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⟨1074⟩ EXCIPIENT BIOLOGICAL SAFETY EVALUATION GUIDELINES

INTRODUCTION

This informational chapter presents a scientifically-based approach for the safety assessment of new pharmaceutical excipients (i.e., those excipients that have not been previously used or permitted for use in a pharmaceutical preparation). The guidelines presented herein provide a protocol for developing an adequate database upon which to establish conditions for the safe use of a new excipient intended for use in products administered by various dosage routes. [Note—The final section of this chapter, *Definition of Terms*, lists some terms referred to in this chapter.]

An excipient may perform a variety of functionality roles in a pharmaceutical product; but, unlike pharmacologically active drug entities, the excipient displays either no pharmacological activity or very limited and directed activity. Because of these differences between excipients and active drug substances in terms of risk and benefit relationships and expected biological activities, the approaches for safety assessments of excipients and active drug substances will differ. Therefore, it is important to note that the guidelines presented in this informational chapter apply only to the safety assessment of excipients, not to the safety assessment of active drug substances.

These testing guidelines are informational in nature and are intended to be used by professionals having a knowledge of toxicology and associated sciences. It is also intended that the applicable safety test method requirements of the receiving regulatory authority would be used in a proposal for market entry. For example, if a proposal is to be submitted to the U.S. Food and Drug Administration, that agency's safety test requirements would have to be met. These guidelines do not provide specific details regarding test methodology and data interpretation. Test procedures that are generally recognized by experts and by the regulatory agencies should be used. Alternatives to the use of living animals are encouraged wherever these alternative procedures have been validated for the intended purpose and where it is known that the alternative procedure will provide sufficient data upon which to base a safety judgment. It is recommended that the *Guiding Principles on the Use of Animals in Toxicology* of the Society of Toxicology (1996) and, in other countries, the appropriate legal and professional codes, be adhered to in the conduct of all test procedures. All studies must meet the requirements of the appropriate national good laboratory practice guidelines in effect in the country where the studies are being conducted.

In cases of extensive human experience based upon food use, there may be sufficient information to fulfill the requirements of the guidelines for orally-ingested excipients only. In addition, there may be animal-based data, which was developed for other purposes, that may be used to fulfill the testing guidelines requirements. If the data requirements have been met through prior human use experience and pertinent human data have been collected in a scientifically sound manner, there is no need to provide animal data for those endpoints evaluated by prior clinical experience.

Some dosage routes offer unique toxicological challenges, and the guidelines include provisions for these routes (e.g., inhalation). Also, further explanation is provided regarding numbers of species and other basic information (e.g., two species, one rodent and one nonrodent).

The extent of information required to define a set of baseline data, which constitute a toxicological and chemical database, is dependent upon the intended use of, and duration of, dosing of the candidate excipient material. It is critical that a thorough review of background information be conducted before embarking on a testing regimen. In addition to literature database reviews, information should be obtained regarding the physical and chemical properties of the compound; its manufacturing process (or processes); and product specifications including limits of impurities, potential for pharmacological activity, exposure conditions (i.e., dose, duration, frequency of use, dosage formulation, and route of administration), and potential user population. Also, base toxicity information covering the topics is fundamental. Particular attention should be addressed to the absorption/distribution/metabolism/excretion/pharmacokinetics (ADME/PK) studies because much of the later decision process will be dependent upon these data.

These guidelines provide a mechanism for obtaining sets of baseline data for all candidate excipient materials. The background information and baseline toxicity information alone may support the use of the candidate excipient either in a short half-life product that is not administered in a frequency that results in a residual excipient build-up in body tissue or in a product used only once or twice in a lifetime, such as a diagnostic agent. Additional tests, listed under *Step 4* of the *Safety Assessment Guidelines*, are necessary for candidate excipient material that is to be used in a manner that will result in short- or intermediate-term repeated exposure in humans—that is, a pharmaceutical product that will be administered for less than 10 days or for 30 to 90 consecutive days, respectively. For a candidate excipient material that is intended for use in a pharmaceutical product intended for either intermittent or chronic administration over a long time period, such as a treatment for psoriasis or an insulin preparation, further tests are required. These tests are listed under *Step 7* of the guidelines and in the appropriate section under *Additional Requirements for Specific Exposure Routes*. While providing guidance for consumer safety, some of the required tests are intended to provide information to address occupational safety (e.g., skin and eye irritation).

The guidelines are summarized in *Table 1*. Tests that are required (R) by the guidelines are distinct from those that are recommended conditionally (C). Whether conditional tests are conducted is dependent upon the conditions of use and available biological data. Consideration must also be given to the requirements of the regulatory authorities when making the decision to test.

