

Toxicity of Excipients—A Food and Drug Administration Perspective

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Excipients are essential components of drug products. They are also potential toxicants. Examples of known excipient-induced toxicities include renal failure and death from diethylene glycol, osmotic diarrhea caused by ingested mannitol, hypersensitivity reactions from lanolin, and cardiotoxicity induced by propylene glycol. Proposals to test or market new drug products in the United States should adequately address the safety of the proposed exposure to the excipients in those products. The specific safety data that may be needed will vary depending upon the clinical situation, including such factors as the duration, level, and route of exposure, but may include acute, repeat-dose, reproductive, and genetic toxicity data, carcinogenicity data, and specialized toxicology information, such as sensitization or local irritation data. Many guidances exist to aid in the development of pharmaceuticals, including the International Conference on Harmonization (ICH) documents and various Food and Drug Administration/Center for Drug Evaluation and Research (FDA/CDER) pharmacology and toxicology guidances. The FDA/CDER has recently adopted a new guidance for industry, “Nonclinical Studies for Development of Pharmaceutical Excipients,” which focuses on issues associated with development of safety databases that will support clinical use of excipients in drug products. The new guidance document is introduced and discussed in this article.

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Excipients are essential, but often neglected, components of drug products (de Jong 2001). Examples of excipients include fillers, extenders, diluents, wetting agents, solvents, emulsifiers, preservatives, flavors, absorption enhancers, sustained-release matrices, and coloring agents. Excipient use can be traced back thousands of years. In the Bible and other ancient texts, it was mentioned that substances such as honey, various alcoholic beverages, and certain tree saps were used in medicines. Most

likely these substances were used to make the often-bitter herbal medicaments available in those days more palatable. Successive generations of traditional medicine practitioners experimented and passed down their recipes for medicines and ways of making them more palatable. The importance of excipients in drug products is evidenced by the term often used to describe them “pharmaceutical necessities.” Besides their use in making drugs palatable, excipients can be added to parenteral formulations to maintain active ingredient solubility and/or stability but they can also assure safety (antimicrobial preservatives), minimize pain and irritation upon injection (tonicity ingredients), and control or prolong drug delivery (polymers) (Akers 2002).

EXCIPIENT TOXICITY

Like all chemicals, excipients are potential toxicants and they are not inert substances (Golightly, Smolinske, Bennett, Sutherland, and Rumack 1988). Absolute safety from a specific chemical can only be accomplished through avoidance of exposure to that chemical. If a pharmaceutical manufacturer considers using a particular excipient in a product, the manufacturer should be prepared to demonstrate the safety of the proposed exposure to the excipient by citing suitable safety data that can be considered by the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) in a risk-benefit assessment. The importance of assessing the safety of proposed exposures to excipients can be illustrated by examining some examples of excipient-induced toxicities.

When elixir of sulfanilamide was formulated in 1937, diethyleneglycol (DEG) was used to solubilize the antibacterial drug. The elixir contained 72% DEG, 10% sulfanilamide, and about 15% water. DEG also improved the taste of the medication and made it esthetically pleasing to children. The first batches of the product were distributed in September of 1937. More than 100 children died from its consumption as a result of kidney failure (Rossoff 2002; Ruprecht and Nelson 1937). This incident induced the U.S. Congress to pass the *Federal Food, Drug and Cosmetic Act* of 1938, which mandated that safety testing be performed by drug manufacturers prior to marketing. Examples of excipient-induced toxicities include the hypersensitivity reactions produced in susceptible individuals by such excipients as

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acacia, parabens, lanolin (hydrous wool fat), polyethylene- and propylene-glycols. If given intravenously, propylene glycol can be cardiotoxic and could induce thrombophlebitis. In infants, benzyl alcohol has produced severe adverse reactions.

