The International Pharmaceutical Excipients Council

Safety Guide

For Pharmaceutical Excipients

First Version
2021

This document represents voluntary guidance for the excipient industry and the contents should not be interpreted as regulatory requirements. Alternatives to the approaches in this Guide may be used to achieve an equivalent level of assurance for excipient quality.

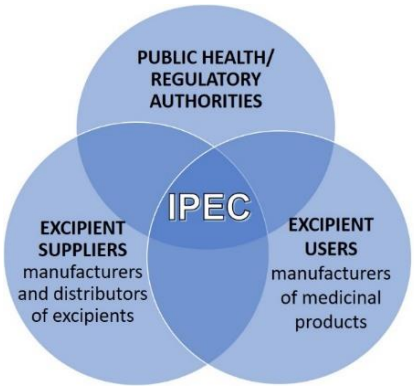
This guide was created to help companies understand current expectations on this topic and is not intended for use by third party certification bodies to conduct audits or to certify compliance with the guide.

FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors and users. At the current writing there are regional pharmaceutical excipient industry associations located in the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to the international excipient standards development and harmonization, provide information useful for new excipient development and introduction, and offer best practice and guidance concerning excipient development.

IPEC has three major stakeholder groups:

1. excipient manufacturers and distributors, defined as suppliers in IPEC documents,
2. pharmaceutical manufacturers, defined as users in this document, and
3. public health and regulatory authorities.



This guide offers best practice and guidance for the safety assessment of new pharmaceutical excipients. Recommended safety testing is based upon the best currently available toxicological science and has taken Guidelines of the International Council for Harmonization (ICH) into consideration. These guidelines were developed to address the toxicological testing of a material intended for use as an excipient in medicinal products.

NOTE: Refer to the "International Pharmaceutical Excipients Council Glossary: General Glossary of Terms and Acronyms[1] for definitions. The first use of a term found in the glossary will be in **BOLD**.

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1 INTRODUCTION

Excipients are **components** in a drug formulation having a functional purpose related to the performance of a **drug product**. Excipients can be macromolecular substances such as albumin, or substances such as amino acids and sugars that are used in drug and biological products. With advances in the technology of drug **dosage forms** and drug delivery systems, functional properties including preservation, solubility, release control, and disintegration have become more critical to issues of safety and bioavailability in modern drug products. Accordingly, a more appropriate definition for an excipient is:

"*A substance other than the active ingredient, which has been appropriately evaluated for safety and is included in a drug delivery system to:*

1) *aid in the processing of the drug delivery system during its **manufacture**;*
2) *protect, support, or enhance stability, (formulation feasibility,) bioavailability, or patient acceptability;*
3) *aid in product identification; or*
4) *enhance any other attribute of the overall safety and effectiveness of the drug during storage and use[2]"*

Recent advances in formulation technology have increased the need for new materials with enhanced properties to facilitate and improve active delivery. Excipient(s) used for the first time in a drug product or in a new route of administration are currently considered "novel**.**"[3]

Novel Excipients

A **novel excipient** generally refers to an inactive ingredient that has not been previously used in an approved drug product. However, regulators may view an excipient that has not been used in a particular route of administration or at levels above the precedence of use in an approved drug product as "novel." Even if an excipient has been extensively used in other approved, non-pharmaceutical applications, such as food or over-the-counter (OTC) products, it is still considered "novel" when used in drug products subject to regulatory approval. In general, excipient **users** are reluctant to use a novel excipient in a drug product as there is no certainty that a regulatory agency would find the available excipient safety information adequate. This uncertainty is greater for generic drugs as nonclinical and clinical studies are not required for regulatory approvals.

In the US, the FDA lists some excipients previously used in **synthetic** drugs in the FDA Inactive Ingredient Database (IID) for the intended route and level of administration.[4] However, the IID does not include excipients used in OTC and biologic drug products. Databases similar to the IID do not typically exist in other countries.

At the time of publication of this guide, with the exception of a pilot program for novel excipients review recently introduced by the US FDA, there is no independent review of novel excipients and

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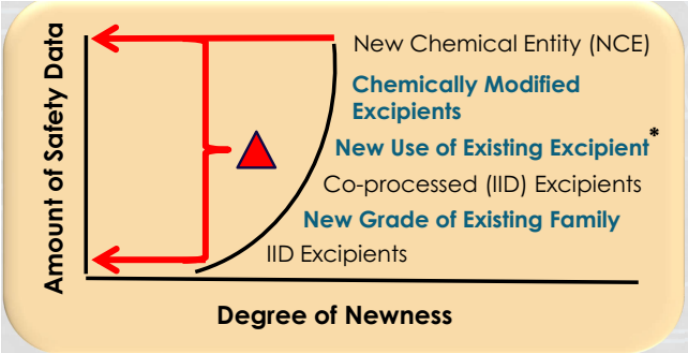
this guide is intended to provide information to assist in determining the level of safety information necessary to support the use of a novel excipient. Based on the type of novel excipient, different levels of safety information may be required, as shown in Figure 1.

Various types of excipients are currently considered novel excipients. For example:

- New chemical entities
- Modified excipients (generally polymers of the same family with varying chain length/molecular weight/substitution)
- New **co-processed excipients** made from two or more previously approved excipients
- Previously used excipients that are employed in a new route of administration or patient population
- Excipients used in an approved drug product but at a higher level of use than previously listed in the IID
- Approved food-use/cosmetic-use ingredient.

Figure 1 Safety data requirements are proportional to "degree of newness"



Target for bridging process/documentation support

* Higher level of use and/or different route of delivery/different patient population

A co-processed excipient is not a simple blend. Co-processed excipients are defined as follows:

> A co-processed excipient is a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without **significant** chemical **change**. However, in some instances, formation of necessary components may occur, such as in-situ salt formation. (IPEC Glossary[1] and Co-Processed Excipient Guide[5]).

The safety of a novel co-processed excipient may be based on the safety and toxicology of the individual components. It should be demonstrated that the components have only been physically combined, and not covalently altered in comparison to the corresponding physical blend. That is, the co-processed excipient component individual chemical identities are preserved. The safety of the co-processed excipient can then be bridged to the safety of the individual components, by analytical rather than toxicological means.

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Since there is currently no pathway for excipients to be evaluated independently from a drug product application, the current regulatory landscape, or lack of an independent excipient approval pathway is limiting the entrance of new excipients in the market and, subsequently, new drug products.

The **guidelines** discussed within this guide provide toxicological approaches to define safe conditions of use of new excipients. This tiered approach permits early evaluation of a new excipient in humans as soon as warranted by the safety data in animals. Provision has also been made for limited use as the excipient is developed.

Excipient Composition and Impurity Profile

Excipients are different from drug substances, and their composition can be very complex; therefore, it is important to have appropriate characterization of the excipient **composition profile**.[5] Defining excipient composition, including impurities, can be complicated. An excipient composition profile defines the material that is considered in the safety assessment and includes a description of the components present in typical excipient **lot**s produced by a defined manufacturing process. The primary excipient components contribute to excipient performance in drug products (also known as "**nominal**" components). Other potential components (e.g., **concomitant components**, **additives**, and **processing aids**) may also contribute to excipient performance. Unreacted starting materials, reaction by-products, degradants, elemental impurities, and residual solvents also may be present as a result of the excipient manufacturing process. These components may arise at different stages during excipient manufacture and are considered part of the excipient composition profile.

ICH M7 states that safety risk assessment principles of the guideline *can be used if warranted for impurities in excipients that are used for the first time* (novel excipients*) in a drug product and are chemically synthesized*.

1.1 Purpose and Scope

Building off of articles published by both IPEC-Americas (A New Approach to the Safety Assessment of Pharmaceutical Excipients[6]) and IPEC Europe (The Proposed Guidelines for the Safety Evaluation of New Excipients[7]) in 1996 and 1997, respectively, the IPEC Safety Guide gives an overview on recommended toxicological studies for different application forms, routes of administration and treatment periods. Toxicological safety studies described in this guide are intended for consideration by excipient **manufacturers** who market excipients for use in drug formulations and excipient users who conduct toxicology studies required for the initial approval of a novel excipient in a drug formulation. Excipient users formulating an excipient beyond its approved, prior use are responsible for conducting the appropriate safety studies.

Furthermore, the guide includes considerations for novel excipients based on their intended use in special patient populations when specific characteristics are necessary to address potential excipient hazard(s) such as: endocrine activity, nano character and biological occurrence. In

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addition, several recent approaches are discussed to demonstrate the safety of novel excipients in a state-of-the-art Weight of Evidence (WoE) approach.

A WoE approach should consider the following principles in safety evaluation of excipient(s).

1) Current regulatory guidelines
2) Existing safety data sets for the excipient under evaluation, conducted according to regulatory guidelines and in compliance with good laboratory practice (GLP) principles.
3) Studies designed to obtain the maximum amount of safety information with minimal use of animals (per 3Rs principles: Replacement, Reduction, Refinement).
4) Studies used the expected route of human exposure.
5) The duration of the safety studies determined by the intended use.
6) Selection of the most appropriate species begins with rodent and non-rodents. Further refinement of species selection also depends on data obtained from preliminary pharmacology/pharmacokinetics, ADME and short-term systemic or topical toxicity results or other relevant data.
7) Stepwise toxicological safety testing requirements serve as the global regulatory approach by considering 3Rs principles.
8) New Approach Methodologies (NAMs) should be considered for safety assessment of novel excipients on a case-by-case situation, when appropriate.

The guidelines referenced are intended to be used by scientists having a knowledge of toxicology and associated scientific and regulatory disciplines.

Extensive human experience based on food or cosmetic use could minimize some of the needed testing for oral and topical dosage forms, respectively. In addition, animal-based data developed for other purposes may be used to fulfil toxicology safety testing guideline requirements. Relevant human data collected in a scientifically sound manner may preclude the need to collect animal data for those endpoints.

