Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route

Guidance for Industry and Review Staff

Good Review Practice

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmacology/Toxicology

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Contains Nonbinding Recommendations

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for the nonclinical evaluation of previously approved drug substances when a new formulation or a new route of administration for a previously approved formulation is proposed by the sponsor. This guidance is intended for sponsors and review staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) involved in the development and review of new formulations of previously approved drug substances and proposals for existing formulations to be used by a new route of administration.

The goals of this guidance are to:

- Communicate to industry the FDA's current thinking pertaining to safety data needed to support approval of these drug products
- Increase uniformity within CDER on recommendations for the nonclinical development of reformulated drug products and products being used by an alternate route

This guidance assumes that the drug substance has already been used in an approved drug product. It outlines the nonclinical information generally recommended to support the development of a new product even if there is no change in the composition of the formulation.

[1] This guidance has been prepared by the Pharmacology/Toxicology Coordinating Committee in the Center for Drug Evaluation and Research at the Food and Drug Administration.

For example, the same formulation might be used by a new route, prompting a reevaluation of the toxicity information using considerations outlined in the guidance.

This guidance does not absolve the sponsor from providing complete nonclinical information for a drug product, either directly (i.e., literature or study reports), through a right of reference to such information, or by relying on the finding of safety and effectiveness for a listed drug and establishing a clinical bridge to that listed drug.[2]

This guidance does not fully address the complete safety evaluation that may be appropriate for excipients that are being used in a new formulation but that have not been previously used in FDA-approved products. The studies described in this guidance may help support the safety assessment of an excipient being used by a new route of administration. For recommendations regarding nonclinical issues that apply to excipients that have not been previously used in FDA-approved products, see the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.[3]

In general, FDA's guidance documents 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. Although guidance documents do not legally bind FDA, review staff may depart from guidance documents only with appropriate justification and supervisory concurrence.

II. BACKGROUND

Generally, nonclinical data support use of a drug product by a particular route and also reflect the planned duration of use. For example, carcinogenicity studies usually are not conducted to support approval of antibiotics intended for short-term use. Much of the available nonclinical information used to support approval of an initial formulation can be used to support the safety of new formulations, but in some cases these data may not be sufficient to support additional approvals because changes in the formulation could produce a new toxicity or more commonly because the new formulation will be used in a different way. This is particularly true if the drug product's route of administration is different or the duration of use changes markedly. In those cases, additional nonclinical studies might be recommended to ensure that the toxicity of a new formulation, as it is to be used, is fully characterized.

[2] The term *listed drug* is defined as "a new drug product that has an effective approval under 505(c) of the act for safety and effectiveness or under 505(j) of the act, which has not been withdrawn under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined as reasons of safety or effectiveness" (21 CFR 314.3).

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

If the new formulation is to be used in a manner similar to previous formulations, the need for additional nonclinical data generally will be limited. However, if the new formulation will be used in a substantially different way (e.g., new route, longer duration), the need for additional nonclinical data becomes greater and additional nonclinical information may be needed even if no change is made in the composition of the formulation. For example, if a topical cream originally used on the skin will be used intravaginally, the safety database should be assessed to determine if this new route is safe or if additional studies are needed.

III. GENERAL CONSIDERATIONS

The recommendations provided in this guidance assume that the nonclinical evaluations of the previously approved drug products were adequate by current standards. If this is not the case, and the change in formulation or route of administration triggers the need for additional studies, then additional nonclinical studies might be recommended to address any preexisting deficiencies.

Sponsors should review available toxicity information to determine whether it supports the proposed clinical use of the new formulation or new route of administration. This review should include considering whether additional data (e.g., chronic toxicity, carcinogenicity studies) are recommended for new products indicated for long-term use.

We recommend that the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* or *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* and the appropriate review division be consulted regarding the timing of submission of nonclinical data relative to clinical development. Toxicology studies used to support clinical use of a drug product should be conducted under the good laboratory practice regulations.[4]

IV. SYSTEMIC TOXICITY CONSIDERATIONS

All routes of administration can result in systemic exposure. Therefore, the adequacy of the available systemic toxicity information should be evaluated based on a comparison of the systemic exposure obtained after administration of a proposed new formulation to the systemic exposure with use of the previously approved formulation. Changes in the formulation can alter the pharmacokinetics of an active ingredient. Additional toxicity studies might be recommended if the available toxicity information is not sufficient to support the exposure associated with the new formulation or route or if a significantly different pattern of exposure results from the new formulation or route.

An adequate evaluation of the pharmacokinetics and absorption, distribution, metabolism, and elimination (PK/ADME) of the drug substance is recommended for new formulations. These data and any available human data can be helpful in determining what additional nonclinical

[4] See 21 CFR part 58.

toxicity data, if any, are recommended. When comparing the PK/ADME of a new formulation or route with a previously approved product it is important to examine the shape of the concentration/time curve in addition to the total area under the curve. For example, alterations in absorption or the dosing frequency can produce significantly different concentration/time profiles that might lead to different toxicological effects. In some cases, PK/ADME for the new formulation or route might not be available. In these cases, an assumption of 100 percent bioavailability from the proposed clinical dose might be used to judge the adequacy of available systemic toxicity information.