As with many substances, excipient toxicities resulted in people as a result of their excessive consumption. Ethanol is a widely used excipient in liquid cough and cold preparations and can constitute from 5% to 25% of the product by volume. In sufficiently large amounts, ethanol can produce central nervous system depression, drunkenness, and death following ingestion. Osmotic diarrhea has been associated with the excessive ingestion of syrups containing large amounts of sucrose, glycerin, mannitol, and sorbitol (Winek 1969, 2000).

During the period 1995 to 1996, 88 Haitian children were poisoned from DEG-contaminated glycerin used to make acetaminophen syrup (Winek 2000). Similar toxicities from DEG-contaminated drug products were reported in children in South Africa in 1972 and in Bangladesh in 1995. For a definitive list of toxicities and the associated excipients, see Winek (2000).

EXCIPIENT TOXICITY GUIDANCE

The FDA CDER, through its Inactive Ingredients Subcommittee, has developed a guidance document that addresses the safety testing of potential excipients. The guidance was influenced by ideas from the International Pharmaceutical Excipients Council (IPEC; Steinberg et al. 1996) and the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). In September of 2002, the FDA published its draft guidance for industry entitled “Non-clinical Studies for Development of Pharmaceutical Excipients” to solicit comments from the public (*Federal Register* 2002).

The draft guidance lists safety-related issues that should be addressed under an investigational new drug application (IND) or new drug application (NDA) in support of proposals to use excipients in new drug products in the United States. The issues that should be addressed under various exposure conditions are presented below. It is important to understand that these “issues” are viewed by the CDER not as a concrete list of non-clinical studies that must be submitted, but rather as a series of topics that should be adequately addressed in some manner within an IND or NDA. The draft guidance emphasizes that the need to submit suitable supporting data that lead to a positive risk-benefit assessment is not limited to excipients that are new molecular entities (NMEs). The safety issues identified in the draft guidance should be addressed for all proposed exposures to excipients, regardless of previous use.

For excipients with a history of use, it may be possible to adequately address some or all of the safety issues through citation of the existing nonclinical and clinical database, marketing history, or regulatory status of the compound (e.g., “GRAS” [generally-recognized-as-safe] status as a direct food additive may adequately support oral administration of that compound up to the levels permitted in foods). Any gaps in the database,

however, should be filled by conducting new nonclinical studies. Prior use in humans says relatively little about some safety issues, such as genotoxicity and carcinogenicity potential. There is a common misperception that once an excipient is used in an approved product (and is therefore listed in the CDER’s Inactive Ingredient Guide), it is automatically assumed by the agency to be safe for use in any product thereafter that involves the same route of administration and level of exposure. If an excipient was used in a previously approved product (excipients are never “approved” themselves), it is likely to be deemed safe for use in other products that involve use under similar circumstances, but the agency may ask that the database be brought up to current standards in relation to even that “similar” use.

Any attempt by the manufacturer to justify a proposed human exposure to an excipient by discussing prior use of the excipient should carefully consider differences between the proposed use and the prior use. For example, just because the database associated with an excipient is deemed to support use associated with short-term treatment of cancer patients does not necessarily mean that the database would support chronic treatment of acne patients, or even short-term treatment of acne patients. Different use scenarios are associated with different risk-benefit assessments. In other words, the CDER uses a “cause for concern” approach when assessing the scope of the database necessary to support a given use of an excipient. The approach is somewhat analogous to that described in the ICH-S1A document (1996) in association with deciding if carcinogenicity data are needed to support marketing of a drug product. The decision can be affected by mitigating circumstances, such as the duration of exposure, levels of local and systemic exposure, patient population (e.g., use in pediatrics, use in severely debilitated individuals, use in young, essentially healthy individuals), route of administration (which affects systemic and local exposure considerations), what is known about other compounds in the same class or chemical family, and what is known about the excipient itself from studies conducted to date (i.e., safety pharmacology or previously conducted toxicology studies may point to areas that require further study). All these factors are considered in the risk-benefit assessment. The “benefit” aspect of the equation is, of course, derived from the therapeutic effects of the drug product. But if one has documented the benefits that an excipient enhances the therapeutic properties of a product (e.g., by enhancing absorption or affecting the rate of release of the drug substance, especially if the effect is deemed critical and unique to that excipient), the agency will weigh that benefit to the patient (therapeutic enhancement) against any risk to the patient attributed to the excipient. Each proposed use of an excipient must be considered on a case-by-case basis and must be consistent with a positive risk-benefit assessment.