1.2 Principles Adopted

This guide was developed with US and European focus, but the scientific principles applied should support the usage of the excipient internationally, acknowledging that chemicals used as excipients in pharmaceutical drug products often have uses other than as pharmaceutical ingredients. In addition, excipients are often used within broad and diverse finished dosage form ranges. As an international guide, this document does not specify legal requirements, include excipient safety requirements for every nation or locality or apply to particular characteristics of all excipients. Current safety related guidelines of the ICH of Technical Requirements for Pharmaceuticals for Human Use do not apply to either existing or novel excipients. This IPEC guide was developed to provide appropriate safety evaluation concepts for all excipients.

New methodologies for safety assessment are being developed and this guide includes information related to some potential alternative methodologies that can be considered when

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evaluating the safety of an excipient. New programs, such as Tox21[8], EU-ToxRisk[9] and The European Partnership for Alternative Approaches to Animal Testing,[10] are exploring these new methodologies.

2 SAFETY TESTING GUIDELINES FOR EXCIPIENTS

The type of exposure experienced for excipients differs from APIs and food additives. The safety of excipients is based upon regulatory review, applying the principles of basic regulations on medicinal products like the European Union (EU) Directive 2001/83/EC,[11] Japan's Pharmaceutical and Food Safety Bureau (PFSB), Ministry of Health, Labour and Welfare (MHLW) Notification No. 1121-2[12] or the US Food, Drug, and Cosmetic Act[13] and approval of drug products.

This guide does not specifically address the toxicology safety assessment of excipient **mixtures**, or co-processed excipients; however, many of the published FDA and ICH toxicology guidelines can be applied for evaluation and should be considered on a case-by-case basis. Although exposure to an excipient parallels the drug exposure categories, the overall exposure is less well controlled because patients can be exposed to a given excipient in several different dosage forms for different clinical indications and for varying lengths of treatment times. Food additives are similar to excipients in that they are added to foods in low levels to impart specific functional characteristics, but exposure is even less well controlled. Appropriate safety assessment should be based on realistic exposure.

2.1 Study Overview

Studies to be conducted are determined by the adequacy of available data, route of administration and duration of intended human exposure. This guide provides for a tiered approach based on the chemical and physical properties of the excipient, review of the scientific literature, exposure conditions (including dose, duration, frequency, route, and user population), and absence or presence of pharmacological activity.

Alternatives to the use of living animals are encouraged wherever these alternatives procedures have been validated, will provide sufficient data upon which to base a safety judgment, and will be acceptable to a regulatory agency. It is strongly recommended that the *Guiding Principles of the Use of Animals in Toxicology* of the Society of Toxicology,[14] and, in other countries, the appropriate legal and professional codes be followed in the conduct of all tests. All studies should be conducted according to best practice; e.g., those that are in effect in the country in which the studies are being conducted or according to the requirements of the agency/agencies which will receive this data.

2.2 Excipient Characterization

2.2.1 *Physical/Chemical Composition and Characterization*

An excipient composition profile may be defined as a description of the components present in typical excipient lots produced by a defined manufacturing process. The primary excipient

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components are those which, in most cases, contribute to excipient performance in drug products where used (also known as "**nominal**" **components**). Other necessary components may also be present, i.e., concomitant components, additives, and processing aids, which contribute to excipient performance. Unreacted starting materials, reaction by-products, **degradants**, elemental impurities, and **residual solvents** also may be present as a result of the excipient manufacturing process. These components may arise at different stages during excipient manufacture and are considered part of the excipient composition profile.[15]

For many excipients, it may not be possible to classify and quantify all components. The composition-related methods and **specifications** should be justified. There are many well-established excipients for which it is neither feasible nor necessary for safety purposes to identify all components and to (re-)evaluate safety unless scientific evidence becomes available that suggests otherwise. Where feasible, composition profile generation should involve identification, classification, and quantification (expressed as a range) of each component or, if unidentified, an appropriate qualitative description such as peak retention time. A reasonable reporting threshold should be no more prescriptive than for APIs as found in ICH **impurity** guidelines.

2.2.2 *Pharmacokinetics/Toxicokinetics*

It is recommended to obtain information on the toxicokinetics (TK) and/or pharmacokinetics (PK) in the body, i.e., on its absorption, distribution, metabolism and excretion (ADME) in order to decide what safety data are needed for excipients.

A literature search should be conducted and all available published data should be reviewed before the **commissioning** of animal testing. A number of databases (e.g., ECHA[16] , WHO[17], OECD[18]) from where TK/PK data may be retrieved, for example a complete list of synonyms, together with the CAS number and Unique Ingredient Identifier Number (UNII) [19] of the excipient, when available, enables a thorough literature search for PK data of the excipient and/or related compounds. Ingredients in the same chemical class that have been demonstrated to be very similar in their chemical structures and physicochemical properties should also be included in the search.[20]

There are also cases where a complete ADME/ TK/PK study cannot be conducted because of complex nature of the excipient (e.g., co-processed excipients, excipients from botanical origin), analytical challenges or biotransformation to physiological products (e.g., sugar esters), etc., these indications may trigger a WoE approach in the absence of ADME/TK/PK test results. A strong, well-documented argument will be required using existing data. In order to facilitate a transparent and systematic approach for read-across exercise, more discussion is presented in Section 1.1 of this guide.

In recent years TK/PKs prediction have made a great progress, including *in silico* tools[21] and physiologically-based pharmacokinetic models (PBPK)[22,23,24] to estimate ADME/PK properties of compounds. Some models predict TK/PK behavior of a substance based on properties, e.g., molecular weight[25], water solubility, n-octanol/water partition coefficient, acidity, electrophilicity[26],

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surfactant activity, membrane irritation, skin permeability and toxicity data, *etc.*, in certain instances, *in vitro* techniques[27] provide confirmation of the TK/PK effects.

Based on all the previous steps, a decision should be made as to whether the available information is sufficient and adequate to properly conclude on ADME/TK/PK, or the definitive evidence should be conducted in whole animals. The studies may employ the same species that are used in the nonclinical safety studies, routes of administration, duration and frequency of exposure to correlate with the clinically relevant route(s), frequency and duration.[28,29] The route of administration may place a limitation on the amount of a substance absorbed, because it is not necessarily equivalent to systemic bioavailability, i.e. the oral profile of the excipient can be influenced by its intestinal and hepatic first-pass effect.[30] Although first pass metabolism is less significant for topical and transdermal administrations, cutaneous absorption depends on various factors (e.g. application at a specific body region, surface area, rheological behavior, *etc*.),[31] different *in vitro*[32] or *in vivo* methods have been developed to assess skin penetration and permeation.

The base toxicity set and additional data are shown in the table below. Overall, ADME/TK/PK data should be generated on a case-by-case basis with justification for the conclusion drawn.

Table 1: Pharmacokinetic/Toxicokinetic Profile

List of global regulatory Guidance to consider:
ICH S3A: Note for Guidance on Toxicokinetic: The Assessment of Systemic Exposure in Toxicity Studies.28
ICH S3B: Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies. [29]
ICH M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals[33]
OECD TG 417: Toxicokinetics.[34]
OECD TG 427: Skin Absorption: *in Vivo* Method.[35]
OECD TG 428: Skin Absorption: *in Vitro* Method.[36]
Other dermal absorption studies to consider:
ECETOC Monograph 20: Percutaneous Absorption.[37]
EFSA Guidance on dermal absorption for plant protection products.[38]
EPA/600/R-07/040F: Dermal Exposure Assessment: A Summary of EPA Approaches.[39]
OECD TA 156: Guidance Notes on Dermal Absorption.[40]
OECD TA 28: Guidance Document for the Conduct of Skin Absorption Studies.[41]
WHO/IPCS EHC 235: Dermal Absorption.[42]

2.3 Methods – Duration

The following sections provide a tiered approach to evaluating the safety of excipients. Factors such as dose, duration of exposure, frequency, administration route, and potential user population should be considered when designing a study program for excipients.

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The duration of exposure tiered testing strategy is based on the length of proposed clinical exposure to a drug product containing the excipient. It is defined by three categories:

1. Excipient intended for single clinical exposure: For use in a drug product that may be used only once or twice in a lifetime, e.g., a diagnostic agent.
2. Excipient intended for repeat clinical exposure: For use in a drug product to be used more extensively, but not considered to be long-term.
3. Excipient intended for long-term clinical exposure: For use in a drug product to be taken intermittently or chronically over a long period of time as in an insulin treatment or treatment for psoriasis or migraine headache.

Note that the tiered testing strategy builds upon the previous category. For example, testing for an excipient intended for repeat clinical exposure would include the testing outlined in 2.3.3 as well as 2.3.1 Safety Pharmacology and 2.3.2 Excipient intended for single clinical exposure. Studies for consideration under each of these durations of clinical exposure are further highlighted in Table 10.

Table 2: Comparison of Clinical Exposure Terminology and Description

2021 IPEC Safety Guide	Steinberg et al, 1996[6]	FDA Guidance, 2005[43]
2.3.2 Excipient intended for single clinical exposure	Single or limited exposure in humans "…product that may be used only once or twice in a lifetime, e.g., a diagnostic agent"	Short term use. "…products that are limited by labeling to 14 or fewer consecutive days per treatment episode and are infrequently used…"
2.3.3 Excipient intended for repeat clinical exposure	Limited and repeated exposure in humans. "…if the candidate material is to be used more extensively…"	Intermediate use. "…drug products that are labeled for clinical use of more than 2 weeks but less than or equal to 3 months per treatment episode…"
2.3.4 Excipient intended for long-term clinical exposure	Long-term exposure in humans. "…product to be taken intermittently or chronically over a long period of time as in an insulin treatment or treatment for psoriasis or migraine headache..."	Long-term use. "…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…"

2.3.1 *Safety Pharmacology*

Evaluation of pharmacological activity on major organ systems (e.g., central nervous system, cardiovascular, respiratory systems) can provide valuable information during the early stages of development and inform the appropriateness of the excipient. Although not specifically listed in base set of toxicology studies (refer to Tables 1, 3, 4 and 5), the FDA recommends[43] that all new excipients, in which no prior human exposure has been documented, be evaluated for safety pharmacology using standard tests as described in ICH S7A[44] or as part of standard repeat dosing toxicology studies in-life assessments.

