

# The Development of IPEC's Excipient Qualification Guideline

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IPEC is developing a guideline about **excipient qualification to address the overall process needed** for makers and users to fully qualify their excipients.

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**P**harmaceutical excipients users and manufacturers must take more time to understand each other's needs and controls than they have traditionally done in the past. It is a changing world for the pharmaceutical and excipient industries because of issues such as bioterrorism, drug counterfeiting, bovine spongiform encephalopathy/transmissible spongiform encephalopathy concerns, genetically modified organisms, allergens, corporate mergers, and the need to control and lower costs. These issues have caused a need for increased supply chain controls and traceability. If there ever was a time when improved communication was needed, it is now!

In the past, the lack of good, clear communication between the users and makers of excipients has resulted in many technical and commercial problems in the industry. Many of these problems probably could have been averted if appropriate information had been shared earlier about the way in which a specific excipient was to be used or

the way in which it was made. In today's world, it is critical that there be improved openness between the user and maker to avoid pitfalls in the future.

So, where do we start? This answer depends on whether you are an excipient maker or a user. The maker's desires are for the excipient to meet the minimum regulatory compliance requirements needed for entry into the market and to generally meet their customers' needs. The user's desires are to minimize variation in product quality and performance with excipients that will not create any registration issues. Makers and users have different business goals as well. Makers are usually chemical companies whose main business is not pharmaceutical. Users are usually focused entirely on pharmaceuticals but tend to minimize the importance of excipients (until problems occur).

### Key characteristics of an excipient

The maker's desired characteristics of an excipient are

- for the excipient to have the potential to meet the compendial/regulatory requirements for their targeted market regions based on sales goals for premium products
- for the testing to be performed related to premium pricing
- that the lot-to-lot variability in chemical and physical properties be based on their process capability
- appropriate good manufacturing practices (GMPs) be used for their target market (e.g., pharmaceutical, food)

- that the shelf life and storage requirements be communicated to customers to minimize the maker's liability
- that there be flexibility to make process improvements
- that there be interaction with customers that do not unnecessarily disclose intellectual property
- that the participation in the target market return a reasonable profit margin.

The user's desired characteristics of an excipient are

- that the excipient meet all compendial/regulatory requirements for desired global market regions
- that the excipient exhibit no lot-to-lot variability in performance-indicating properties (whatever they happen to be)
- that the excipient be well characterized for pharmaceutical type applications and made under excipient GMPs
- that the stability, packaging, and storage conditions be well defined and include an expiration or reevaluation period
- that the user be notified of all significant changes
- that the specific grade of the excipient from the same manufacturing location be available worldwide through a distribution network
- that the excipient be available from multiple suppliers (that provide equivalent materials)
- that the excipient be inexpensive because it is the inactive part of the formulation.

As you can see from these lists of desirable characteristics, it is no sur-

prise that makers and users have difficulties in understanding each other's issues when trying to set up a mutual agreement between them regarding specifications and supply agreements. It is very important that each party provide clear communication to the other party what their realistic needs are and that the negotiations be a win-win situation for both parties.

In many cases, excipients are selected by users simply on the basis of some type of performance testing that was conducted to solve a particular formulation problem, but without an understanding of the overall regulatory and supply chain control situation. Before a user can select an excipient, it is critical to define the true target market for the application.

### Target market considerations

Users should identify their target market by addressing a number of questions that can affect what excipients may be acceptable for their applications. Some of these questions include the following:

- Is the product going to be regulated as a pharmaceutical or as a dietary supplement?
- What are the desired regions for marketing the drug now and in the future (i.e., the specific countries)?
- In what route of administration will the excipient be used?
- In what type of dosage form will the excipient be used (e.g., tablet)?
- What will be the frequency of the dose?

It is important that this type of information be known before selecting an excipient for the formulation because many excipients have

certain restrictions in some countries. These restrictions must be fully understood before significant research and development (R&D) work is completed. In many cases, companies have spent a lot of time developing a formulation only to find out afterward that regulatory issues regarding the excipient they used in their formulation limited their ability to market the product in certain regions.

For example, many excipients have significantly different tests and limits in the major pharmacopeias. The pharmacopeial harmonization process is helping to align some of the nonharmonized attributes. However, this is a slow process and there will still probably be nonharmonized requirements in many of the monographs after they complete the harmonization process. To use an excipient in any particular country, compliance with all of the requirements for that country's local pharmacopeia must be met. This may go beyond the standard compliance to the *United States Pharmacopeia–National Formulary*, *European Pharmacopeia*, and *Japanese Pharmacopeia/Japanese Pharmaceutical Excipients*, which many companies use as a global specification. Other pharmacopeias such as the *Chinese Pharmacopeia* and *Indian Pharmacopeia* take precedence in their countries, as do a number of other pharmacopeias.

