The Proposed Guidelines for the Safety Evaluation of New Excipients.

By IPEC Europe Safety Committee

The **International Pharmaceutical Excipients Council** (IPEC) is an industry association with distinguished worldwide membership including over 150 pharmaceutical, chemical, and food processing firms that develop, manufacture, sell, and use pharmaceutical excipients.

IPEC comprises 3 regional organisations, in the United states, Europe (IPEC-Europe) and Japan (JPEC), each with the same objective regarding the international harmonisation of excipients standards, introduction of useful novel excipients to the market place, and the development of safety evaluation guidelines for excipients.

The present safety evaluation guidelines are an approach to the safety assessment of pharmaceutical excipients. They are considered to be a guide for professionals familiar with safety and regulatory aspects, but not normally experienced with the complex nature of excipients. The main premise is that excipients themselves display no pharmacodynamic activity. Accordingly, a more appropriate definition for an excipient is: any substance other than the active drug or product which has been appropriately evaluated for safety and is included in drug delivery systems to either:

- Aid processing of the drug delivery system during manufacture;
- Protect, support or enhance stability, bioavailability or patient acceptability;
- Aid in product identification; or
- Provide any other attribute of the overall safety and effectiveness of the entire drug product during storage and use.

A new pharmaceutical excipient can be either:

1 A New Chemical Entity.
2 A chemical entity which is not used in medicinal products for humans, in foods or cosmetics.
3 A chemical entity which is already used in foods or cosmetics, but not in human medicinal products.
4 A chemical entity which is already used in human medicinal products but at a lower exposure or via a different route of administration.
5 A chemical entity which is already used in veterinary medicinal products but not in human applications

The products covered by points 1. and 2. will require a full evaluation, as for a new active ingredient.

The safety assessment for the excipient per se should not necessarily be as complex or far reaching as that for an active ingredient. The present guidelines specifically cover points 3. and 4. above and are intended to design a safety programme adapted to excipients using the existing guidelines for toxicity testing for new chemical entities. They do not cover workplace or transportation safety requirements.

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Rationale

Currently, the acceptance procedure for an excipient is not specifically addressed in most developed countries, unless one takes a maximalistic approach. Authorities generally favour the use of compendial, commercially established excipients, food additives and substances that, for example, have been designated as Generally Recognised As Safe (GRAS) in the United States.

The objective of the current proposal is to provide a logic rationale approach to cover the field between ""nothing is needed" and "full testing".

The final aim of these Safety Evaluation Guidelines for Excipients is to provide an important element in the acceptability of a new excipient by Health Authorities independently of the approval of a specific drug formulation.

Overview

These guidelines are based upon the best available science and are not intended to replace any toxicity guidelines, but rather to provide a stepwise process in defining a safety programme for excipients:

- The guidelines provide the extent of testing required for any excipient, after a proper review of its current use and applications in the market place, review of the database and relevant background information.

As detailed below, the guidelines indicate what type of ***background information*** is needed to be able

to decide whether toxicity studies should be performed or not. A subsequent ***Decision Tree*** for the various routes of administration goes into greater detail and includes biological information and previous uses in food, cosmetics etc., and will further help in the choice of toxicity testing.

In the last section, the ***Summary of Toxicity Tests*** for the various routes of administration is listed and grouped into three subgroups in order to indicate a ***step-by-step procedure*** related to the duration of administration of an excipient.

This step-by-step procedure should also be applied in those cases where a well-known excipient has been varied in the concentration of its components, or slightly modified in its chemical structure.

It is important to obtain information on the bioavailability and biotransformation in the body

Background Information

Studies to be conducted are determined by the relevance of available data and the intended use in humans. The guidelines provide a tiered approach based on the chemical and physical properties of the excipient, review of the scientific literature and exposure conditions (including dose, duration, frequency, route, and user population).

It is therefore critical to proceed with the identification of the excipient and its characterisation in order to define its current status. Once well characterised, determining the design of the safety programme using the Decision Tree and the step-by-step procedure becomes easier.