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2.3.2 *Excipient Intended for Single Clinical Exposure*

Data to be developed should define safe exposure conditions and potential adverse effects for the user and for workers involved in manufacturing the excipient. The base set should include measurement of the effects of acute exposure by intended routes and mutagenicity/genotoxicity assays.[45,46] Absorption, distribution, metabolism, excretion, and pharmacokinetic (ADME/PK) assays by oral and/or appropriate routes should be conducted following single-dose. Data from existing single-dose studies (including six-pack studies[47]) can be leveraged whenever they are available according to a WoE approach [refer to Section 1.1]. Single-dose studies may not be necessary if sufficient data to support a single-dose can be obtained from repeat-dose studies, although single-dose studies may be necessary for other regulations (transportation, safety data sheet, etc.). The data are critically evaluated and may support the use of the new excipient either in a product with a short half-life that will not be given at a frequency that would provide for residual excipient in body tissues or in a product that may be used only once or twice in a lifetime, e.g., a diagnostic agent.

Various regulatory agencies globally have different requirements for specific genotoxicity test batteries. To rapidly assess a chemical's genotoxicity potential, a preliminary mutagenic screening approach may be used. This approach is based on following ICH M7 (R1).[48] This guidance outlines a computational assessment employing a QSAR platform to classify a chemical's mutagenicity potential based on results from the Ames Assay. This classification starts with a Class 1 designation for a known mutagenic carcinogen to a Class 5 designation as a non-mutagen. This *in silico* approach does not addresses the issue of the potential for non-genotoxic carcinogens. If a mutagenic impurity is found, further *in-vitro* or *in-vivo* studies would be necessary. Any proposed QSAR models[49,50,51,52] should be validated and built using the current best practices for regulatory acceptance.

To evaluate genotoxic potential, the minimum data set should include the assessment of genetic mutations and chromosomal damage.[53] A combination of both *in vitro* and *in vivo* tests may allow a WoE assessment to help define the concern for potential human safety. Two options for equally acceptable test batteries are provided in the ICH S2(R1) guidance.[54] Where there are equivocal results or positive results, confirmatory testing[55,56] may be conducted.

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 route(s) may be appropriate.

(2) The comparison of toxicity and ADME/PK data between oral and intended routes is critical at this point because that knowledge may determine 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. Refer to ICH S3A/S3B and OECD TG 417 for additional

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considerations. For most compounds, it is expected that single-dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation.

(3) The Table 3 below and Table 10 lists studies for consideration; however, not all studies may be required and the studies selected should align with and be based on a company's regulatory assessment and safety testing strategies.

Table 3: Intended for Single Clinical Exposure

List of global regulatory Guidance to consider:

ICH S2 (R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use.[54]

ICH S3A: Note for Guidance on Toxicokinetic: The Assessment of Systemic Exposure in Toxicity Studies.28

ICH S3B: Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies.[29]

ICH M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals[33]

OECD TG 417: Toxicokinetics.[34]

OECD TG 471: Bacterial Reverse Mutation Test.[57]

OECD TG 473: *In Vitro* Mammalian Chromosomal Aberration Test.[58]

OECD TG 474: *In Vivo* Mammalian Erythrocyte Micronucleus Test.[59]

OECD TG 476: *In Vitro* Mammalian Cell Gene Mutation Test using the HPRT and XPRT genes.[60]

OECD TG 487: *In Vitro* Micronucleus Study.[61]

OECD TG 490: *In Vitro* Mammalian Cell Gene Mutation Test using the Thymidine Kinase Gene.[62]

Additional genetic toxicology tests to consider based on results from standard test above:

OECD TG 488: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays.[55]

OECD TG 489: *In Vivo* Mammalian Alkaline Comet Assay.[56]

2.3.3 *Excipient Intended for Repeat Clinical Exposure*

Repeat dosing refers to testing from 10-14 days up to chronic exposure. Prior to conducting repeat-dose studies, appropriate genetic toxicity studies should be performed as per Table 3. If the candidate material is to be used more extensively, additional testing is recommended (Table 4). This should include effects of sub-chronic exposure in appropriate species via the intended route of use. Most common species for the repeated dose studies are the rat (rodent) and the dog (non-rodent), however, alternative species may be used if scientifically justified. Embryo-fetal development (EFD) should be performed in rats and rabbits according to ICH requirements.[63] Assessment of mutagenicity data from the base set may trigger additional *in vitro* or *in vivo* studies on a case-by-case basis.[54, 33,64,] All studies proposed should be based on previous findings, identified toxicokinetic properties and the intended use of the new excipient.

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Specific safety concerns may require repeated-dose tissue distribution studies; however, they should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated-dose distribution studies may be appropriate under certain circumstances based on the data from single-dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half-life, incomplete elimination or unanticipated organ toxicity. (ICH S3A).

Note:

(1) Table 4 and Table 10 list studies for considerations; however, not all studies may be required. Studies selected should align with a company's regulatory assessment, existing guidance[33] and safety testing strategies.

Table 4: Intended for Repeat Clinical Exposure

List of global regulatory Guidances to consider:
Refer to Table 3 for relevant genotoxicity studies, studies below are most relevant to repeat dosing.
OECD TG 407; Repeated 28-day Oral Toxicity Study in Rodents.[65]
OECD TG 408: Repeated Dose 90-day Oral Toxicity Study in Rodents.[66]
ICH M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals[33]
Special population considerations:
ICH S5(R3); Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.[63]
OECD TG 414: Prenatal Development Toxicity Study (rat, rabbit).[67]

2.3.4 *Excipient Intended for Clinical Long-Term Exposure*

Long-term exposure refers to testing, generally 6-24 months in duration. Prior to conducting long-term studies, appropriate genetic toxicity studies should be performed. If the excipient is to be used in a product that is to be taken intermittently or chronically over a long period of time, as in an insulin preparation or treatment for psoriasis or migraine headache, additional data will be necessary (see Table 5). Long-term studies should be conducted in appropriate rodents and non-rodents, and the experimental conditions should be established by the sub-chronic studies. Chronic toxicity testing for excipients can be considered using the ICH development plan.[33] A 6-month rodent study and a 9-month non-rodent study are discussed in the ICH Guidelines.

Performing carcinogenicity studies for an excipient should take into consideration, on a WoE basis, factors including potential results from studies such as genotoxicity (Table 3, ICH M7), ADME, repeat-dose and in-life findings. These studies and findings can be used to support a waiver for conducing rodent life-time study.[68] Another evaluation factor may include previous toxicological data related to the carcinogenic potential of a specific product class. It is

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recommended that proposed carcinogenicity studies for an excipient be discussed with the regulatory authorities prior to study initiation.

Fertility and Early Embryonic Development (FEED) studies should be conducted to assess any excipient-induced effects in mating behavior/fertility. Embryo-Fetal Development (EFD) and a Pre-and Post-Natal Development (PPND) studies are generally required.[63] The ICH Guidelines provide various options for evaluating reproductive risk, including the conduct of a single study with a combination of fertility, gestation, and postnatal development endpoints. The number of animals tested can be reduced by conducting a *Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test*.[69]

Note:

(1) Table 5 and Table 10 list studies for considerations; however, not all studies may be required. Studies selected should align with a company's regulatory assessment and safety testing strategies.

Table 5: Intended for Clinical Long-Term (Chronic) Exposure

List of global regulatory Guidances to consider, in addition to testing conducted in repeat dosing:

Refer to Table 3 for relevant genotoxicity studies. Studies below are most relevant to long-term dosing

ICH S4; Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing).[70]

ICH S5(R3); Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.[63]

ICH M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals[33]

Special considerations for novel excipients:

ICH S1A: Guideline on the Need for Carcinogenicity Study of Pharmaceuticals.[71]

ICH S1B: Testing for Carcinogenicity of Pharmaceuticals.[72]

ICH S1C(R2): Dose Selection for Carcinogenicity Studies of Pharmaceuticals.[73]

OECD TG 416: Two-Generation Reproduction Toxicity[74]

OECD TG 421*: Reproduction/Developmental Toxicity Screening Test.[75]

OECD TG 422*: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test.[69]

OECD TG 443: Extended One-Generation Reproductive Toxicity Study[76]

OECD TG 451: Carcinogenicity Studies[77]

0ECD TG 452: Chronic Toxicity Studies[78]

0ECD TG 453: Combined Chronic Toxicity/Carcinogenicity Studies[79]

**** when also considered to be sold as a chemical***

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2.4 Methods – Route of Administration

In addition to studies outlined in Table 5 for long-term exposure, alternative clinically relevant routes of administration must be considered in addition to the previous long-term toxicity studies.

EMA further specifies[80] that antimicrobial preservatives must not be added to medicinal products intended for use by any route of administration that will give access to the cerebrospinal fluid or in products that will be injected retro-ocularly.

Some testing regimes, although currently recommended by regional regulators may not be acceptable in all regions.

2.4.1 *Transdermal and Topical Exposure*

The base set and additional studies described and delineated in Tables 1, 3, 4 and 5 are all that are necessary if the route of use is oral or mucosal. If the intended route is transdermal, then the base set is adjusted accordingly (Table 6).

Acute dermal irritation represents a local, reversible inflammatory response of the living skin after a single or short-term application of an irritant substance. By contrast, skin corrosion is defined as an irreversible damage of the skin. To study irritant and corrosive effects of chemicals, a study on animals such as OECD TG 404[81] is no longer recommended. If a primary dermal irritation/corrosion assay is warranted, then a 3-dimensional reconstructed tissue model is (OECD TG 439[82]) is to be considered. The reconstructed human epidermis model closely mimics the biochemical and physiological properties of the upper parts of the human skin and several commercially test methods adhere to this test guideline. The potential for milder forms of dermal irritation could, for example, be evaluated during the repeat-dose dermal toxicology study; a standalone skin irritation study is therefore not considered to be needed.[83]

Regarding skin sensitization, generally, three *in vivo* animal test methods accepted by regulators have been used to evaluate the potential of a substance to cause skin sensitization, the Local Lymph Node Assay (LLNA) in mice, the Magnusson Kligman Guinea Pig Maximization Test (GPMT) and the Buehler test. The GPMT and Buehler tests are able to provide results on induction and elicitation; the LLNA only addresses induction.[40] The US FDA is now recommending an alternative to LLNA for topical drug products.[84,85] Compared to the Guinea pig tests, the LLNA reduces the number of animals used and refines the treatment and is therefore the method of choice for animal welfare reasons. Moreover, the LLNA provides dose-response information which can be later used for risk assessment.