V. ROUTE OF ADMINISTRATION CONSIDERATIONS

In addition to evaluating the adequacy of the available toxicity information, possible toxic effects relevant to the particular route of administration should be considered. Information on toxic effects might be insufficient when there is a change in the route of administration with a new formulation. Even reformulations that do not change the route of administration might have local toxic effects not previously observed, because new combinations of active and inactive ingredients can produce additive or new effects. For example, two ingredients (active or inactive) that produce only mild irritation when used separately might produce more pronounced irritation when used together or one ingredient may alter the metabolism of another and consequently change its toxicity.

A. Considerations for All Routes of Administration

For all drug product reformulations and for all drug products with new routes of administration, acute and/or repeat-dose toxicity studies with complete histological evaluation should be conducted using the clinical route of administration. Acute studies may not be needed when repeat-dose studies are conducted. In general, durations of the toxicity studies should follow the recommendations outlined in ICH M3(R2) or ICH S9. For a new formulation that will be used by the same route as the previously approved product, shorter duration toxicity studies than those outlined in ICH M3(R2) may be appropriate.

If systemic exposure by a new route of administration is equivalent to or less than that of the approved route, histological evaluation may be limited to locally exposed tissues. If there are insufficient data or a safety concern about any of the excipients in the formulation, the inclusion of a saline, water, or untreated control in the safety studies should be considered.

B. Route-Specific Considerations

In addition to the considerations for all routes listed in sections IV. and V.A., the route-specific recommendations described in the following sections should be considered for all new formulations, whether they are proposed for a new route or the same route as a previous formulation. Note that as with systemic toxicity, new studies may not be needed if existing information is already sufficient. Similar recommendations can be considered for any route not mentioned here.

1. Oral

No studies are recommended in addition to the toxicity studies listed in section V.A.

2. Dermal (Including Patches)

- The potential for delayed hypersensitivity of the new formulation should be evaluated.

- The potential for phototoxicity should be evaluated according to the principles outlined in the ICH guidance for industry *S10 Photosafety Evaluation of Pharmaceuticals.*

- If the new formulation contains a drug substance that has not been evaluated for ocular irritation, then the potential of the topical drug product to induce irritation of the eyes if the eyes were inadvertently exposed to the product should be appropriately addressed. The topical drug product's ocular irritation potential should be evaluated through the use of appropriate in vitro or ex vivo methods. The in vivo rabbit ocular irritation test method is no longer recommended for topical drug products.

- If the new formulation contains a drug substance that has not been used by the dermal route, the repeat-dose local toxicity study mentioned earlier should be conducted in a nonrodent species (preferably minipig). This study should be of the same duration as clinical use (up to 9 months for chronically used drugs) and include both local and systemic evaluation.

- The skin dose from topically applied drug products can be orders of magnitude higher than the skin dose after systemic administration. Therefore, a dermal carcinogenicity study might be recommended for drugs with a chronic indication even if systemic carcinogenicity studies are available. However, a dermal carcinogenicity study might be waived if a chronic dermal study in an appropriate nonrodent species shows no preneoplastic effects and there are no other causes for concern (i.e., there are no genotoxicity signals and systemic carcinogenicity data show no concern.)

- Dermal studies generally should be conducted with untreated control, vehicle control, and complete formulation groups.

3. Intravenous

- Compatibility with blood (e.g., in vitro hemolysis, protein flocculation, platelet activation) should be evaluated.

4. Ocular

- If the drug substance has not been previously administered by the proposed ocular route, then toxicity studies in two species with complete ocular and systemic evaluation for the appropriate duration should be carried out with the new formulation. A study in a single most appropriate species may be adequate if the drug substance has been previously administered by the proposed ocular route. Ocular toxicity can be assessed using slit lamp

biomicroscopy (with and without fluorescein staining), funduscopy, tonometry, electroretinography, and histopathology.

- Ocular studies generally should be conducted with vehicle control and complete clinical formulation groups.

- These studies should include the evaluation of systemic exposure. Ocular tissue distribution should also be assessed.

5. Otic

- The dermal irritation and potential for delayed contact hypersensitivity of the new formulation should be evaluated.

- The ability of the drug product to penetrate an intact tympanic membrane should be determined and the exposure to the middle and inner ears in an animal model should be estimated when this barrier is or is not intact.

- If the drug product is expected to reach the middle or inner ear during clinical use or is introduced directly to those regions, evaluation of the auditory brainstem response, as well as microscopy of relevant otic tissues, including a cytocochleogram, should be included in acute and/or repeat-dose studies conducted by intratympanic administration.