Chemical Identification

Apart from the chemical name and the CAS number, all synonyms of the excipient should be given to facilitate its identification in various parts of the world. It has to be made obvious that; for example, Tweens® and polysorbates refer to the same compounds. In addition, the excipient has to be clearly characterised and described. The excipient can firstly be a single chemical entity such as Sodium Chloride, or secondly a mixture of related substances like glycerides, which contain mono- and diglycerides. In a third case the excipient can be a fixed combination of two or more defined excipients, or a mixture of polymers where molecular distribution may be key to understand. Whenever possible, information on the impurity profile and manufacturing procedures will be collected.

Status of the Excipient

A search in the Pharmacopoeias and pharmaceutical compendia such as PDR (US), Vidal (France), Rote Liste (Germany) etc. will give information on the use of the excipient(s) in drugs. Excipient lists such as the 'Inactive Ingredients Guide' of the FDA and lists of other countries and regions (Europe and Japan) indicate whether or not the excipient is already known and by which route of administration it is used. If an excipient is to be used orally it is valuable to know if and where it is used as a food additive. When the excipient is to be used beyond the usual daily average intake, or at levels above the normal human exposure, consideration should be given in evaluating the existing safety data within the scope of the new doses (table 2). Similarly, if the excipient is to be used dermally, it will be useful to know whether the excipient is already widely used in cosmetics and toiletries. Only after collecting all the relevant information, will it be possible to decide which additional documentation is required to allow the use of the excipient through the intended route of administration.

Bioavailability

It is important to obtain information on the bioavailability and biotransformation in the body, i.e. on its absorption, distribution, metabolism and excretion (ADME) in order to decide what safety data are needed.

A complete list of synonyms, together with the CAS number of the excipient, when available, enables a thorough literature search for pharmacokinetic data of the excipient and/or related compounds.

However, there are cases where a complete ADME study cannot be performed because of the complex nature of the excipient, analytical challenges or biotransformation to physiological products (e.g. sugar esters), etc. In such cases, a strong, well-documented argumentation will be required using however a maximum of existing data, also from similar compounds, if extrapolations are meaningful..

Points to Consider

The information reviewed may show that the excipient is already used by the oral route, for example, but not in the intended topical route of administration. This means that the available safety data can be used, but that additional safety studies to support the new route (e.g skin penetration, local toxicity, phototoxicity, allergogenicity, etc...) will have to be performed. The collected information may also reveal that the available animal data do or do not cover the dose range and/or duration of treatment intended for the new dosage form, suggesting the need for some bridging studies.

Safety pharmacology information (action on major organ systems e.g. central nervous system, cardiovascular, respiratory systems...) can give valuable information on the necessary programme to carry on.

Furthermore, there is the possibility that an excipient is used in one area of the world but not in another. In this case, all data available from the area where this excipient is already used should be given, including in certain instances health industrial exposure data.

Older studies which have not been performed under GLP condition or studies run under old pro-

tocols should be used as long as the overall quality is acceptable. Bridging studies might be necessary here.

In addition, clinical data will have to be generated with the formulated drug using the particular excipient(s) when an application for registration is submitted.

All data, whether published or generated by the applicant's facilities or elsewhere, can be used in the assessment process and will have to be made available. All this information does not only help to set up an appropriate toxicity programme, but will also be a good basis for the Authorities to understand the reasoning for the design of the safety programme.

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Decision Tree

In the ***'Background Information'*** section, it was shown that the excipient has to be chemically defined. A Decision Tree is provided to assist the choices in the development of a candidate excipient. This decision will be based on the anticipated duration of treatment. In the case of extensive human experience with an ingredient in the food industry (for oral route) and/or cosmetic industry (for topical route), there may be sufficient information either to fulfill the requirement of the guidelines or to preclude their application. If not, bridging studies should be planned along with the safety evaluation.

In addition, there may be animal data which has been developed for other purposes which also can be used to fulfill the regulatory requirements. If the data requirements have been fulfilled for prior human use and if the experience and pertinent human data have been collected in an adequate scientific manner, there may be no need to provide further animal data.

Toxicity programme

Data to be developed should define safe exposure conditions and potential adverse effects for the user.