Recently, several alternative approaches have been developed, validated and accepted by regulatory agencies that assess different key events on the skin sensitization Adverse Outcome Pathway (AOP).[83,86,] An integrated testing strategy combining *in silico* read across, *in chemico* and *in vitro* studies using human derived cells should therefore also be acceptable for **hazard** identification of skin sensitization.

Phototoxicity/allergy testing is only required if the excipient is both dermally applied and absorbed in the UVB/A/vis range to a relevant extent and generates reactive species following absorption

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of UV/vis light.[83,87] The 3T3 Neutral Red Uptake Photo-toxicity Test (3T3 NRU PT) is a validated *in vitro* method based on the comparison of the cytotoxicity of a chemical in presence and in the absence of exposure to a non-cytotoxic dose of UV/vis light (SCCS 2019). It may be used as a screen, followed by *in vivo* test(s) to confirm positive *in vitro* results.[83] However, no standardized study design has been established for phototoxicity testing in laboratory animals.[87]

The ADME/PK studies are important when considering potential systemic toxicity. In the absence of data, 100% dermal absorption can be assumed to cover a 'worst case' scenario. For cosmetic applications, many regulatory authorities consider an arbitrary default value to be 10% if the molecular weight is greater than 500 and log P_{ow} is either below –1 or above 4,[40,86] suggesting that insufficient material is absorbed transdermally to produce systemic effects.

According to ICH (ICH S10 2015 note 2 and ICH M3(R2) 2009 note 6), testing for photo-genotoxicity and photocarcinogenicity in rodents is currently not recommended or considered useful for support of human pharmaceutical development. If the phototoxicity assessment suggests a potential photocarcinogenic risk and an appropriate assay becomes available, the study should be conducted, and the results should be considered in the human risk assessment.

Much of what has been written here regarding the transdermal route of exposure applies to use of the candidate material in a topical preparation (e.g., sun screen). The specific addition to the base set found in the table below.

Note:

(1) Table 6 and Table 10 list studies for considerations; however, not all studies may be required. Studies selected should align with a company's regulatory assessment and safety testing strategies.

Table 6: Transdermal and Topical Exposure

List of global regulatory Guidances to consider in addition to studies outlined in Table 1, 3, 4 and 5:
ICH S3B: Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies.[29]
ICH S10: Photosafety Evaluation of Pharmaceuticals.[87]
Neutral Red Uptake Assay for the estimation of cell viability/cytotoxicity.[88]
OECD TG 402: Acute Dermal Toxicity.[89]
OECD TG 404: Acute Dermal Irritation.[81]
OECD TG 406 Skin Sensitisation (Guines-Pig Maximisation Test method, Buehler Test method).[90]
OECD TG 429: Local Lymph Node Assay.[91]
OECD TG 430: *In Vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test method (TER).[92]
OECD TG 431: *In Vitro* Skin Corrosion: Reconstructed Human Epidermis Test method.[93]
OECD TG 432 *In Vitro* 3T3 NRU Phototoxicity Test.[94]
OECD TG 439 *In Vitro* Skin Irritation Reconstructed Human Epidermis Test method.[82]

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OECD TG 442C: In Chemico Skin Sensitization Assays addressing the Adverse Outcome Pathway key event on covalent binding proteins.[95]

OECD TG 442D: *In Vitro* Skin Sensitization Assays Addressing the AOP Key Event on Keratinocyte Activation.[96]

OECD TG 442E: *In Vitro* Skin Sensitization assays addressing the Key Event on activation of dendritic cells on the Adverse Outcome Pathway for Skin Sensitization.[97]

FDA Guidance: Transdermal and Topical Delivery Systems – Product Development and Safety Considerations.[98]

FDA Guidance: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs.[99]

Additional studies to consider:

Human repeat insult patch test (HRIPT).[100]

OECD TG 427: Skin Absorption: *in Vivo* Method.[35]

OECD TG 428: Skin Absorption: *in Vitro* Method.[36]

Refer to IVRT in Section 3.4.2.1.2

2.4.2 *Parenteral Dose Forms*

Similar to other routes of administration there is a base toxicity study set required to qualify the excipient for parenteral administration even if the excipient has been qualified by other routes. Unique assessments to the parenteral route (e.g., I.V., I.M., S.C.) include an evaluation of the injection site toxicity performed in rabbits or dogs and evaluation of the impact of rate of administration (e.g., bolus vs infusion). See Table 7 for additional toxicology studies to consider when assessing longer durations of exposure (e.g., short- or intermediate-term repeat use and intermittent long-term or chronic use).

Other important considerations prior to qualification should include:

- Low bioburden or be produced as pyrogen-free
- Define compatibility of dose form with blood (hemolytic potential)
- Define pH and toxicity of injectable dose form

Note:

(1) Table 7 and Table 10 list studies for considerations; however, not all studies may be required. Studies selected should align with a company's regulatory assessment and safety testing strategies.

(2) Acute toxicity may also be obtained by performing repeat-dose studies (ICH M3(R2)).

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Table 7: Parenteral Dose Forms

List of global regulatory Guidances to consider <u>in addition to studies outlined in Table 1, 3, 4 and 5</u>
FDA Guidance. Single Dose Acute Toxicity Testing for Pharmaceuticals.[101]
USP <85> Bacterial Endotoxins Test.[102]
USP <151> Pyrogen Test (USP Rabbit Test).[103]
ASTM F756: Hemolytic Potential.[104]

2.4.3 *Inhalation or Intranasal Exposure*

For excipients to be used in products intended to have inhalation or intranasal exposure, apart from the base set toxicity studies (Tables 1, 3-5), additional studies are required to evaluate safety towards respiratory system. In addition, the systemic exposure following administration of excipient through inhalation route needs to be characterized. In general, if the toxicokinetics (TK) and systemic exposure after inhalation administration is known, route-to-route extrapolation can be performed to evaluate dose equivalence and systemic toxicity studies by oral route can be leveraged to waive certain studies by inhalation route.[105]

Prior to the use of an excipient for inhalation, the following studies should be conducted:

The MMAD (mass median aerodynamic diameter) of particulates and aerosol needs to be evaluated to ensure appropriate exposure. The particle size (MMAD) should be between 1-4 microns to ensure particles are respirable.[106] The duration of exposure should be minimum 4 hours in pharmacokinetic and acute inhalation toxicity studies.

For this route of delivery, single-dose pharmacokinetic studies are required to be conducted at different doses by inhalation or intranasal route and compared with oral route to understand the absorption and disposition kinetics to evaluate the systemic exposure and establish ADME properties. If route to route extrapolation is not used, a comparison of ADME though inhalation exposure should be performed with other routes.

Repeat-dose inhalation toxicity studies of appropriate duration should be conducted in two mammalian species (one rodent and one non rodent) using vapors/particulates/aerosols with appropriate particle size and size distribution.[105] The particle size needs to be characterized during inhalation toxicity studies. The inhalation toxicity studies should be able to establish appropriate safe doses for local lung toxicities as well as systemic effects. Toxicokinetics should be an integral part of inhalation toxicity studies.

Bioequivalent studies that demonstrate systemic equivalence exposure by different routes of administration supports further discussion with regulatory agencies for a biowaiver to conduct additional reproductive and carcinogenicity studies. With the exception of pulmonary toxicity studies, which fall into their own special classification of safety assessment.

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The local effects on lung and nasal mucosa need to be evaluated which is usually assessed during repeat-dose inhalation toxicity studies and no separate studies would be required. The possibility of leveraging ocular or oral mucosal irritation studies for mitigating nasal irritation can also be explored if the proper concentrations and chemical forms can be compared.

Limit tests; e.g., use the highest achievable concentration in 4-hr exposure to vapor, aerosol, or solid particulate. Pulmonary sensitization potential should be assessed, if deemed necessary, along with generating other appropriate particulates of appropriate mass median diameter.

Note:

(1) Table 8 and Table 10 list studies for considerations; however, not all studies may be required. Studies selected should align with a company's regulatory assessment and safety testing strategies.

Table 8: Inhalation or Intranasal Exposure

List of global regulatory Guidances to consider <u>in addition to studies outlined in Table 1, 3, 4 and 5</u>
OECD TG 433: Acute Inhalation Toxicity – Fixed Concentration Procedure.[107]
OECD TG 436: Acute Inhalation Toxicity – Acute Toxic Class Method.[108]
ICH S5(R3): Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.[63]
OECD 412: Subacute Inhalation Toxicity: 28-day Study.[109]
OECD TG 413: Sub-chronic Inhalation Toxicity: 90-day Study.[110]
ICH M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals[33]

2.4.4 *Ophthalmic Exposure*

Excipients intended for use in topical ocular preparations require additional tests and modifications to the base set. These are delineated in Table 9. The pH, tonicity and local and systemic toxicity of the intended topical ocular dose formulation should be evaluated, rather than for the excipient in isolation. Ocular irritation can be assessed primarily by cell-based and alternative, non-animal method examples of which are listed in Table 9 below.

Alternative, non-animal methods have made significant progress in the area of topical ocular irritation to the point they have effectively eliminated *in vivo* animal tests for monitoring ocular irritation.

