

General Principles for the Safety Assessment of Excipients

- ◆ General Characteristics of the Pharmaceutical Excipients
- ◆ Classification of excipients
- ◆ The Safety Assessment of Pharmaceutical Excipients : how to conceive a Safety Program?
- ◆ **But**
 - Many excipients are not only of Pharmaceutical use
 - Are excipients of Well-Established use definitively safe?
 - What is a “relevant information”?
 - Many difficulties occur for the ADME Evaluation
 - What is the value of human data?
- ◆ IPEC guideline
- ◆ FDA guideline
- ◆ EMEA guidelines

This presentation is not focused on the safety of excipients from living origin (gelatin...) which pose very specific problems (TSE)

General Characteristics of the Pharmaceutical Excipients

- ◆ Large number of products, structurally very simple to very complex (mixtures) used for various technological reasons (ballast, lubricant, vehicles, sweeteners, antioxidants...)
- ◆ No pharmacological or therapeutic activities (sometimes debatable by topical route)
- ◆ Possibility to be used by various route of administration
- ◆ Large safety margin

Classification of Excipients

Several classifications have been proposed, according to:

- ◆ Their chemical structure: sugars, polyols, starches, inorganic salts...
- ◆ Their technological properties: ballast, lubricant, sweeteners, antioxidants...
- ◆ Their technological properties for a given route of administration and for a given formulation : oral medicines (tablets, capsules...), parental systems, topical and transdermal delivery systems... *(see « Excipients Toxicity and Safety » ML Weiner and LA Kotkoskine – M Dekker Ed 2000)*