This stepwise procedure of safety testing is proposed taking the chemical nature of the excipient, its absorption and biodisposition, as well as the intended amount, route and duration of administration into account (table 3). The content of the safety programme to be conducted has to refer to the potential absorption or not of the excipient, therefore common sense should be used prior to planning extensive long term studies (table 2).

Step 0: ADME/PK assays by oral and/or appropriate routes should be evaluated prior to designing the safety programme. When ADME/PK data cannot be produced for technical reasons, step 1 package may be requested as a prerequisite. For the oral route, absorption or non-absorption is essential to decide which studies are to be performed. Moreover, such data can validate animal toxicity data when a higher daily average intake in humans is planned.

Step 1: The base set (Step 1) should include measurement of the effects of acute and repeated exposure by oral and/or intended routes and mutagenicity assays. The data are critically evaluated and may support the use of new excipients in a product to be marketed during a short period of time (up to two weeks) or up to one month for excipients to be used in clinical Phase I/IIa studies. The same package can be used as bridging studies when a different route of administration is intended, for excipients with a chemical structure closely related to accepted ones. In this case, the purpose is to demonstrate that the toxicity profile is not different from the accepted one.

In the case where non-expected effects (for example, impact on weight and histopathology of reproductive

Table 1:STATUS OF EXCIPIENTS AND CONSEQUENT REQUIREMENTS

USED IN MEDICINES, FOOD OR COSMETICS IN EU, USA OR JAPAN AND USED IN THE INTENDED ROUTE, DOSE, DURATION OF TREATMENT.	USED IN MEDICINES, FOOD OR COSMETICS IN EU, USA OR JAPAN BUT NOT USED IN THE INTENDED ROUTE, DOSE OR DURATION OF TREATMENT	NOT USED IN MEDICINE, FOOD OR COSMETICS.
↓	↓	↓
NO TOXICITY STUDIES NECESSARY	BRIDGING TOXICITY STUDIES ACCORDING TO INTENTED ROUTE OF ADMINISTRATION	PROVIDE COMPLETE TOXIXITY DATA (SEE TABLE 3)

Note: For excipients already used in veterinary medicines, check the available animal safety information and generate relevant complementary data

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organ) are observed, further investigation should be carried out.

Step 2: If the candidate material is to be used in a product to be marketed (up to 4 weeks), additional testing is recommended (Step 2). For excipients to be used in clinical Phase I/IIa studies, completing Step 2 allows the drug use for up to 3 months. This should include effects of sub-chronic exposure in appropriate species via the intended route of use. Consideration should be given to conducting additional in vivo and in vitro studies. Segment II studies (teratology) should be performed in rats and rabbits, in case of exposure of the embryo and foetus foreseen. All studies proposed should be based on findings from the previous steps and intended use of the new excipient.

Step 3: If the new excipient is to be used in a product that is to be taken intermittently or chronically over a long period of time, i.e. longer than 4 weeks, additional data will be necessary. Long term studies should be conducted in appropriate rodents and mammalian non-rodents and the experimental conditions should be established by the sub-chronic studies. One-generation reproduction studies (Segment I) should be conducted to assess any excipient-induced effects/disturbances in mating behaviour, development/maturation of gametes, fertility and pre-implantation/implantation of the embryo. Should the data give rise for some concern for either reproductive or developmental toxicity and/if treatment during late gestation and lactation cannot be excluded, a segment III or a two generation study might be appropriate. Tests to reveal carcinogenic effects have to be required for substances having a close chemical analogy with known carcinogenic compounds, for substances which have given rise to suspicious results in the long term toxicology studies, and in the tests for mutagenic potentiel (interference with hormones, immunomodulation etc...).

Further more, if the candidate circulates systematically and is likely to be given for more then 6 months during a patient lifetime, carcinogenicity studies have to be envisaged. Depending on the individual case, the contents of this programme have to be discussed with the relevant authorities. One should discuss the possibility to do only one rodent carcinogenicity study in the most appropriate species and depending on previous findings possibly other studies helping to evaluate the risk for carcinogenicity.