In vivo ocular irritation studies are no longer recommended as a measure of excipient safety evaluation in topical ocular drug formulations; however, these tests may be necessary to meet other regulatory requirements. When necessary to conduct animal studies it should be noted that

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rodents are not appropriate for ophthalmic toxicity evaluation and that two non-rodent species should be used in excipient studies. Additionally, a toxicokinetic/pharmacokinteic arm should be included in ophthalmic studies to properly evaluate ADME via this route of exposure (see section 2.2.2).

Other ocular considerations, when designing a safety testing paradigm include considering the pH, tonicity, and physical form of the dosing formulation (e.g., solution, suspension, ointment). If the pH value is too high or too low, irritation of the conjunctiva and corneal epithelium may occur. The concept of Integrated Approach to Testing and Assessment (IATA) is possible for the ophthalmic endpoint due to the number and validity of *in vitro* methods. The OECD guidance[111] IATA for serious eye damage and irritation is a useful guide in assessing ocular toxicity.

Note:

(1) Table 9 and Table 10 list studies for considerations; however, not all studies may be required. Studies selected should align with a company's regulatory assessment and safety testing strategies. Consideration should be given to combinations of multiple studies to fully investigate the ocular toxicity endpoint.

Table 9: Ophthalmic Exposure

List of global regulatory Guidances to consider <u>in addition to studies outlined in Table 1, 3, 4 and 5</u>
pH and Tonicity of Ophthalmic Solutions.[112]
OECD TG 405: Acute Eye Irritation/Corrosion.[113]
NIH 07-4517: *In Vitro* Ocular Toxicity Test Method for Identifying Severe Irritants and Corrosives.[114]
OECD TG 460: Fluorescein Leakage Test Method for Identifying Ocular Corrosives and Severe Irritants.[115]
OECD TG 437: Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants.[116]
OECD TG 438: Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe irritants.[117]
OECD TG 491: Short Time Exposure *In vitro* Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage.[118]
OECD TG 492: Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage.[119]
OECD TG 496: *In vitro* Macromolecular Test Method for Identifying Chemicals Inducing Serious Eye Damage and Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage.[120]

2.5 Other routes of delivery

The routes of delivery reviewed in this guide are considered to be the primary routes of delivery; however, the authors recognize that there are other routes of delivery which are not discussed here.

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2.6 Discussion

Table 10 is a synopsis of proposed and/or existing excipient safety assessments first developed and published in 1997 by IPEC Europe.[7]

Table 10: Safety Assessment of Excipients[a]

	Routes of Human Exposure					
Tests	**Oral**	**Mucosal**	**Transdermal/ Topical**	**Parenteral**	**Inhalation/ intranasal**	**Ophthalmic**
Single Clinical Exposure						
Acute oral toxicity [b, c]	R	R	R	R	R	R
Acute dermal toxicity [b, c]	R	R	R	R	R	R
Acute inhalation toxicity [b, c]	C	C	C	C	R	C
Eye irritation [b, c]	R	R	R	R	R	R
Skin irritation [b, c]	R	R	R	R	R	R
Skin sensitization [b, c]	R	R	R	R	R	R
Acute parenteral toxicity [c]	-	-	-	R	-	-
Application site evaluation [c]	-	R	R	R	R	-
Phototoxicity/photo-allergy [c]	-	-	R	-	-	-
Genotoxicity assays	R	R	R	R	R	R
ADME- intended route	R	R	R	R	R	R
Repeated Clinical Exposure						
28-day toxicity (2 species) intended route	R	R	R	R	R	R
90-day toxicity (most appropriate species)	R	R	R	R	R	R
Embryo-fetal development, EFD (rat and/or rabbit)	R	R	R	R	R	R
Long-term Clinical Exposure						
Chronic toxicity (rodent, nonrodent)	C	C	C	C	C	C
Additional developmental and reproductive toxicity	R	R	R	R	R	R
Carcinogenicity	C	C	C	C	C	-

Note. R, recommended based on regulatory guidance; C, conditional

[a] "Extent of testing is dependent upon conditions and duration of exposure: single exposures less than 2 weeks, repeat clinical exposures of 2 weeks to 3 months, and long-term for exposures greater than 3 months (refer to Table 2).

[b] A battery of animal tests that evaluates acute systemic toxicity by the oral, topical, and inhalation routes of exposure, as well as skin and eye irritation/corrosion, and skin sensitization, is commonly referred to as the "six-pack"[47]

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[c] These studies are currently being replaced by *in vitro* and computational methods in order to replace animal testing. Acute toxicity may also be obtained by repeat-dose studies that may be performed (ICH M3(R2)).

Specific details regarding test methodology and data interpretation are not addressed by these guidelines. Practical considerations for study design have been previously published. (Weiner and Kotkoskie, 2000[121]). Test procedures generally recognized by experts and by the regulatory agencies should be used. Each test should be designed to address a specific issue and the data should be evaluated accordingly.

3 SPECIAL CONSIDERATIONS AND ALTERNATIVE TECHNOLOGIES

This is a rapidly developing and emerging area and the content below is only intended to be a point-in-time snapshot based on the information available at the time the guide is published.

3.1 Special Assessments/Considerations for Excipient Families

For some routes of administration (e.g., oral, dermal), polymers, especially those that are not metabolized or absorbed, create a special case. Generally, polymers with a molecular weight >1,000 Da are considered "…very unlikely to be absorbed by the gastrointestinal tract and thus are not considered to present a toxicological risk."[122] FDA offers a possible exemption requiring less safety data for large polymers if the new polymeric excipient:

- differs from other characterized polymer excipients only in molecular weight
- has similar physical state, pharmacokinetics, impurities including unreacted monomers

3.1.1 *Read Across*

Read-Across (RAx) is one of the most frequently used alternative tools for conducting safety assessments with reference to complex toxicological and pharmacological endpoints found in repeat-dose toxicity studies.[123] The RAx approach has evolved over past decades as an important safety assessment tool to fill data gaps without performing additional animal testing. Read-Across is being adopted by industrial chemical regulatory agencies (e.g., ECHA[124], US EPA) and to some degree by pharmaceutical regulatory agencies (e.g., EMA and US FDA[129]). Currently, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which includes FDA's CFSAN and CDRH as members, is actively working to "build read-across capacity, raise awareness of the state of the science, and work towards a harmonization of read-across approaches across U.S. agencies."[125]

The RAx process begins with identifying structural/physiochemical similarities between Source chemicals (also known as Surrogates) with a known toxicological profile and a target chemical of interest whose toxicity profile is unknown.[129] The basic premise is that similar structural features lead to similar pharmacological and toxicological effects. Both ECHA and EPA have extensive

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framework documents, presentations and websites that provide guidance on how to select robust surrogates.

The criteria for similarity, to be scientifically meaningful, has been expanded to include biological, pharmacological/pharmacodynamic, toxicokinetic, ADME and standard toxicological systemic toxicity endpoints. To better characterize these properties, New Approach Methods (NAMs, see Section 3.4 of this guide) are being used to incorporate mechanistic information related to adverse outcome pathways (AOP) with reference to toxicokinetic modeling. This modeling by including various *in vitro* parameters such as plasma protein binding and hepatocellular clearance emphasizes either the similarity or dissimilarity between Source and Target compounds. When appropriately applied, the RAx approach can potentially reduce *in vivo* testing.

3.1.2 *US FDA Bridging Arguments and Justification*

Historically, a bridging approach was an initial method proposed by the FDA[126,127,128] to assist in evaluating the safety profile of an unknown molecule by comparing to the chemical class (family) to which it belonged. Well-established legacy data could be used to characterize the toxicity profile of the unknown molecule. Since then, "bridging" has been replaced in the world-wide regulatory community by RAx as the preferred method using NAMs that provide robust data sets to increase the probability that the safety assessment for the target chemical was highly consistent with the available toxicological data.

Specifically, the bridging approach has been used to qualify the safety of excipients that are polymers (e.g., hypromellose and other cellulosics, polyethylene glycol, dimethicones, polyethylene oxides). These chemicals have in common functional groups or chemical similarity within the group (e.g., C14-16 linear and C16 branched) saturated and unsaturated aliphatic hydrocarbons. For this class of excipient, extensive toxicology datasets are available for either specific molecules within the chemical family, or an extensive toxicology dataset across the entire chemical family that can be used to facilitate toxicological safety assessments.[129] Therefore, for polymer qualification, the need to identify appropriate Surrogates for a Target chemical is structurally less challenging since structural similarity in a given polymer family is intrinsic. This bridging method for polymeric excipients is an acceptable regulatory approach with ECHA and is consistent with the REACH Guidance.

ECHA has defined what is a "family" of chemicals. This definition indicates that a family is structurally similar with physicochemical, toxicological, ecotoxicological and/or environmental fate properties that are likely to be similar or to follow a regular pattern may be considered as a group of substances (Regulation (EC) No 1907/2006 as amended). This definition includes, but is not limited to:

- Common functional group (*i.e.,* chemical similarity within the group) C14-16 (even numbered) and C16 (branched) saturated and unsaturated aliphatic hydrocarbons
- Common precursors and/or likely common breakdown products *via* physical and/or biological processes which result in structurally-similar degrading chemicals

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- A constant pattern in the properties across the group (*i.e.*, of physico-chemical and/or biological properties) such as chelants – PDTA (phenyldiaminetetraacetic acid), NTA (nitrilotriacetic acid), EDTA (ethylenediaminetetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), sodium, zinc, iron, ammonium EDTA.
- Polymeric substances

FDA has discussed recommendations for conducting safety assessments for an excipient family. End points to take into consideration include usage levels and routes of administration outside of FDA IID levels. The bridging approach was recommended when specific toxicity data were not available for all of the **grades** of a family of excipients. Similar to ECHA, OECD and EPA requirements, structural, toxicological, pharmacokinetic/ADME, physicochemical and biological properties should be used to build a WoE between various grades of the excipient family.

The importance of adopting the excipient family approach based on scientific rational using pharmacology, toxicology and ADME considerations supports justification of its use. This approach has been discussed with FDA and at scientific meetings.[126] IPEC maintains that requiring toxicology data for every grade of an excipient is not needed and is not aligned with a risk-based approach.