Table 1. Summary of Excipient Guidelines

	Routes of Exposure for Humans					
Tests	**Oral**	**Mucosal**	**Dermal/ Topical/ Trans-dermal**	**Injectable***	**Inhalation/ Intranasal**	**Ocular**
Baseline Toxicity Data						
Acute Oral Toxicity	R	R	R	R	R	R
Acute Dermal Toxicity	R	R	R	R	R	R
Acute Inhalation Toxicity	C	C	C	C	R	C
Eye Irritation	R	R	R	R	R	R
Skin Irritation	R	R	R	R	R	R
Skin Sensitization	R	R	R	R	R	R
Acute Injectable Toxicity	—	—	—	R	—	—
Application Site Evaluation	—	—	R	R	—	—
Pulmonary Sensitization	—	—	—	—	C	—
Phototoxicity/Photoallergy	R	—	R	R	R	—
Genotoxicity Assays	R	R	R	R	R	R
ADME/PK-Intended Route	R	R	R	R	R	R
28-Day Toxicity (2 Species)-Intended Route	R	R	R	R	R	R
Additional Data: Short- or Intermediate-term Repeated Use						
90-Day Toxicity (Most Appropriate Species)	R	R	R	R	R	R
Embryo-Fetal Toxicol.	R	R	R	R	R	R
Additional Assays	C	C	C	C	C	C

	Routes of Exposure for Humans					
Tests	**Oral**	**Mucosal**	**Dermal/ Topical/ Trans-dermal**	**Injectable***	**Inhalation/ Intranasal**	**Ocular**
Genotoxicity Assays	R	R	R	R	R	R
Immunosupression on Assays	R	C	C	R	C	C
Additional Data: Intermittent Long-term or Chronic Use						
Chronic Toxicity (Rodent, Nonrodent)	C	C	C	C	C	C
Reproductive Toxicity	R	R	R	R	R	R
Photocarcinogenicity	C	—	C	C	C	—
Carcinogenicity	C	C	C	C	C	C
R = Required C = Conditional						

* Intravenous, intramuscular, subcutaneous, intrathecal, etc.

SAFETY ASSESSMENT GUIDELINES

Background Information

Before proceeding to the steps under *Data Requirements and Checkpoints*, the following points should be reviewed and defined:

- Review literature information using all appropriate databases
- Define chemical and physical properties
- Define manufacturing process
- Define product specifications, including impurities and residual solvents (see applicable ICH guidelines)
- Estimate exposure conditions (dose, duration, frequency route)
- Define user population
- Assess potential for pharmacologic activity.

At this point evaluate what is known, and develop the initial approach to testing.

Data Requirements and Checkpoints

STEP 1

Toxicity Data (see *Baseline Toxicity Data*)

The toxicity data should take into account the following information:

- Effects of acute exposure by oral and intended routes
- Effects of repeated exposures by intended routes
- Effects of in vitro genotoxicity assays
- ADME/PK by oral or appropriate routes; single or multiple doses.

STEP 2

Depending on results of above, evaluate effects of a single dose in humans.

STEP 3

Checkpoint: Evaluate results of above and proposed exposure conditions and exposed population. The above data might allow use in a single product with a short half-life (e.g., a diagnostic agent).

STEP 4

Gather the following additional data:

- Effects of subchronic exposure in appropriate species and routes
- Embryo-fetal development studies via appropriate route of exposure
- Additional in vitro and in vivo genotoxicity tests.

STEP 5

Depending on results of above, consideration should be given to testing in humans as part of the clinical trials of an active ingredient or as a stand-alone procedure.

STEP 6

Checkpoint: Evaluate all of above information. Data might allow use in a variety of products intended for short-term, repeated intake (e.g., an antibiotic). If the ADME/PK studies for a noninjectable excipient show no absorption, data may permit using a product for 30 to 90 consecutive days.

STEP 7

Additional data should be obtained for use in a product taken chronically, either daily or intermittently, over a long time period depending on:

- Results of subchronic studies and long-term toxicity in appropriate mammalian nonrodents
- Reproductive toxicity studies
- Other test results and human exposure data and long-term toxicity or carcinogenicity in rodents.

Baseline Toxicity Data

The following data should be taken into account:

- Appropriate acute toxicity by intended dose routes: skin sensitization, approximate lethal dose method, limit test, etc.
- Other appropriate acute toxicity studies: oral toxicity by limit test or approximate lethal dose method, skin irritation, etc.
- ADME/PK: single or multiple doses.
- Genotoxicity: for example, Ames Test, in vitro chromosome aberration test, mammalian cell mutation assay.
- 28-day repeated dosing studies in two species by appropriate routes (one rodent, one mammalian nonrodent): evaluation of injection site or similar considerations might be necessary depending on route of administration.