With proper planning, it is often possible to assess the toxicology of a new excipient in a relatively efficient manner. For example, sponsors may be able to develop new excipients concurrently with the development of new therapeutic substances by adding satellite groups of animals that receive the excipient

to studies that would have been conducted anyway to develop a drug substance, effectively conducting a study within a study. The advantage of this approach is that, presumably, it would be less expensive to conduct one larger study than it would be to conduct two separate studies. It may be possible to partially qualify excipients in some drug products by including in appropriate studies both a control group that is either untreated or treated with water or saline and a “vehicle”-treated group (which is treated with the vehicle of the clinical formulation). Comparison of these groups could help to qualify the proposed clinical exposure to the excipients, although additional studies conducted with individual excipients may be needed if either a higher exposure to an excipient was deemed necessary or if the vehicle induced toxicity. Useful safety data (e.g., data about local tolerance) may also be obtained in clinical trials conducted with the to-be-marketed formulation of the drug product. It may be possible to find useful safety data in the scientific literature. Suitable data may also be present in drug master files and approved new drug applications or their equivalent, although it may be necessary to document a right to reference such data by submitting to the agency written permission from the owners of the data allowing the agency to review the information.

Excipients used in over-the-counter (OTC) drug products should not interfere with the effectiveness or quality of a product and for narrow therapeutic index drugs, such as digoxin and coumadin, excipients should not exert any influence on the therapeutic effectiveness of the product for reasons of safety.

The regulations (21 CFR 314.94 (a) (9)) state that generic drug products intended for parenteral, ophthalmic or otic use should contain the same excipients in the same concentrations as their referenced listed drug products with the exception of antioxidants, buffers, and preservatives. However, in these exceptions, the inactive ingredients should not change the safety of the drug product. Excipients formulated in drug products intended for use with other routes of administration can differ, but they must be safe for the indication and patient population.

There are exceptions to the extent and type of safety requirements pertaining to the permitted use of a new excipient. For example, it may be justifiable in the development of an excipient intended for inclusion in life-saving therapies that toxicity data requests be reduced (as opposed to low-morbidity indications) or completed post approval. Also, it may be possible to extrapolate relevant information from the database associated with a large polymer to assess similar polymers that differ only in molecular weight (chain length). The agency would analyze such situations on a case-by-case basis. All safety testing should be performed using state-of-the-art protocols and should conform to good laboratory practice regulations.

DEVELOPMENT STRATEGIES FOR NEW EXCIPIENTS

To qualify excipients that have not been previously marketed, the agency will have to review extensive toxicity information. As with unapproved drug substances, safety pharmacology studies should be performed with new excipients to determine potential

pharmacological activity. It is recommended that the ICH safety pharmacology guidance S-7A (2001) be followed, and the focus should be on testing for effects on the central nervous, cardiovascular, and respiratory systems, as these have been identified in the ICH M-3 (1997) document as vital functions. If activity is found in these systems, changes in the subsequent development program could occur. For example, additional activities could involve performing detailed investigations to determine more precisely the effects of the excipient on the affected system(s) and the no-observed-effect levels (NOELs) and to calculate acceptable daily intakes (ADIs).

THERAPEUTIC DURATION

Existing databases to support the specific use of a given excipient should always be considered within the context of the drug product with which the excipient is associated. If the drug product is intended for a 14-day therapy or less and would be used infrequently, the excipient should be tested in acute toxicity studies and in 1-month, repeat-dose toxicity studies in two mammalian species (one being a nonrodent) using the intended route of therapeutic administration. Pharmacokinetic profiling (ICH-S3B 1995) should also be considered. For an assessment of genetic toxicology and reproductive toxicities, the battery of genetic toxicity tests ICH-S2B (1997) and the ICH reproduction toxicity guidances (S5A [1994] and S5B [1996, 2000]) should be reviewed.

