge of other excipients 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 approach described herein be undertaken in consultation with appropriate review division staff.

E. Potential Excipients for Use in Pulmonary, Injectable, or Topical Products

We recommend that the safety evaluation of potential new excipients that are intended for use in injectable, topical (dermal, intranasal, intraoral, ophthalmic, rectal, or vaginal), or pulmonary drug products include the following:¹¹

⁹ ICH guideline for industry *S1A The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals* (<http://www.fda.gov/cder/guidance/index.htm>)

¹⁰ It may be most cost-effective to evaluate excipients for carcinogenicity through inclusion in bioassays that are conducted in support of therapeutic ingredients. In such cases, it may be appropriate for the carcinogenicity assessment of an excipient to be limited to administration of a single dose of the excipient per species (addition of a single *arm* to each bioassay), provided that the dose was either the maximum tolerated dose (MTD) or the maximum feasible dose (MFD).

¹¹ For cases in which a new excipient is being developed in relation to a specific product, sponsors are encouraged to consult with the appropriate review division to determine if additional guidance is available.

Contains Nonbinding Recommendations

1. All studies from Section IV.A., B., C., or D., as appropriate, using the appropriate route of administration. Studies that include the to-be-marketed formulation of the drug product are preferred, if this information is available at the time of excipient evaluation.
2. Sensitization study (e.g., guinea pig maximization study or murine local lymph node assay). Consult CDER guidance for industry *Immunotoxicology Evaluation of Investigational New Drugs* for more information.
3. For excipients intended for injectable use, the following considerations may be appropriate:
 - a. An in vitro hemolysis study could be performed at the intended concentration for I.V. administration (bolus and/or infusion) to determine the hemolytic potential.
 - b. The plasma concentrations of creatinine kinase determined at the intended excipient concentration for I.M. or S.C. administration can provide information on potential muscle damage.
 - c. An evaluation of protein binding in relation to local site tolerability could be done.
4. Excipients intended for topical use may need support from toxicology studies by both the intended clinical route and 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 review division to discuss whether or not this is appropriate for a specific excipient.
5. For topical dermal products and ophthalmic products, it may be appropriate to conduct an ocular irritation study.

F. Photosafety Data

We recommend that excipients be evaluated regarding the need for photosafety testing as described in the CDER guidance for industry *Photosafety Testing*. Either the excipient or the complete drug product could be tested. We encourage consulting the appropriate drug review division prior to initiation of studies.

V. SUMMARY

Acknowledging the need to develop new excipients, we 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

Contains Nonbinding Recommendations

the course of data evaluation, the reasons for additional data or the potential to eliminate some studies may become apparent. In such cases, we recommend consultation with appropriate review division staff to avoid delays in use of the excipient.