Excipient GMP Quality Standards
One is Enough

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In 2001, the International Pharmaceutical Excipients Council (IPEC) updated its 1995 *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients* to incorporate ISO 9000:2000 requirements. Recently, the Institute of Quality Assurance/ Pharmaceutical Quality Group (IQA/PQG) proposed the pharmaceutical excipients application standard PS 9000:2002, which introduces three levels of increasingly stringent quality system requirements. However, the author argues that the additional set of GMP requirements is not necessary and, in fact, will result only in increased complexity for excipient manufacturers.

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Excipients are those materials that when combined with an active pharmaceutical ingredient (API) result in a drug product. Whereas an API has only one function — albeit an extremely important one, that of providing a therapeutic effect — the excipients contained in a drug product play a multitude of roles. Excipients are flavors and colors, coatings and inks, tablet binders and disintegrants, processing aids and lubricants, and so forth. Excipient ingredients enable an API to be compounded into a stable drug dosage form that can be safely stored and administered with assurance of a consistent bioavailability profile.

Clear regulatory standards exist for the manufacture of APIs and for drug products, but no standards have been set specifically for excipients. In the United States, FDA is responsible for enforcing the requirements of 21 *CFR* Parts 210 and 211 for the manufacture of drug products from APIs, excipients, and other components. Over the years, the agency has issued numerous guidance documents concerning the manufacture of drug products. In the past several years the agency also has focused increased attention on the manufacture of APIs, which has led to an additional series of guidance documents. However, to date, no FDA guidance exists that deals solely with the requirements of the excipient quality system.

The International Conference on Harmonization (ICH) has issued several standards applicable to the manufacture of drug products and APIs. Among these are guidelines for specifications, impurities, stability, and residual solvents. ICH also has issued a guideline good manufacturing practices (GMP) standard for the manufacture of APIs. However, of these guidelines, the only one that includes the manufacture of excipients is the guidance for residual solvents.

The IPEC excipient guide

The International Pharmaceutical Excipients Council (IPEC) was organized in 1991 as an industry association comprising manufacturers of excipients and their pharmaceutical formulating customers. One of the initial objectives of the organization was to develop GMP guidelines appropriate for the manufacture and use of excipients. In 1995 this goal was achieved with the publication of the *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients*. In 2001 this guide was updated and reissued to incorporate ISO 9000:2000 requirements.

The IPEC excipient GMP guide was developed by a committee of industry representatives during a period of four years. Quality assurance and regulatory compliance representatives from several excipient manufacturers worked with their counterparts from pharmaceutical dosage form manufacturers to develop a GMP standard appropriate for excipient manufacture. This standard was based on the ISO 9001 standard. The draft guideline was reviewed by IPEC-Europe and the Japanese Pharmaceutical Excipients Council (JPEC). After their comments were incorporated into the draft, a globally accepted excipient standard was established.

Representation from both parties, makers and users, has led to a standard that excipient manufacturers can achieve on a continuing basis. Conformance to the IPEC standard ensures that the excipient produced is both safe and appropriate as required by the Food, Drug, and Cosmetic Act.

The 1995 IPEC GMP guide was incorporated in a general chapter of the *USP–NF* and was published first in *USP 24–NF 19*. The European Pharmacopeia is reviewing the IPEC GMP guide for publication as an information chapter in *PharmEuropa*. In addition, the IPEC guide was provided to the World Health Organization for use in its development of appropriate excipient GMP requirements to be followed by manufacturers in less-developed countries. Finally, IPEC has kept FDA informed of the development of the excipient GMP guide as well as of subordinate guides such as the excipient audit guide and significant change guide.

The IQA/PQG guide

Recently, the Institute of Quality Assurance/Pharmaceutical Quality Group (IQA/PQG) proposed a pharmaceutical excipients application standard, PS 9000:2002. The stated purpose of this guide is to act "as a significant advancement of the IQA/PQG *Pharmaceutical Supplier Code of Practice for Pharmaceutical Raw Materials* to define appropriate standards of good manufacturing practice for the manufacture of excipients for pharmaceutical products" (1). The development of this European excipient GMP standard may slow efforts to achieve a single, globally accepted excipient GMP standard.

The PQG excipient quality standard integrates the organization's pharmaceutical supplier code of practice with the requirements of ISO 9001:2000. The result is a standard for use in third-party certification using the ISO 9000 scheme. The guide consists of two parts:

- Part 1 contains the requirements for ISO 9001 and requirements for conformance to the excipient GMP standard.
- Part 2 contains additional GMP guidance set forth in a similar format to the ICH *GMP Guide for Active Pharmaceutical Ingredients* (Q7A) (2).