3.2 Special Patient Populations/Considerations

The following sections are intended for excipient manufacturers who specifically target and market their excipients for special patient populations/considerations. Excipient users using the excipient beyond an excipient manufacture's intended use are responsible for conducting the appropriate safety studies for their specific intended use.

3.2.1 *Pediatrics*

Pediatric patients who receive pharmaceuticals during periods of rapid growth and/or postnatal development of several organ systems represent a distinct population characterized by unique needs when compared to adults. In addition, children may absorb, distribute, metabolize and excrete the API and excipients in an age-specific manner. The impact of such changes and adverse consequences from adult data may not always be predictable for pediatric patients. In particular, certain excipients safely used in adult formulations (e.g. benzyl alcohol, ethanol, propylene glycol, benzoic acid, parabens, sulfites) have been associated with elevated risks and safety issues when used in children and specific safety information and instructions have to be provided by the excipient users when they are used in pediatric formulations.[130, 131, 132, 133, 134] The selection of a safe, suitable excipient in a pediatric formulation is therefore of particular concern and any excipient that is unsuitable for children should be avoided.

For a well-established excipient, which is for example also commonly used in food, known use experience may already support the use of the excipient in a pediatric formulation. By contrast, when there is an excipient that has never been used in any pharmaceutical formulation for a

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pediatric population, a comprehensive safety assessment of the excipient is required. Literature and database searches should be conducted to determine if safety in pediatric formulation has been established, in which context and which gaps may exist. One available, publicly accessible database is Safety and Toxicity of Excipients for Paediatrics (STEP),[135] which was developed collaboratively by the European and US Paediatric Formulations Initiatives (EuPFI[136] and USPFI). STEP provides non-confidential in-house and published safety and regulatory information for an increasing number of excipients to support pediatric drug development.[137, 138, 139, 140] Other reference sources may be available to provide information for excipients used in pediatrics.

If there is insufficient information for the excipient to be used in a pediatric formulation, it is necessary to perform safety studies during critical periods of the development of the organism. For this purpose, ICH has defined the following age categories and pediatric subgroups: preterm newborn infants, term newborn infants (0 to 27 days), infants and toddlers (28 days to 23 months), children (2-11 years) and adolescents (≥ 12 years).[141,142] Due to this broad developmental range, careful attention should be given to ensure that the ages and duration of treatment in the nonclinical juvenile safety studies cover these critical periods of pediatric development with respect to the use of the excipient in pediatrics (Figure 2; Barrow 2007[143]). Barrow goes on to state that *juvenile animal studies (JAS) are useful for the detection of juvenile-specific toxicities or increased sensitivity of juveniles to excipients and for establishing safe exposures in pediatric age groups. As for active ingredients, JAS should only be performed for excipients if they are likely to contribute valuable data for clinical risk assessment and* ***labeling***.

Guidelines on juvenile animal safety testing and assessment were established by ICH S11[142] and by authorities in various regions, such as the US,[144,145,146] Europe[147,148] and Japan.[149] The nonclinical safety studies which should be available for any novel excipient, including repeated dose toxicity, a safety pharmacology package and the standard battery of genotoxicity tests will characterize the toxicological **hazards** of the new excipient and already indicate a potential concern in juvenile organisms.[33] Reproduction and developmental toxicity studies in animal species, relevant to the age and gender of the pediatric patient populations under study, can also be important to provide information on direct toxic or developmental risks (e.g., fertility and pre-postnatal developmental studies).[150] Embryofetal developmental studies are in general not critical to support clinical studies for males or prepubescent females.

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Figure 2 Cross-species age comparison

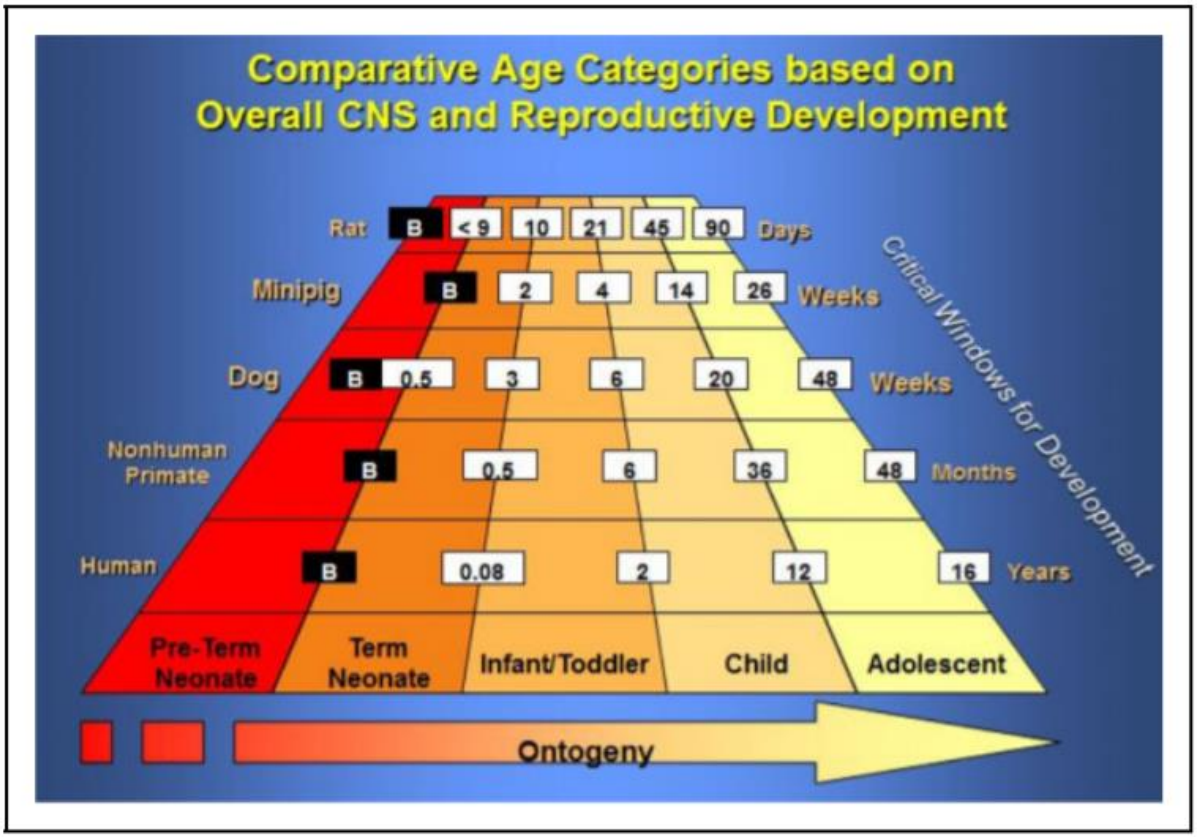

Figure above based on overall central nervous system (CNS) and reproductive development. (Buelke-Sam, 2003[150])

Additional nonclinical safety studies in juvenile animals may be requested by excipient user for excipients to address important concerns which cannot be adequately assessed using the existing animal or human data. Juvenile animal studies are especially relevant when a known target organ toxicity occurs in adults in tissues that undergo significant postnatal development. However, performing juvenile toxicity studies as a standard and as routine should be prevented for excipients and should only be conducted if relevant for clinical risk assessment or when no other sources of information (e.g., *in vitro* or *ex vivo* investigations) provide the necessary data.[143, 147.151] If there are no safety concerns for the intended population from the available toxicological or human safety data, studies in juvenile animals may not be needed. ICH S11[142] suggested that if there are insufficient data to support the use of the excipient in the intended pediatric population, further safety evaluation can be warranted, for example, an additional group evaluating the excipient alone in a juvenile animal study.

If in a WoE approach it is decided to undertake a nonclinical safety study in juvenile animals to address a certain safety concern which cannot be resolved with the existing preclinical and human

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data, then study designs are often developed on a case-by-case basis influenced by age of the target population, available safety and exposure data, relevance of endpoints and feasibility of execution.[152] A majority of nonclinical juvenile studies utilizing the rodent as the animal of choice and in most cases a single species, which is in principle the same species as used in adult repeated-dose studies, is considered sufficient as proposed by ICH.[143] If feasible the route of exposure should match the expected scenario for the pediatric population. It may, for example, also be considered whether dosing can be initiated at a younger age in a repeated-dose study, or whether a developmental toxicity issue could be addressed in a modified pre- and postnatal development study in rats.[133,144]

Toxicological core endpoints to be monitored in a juvenile animal study include postnatal growth and development of specific organ systems, e.g., skeletal, renal, lung, nervous, immunologic, cardiovascular and reproductive.[43,147] Under special circumstances, data on absorption, distribution, metabolism and/or excretion in juvenile animals may be valuable to address an identified specific safety concern.[147]

Finally, if preclinical information does not raise a specific safety concern for the use of the excipient in a pediatric formulation, clinical studies with the final drug product as well as a post marketing monitoring to be conducted by the excipient user could further support the safety of the excipient in a pediatric formulation.

3.2.2 *Endocrine Disruptors*

When the outcome of the standard safety battery of test does not suggest any endocrine related toxicity, further testing would not be necessary. When the outcome does suggest the presence of endocrine disruptors, further testing should be determined on a case-by-case basis. Reference is made to the FDA Guidance[153] which states "*Depending on the outcome of a standard battery of nonclinical tests, additional nonclinical studies may be warranted to more fully characterize the endocrine-related toxicity potential of a drug*."

3.3 Special Excipient Safety Considerations

3.3.1 *Nanomaterials*

The regulatory framework for the use of nanomaterials as excipients in medicines is an emerging area of interest.