Some excipients may have been used in various approved drug applications in certain countries in the past, but they may not have been used for the particular route of ad-

ministration that a formulator may want to use for a particular excipient. Therefore, if the excipient is to be used in a new route of administration in that country, it must be considered a *new* excipient, which requires significant additional toxicology data about the excipient to support its safe use in registration documents. If the excipient is registered as a new excipient, then the approval of the drug may be delayed unless significant additional data is submitted up front.

Other types of regulatory restrictions can occur as well such as quantitative limits regarding the level of use based on prior precedence of the excipient's use in an approved drug in a particular country. In this case, the excipient may be used at a higher level, but it is treated as a new excipient, which requires additional data as discussed previously.

### Supply chain controls

In addition to the types of regulatory criteria that must be assessed when selecting an excipient, a formulator must understand the type of GMPs necessary for a specific excipient. The formulators also need to ensure that their company's quality assurance (QA) and supply chain groups have been actively involved in assessing the supply chain controls that are in place throughout the distribution process before using an excipient in new formulation work. Currently, the excipient supply chain is being affected by bioterrorism concerns and issues related to counterfeiting. It is critical that every pharmaceutical company

be aware of the entire lifecycle of their excipients throughout the distribution chain and know where the material was manufactured and if it was intended for use in drugs. In today's world, it is unacceptable for a pharmaceutical company to use an excipient without having this level of information. The risks are simply too great.

A number of situations in recent years have changed the paradigm related to this issue. The most famous incident occurred in Haiti in 1995 in which more than 80 children died because a child's cough medicine was made with counterfeit glycerin USP that actually contained high levels of diethylene glycol (anti-freeze). The glycerin had been sourced from a company in The Netherlands that had represented themselves as a manufacturer. However, the company was actually a repackager/distributor that had sourced the glycerin from a different repackager/distributor, which had sourced the glycerin from yet another repackager/distributor, and so on. Ultimately, worldwide regulators determined that the glycerin had actually been manufactured in China, but to this day it is not fully known who produced it and for what application it had been originally produced.

It is suspected that the material was actually industrial-grade glycerin, which had been redesignated as glycerin USP at some point in the long distribution chain for profit without full realization of the implications. Questions exist as to whether the material was ever really tested to determine compliance to

the *USP* monograph. However, even if it had been, the tests probably would not have detected the presence of the diethylene glycol. Apparently, some industrial grades of glycerin that are available in third-world countries are sometimes “spiked” with diethylene glycol to save money. The properties of diethylene glycol are similar to those of glycerin when used in most industrial applications. Therefore, this practice maximizes profits.

This situation demonstrates why it is so important that a user understand the full lifecycle of any excipient being used in a pharmaceutical product, and that the GMPs be in place throughout the system. You can no longer just rely on blind faith in a certificate of analysis that says that the material is certified to be *USP-NF* grade. For example, the glycerin used in the Haiti incident came with a certificate of analysis and labels that stated it was *USP* grade. *USP-NF* grade certifications cannot be assigned to an excipient simply on the basis of whether the material passed all the tests listed in the compendial monograph. The GMPs used in the manufacture and the supply chain controls that are in place must be considered before anyone other than the manufacturer can certify compliance to *USP-NF*.

### Excipient functionality

Many pharmaceutical formulators have realized that they may need to develop some type of performance-indicating tests for their excipients to ensure that they will perform in a specific application. However, in

many cases these tests are developed in a vacuum within the pharmaceutical company and not discussed or shared with the supplier of the excipient. This can create severe problems because the properties that the formulator may want to control may not be properties that are routinely controlled by the manufacturer. It is important to assess the potential for these properties to be within the manufacturer's process capability. Otherwise, it may be difficult to obtain an acceptable product when needed. If lot selection is to be used, it should only be conducted very cautiously and with the maker's full understanding of the user's needs. If the maker states that they can meet the criteria needed by the user only for a short period of time, the formulator should redesign the formulation to be more robust as it relates to these properties.

