Guidance for Industry and Review Staff

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

DRAFT GUIDANCE

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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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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. 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 guidance provides recommendations regarding the nonclinical evaluation of a new formulation containing a previously approved drug substance and of a product proposed for use by an alternate route of administration for which the product was not previously approved. This guidance is intended for individuals or organizations 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 products containing previously approved drug substances and proposals for existing formulations to be used in a new route of administration.

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 formulation containing a previously approved drug substance and provides nonclinical evaluation information for formulations intended for use by new routes of administration even if there is no change in the composition of the formulation. Although this situation does not represent a reformulation, it is appropriate in this case to reevaluate 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 or 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

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

listed drug.[2] This guidance pertains to new formulations containing previously approved drug substances only and does not address the safety evaluation of excipients. For recommendations regarding nonclinical issues that apply to excipients, see the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.[3]

The goals of this guidance are to:

- Communicate to industry the FDA's current thinking pertaining to safety data needed to support these drug products

- Increase uniformity within CDER on recommendations for the nonclinical development of reformulated drug products and drugs being used by an alternate route

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

Generally, nonclinical data support use of a drug by a particular route and also reflect the planned duration of use. For example, antibiotics intended for short-term use generally do not have carcinogenicity studies. Much of the available nonclinical information used to support approval of the initial formulation can be used to support the safety of additional formulations, but this may not be sufficient to support such additional approvals because changes in the formulation could produce a new toxicity. This is particularly true if the drug's route of administration is different, or the duration of use changes markedly. Therefore, additional nonclinical studies might be recommended to ensure that the toxicity of a new formulation is fully characterized.

If the new formulation is to be used similarly to previous formulations, the need for further nonclinical data generally will be small. However, if the alternative formulation will be used in a substantially different way (e.g., new route, longer duration) then the need for additional nonclinical data becomes greater. Indeed, further nonclinical evaluation information for drugs to be used by new or alternate routes or greater duration 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

[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 CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

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 generally 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 carcinogenicity data are recommended for new formulations indicated for long-term use or for the original formulation when newly proposed for long-term use.

We recommend that the ICH guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* and the appropriate review division be consulted regarding when nonclinical data should be provided relative to clinical development.

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 the systemic exposure obtained after administration of a proposed new formulation or of a previous formulation by a new route. Additional toxicity studies might be recommended if the available toxicity information is not sufficient to support the exposure measured with the new formulation or if a significantly different pattern of exposure results from the new formulation. 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 toxicity data, if any, are recommended. When comparing the PK/ADME of a new formulation with a previously approved formulation, it is important to examine the shape of the concentration/time curve and not just the total area under curve. For example, alterations in absorption or the dosing frequency can produce significantly different concentration/time profiles that might lead to different toxicological effects. Changes in the vehicle composition or form also can alter the PK of active ingredients. In some cases, PK/ADME for the new formulation 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 relevant to proposed new routes might be deficient when a reformulation results in a change in the route of administration from the one previously used. Even reformulations that do not result in a change of route might still have some local toxic effects not previously observed since 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.

A. Considerations for All Routes

For all reformulations and all routes, depending on the route of administration, acute and repeat dose local toxicity studies with histological evaluation should be conducted either in one species (e.g., skin for dermal formulations or patches; lung for inhaled formulations; gastrointestinal for oral formulations; injection site for intravenous, subcutaneous, intraperitoneal, or intramuscular formulations; extended release injected or implanted formulations; intracavernosal or intraurethral; intrabladder) or in two species (e.g., ocular; intrathecal or epidural).

B. Route-Specific Considerations

In addition to the considerations for all routes listed in section 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 might not be critical for an adequate evaluation of a particular concern, 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 acute and repeat dose toxicity studies listed in section V.A.

2. Dermal (Including Patches)

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

- Photoirritation should be evaluated if the new formulation absorbs ultraviolet or visible radiation (290 nm to 700 nm) and if the product is applied to sun-exposed skin. If the new formulation is a patch, then photoirritation should be considered if the patch is permeable to light and is applied to sun-exposed skin. (See the guidance for industry *Photosafety Testing*.)

- If the new formulation contains an active ingredient that has not been used by the dermal route, the repeat dose local toxicity study mentioned earlier should be conducted in a

nonrodent species. This study should be of at least the same duration as clinical use (up to 9 months) and include both local and systemic evaluation.

- The skin dose from topically applied drug products can be orders of magnitude larger 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.

- The photococarcinogenic potential should be evaluated if the new formulation is used chronically on sun-exposed skin. Evaluation of photococarcinogenicity generally is not recommended for patch products. (See the guidance for industry *Photosafety Testing*.)

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

3. Intravenous

- Compatibility with blood should be evaluated.

4. Ocular

- If the active ingredient has not been used by the ocular route, then toxicity studies in two species with complete eye and systemic evaluation for the appropriate duration should be carried out with the new formulation. In certain cases, studies in one most appropriate species may be adequate. Optimal design of these studies would include the evaluation of ocular and systemic PK. Ocular toxicity can be assessed using slit lamp biomicroscopy (with fluorescein staining), funduscopy, tonometry, and histopathology. Nonclinical ocular studies generally should be conducted with vehicle control and complete formulation groups.

5. Otic

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

- The ability of the drug 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 is expected to reach the middle or inner ear during clinical use, 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 an active ingredient 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 in two species followed by up to a 6-month study in the most appropriate species with the new formulation for a chronically indicated drug. Optimal design of these studies for new formulations would include sham control, vehicle control, and complete formulation groups.

- For drugs 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 and by the oral route (because intranasally administered drugs can be swallowed).

8. Vaginal

- The new formulation should be evaluated for delayed hypersensitivity.

- Reproductive and developmental toxicity of the new formulation should be evaluated 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 acute and repeat dose 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 an active ingredient 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. Optimal design of these studies would include thorough gross and histopathological examination of the gastrointestinal tract.

- 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. As an alternative to this clinical approach, a 28-day nonclinical oral irritation study of the new formulation with a dosing frequency that meets or exceeds clinical frequency can be carried out. 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.

11. Intracavernosal or Intraurethral

- If an active ingredient 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 active ingredient has not been tested in an extended release formulation previously, but all inactive ingredients have been tested by this route, then a single dose 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, studies in two species by both the epidural route and the intrathecal route of administration are still recommended to understand the risks in case unintentional intrathecal delivery occurs in the clinical setting.
- If the drug 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 active ingredient. 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 levels, an evaluation of the neurotoxicity, including gross and histopathological analysis of the central nervous system, is strongly encouraged in all studies.

- The evaluation of the PK of the new formulation should include analysis of the cerebrospinal fluid in addition to systemic levels of the drug.

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

15. Subcutaneous or Intramuscular

No studies are recommended in addition to the acute and repeat dose toxicity studies listed in section V.A.