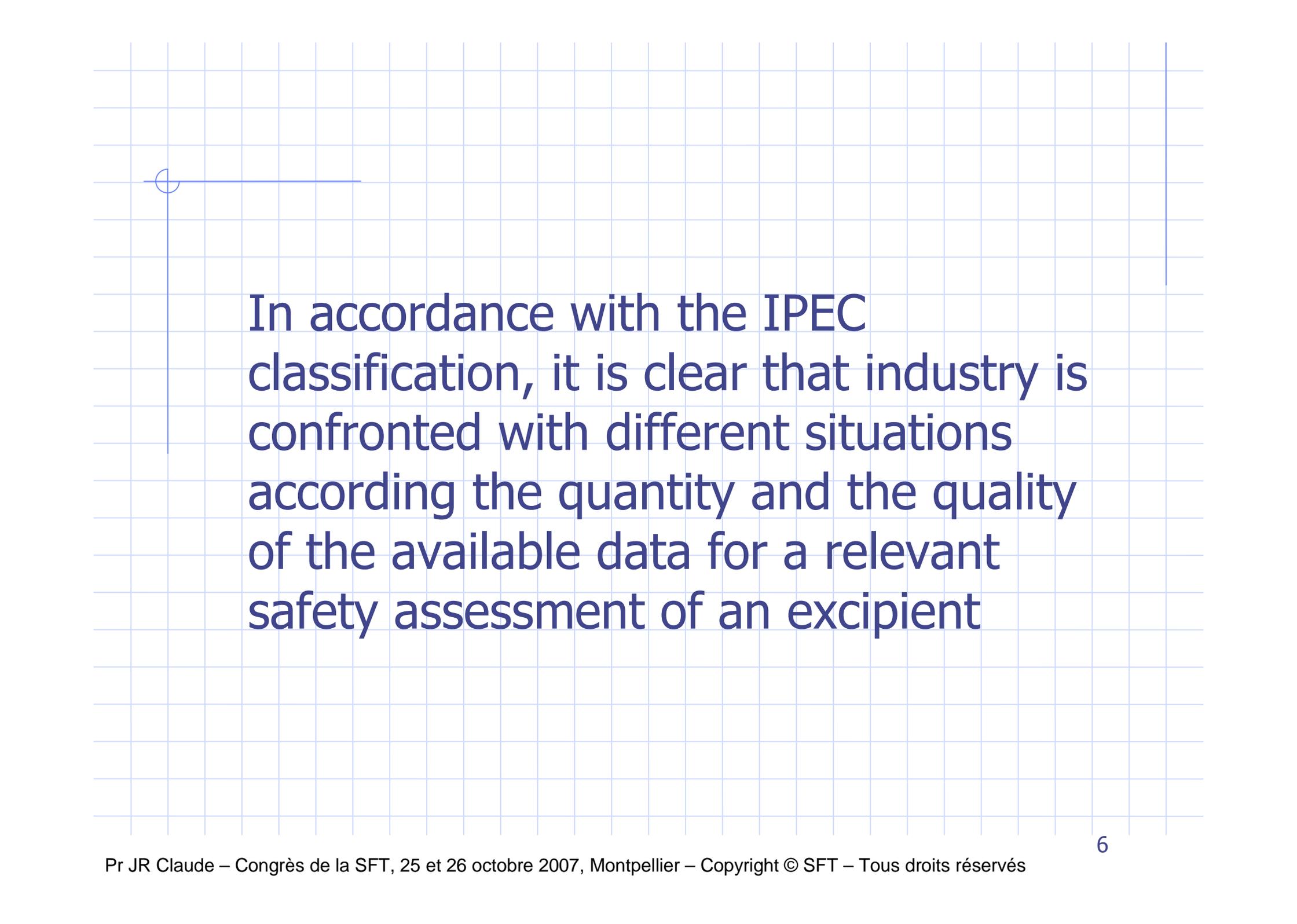
Classification of Excipients

Better applicable for a safety assessment:

- ◆ IPEC (International Pharmaceutical Excipients Council) classification
- ◆ FDA guidance : Non-clinical studies for the Safety Evaluation of pharmaceutical excipients (may 2005). Not providing a classification, but a general strategy based (as for drugs) on the duration and on the route of administration for all new excipients. Very compatible with IPEC classification

Classification (IPEC)

- ◆ New chemical Entity
- ◆ A chemical entity which is not used in medicinal products for humans, in food or cosmetics
- ◆ A chemical entity which is already used in food and cosmetics but not in human medicinal products
- ◆ A chemical entity which is already used in human medicinal products but at lower exposure or *via* a different route of administration
- ◆ A chemical entity which is already used in veterinary medicinal products but not in humans



In accordance with the IPEC classification, it is clear that industry is confronted with different situations according the quantity and the quality of the available data for a relevant safety assessment of an excipient

The Safety Assessment of Pharmaceutical Excipients: How to Conceive a Safety Program?

Very roughly, three possibilities:

- ◆ No data (new compound): **a full program** of toxicology is necessary
- ◆ Well-established use worldwide, no new safety concerns, no modifications in the intended route, dose, duration of treatment: **no studies**
- ◆ Halfway situation: a safety program should be elaborated taking into account the previous knowledge of the product. In some cases, bridging studies (genotoxicity, reprotoxicity...) are necessary. In all cases, this adapted safety program will be scheduled case by case

The Safety Assessment of Pharmaceutical Excipients: How to Conceive a Safety Program?

What kind of data are necessary (or useful) to build a safety program taking into account the previous knowledge of the product?

- ◆ The previous use of the excipient (search in the Pharmacopoeias and pharmaceutical compendia): “Excipient of well-established use”
- ◆ The available relevant informations (studies, scientific papers,...) on the excipient
- ◆ The ADME characteristics of the excipient
- ◆ The existing human data
- ◆ The safety of close compounds (*in silico* toxicology, expert systems...)

But

Many Excipients are not only of Pharmaceutical Use

Consequently:

- ◆ Diversity in the intakes and difficulties to enforce and to control an Acceptable Daily Intake (ADI)
- ◆ Frequently manufactured by non-pharmaceutical companies where the standards are not the same, generating discrepancies in terms of quality and safety that must be taken into account for the risk assessment
- ◆ Nevertheless, the registration on a positive list (GRAS) is an important safety data

Are Excipients of Well-Established Use Definitively Safe?

But

Unfortunately No:

- ◆ Products where metabolic, kinetic or toxicological data are lacking, insufficient, obsolete, debatable,...
- ◆ Product where a toxicological reevaluation has been carried out (phtalates, glycol ethers..)
- ◆ Products inducing allergy (not all inventoried)
- ◆ Mixture of variable composition (PEG, Cremophor..)
- ◆ Presence of impurities, degradation products, catalysts, unknown or toxic
- ◆ Presence of toxic residual solvents (benzene in carbopols) or of solvents (excipient or residual) with a fixed ADI (ICH guideline on residual solvents)
- ◆ Environmental contaminants (CFC,HFC??)
- ◆ Etc...