Globally, nanomaterials are typically defined as intentionally engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range between 1 nm and 100 nm.[154, 155, 156] FDA expanded the definition on nanomaterials to include materials "*engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)*."[153]

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The risk for products containing nanomaterials is based on their potential to alter chemical, physical, or biological properties of the final dosage forms, especially changes impacting bioavailability. Some nanomaterials, whether as primary particles or in an agglomerated or aggregated state, are commonly used as excipients in drug products. Such excipients may serve specific functions and attributes like stabilization, disintegration or disposability (e.g., diluents, surfactants, glidants, emulsifiers, lubricants, targeting or coating agents), improve processability and formulation performance (polymers, amphiphilic substances like lipids or surfactants and substances from mineral sources) and be used as matrices to assemble structures or to stabilize more complex nanomaterials. Nanomaterials can improve the entry of APIs into the systemic circulation and can affect the API distribution, exposure response profile and residence time. Further potential risk can directly result due to nanomaterial properties, especially their uptake, distribution and metabolism within the body.

These materials may require additional evaluation for safety, effectiveness, performance, and quality. For example, FDA issued guidance on the development of nanomaterial containing human drug products[157] which states "*The inclusion of such materials* (nanomaterials) *may result in product attributes that differ from those of products that do not contain such materials, and thus may merit particular examination*" and "*an adequate safety evaluation should be provided when the nanomaterial's safety is not fully demonstrated by existing safety data with respect to level of exposure, duration of exposure, and route of administration*."

European Food Safety Authority (EFSA) proposed a structured pathway[158] for carrying out safety assessment of nanomaterial in food/feed and related applications and provides practical suggestions for the types of testing needed and the methods that can be used for this purpose.

The use of a read-across approach including a justification to compare hazard data between nanoforms and non-nanoform(s) is discussed in depth in the EFSA Guidance document[158] (see Section 3.1 for read-across).

Special prerequisite considerations should be given to the following:

- Identification of the nanomaterial and detailed characterization of the constituting components (including impurities, and any entities on the particle surface).
- Physicochemical parameters of the nanomaterial (e.g., before and after application, agglomeration or high degradation rates)
- Physicochemical attributes of a material transformed into a nanostructure upon formulation.
- Lipid excipients intended for the manufacture of liposomal drug products have special Chemistry, Manufacturing, and Control (CMC) requirements.[159]
- Some state-of-the-art *in vitro* assays may not be appropriate for nanomaterials, or the conditions under which these assays are conducted might need to be adjusted in order to obtain accurate results.

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3.3.2 *Excipients derived from Animal or Human Sources*

Excipients can originate from various sources, including human and animal origin (e.g., lactose, gelatin, stearic acid) and may increase the risk of introducing adventitious agents. Specifically, the use of human and or animal derived materials may lead to safety concerns for issues related to BSE (**Bovine Spongiform Encephalopathy**) or TSE (**Transmissible Spongiform Encephalopathy**) and may restrict acceptance. As such, for excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data). Sponsors should demonstrate that materials used in production of the excipient are considered safe and that the approaches (methods) used to test, evaluate, and eliminate potential risks during the manufacturing are suitable.

3.3.3 *Excipients for Biotechnology-Derived Pharmaceuticals*

Excipients are used in protein-based therapeutics to optimize desirable properties. Like excipients used with small molecule products, the safety, toxicity, and immunogenicity of the excipients should be assessed prior to use. It is important that a new or inadequately qualified excipient proposed for use in any product to be marketed according to a Marketing Authorization Application (MAA) is supported by adequate safety data. Current regulatory excipient guidance[160,80,161] do not distinguish excipient safety based on use in a certain pharmaceutical product (e.g., small molecule versus biologic).

More pronounced in biopharmaceuticals, excipients are used to improve stability, route of administration, dosage form (liquid or lyophilized), or limit immunogenicity potential. There are a number of excipients currently available to protect proteins from chemical and physical degradation pathways as a result of stresses during processing, storage, and administration. In addition to safety, toxicity, and immunogenicity of the excipients, the appropriateness of an excipient(s) should be considered based on their mechanisms of action and with an understanding of degradation pathway(s) of the particular drug product in the dosage form of choice.

3.3.4 *Exposure Assessment and the Use of Human Equivalent Dose (HED)*

The determination of Human Equivalent Dose (HED) can be used when evaluating the toxicology data of a novel excipient. The first step to derive an HED is to identify the No Observed Adverse Effect Level (NOAEL) for each species tested in a toxicology study. The NOAEL is defined as the highest dose level that does not produce a significant increase in adverse effects (AEs) in comparison to the control group. The NOAEL is then converted to an HED using appropriate scaling factors. The species that generates the lowest HED is the most sensitive species. [160]**Error! Bookmark not defined.**

The HED can be used to determine the maximum recommended starting dose (MRSD) of the excipient for first in human clinical trials. A safety factor of at least 10 is applied to the HED to increase assurance in humans that the first dose in humans will not cause adverse effects. [160]

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Alternatively, the HED can be compared to anticipated human exposure to determine if an adequate margin of safety exists for the proposed use of a novel excipient.

3.4 Alternative Methods

3.4.1 *Introduction*

The emergence of alternative approaches (i.e., US TOX21 Initiative[8]) led to the establishment of predictive toxicology that uses individual or combinational *in silico* (also known as computational) and *in vitro* methods to perform safety assessments. Examples of *in silico* platforms are Quantitative Structure Analysis Relationship (QSAR) and Physiologically Based Pharmacokinetic (PBPK) models; for *in vitro* methodologies some of the best-known examples include high throughput screening, tissue-on-a-chip, and organoid cultures. Collectively, these alternatives are designated as New Approach Methods (NAMs) and are being considered to be included into the standard *in vivo* toxicology testing paradigm used to evaluate systemic toxicity potential of chemicals.

3.4.2 *Existing and New Approach Methods*

3.4.2.1 *In Vitro*

There are a variety of existing and *in vitro* NAMs that are either under development by various academic and government research groups or validated and accepted for regulatory application.

3.4.2.1.1 Under Development and Potential Uses

Some *In Vitro* Assays that are Under Development:

- Zebrafish model
- Mixed culture of neuronal and glial cells
- High-Throughput Screening (HTS)
- Organ or Tissue-on-a-Chip
- Organoid cultures

Some Uses of NAMs for the Assessment of:

- Microvesicular liver stenosis
- Prediction of embryo toxic and teratogenic (birth defect) effects
- Inhibition of mitochondrial respiratory chain complex 1 of nigra striatal neurons leading to parkinsonian motor deficits.
- Neurodevelopment outcomes – use of mixed culture of neuronal and glial cells derived from human induces pluripotent stem cells; impairment of learning and memory in children; effects on neurotrophic factor (BDNF) level, neurite outgrowth and synaptogenesis after short (72 hour) or long-term exposure (14 days).

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This brief listing indicates representative examples of *in vitro* NAMs under development with some toxicological applications. Many of these NAMs are being developed with the expectation to increase the predictiveness of human chemical safety evaluation coupled to the reduction in animal use.

3.4.2.1.2 Regulatory Applications

Although designed initially to replace animal testing, most of these tests are not currently accepted by regulatory authorities. However, in a case-by-case circumstance these tests offer an alternative approach that may convince authoritative bodies to replace and/or reduce animal testing. There is some risk to this NAM approach, which should be taken into account when developing a toxicology safety assessment program. Communication is encouraged between the excipient manufacturer, sponsor and/or the regulatory agency.

In Vitro NAMs that have FDA regulatory acceptance to evaluates potential toxicity associated with dermal absorption of topical and transdermal drug products include the following:

- *In Vitro* Permeation Assay (IVPT) [162]
- *In Vitro* Release Test (IVRT) [162]
- *In Vitro* Bioequivalence Studies [163, 164]

These assays determine the pharmacokinetic/toxicokinetic parameters that summarize disposition kinetics of dermal and systemic absorption, and the role of skin metabolism as a prerequisite for conducting more detailed animal studies.

In contrast to the limited number of *in vitro* NAMs recommended by FDA, OECD has a large battery of Test Guidelines using *in vitro* NAMs for acute exposure (see OECD Table 11). These NAMs have been reviewed and established by OECD, European Union Reference Laboratory for Alternative Animals Testing (EURL-ECVAM) and by the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) and meets the Toxic Substances Control Act (TSCA) Section 4(h)(2)(C) criteria for scientific reliability and relevancy. The extensive test method evaluation process developed by EURL-ECVAM and ICCVAM is accepted internationally as described in OECD Guidance Document 34 and designated to identify NAMs for regulatory acceptance. In contrast to the FDA, some of these NAMs represent existing *in vitro* assays or policies within the US EPA.

In addition to the US EPA and OECD, the ECHA's REACH regulation requires the use of animal data only as a last resort. ECHA offers the possibility to industry to fulfill its toxicological data requirements using *in vitro* NAMs in preference to standard animal testing. The level of acceptance depends on the complexity of the toxicological endpoint. For a "simpler" endpoint, such as skin irritation, *in vitro* NAMs are the standard information requirement under REACH. As the "complexity" of the endpoint increases, either more detailed scientific justifications are required or the *in vitro* NAM data becomes supportive only.

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When an adverse effect or endpoint requires "complex" considerations, *in vitro* NAMs may be combined within IATA framework as mentioned for RASAR computational approaches. In this instance, *in vitro* data is considered in conjunction with standard pivotal *in vivo* toxicity data and may be valuable to infer mechanism of action (MoA), molecular initiating events, or mode of toxicity as part of an Adverse Outcome Pathway (AOP).