Application of the PQG standard

An important feature of the PQG standard is the introduction of three levels of increasingly stringent quality system requirements: foundation, intermediate, and high. These levels range from basic GMP conformance, as denoted in the standard, to GMP requirements for the manufacture of the excipient akin to that specified in the ICH API GMP guide. Determination of the appropriate GMP level involves the evaluation of two main risk factors:

- the route of administration of the final drug product
- several inherent properties of the excipient and the excipient's method of manufacture.

Route of administration. The GMP level associated with the route of administration ranges from foundation for oral and topical drug products to high for dosage forms that are meant to bypass the body's natural defenses (e.g., parenteral dosage forms). Thus tablets typically would require excipients with a low GMP level (foundation) because tablets are ingested, whereas injectable dosage forms would require a high GMP level because they bypass the defenses of the skin.

Application of the PQG standard begins with a determination of the level of patient risk associated with a drug product's route of administration. The proposed standard would require that a pharmaceutical company inform its excipient manufacturer about the drug product that would use the excipient. In other words, this approach requires that the company work closely with the excipient manufacturer early in the drug development process to ensure that an appropriate grade of excipient for the intended route of administration is available from the manufacturer. However, this coordination may not be feasible because of issues such as confidentiality, competition, pricing, and so forth.

Nature and manufacture of the excipient. If the route of administration for the drug product containing the subject excipient caused the GMP level to be categorized as "high," no further evaluation is necessary. Otherwise the inherent nature of the excipient and its method of manufacture then must be assessed because these factors can cause the required GMP level to increase. The inherent nature of an excipient and its production involves consideration of the excipient's functionality in the drug product, evaluation of the excipient's toxicity, and the potential for cross-contamination during its manufacture. As noted in the PQG guide, the functionality of the excipient, its toxicity, and its potential for cross-contamination during its manufacture can raise the requirements for GMP compliance.

Functionality. The first inherent property of the excipient is its functionality in the dosage form. Determination of the functionality also requires close communication with the pharmaceutical developer because it is not uncommon for an excipient to have various functionalities that depend on the dosage form. For instance, Povidone is a tablet binder in solid dosage products but functions as a thickener in liquid preparations. Close communication also is needed because the pharmaceutical developer may have found a new functionality for the excipient of which the manufacturer is not aware. Determination of an excipient's functionality is important to the excipient manufacturer in its assessment of the proper level of GMP, and yet the drug maker may withhold this information until well into the development process.

Toxicity. The excipient manufacturer also should determine the toxicity of an excipient on the basis of the daily dose of the excipient in the drug product. Although the excipient manufacturer will have determined the toxicity of the excipient, it is the drug formulator that is ultimately responsible for the safety

of the drug product. To determine the GMP level, the pharmaceutical company must disclose to the excipient supplier an approximation of the level of the excipient in the drug product as well as the frequency with which the patient may take the drug. The pharmaceutical manufacturer may not be inclined to disclose this information, but without knowledge of the usage level, an incorrect level of risk may be assigned.

Manufacture. The final factor inherent in the excipient is attributed to its manufacture. Excipients produced in a dedicated plant are treated differently from those made in a multipurpose plant; the latter raises the possibility of cross-contamination. The PQG guide does not qualify what is meant by *multipurpose*, and thus leaves its interpretation to the excipient manufacturer and pharmaceutical customer. Generally speaking, only excipients that are also used as food ingredients are produced in dedicated plants because of their large market and economies of scale.

Typically, excipient ingredients — except those that also are used in food applications — are produced in multipurpose plants. Many are made in large chemical complexes along with numerous other chemicals. However, the manufacture of these synthetic chemicals generally requires highly controlled environmental conditions. Synthetic excipients typically are produced in closed manufacturing facilities because of the sensitivity of chemical reactions. Because the equipment often is dedicated and the excipient is packaged in controlled environments, one may question whether the likelihood of cross-contamination is higher for the processing of these excipients than for the refining of foodstuffs to produce excipients such as sugar or starch. The IPEC guide leaves the evaluation of the potential for cross-contamination to the excipient manufacturer with oversight by the pharmaceutical manufacturer during on-site audit.

Clearly, the proper application of the principles in the PQG guide to determine the level of GMP for excipient manufacture requires a combination of good communication between a drug developer and an excipient producer (preferably early in the development process) as well as personnel at the excipient manufacturing site who can properly evaluate the information to determine the GMP level. The need for clear and complete communication with a pharmaceutical developer represents a paradigm shift for an industry in which an excipient supplier typically is unaware of the products into which an excipient is compounded, the excipient usage level, and the anticipated daily dose. In addition, many excipient manufacturers would not have the expertise to evaluate the pharmaceutical compounders' information should they make it available.