[Note—1. In those cases where intended route restrictions (e.g., volume, concentration) preclude an adequate assessment of the toxicity of the excipient, development of a toxicity profile by other relevant routes may be needed.
2. The comparison of toxicity and ADME/PK data between oral and intended routes is critical at this point because that knowledge may set the direction for future toxicity testing (e.g., reproductive toxicity testing conducted by oral route rather than intended route). In addition, relevant studies using the intended route and anticipated duration of exposure may preclude performance of additional studies.]

Additional Requirements for Specific Exposure Routes

FOR ORAL EXPOSURE

No additional requirements beyond those presented for *Baseline Toxicity Data*.

FOR MUCOSAL EXPOSURE

No additional requirements beyond those presented for *Baseline Toxicity Data*.

FOR DERMAL, TOPICAL, OR TRANSDERMAL EXPOSURE

Baseline Toxicity Data

- *Effects of Acute Exposure by Transdermal Dose Route:* dermal sensitization study for repeat applications
- *Effects of Repeated Exposures by Transdermal Route*
    1. Photoallergy/phototoxicity study
    2. Studies in two species (one rodent, one mammalian nonrodent) by transdermal route.

- *Effects of Subchronic Exposure, Reproductive Toxicity Effects*—Initial toxicity studies may be performed by the IV route to adequately profile the toxicity of the excipient. This will provide an assessment of potential target organs if an adequate amount of the compound cannot be delivered via a transdermal dosage form. This is dependent upon the results from the ADME/PK studies.

Reproductive studies may also be conducted via oral or IV route with demonstration of absorption (oral) and pharmacokinetic comparisons of the chosen route versus transdermal.

Photocarcinogenicity studies may be required and should be considered if data and the proposed use indicate when evaluating materials to be placed on the skin for prolonged periods of time and exposure to UV light is a factor (e.g., sun block). This also applies to oral, parenteral, and inhalation products where skin drug concentrations exceed plasma drug concentrations for a substantial period of time, or where the candidate material would appear to have the potential for photo-activity or has demonstrated photo-activity.

FOR INJECTABLE DOSAGE FORMS

Background Information

1. Define compatibility of the dosage form with blood, if appropriate, based on route of exposure.
2. Define the pH and tonicity of injectable dose form, if appropriate, based on the route of exposure.

Baseline Toxicity Data

- *Effects of Acute Exposure by Intended Injectable Dose Routes*
    1. Include evaluation of injection site irritation in rabbit or dog
    2. Include evaluation of rate of administration.

FOR INHALATION OR INTRANASAL EXPOSURE[1]

Baseline Toxicity Data

- *Acute Inhalation Toxicity*—A limit test that would, for example, use the highest achievable concentration in a 4-hour exposure to vapor, aerosol, or solid particulate. Pulmonary sensitization may be performed along with other appropriate studies. If exposure is to be to an aerosol or solid particulate, particulates of appropriate mass median diameter should be generated.
- *Single and Repeated Dose ADME/PK by Inhalation or Intranasal and Oral Routes*
- *28-Day Repeated Dose Inhalation Study in Two Mammalian Species Using Vapor or Particulates of Appropriate Mass Median Diameter:* compare to similar oral toxicity data.

FOR OPHTHALMIC EXPOSURE

Background Information: define pH and osmolarity of topical ocular dose form.

Baseline Toxicity Data

- *Effects of Acute Exposure by Ophthalmic Routes:* cytotoxicity tests (e.g., agar overlay)
- *Effects of Repeated Exposures by Ophthalmic Routes*
    1. Studies in two species (one rodent, one mammalian nonrodent)
    2. Examination of anterior and posterior segments of the eye
    3. Studies on allergenicity potential.

Other Data—Comparison of pharmacokinetic parameters of the route chosen for reproductive studies and the ophthalmic exposure are essential for extrapolation of potential toxicity via the ophthalmic route.

GLOSSARY

Acute:
exposure to a test agent within a single, 24-hour period. Doses may be single, multiple or continuous during a 24-hour period.

Subacute:
repeated dosing of a test agent for up to 29 days. Daily doses may be single, multiple or continuous during a 24-hour period.

Subchronic:
repeated dosing of a test agent for 30 days to 10% of the lifespan of the test species (90 days in rodents). Daily doses may be single, multiple or continuous during a 24-hour period.

Chronic:
repeated dosing of a test agent for more than 10% of the lifespan of the test species (more than 90 days in rodents). Daily doses may be single, multiple or continuous during a 24-hour period.

[1] When designing studies to evaluate use in products intended for use by the inhalation or intranasal route, consideration should be given to the dosing regimen that will be used by humans. The appropriate study protocol for a product intended for inhalation therapy that will result in prolonged exposures (e.g., several hours per day) may differ from that used to evaluate a product that would result in exposure to several metered doses per day.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
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