6. Inhalation

- If a drug substance in the new formulation has not been tested by inhalation, then inhalation toxicity studies should be conducted. These studies should consist of short-term studies (2 to 4 weeks) in two species (at least one nonrodent) followed by up to a 6-month study in the most appropriate species with the new formulation for a chronically indicated drug. Studies for new formulations should include sham (air) control, vehicle control, and complete formulation groups.

- For drug products administered chronically by inhalation, carcinogenicity studies by the oral route can be sufficient when no toxicity suggesting proliferative or preneoplastic changes is observed in chronic inhalation toxicity studies and when adequate local airway exposure by the oral route is demonstrated.

7. Intranasal

- The nonclinical studies carried out to support a new intranasal formulation generally should be similar to the studies for new formulations administered by inhalation.

- These studies should consist of short-term studies (2 to 4 weeks) in two species (at least one nonrodent) followed by up to a 6-month study in the most appropriate species with the new formulation for a chronically indicated drug product. Studies for new formulations should include vehicle control and complete formulation groups. Vehicle and complete formulation

groups generally should be treated by the intranasal route (e.g., intranasal instillation) to maximize direct exposure of nasal tissues. Histological assessment should include local tissues and potentially affected brain areas. Inhalation studies may be adequate to assess intranasal safety if adequate local exposure can be demonstrated.

- An inhalation study also may be recommended if the particle size (less than or equal to 5 micrometers) results in lung deposition.

8. Vaginal

- The new formulation should be evaluated for delayed hypersensitivity.

- Reproductive and developmental toxicity of the new formulation should be evaluated by the vaginal route in one species if exposure in previous studies was inadequate to cover exposure from the vaginal route and the previous studies did not show a developmental risk.

9. Rectal

No studies are recommended in addition to the toxicity studies listed in section V.A.

10. Intraoral (Including Buccal or Lingual, or Periodontal)

This route applies to products intended to deliver the drug substance within the mouth. The following recommendations should be considered for the intraoral route:

- The possibility of accidental swallowing should be considered when comparing systemic exposure from the proposed new formulation with toxicokinetic data obtained using a different route or formulation. Previously conducted oral studies to support an oral dosage form may be sufficient. If the new formulation contains a drug substance not previously tested by oral administration, or if exposure associated with the new formulation is not qualified by data obtained previously, then toxicity studies conducted by the oral route (i.e., gavage, dietary, or drinking water) should be conducted. Studies should include thorough gross and histopathological examination of the gastrointestinal tract.

- An intraoral local tissue toxicity study in one species of the new formulation with a dosing frequency that meets or exceeds clinical frequency can be conducted. If this study includes animals with abraded oral mucosa then an assessment of the effect of the drug on the healing of oral lesions is possible. Alternatively, frequent clinical monitoring of the oral cavity in early phases of clinical development can be used to ensure that excessive local irritation of the oral cavity does not occur in humans.

11. Intracavernosal or Intraurethral

- If a drug substance has not been tested for the effect on male fertility then the new formulation should be evaluated for its effect on male fertility in the most appropriate species.

12. Intravesicular (Intrabladder)

- Reproductive and developmental toxicity of the new formulation should be evaluated if exposure in previous studies was inadequate to cover exposure from the intravesicular (intrabladder) route and the previous studies did not show a developmental risk.

13. Extended Release Injected or Implanted Formulations

- If the drug substance has not been tested in an extended release formulation previously, but all inactive ingredients have been tested by this route, then a toxicity study of the proposed new formulation should be carried out in the most appropriate species. The animals should be monitored for a period of time after administration sufficient to assess the entire duration of the extended release.

- The fate of any materials associated with the formulation (e.g., solid material from an implant) should be determined.

14. Intrathecal or Epidural

- If the drug substance has not been previously approved for use by either the intrathecal or epidural route of administration, toxicity studies in two species (at least one nonrodent) with the intended clinical formulation should be conducted.

- If the drug is under development for epidural route of administration only, the studies in two species should include dosing by both the epidural route and the intrathecal route of administration to understand the risks in case unintentional intrathecal delivery occurs in the clinical setting.

- If the drug product is under development for intrathecal route of administration only, nonclinical studies via the epidural route should not be necessary.

- Toxicity studies of a new formulation should be conducted in two species for the appropriate duration for a reformulation of a currently approved intrathecal or epidural drug product in which the new formulation contains a higher concentration of drug substance. If one species has been determined to be the most sensitive species, sponsors should provide the review division with justification for use of a single species for evaluation.

- Because of the localized high drug product levels, an evaluation of the neurotoxicity, including behavioral observations and gross and histopathological analysis of the central nervous system, is strongly encouraged in all studies. Such analysis may require special techniques and stains.

- The evaluation of the pharmacokinetics of the new formulation should include analysis of steady-state levels in the cerebrospinal fluid in addition to systemic levels of the drug substance.

- The design of nonclinical studies should reproduce as closely as possible the intended clinical dosing regimen, taking into consideration the drug substance concentration, the volume to be administered, and the rate of infusion.

15. Subcutaneous or Intramuscular

No studies are recommended in addition to the toxicity studies listed in section V.A.