Excipients: Safety, toxicological, and precedence of use issues

An excerpt from the GMP MANUAL

by Iain Moore, Ph.D.

In this chapter you will find answers to the following questions:

- How can precedence of use be assessed for marketed excipients?
- How can safety be assessed for a chemical to be used as new excipient?

1. Marketed excipients

Potentially any substance could be used as an excipient as long as it has no therapeutic effect and is safe to the patient. However, there are several safety related issues that should be assessed by the potential excipient manufacturer as part of its decision to introduce an excipient to the pharmaceutical market.

First an assessment should be made as to whether there is a precedence of use for the material in a drug product or a similar application such as a food additive or food contact packaging component. If a precedence of use can be shown in applications where there is human exposure, the safety of the material might already be appropriate for potential application as an excipient in the pharmaceutical industry.

In the U.S., the Food and Drug Administration (FDA) maintains a database of excipients that is posted on their website as the Inactive Ingredient Database (IID). The IID should be used to establish precedence of use since it lists each excipient which has been allowed as a consequence of its presence in an approved innovator drug product. Each excipient is listed by name, dosage form, and the maximum amount of excipient contained in an approved drug of that listed dosage form. Care must be exercised in searching the database because an excipient can be listed by various names, including trade name, compendia name, chemical name, or generic description (for dyes and flavours).

In Japan, an assessment for precedence of use can be made by referring to the Japanese Pharmaceutical Excipients Dictionary (JPED) which is edited by the Japan Pharmaceutical Excipients Council in conjunction with the Ministry of Health, Labor, and Welfare. The JPED is a compilation of all excipients for which there is a precedence of use in drug products in Japan. It includes monographs from the JP or Japanese Pharmaceutical Excipients (JPE) as well as all non-monograph excipients that have been previously used. Each monograph lists the nonproprietary name and synonyms along with the application and maximum dosages for the various routes of administration in approved drugs.

In Europe, there is no comprehensive European Union list of excipients that have been approved in drug products. Therefore, in order to establish precedence of use, it is necessary to review the drug catalogues such as the “Dictionnaire Vidal” (France), “Die Rote Liste” (Germany), or “The Electronic Medicines Compendium” (UK).

Note: If there is no precedence of use in a drug product, then the material is to be considered a new excipient and should be introduced according to local regulations.

2. New (novel) excipients

An excipient used for the first time in a drug product or by a new route of administration is classified as new according to the ICH Guideline M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use. Conversely, this guideline defines known excipients as “excipients that are well-established and commonly used in registered drug products and are usually included in pharmacopoeias”.

When an excipient has not previously been used in a pharmaceutical dosage form then there are a number of conditions set out by
the US and European regulatory authorities to allow for its use. The U.S. FDA has issued a Guidance concerning the safety testing required for novel excipients\cite{U.S. FDA, Nonclinical Studies for Development of Pharmaceutical Excipients (final version May 2005)} as has IPEC in their IPEC New Excipient Safety Evaluation Procedure\cite{http://ipecamericas.org/content/ipec-novel-excipient-safety-evaluation-procedure}. The latter were the basis for the USP-NF 26 General Chapter <1074> Excipient Biological Safety Evaluation Guidelines on this topic. The information contained in these documents is useful for assessing the safety of a chemical for use as an excipient. The IPEC Europe Safety Committee has published a similar guideline\cite{The Proposed Guidelines for the Safety Evaluation of New Excipients (European Pharmaceutical Review, November 1997)}. The manufacturer of a new or novel excipient should develop the safety information recommended in these guidelines appropriate to their intended use. This information provides the basis for establishing the suitability of the material for use as an excipient in a particular type of dosage form.

The terms “new” and “novel” as related to excipients are difficult to define precisely. Clearly an excipient is new if it is not listed in the FDA Inactive Ingredient Database, any of the 3 major compendia, U.S. Pharmacopeia (USP-NF), European Pharmacopoeia (Ph. Eur.), or Japanese Pharmacopoeia (JP), or other widely known compendia such as the Handbook of Pharmaceutical Excipients or Fiedler: Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete (Encyclopedia of excipients for pharmaceutical, cosmetic and related use).

The industry recognizes that any change in the chemical composition of an excipient produces a new excipient, no matter how minor the modification to the chemical composition is in fact. Mixtures of excipient ingredients can result in a “new” excipient when the subject mixture is to be used in a dosage form for which its constituent excipients have not already independently been used in that intended route of administration. Physical modification of an excipient, such as micronizing or compaction does not generally produce a new or novel excipient.

However, co-processing can produce a synergistic physical interaction between two or more excipients that is patentable and create unique properties that cannot be achieved through simple blending. The safety assessment for these co-processed excipients made with commonly used pharmaceutical excipients will generally be less stringent than for a new chemical entity.

If the excipient is already described in a pharmacopoeia or used as such in other pharmaceutical dosage forms, the excipient is neither new nor novel and the detailed safety review recommended in the above guidelines will not be necessary.

**Summary:**

For marketed excipients, precedence of use can be assessed by reference to FDA’s Inactive Ingredients Database (IID), the Japanese Pharmaceutical Excipients Dictionary (JPED), and drug catalogues such as Dictionnaire Vidal or Rote Liste. If a precedence of use can be shown in applications where there is human exposure, the safety of the material might already be appropriate for potential application as an excipient in the pharmaceutical industry.

When an excipient has not previously been used in a pharmaceutical dosage form then there are a number of conditions set out by the US and European regulatory authorities to allow for its use. Relevant guidance is given by FDA, IPEC and US/NF. The manufacturer of a new or novel excipient should develop the safety information recommended in these guidelines appropriate to their intended use. This information provides the basis for establishing the suitability of the material for use as an excipient in a particular type of dosage form.

**Author:**

Iain Moore, Ph. D., Croda Europe Ltd, UK

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\[ i \] Database: [www.accessdata.fda.gov/scripts/cder/iig](http://www.accessdata.fda.gov/scripts/cder/iig)

\[ ii \] Maximum dosage information is only contained in the Japanese language version of the JPED.

\[ iii \] U.S. FDA, Nonclinical Studies for Development of Pharmaceutical Excipients (final version May 2005)

\[ iv \] [http://ipecamericas.org/content/ipec-novel-excipient-safety-evaluation-procedure](http://ipecamericas.org/content/ipec-novel-excipient-safety-evaluation-procedure)

\[ v \] The Proposed Guidelines for the Safety Evaluation of New Excipients (European Pharmaceutical Review, November 1997)