But

What is a "relevant" information? (essential to decide of the need of bridging studies)

- ◆ Toxicological data are not published in many cases and are very difficult to obtain (industrial protective measures). Big difficulties when an excipient is used in one area of the world but not in another
- ◆ What is the value of "old " studies (not in accordance with up-to-date guidelines, and not performed under GLP conditions)? Bridging studies or new studies (if there is a cause of concern)?
- ◆ Debatable value of scientific papers, and difficulties to reproduce the results in some cases (not performed for a regulatory purpose)

But

Difficulties for the ADME Evaluation

- ◆ The Safety Evaluation and a rationale safety program strongly depend on the ADME
- ◆ However, the ADME evaluation is sometimes extremely difficult or impossible (complex mixtures, analytical challenges...)

But

What is the Value of Human Data?

- ◆ High value for excipients used previously as food additives or cosmetics, if correctly collected and evaluated
- ◆ High value for excipients used previously in chemical industry (solvents) if occupational data were correctly collected and evaluated
- ◆ For excipients already used in pharmaceuticals: difficulties to detect undesirable effects by the pharmacovigilance if these effects are weak, with a low incidence and /or of allergic origin....

In practice:

- ◆ For NCE and for products never used in medicine, food or cosmetics: full toxicity studies should be provided
- ◆ For products already used but not sufficiently documented: bridging studies or complementary studies should be provided

The IPEC guideline

○ (European Pharmaceutical Review, 1997, 2, issue 4)

Excellent document, still of value.
According to 3 steps procedure, the requirements are related to the route of exposure for humans and to the duration of exposure. ADME is required (except for complex mixtures)

The FDA guideline: Non-clinical studies for the Safety Evaluation of Pharmaceutical Excipients – May 2005

- ◆ Very close to the IPEC guideline
- ◆ **The most important point:** the recommended strategies to support marketing of new excipients in drug products, including:
 - Safety pharmacology (not existing in IPEC)
 - Studies for short term use (14 days): ADME, acute toxicity, 1-month study (2 species), genotoxicity, reproductive toxicology (3 segments)
 - Studies for intermediate use (2 weeks- 3 months): the same + 3month study (2 species). Additional studies may be asked (parenteral)

The FDA guideline:

Non-clinical studies for the Safety Evaluation of Pharmaceutical Excipients – May 2005

- ◆ Studies for long term use (more than 3 months, single treatment or multiple cures): the same + 6 month study in rat + 6-9-12 study in non rodent depending on the toxicity. If appropriate, carcinogenicity studies.
- ◆ Studies for use in pulmonary, injectable or topical products
- ◆ Need for photosafety data

EMA guidelines

- ◆ Excipients in the label and package leaflet of Medicinal Products for Human Use (July 2003): the well-known guideline containing warning statements relating to the presence of certain excipients. In French « excipients à effet notoire », starting with Aprotinin and finishing with Xylitol
- ◆ Excipients in the dossier for Application for Marketing Authorisation of a Medicinal Product, (deadline for comments, February 2007). Two lines are related to toxicology. **Nervertheless Quality is the first step of the safety assessment**
- ◆ Metal catalysts (deadline for comments May 2007)
- ◆ Limit for Genotoxic impurities (into operation January 2007)
- ◆ Carcinogenicity, mutagenicity and reproductive toxicity of excipients (CMR) (consequence of REACH). In progress.

Risk Assessment for Pharmaceutical Excipients

Can be established if:

- ◆ The requirements related to the quality (impurities and degradation products, residual solvents, catalysts,..) are respected
- ◆ A relevant knowledge of the products is available (previous studies, studies kept up-to-date, good scientific information...)
- ◆ A safety program (or an adapted one) allows the determination of a non-effect level (NOEL) or a non observed adverse effect level (NOAEL)
- ◆ Eventually human data are available, relevant and clean.
- ◆ The general condition of the exposure in a pharmaceutical product are well defined (route, dose,...)

Risk Assessment for Pharmaceutical Excipients (con't)

- ◆ Finally, the risk assessment allows the proposal of an Acceptable Daily Intake (ADI) or a Permitted Daily Exposure (PDE), and the assessment of a safety margin.
- ◆ A question: can we discriminate an ADI for a short term and for a long term exposure?
- ◆ A practical consequence for the excipients with a recognized effect on the general population (ethanol), or populations at risk: juveniles (benzyl alcohol), elderly, genetic disorders (fructose, galactose, lactose), sensitized individuals (allergy)...: **The European (EC) list of excipients with notorious effects**