If the intended therapeutic duration is less than or equal to 90 days, all of the above studies should be performed plus two 90-day repeat-dose studies, which would be conducted as previously mentioned.

If the intended use is greater than 90 days, all of the above studies should be conducted plus chronic toxicology studies in both a rodent species (usually 6-month duration) and an appropriate mammalian nonrodent species (usually 9-month duration). Under certain circumstances the agency will request chronic toxicology studies of different duration (see the ICH guidance S4A [1999]). In addition, for those excipients intended for use in chronically administered drug products, a carcinogenicity evaluation should be made. The sponsor has the option of conducting two 2-year bioassays in rodents, or one 2-year bioassay in rats and an alternative assay as per the ICH documents S1A (1996) and S1B (1997). However, if the sponsor can document adequate scientific justification that carcinogenicity data are not necessary, the need for such data could be waived (see ICH-S1A). Such strategies will be evaluated on a case-by-case basis. An evaluation of a strategy and a decision will be made by the appropriate division-level staff in conjunction with the center's Pharmacology and Toxicology Coordinating Committee's (PTCC) Executive Carcinogenicity Assessment Committee (ECAC). The factors in the sponsor's strategy that will be reviewed involve:

- a. Any previous demonstration of carcinogenic potential in the excipient class that is considered relevant

- b. Structure-activity relationships suggesting a carcinogenic risk
- c. Evidence of preneoplastic lesions in repeated-dose toxicity studies
- d. Long-term tissue retention of the excipient or a metabolite of the excipient resulting in local tissue reactions or other pathophysiological responses that are suggestive
- e. Genetic toxicity data

In some situations, data from a properly performed cell-transformation assay could assist in this evaluation.

For excipients that will be used in drugs administered by inhalation or by topical routes, sponsors may need data generated from all of the above tests. The appropriate review division should be contacted for a decision. In addition, data on sensitization potential by either route would be needed. If systemic exposure is identified in the pharmacokinetic studies, data obtained from a parenteral or oral (if supported by toxicokinetic data) study may be necessary to evaluate the excipient's potential for producing systemic toxicity. As part of any safety evaluation, the excipient should be evaluated for its ability to absorb ultraviolet (UV) light (i.e., UVA, UVB) and visible wavelengths. If such a capacity were determined, it would be prudent to evaluate the excipient for its phototoxicity potential.

Depending on the results of toxicological testing, the agency could request additional studies to examine more closely the toxicity in question to understand the level of risk that the compound may pose. For example, the agency could request special studies to elucidate an observed cardiovascular event or an ocular finding. The potential may also exist to eliminate some studies during the course of product or excipient development. In these situations, it is appropriate to consult with the appropriate FDA division for a decision.

Guidance concerning the development of specific excipients can generally be obtained from the agency. Information requests in relation to use in a specific drug product should be made to the division that handles products of that indication, either during a pre-IND interaction or in a submission to an IND or NDA, depending on the regulatory status of the product. Requests for guidance on excipient issues that do not pertain to a specific drug product (e.g., general excipient issues), or questions that pertain to potential excipients not yet associated with a drug product can be directed to the Inactive Ingredient Subcommittee of the Pharmacology and Toxicology Coordinating Committee of CDER.

In summary, CDER has recently adopted a guidance for industry that relates to the nonclinical development of excipients,

and that document discusses associated issues and outlines recommendations concerning the safety database that may be appropriate to support use of excipients under various clinical use scenarios. These issues and recommendations should not be viewed as a concrete list of nonclinical studies that must be submitted, but rather as a series of topics that should be addressed in an acceptable manner. This may or may not require conduct of nonclinical studies, depending on the proposed clinical use and the scope of the existing database. Information or guidance specific to a particular excipient or drug product concerning the development of a safety database is usually available from CDER. Readers should consult the guidance for further details.

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