IPEC and PQG standards comparison

A review of the PQG standard would indicate that the IPEC standard is comparable with the PQG intermediate level of GMP compliance. This level is appropriate because conformance to the foundation level would be sufficient only in cases in which the excipient is produced in a dedicated facility (e.g., the manufacture of large-scale materials such as sugar and starch). Conformance to the requirements for the high level of GMP, equivalent to that needed for API manufacture, would serve only to increase the complexity of the GMP quality system without a commensurate increase in excipient safety and appropriateness.

In many cases, application of the PQG standard means that an excipient would be manufactured at multiple GMP levels within one manufacturing facility. The excipient manufacturer often would have to choose whether to double or triple the number of grades of excipient offered or to manufacture the excipient at the highest GMP level anticipated, regardless of the dosage form in which the excipient is used. Relative to the requirements of the IPEC standard, each approach increases the complexity of the quality system under which the excipient is produced.

A manufacturer that produces an excipient to multiple GMP levels must support multiple GMP quality systems, provide manufacturing instructions specific to each grade, inventory multiple grades of product, and ensure that the pharmaceutical customer orders and receives the proper GMP grade. In turn, the pharmaceutical company using the excipient in various dosage forms must inventory multiple grades of the excipient and ensure that the proper grade is used in the manufacture of the dosage form.

A company that elects to manufacture at the high GMP level will have a more complex GMP system to support. This decision will place that manufacturer at a disadvantage to the competitor that decides not to offer an excipient grade produced at the high GMP level. The effect of such a decision on the pharmaceutical customer would be a loss of competition for the excipient produced to high GMP standards.

The alternative to the PQG approach, on the basis of the IPEC standard, begins with the manufacture of an excipient to a common GMP standard. A customer requiring additional GMP compliance would reach a contractual agreement with a manufacturer to offer an excipient grade that conforms to an appropriate specification. For example, in cases in which an excipient has functionality in both oral and parenteral applications, the excipient manufacturer would be expected to offer a parenteral grade with specifications appropriate to its intended use. This expectation may coincide with enhanced manufacturing and GMP requirements that should meet the need for excipient manufacture to conform to appropriate GMP standards. In the less common instance in which the pharmaceutical customer has identified the need for enhancements to the IPEC standard, these changes would be detailed in contractual agreements concerning GMP requirements or mutually agreed upon specifications.

FDA requires pharmaceutical companies to ensure excipient ingredients are made under appropriate GMP standards. The company has the responsibility of ensuring that the excipients it uses meet GMP requirements. One must remember that the manufacturer of the drug product is ultimately responsible for the safety of the marketed drug.

Conclusion

IPEC has worked for 10 years to develop excipient GMP standards acceptable to FDA. The introduction of a new set of quality standards for excipient manufacture will create the need for a closer relationship between an excipient supplier and its cus-

tomer. The pharmaceutical customer will have to disclose to the supplier far more details about the use of the excipient in the drug product than it does currently. In turn, the excipient manufacturer will need staff that can appraise the information received from its pharmaceutical customer along with the inherent nature of the excipient to determine the commensurate level of risk. The PQG standard will result in increased complexity for the excipient manufacturer as a consequence of producing excipient grades to various GMP standards. Likewise, the pharmaceutical compounder will have the added burden of ensuring that the stated GMP level for the excipient has been followed. Finally, this approach to GMP compliance places the burden of assessing the safety of the excipient in the dosage form with the excipient manufacturer, which runs counter to FDA's expectations.

Is there any value added for the extra level of compliance? Although it would seem that a new set of standards would improve the safety of drug products for the consumer, is there any evidence of an adverse drug reaction attributable to an excipient produced under CGMP conditions in conformance with the IPEC requirements? I suggest that the answer to both questions is no. Therefore, the introduction of another set of GMP requirements does not serve the industry well. The simplicity of conforming to the IPEC excipient GMP, which is adequate to ensure safe and appropriate excipients, makes a second GMP standard unnecessary.

References

1. IQA/PQG PS 9000:2002, *Pharmaceutical Excipients: The Application of ISO 9001:2000 to Pharmaceutical Excipients* (Institute of Quality Assurance, London, England).
2. ICH, *Harmonized Tripartate Guideline: Good Manufacturing Practices for Active Pharmaceutical Ingredients* (International Conference on Harmonization, Geneva, Switzerland, 2000). **PT**

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