

Qualification of Excipient Vendors

In his guest editorial in *Pharmaceutical Technology's* January 1998 issue, Michael Groves described the gruesome outcomes caused by the use of contaminated or counterfeited glycerin. Although I agree with the contention that testing should prevent such incidents, we at the International Pharmaceutical Excipients Council (IPEC) believe that a more holistic approach to the control of these vendors is in order. Investigation of the incident in Haiti revealed that not only did the manufacturer fail to seek assurance that the vendor's manufacturing practices met GMP standards, but also that several different entities handled the material during its life cycle from manufacture in China through several agents in the Netherlands and eventually to Haiti. This serves as a wake-up call to the industry. In response, IPEC prepared a white paper to serve as a guide during the qualification of vendors.

Background. There is no question that the standards and specifications established for excipients, either by the pharmacopeia or by the user and maker of an excipient, provide a series of tests designed to ensure the safety, purity, and key characteristics of the material. During the past three decades, the technology of standardization has undergone a remarkable transition. Chemical analyses have attained new levels of precision and sensitivity, and advances in chromatography have permitted new and more rigorous definitions of purity. At the same time, improved dissolution technology and bioavailability-bioequivalence analysis of drug products permit more thorough analysis of the potential impact that excipients may have on the products and reconfirm the importance of the consistency of their characteristics. The development of the SUPAC guidelines has begun to establish minimum requirements to ensure that changes in the manufacture (including excipients) of the final drug product are considered and controlled.

Despite our advancing technology, one principle that has not changed is that quality cannot be tested in. It is through consistent adherence to current GMPs, as detailed in such documents as IPEC's Guide for Bulk Pharmaceutical Excipients and FDA's guide on BPCs (APIs), that we can best ensure the safety, purity, and consistency of excipients.

Guideline. IPEC recommends that once a supplier is identified as a source or potential source of a material to be used as an excipient, the drug manufacturer should confirm the supplier's ability to adhere to GMPs. Should the supplier turn out to be a distributor, the excipient manufacturer's adherence to GMPs should be confirmed by a suitable means. It should be determined whether all operations are performed by the manufacturer or by subcontractors (e.g., contract packagers) or whether the material is sold to repackagers before acquisition

by the user company. In the event such contractors or repackagers are used, their adherence to GMPs should be confirmed. If the excipient distributor or manufacturer has an adequate GMP confirmation program and is willing to share the results such results may be used to accomplish this purpose. Adherence to GMPs should then be reconfirmed periodically.

If the material is in a compendium, it should be verified that the manufacturer's tests and specifications conform to the compendium. If a modified or noncompendial method is used it should be verified that appropriate method validation has been performed to ensure that the results are reliable and equivalent to the compendial method.

With the exception of the tests for description and identification, all tests on a supplier's certificate of analysis (C of A) may be qualified for reduced testing by the purchaser. To accept the C of A and implement a reduced testing program, the following criteria must be met.

- The supplier's ability to adhere to GMPs should be confirmed
- Analytical methods should be identical or deemed equivalent
- An adequate number of lots should be evaluated to compare results with the C of A. Results for quantitative assays must be comparable and within specifications. For tests other than quantitative assays, all results must be within specifications.
- Each raw material qualified by the above procedure should be subjected periodically to complete testing to reconfirm the reliability of the supplier's C of A results.

Finally, as part of the procurement process, an agreement should be formalized stating that all material must be traceable during its distribution life cycle and that the user will be notified of all significant changes.

As a follow-up to the above guidance, IPEC is currently working on more detailed guidelines covering some of the key topics for qualifying vendors, including

- an excipient vendor GMP audit guide
- specification development
- a certificate of analysis guide
- definition of significant changes
- third-party certification of excipient vendors.

Several of these guidelines should be available during 1998. Readers who are interested in these or any other IPEC activities can contact Alan Mercill by phone at (703) 521-3338 or e-mail at (amercill@aol.com).

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