Unfortunately, formulators are sometimes reluctant to take this approach because it may mean spending a lot of additional time on a formulation that they thought was finished. However, formulators must carefully assess this need if they have their company's best interest in mind. If the performance-indicating test requirements for the excipient are not within the maker's process capability, significant operational problems may result in the future if the user cannot source material to meet this criteria.

Process improvements that makers may need to implement in their operation also can affect their ability to meet these requirements. For example, the excipient manufacturer may

need to make these improvements to satisfy other customers' needs who may have purchased the bulk of the excipient to standard sales specifications. Remember, the pharmaceutical uses of most excipients are usually only a very small portion of what the maker is actually producing. The rest of the product may go into food or industrial applications where tolerances may be much more flexible. It is important that there be a mutually agreed upon change notification program in place. However, there also must be a realization by the pharmaceutical industry that these types of changes typically are necessary and that the pharmaceutical uses of the excipient will rarely dictate whether changes of this type will be made. Therefore, it is important that pharmaceutical companies have a good raw material validation program in place to evaluate these types of changes when they occur. This may sometimes result in a need to reformulate the drug product when these changes affect the performance of the excipient in a specific drug.

### **How can communication be improved?**

As seen from the issues discussed previously, there must be good communication between excipient users and makers for everything to go smoothly. Therefore, it is necessary to have a well thought-out process to qualify an excipient both by the maker and by the user. Each party has different needs that must come together when mutually agreeing on quality specifications and supply contracts. The Interna-

tional Pharmaceutical Excipients Council (IPEC) has decided to take on the task of developing a detailed guideline about excipient qualifications that will address the overall process needed for excipient makers and users to fully qualify their excipients before they either launch the product for pharmaceutical applications or use the excipient in their formulations, respectively.

The guideline will include several sections that can each be used as stand-alone guidances or as part of an overall approach. The first section will contain a standard process that excipient manufacturers can use to assess their product and develop all the supporting information and controls needed to sell their product into the pharmaceutical industry as a viable excipient. The second section will provide a standard approach that pharmaceutical users should use to select excipients for a formulation project on the basis of their target market needs and how to fully qualify the selected excipients for use in their particular application. The guideline will discuss the process to be used, and not specific test criteria because this process is extremely application-dependant. This section will contain significant guidance about how best to enhance the communication of the user's needs to the excipient maker so that problems can be avoided. The third section will contain guidance about the negotiation process that can be used between the user and the maker to come to a win-win agreement on

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# Glossary

**Excipient:** a substance other than the active pharmaceutical ingredient contained in a finished pharmaceutical product dosage form. Common types include binders, disintegrants, fillers, lubricants, glidants, compression aids, colors, sweeteners, preservatives, suspending/dispersing agents, film formers/coatings, and flavors.

**Direct compression:** a method of tableting in which the blended dry ingredients are formed into tablets by pressing them together on a tablet press. See also **wet granulation**.

**Disintegrant:** an excipient added to a tablet or capsule blend to help break up the compacted mass when it is in a fluid environment.

**Friability:** the ease with which a

material is crumbled, pulverized, or reduced to powder.

**Particle-size distribution:** the weight or net volume of solid particles that fall into each of the various size ranges, given as a percentage of the total solids of all sizes.

**Polymorphism:** the property of a chemical substance crystallizing into two or more forms with different structures.

**Spray-drying:** to dry by bringing into the form of a spray through contact with a hot gas.

**Wet granulation:** a tableting technique in which the active ingredients and excipients are mixed together and then agglomerated with a wetting solution. The mixture is then dried and granulated, and formed into tablets on a tablet press. **PT**

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the requirements that satisfy both the user's needs and that address any of the maker's concerns about their capability to supply to the agreed-upon requirements.

There will be several appendices to the guideline that will contain standard templates, which can be used for regulatory assessments, excipient specification formats, and supplier questionnaires. Many people are interested in standardizing these types of documents throughout the industry to minimize the redundancy that currently exists when every user requests similar information in many different ways, which then creates a huge workload burden for the excipient makers without any real benefit.

There will be a significant benefit to makers and users if the transfer of this type of required information can be completed in a standardized way throughout the industry.

The IPEC Excipient Qualification Guideline is currently being developed and some sections should be ready for publication later this year. The full guideline is expected to be completed in 2005. If your company is concerned about the issues described above and would like to be involved in the development of this guideline, you should get involved by becoming an IPEC member and by participating on the Excipient Qualification Committee. To obtain information about IPEC membership, visit [www.IPECamericas.org](http://www.IPECamericas.org). **PT**