Other testing that are area specific must be considered, for example immunogenicity testing in Japan.

Consideration should be given to the route of administration when using the ***Summary Toxicity Table,*** where not all the tests are deemed necessary (table 2).

Summary

A synopsis of the new, proposed Guidelines for Excipients is shown in Table 3. Tests that are recommended as required by the guidelines are distinct from those which are recommended conditionally. Whether or not conditional tests are conducted is dependent upon the conditions of use and available biological data.

The test guidelines have been developed with the premise that the excipient is pharmacologically inactive. The risk/benefit ratio for a pharmaceutical active ingredient is different from that of an excipient.

Specific details regarding test methodology and data interpretation are not addressed by these guide-

Table 2: Example of Use of the Decision Tree for Cases of Route of Administration Switching

			FOR ORAL USE		TOPICAL USE
STEP 0	A D M E	Not Absorbed	Absorbed		
			Metabolised		
			Physiological Product(s) (Before absorption)	Non-Physiological Products	
STEP 1/2/3	Food Additive < daily average intake	No new studies*	No new studies*	No new studies*	Steps 1&2 or 3 Bridging studies according to duration of treatment
	Food Additive > daily average intake	No new studies*	STEP1 to evaluate safety margin		Steps 1&2 or 3 Bridging studies according to duration of treatment
	Excipient already used in cosmetic industry	Step 1 Bridging studies	Steps 1&2 Bridging studies according to duration of treatment		No new studies*

*providing the data evaluation is satisfactory, otherwise bridging studies may be needed

Each test should be designed to address a specific issue and the data should be evaluated accordingly.

lines. Test procedures generally recognised 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.

Alternatives to the use of animals are encouraged wherever these alternatives have been validated, and where it is known that the alternative procedure will provide sufficient data for an adequate safety assessment acceptable to regulatory agencies.

These guidelines will provide sufficient data to define safe conditions of use for 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.

It is recommended that the guiding principles on the use of animals in toxicology of the relevant scientific societies from the various countries, and the appropriate legal and professional codes be adhered to in the conduct of all test procedures. All studies will be carried out according to the appropriate Good Laboratory Practice Regulations.

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Table 3: Summary of Excipient Toxicity Guidelines
ROUTES OF EXPOSURE FOR HUMANS

TESTS	Oral	Mucosal	Trans-dermal	Dermal/ Topical	Parenteral	Inhalation/ Intranasal	Ocular
STEP 0 : ADME	R	R	R	R	R	R	R
STEP 1 : BASIC SET							
Acute Toxicity (Intended Route)	R	R	R	R	R	R	R
Eye Irritation		R	R	R	R	R	R
Skin Irritation		R	R	R	R	R	R
Skin Sensitisation	R	R	R	R	R	R	R
Acute Parenteral Toxicity	-	-	-	-	R	-	-
Application Site Evaluation	-	R	R	R	R	R	R
Pulmonary Sensitisation	-	-	-	-	-	C	-
Photo-toxicity/ Photo-allergy	-	-	C	C	-	-	-
Ames test	R	R	R	R	R	R	R
Chromosome damage	R	R	R	R	R	R	R
Micronucleus Test	R	R	R	R	R	R	R
4 weeks Toxicity (2 species) Intended Route	R	R	R	R	R	R	R
STEP 2:							
3 months Toxicity (most appropriate species)	R	R	R	R	R	R	R
Teratology (Rat & Rabbit)	R	R	R	R	R	R	R
Genotoxicity Assays	R	R	R	R	R	R	R
STEP 3:							
6 - 9 months: Chronic Toxicity (Rodent ,Non-rodent)	C	C	C	C	C	C	C
Segment I	R	R	R	R	R	R	R
Segment III	C	C	C	C	C	C	C
Photo-carcinogenicity	-	-	C	C	-	-	-
Carcinogenicity	C	C	C	C	C	C	C

R: Required
C:Conditional

Extent of testing is dependent upon conditions and duration of exposure: Step 1 for exposures of less than 2 weeks, step 2 exposures for less than 4 weeks, step 3 exposures greater that 4 weeks.