Table 11: Validated Acute Alternative Methods available

Toxicology area/endpoint	Methods	OECD
Ocular toxicity	Bovine corneal opacity and permeability test method to identify chemicals inducing serious eye damage and chemicals not requiring classification for eye irritation or serious eye damage (BCOP)	TG 437 2017
	Fluorescein leakage test method to identify ocular corrosives and severe irritants (FL)	TG 460 2017
	Short time exposure *in vitro* test method to identify chemicals inducing serious eye damage and chemicals not requiring classification for eye irritation or serious eye damage (STE)	TG 491 2018
	Reconstructed human cornea-like epithelium (RhCE) test method to identify chemicals not requiring classification and labelling for eye irritation or serious eye damage (EpiOcular, SkinEthic, LabCyte CORNEA-MODEL24 EIT)	TG 492 2018
	Collagen gel - eye irritation test (Vitrigel-EIT): allows the identification of test chemicals not requiring classification and labelling for eye irritation or serious eye damage	TG 494 2019
	In vitro Macromolecular Test Method for Identifying Chemicals Inducing Serious Eye Damage and Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage	TG 496 2020
Dermal corrosion/irritation	*In vitro* skin corrosion: Transcutaneous electrical resistance test method (TER)	TG 430 2015
	In vitro skin corrosion: Reconstructed human epidermis (RHE) test method (Episkin, EpiDerm, SkinEthic, epiCS)	TG 431 2016
	In vitro skin irritation: Reconstructed human epidermis test method (Episkin, EpiDerm, SkinEthic, LabCyte, EPI-MODEL24)	TG 439 2015
Skin sensitization	In chemico skin sensitization: Direct peptide reactivity assay (DPRA)	TG 442C 2015
	In vitro skin sensitization: ARE-Nrf2 luciferase test method (KeratinoSens, Lu-Sens)	TG 442D 2018
	In vitro skin sensitization assays addressing the key event on activation of dendritic cells on the adverse outcome pathway for skin sensitization (h-CLAT+U-SENS+IL-8)	TG 442E 2018
Skin phototoxicity	*In vitro* 3T3 NRU phototoxicity test	TG 432 2004

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	Reactive oxygen species assay（ROS）	TG 495 2019
Skin absorption	*In vitro* Skin Absorption Test	TG 428 2004

3.4.2.2 Computational Assessment – Quantitative Structure Analysis Relationship (QSAR)

One of the most widely used computational NAMs is a QSAR assessment recommended in the ICH M7(R1) guidance.[48] This NAM characterizes the mutagenic potential of unknown chemicals by employing two platforms, an expert rule-based and statistical-based. This *in silico* approach is accepted throughout the ICH regulatory community as an alternative for the bacterial mutagenicity (Ames) assay. The basis for this computational toxicology assessment is the comparison of an unknown chemical to known chemicals that share similar structural alerts identified as mutagenic with or without carcinogenic potential. This computational comparison is called read across. The result of this read across QSAR assessment is to classify an unknown chemical to one of five classes. Class 1 designation indicates a known mutagenic carcinogen; Class 5 designation indicates a non-mutagen. This read across approach was the subject of OECD guidance 211[165] and was a component of the ongoing FDA's Predictive Toxicology RoadMap.[166]

The computational approach also has been applied to assessing acute toxicity. For this application, QSAR's read across method was modified. Instead of identifying structural alerts in common between known and unknown molecules, structural similarities based on Tanimoto indices were used as important criteria for comparison. Modification of QSAR's read across approach is referred to as Read Across Structure Analysis Relation (RASAR). This change increased the accessible chemical universe from several hundred chemicals to 10 million structures with a concomitant increased probability to predict systemic toxicity. In addition, RASAR has been integrated into Artificial Intelligence based big data machine learning paradigm. This added capability has incorporated several reliability measures such as structure, property, metabolism, pharmacodynamics and pharmacokinetics leading to a consequential accuracy increase from 81% with *in vivo* assays to 87% with *in silico* RASAR approach. Sensitivity also increased notably from 69% to 89%.[158,167] Acute toxicology tests employing this computational RASAR approach are referred to as the *Six-Pack* and include oral, inhalation, dermal, skin irritation/corrosion, sensitization, and eye irritation/corrosion.

Currently, the RASAR *in silico* approach to assess acute toxicity is not accepted as a stand-alone replacement for acute oral animal tests[168] by any regulatory agencies world-wide.

However, this computational assessment can be used on a case-by-case basis by OECD and ECHA as supportive part of a WoE approach that justifies longer term standard *in vivo* animal toxicology studies.

Another area for the application of an *in-silico* approach is the preparation of toxicological safety assessments for APIs, impurities, process degradants, extractables and leachables, and novel excipients based on repeat dosage animal toxicity data. This is a regulatory challenge since

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qualification of these chemicals is based on ICH's Q3A[169] and Q3B(R2)[170] Guidances. Qualification recommendations involve conducting two *in vitro* genotoxicity assays that evaluate the potentials for point mutation (Ames Assay) and chromosome aberration and one *in vivo* repeat dosage toxicity study of 14 to 90 days using a standard toxicological animal model.

Genotoxicity qualification requirements can be met by following the NAM outlined in the M7 QSAR guidance.[48] Repeat dosage toxicity studies for assessing systemic toxicity can be met by accessing prior animal toxicology data that is proprietary or available in the peered reviewed literature. In cases where nonclinical data is not available, an alternative is to conduct a RASAR assessment that identifies surrogates with a very high level of structural similarity using Tanimoto coefficients. Since the FDA and other European regulatory agencies considers that structural similarity alone may not be a reliable bridge to accurately define systemic toxicity, this is compensated by including pharmacodynamic, ADME and pharmacokinetic data into a WoE argument to establish an Adverse Outcome Pathway (AOP). Such a toxicological argument employing multiple assessment tools is termed an Integrated Approach to Testing and Assessment (IATA). This broad-based big data approach builds a toxicity profile that identifies potential target organs and NO(A)EL values needed to calculate a Margin of Safety (MoS) to justify the clinical safety of a given chemical.

At present, the RASAR surrogate approach of applying big data machine learning to repeat dosage toxicity studies is being cautiously reviewed by the FDA on a case-by-case basis. It is anticipated that using the RASAR surrogate approach in conjunction with relevant biological data may be valuable to infer a mechanism of action (MoA), molecular initiating events or mode of toxicity as part of an AOP for a given chemical or class of chemicals.

In contrast, this computational RASAR toxicological approach is being considered more favorably by OECD and ECHA regulatory agencies under the integrative European large-scale EU-ToxRisk project. The goal of this project is to fulfill data requirements directly for acute studies and provide support for more complex toxicological endpoints (e.g., reproductive toxicity) as part of the REACH Regulation.

3.5 Formatting and Tabulation of Toxicological Data and Summaries

When filing confidential excipient safety information for review along with a MAA (e.g., a U.S., Japan or Canadian "excipient" **Drug Master File** (DMF), a Europe "excipient" **Certificate of Suitability** (CEP) or a China "excipient" registration dossier), the Common Technical Document (CTD) format is often required. For counties/regions not currently having a process in-place to separately submit confidential excipient information, the safety information should be provided directly to the Marketing Authorization Holder (MAH) to submit along with their application.

3.5.1 *Nonclinical written and tabulated summaries*

Nonclinical written and tabulated summaries can be provided in Module 2; however, these summaries are more applicable for drug products and drug substances (APIs) due to the

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information detail contained in Modules 3 and 4 for these types of submissions. However, if included to justify the use of a novel excipient, the intent should be to provide a high-level "Nonclinical Study summary" of studies which may be included in Module 2.

Based on ICH CTD Guidelines:

> **Section 2.4 Nonclinical overview** *should include a nonclinical overview that presents a critical assessment of the excipient toxicological evaluation. The study's nonclinical testing strategy and Good Laboratory Practices (GLP) status should be discussed and justified. An assessment of the excipient composition including impurities and degradants present in the excipient should be included as well as what is known regarding potential toxicological effects. Relevant scientific literature and the properties of related excipients should be considered.*
>
> **Section 2.6 Nonclinical written and tabulated summaries** *should follow ICH Safety Guideline M4S (R2).*[171] *Appropriate tables and figures should be used to effectively communicate information about the studies. Studies should be presented for the intended excipient administration routes.*

3.5.2 *Nonclinical Toxicology Data Organization and Format*

The ICH M3(R2) Safety Guideline[172] provides information for the types of nonclinical safety studies that should be considered for novel excipients. The nonclinical safety assessment for a novel excipient includes safety pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction and developmental studies, genotoxicity studies and an assessment of carcinogenic potential. Other nonclinical studies to assess phototoxicity and juvenile animal toxicity can be considered if appropriate. The ICH Guideline presents tables, figures and tabulated summary templates in appendices as examples.

Table 12 outlines the format and high-level sections of Module 4, based on the ICH M4S(R2) Safety Guideline.[171] For further organization and level of detail for nonclinical study reports in the CTD submission to the U.S. FDA, refer to the U.S. FDA Guidance.[173]

Table 12: Module 4 Content

Section	Title
4	Nonclinical Study Reports
4.1	Table of Contents for Module 4
4.2	*Study reports*
4.2.1	Pharmacology
4.2.2	Pharmacokinetics
4.2.3	Toxicology
4.3	*Literature References*

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3.5.3 *U.S. Type IV DMF (Excipient)*

In the US, excipient manufacturers generally submit a Type IV **Drug Master File** (DMF) to the FDA for novel excipients used in the US. The IPEC-Americas U.S. Drug Master File Guide for Pharmaceutical Excipients[174] provides excipient manufacturers with information pertaining to the DMF system in the US as well as information on the excipient DMF submission process. The guide utilizes the ICH Common Technical Document (CTD) format for the DMF file structure.[3]

Although not required, a U.S. **DMF holder** can choose to submit toxicology summaries (in Module 2) and study reports (in Module 4) in an excipient DMF. Typically, DMFs for well-established excipients do not include toxicology summaries or reports; however, a DMF holder should consider including these summaries and/or reports to justify the use of novel excipients.

Effective May 5, 2017, all DMF Submissions to the FDA were required to be in the electronic eCTD format. FDA guidance documents outline the requirements for DMF submissions in electronic format using the eCTD specifications.[175],[176] The guidance document provides recommendations regarding the use of the eCTD backbone files developed through ICH. The FDA Data Standards Catalog[177] provides specifications for the eCTD submission. Additional guidance is available at the FDA website.[178]

The CDISC Standard for Exchange of Nonclinical Data (SEND) is a required standard for data submission to the FDA and specifies the method to collect and present nonclinical data.[179] The format consists of several components for individual study endpoint data which are typically mapped to datasets in domains with several variables in each study dataset. Version 3.0 of SENDIG is intended to guide the organization, structure, and format of standard nonclinical tabulation datasets for drug application submissions to regulatory authorities.

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