

PQRI Survey of Pharmaceutical Excipient Testing and Control Strategies Used by Excipient Manufacturers, Excipient Distributors and Drug-Product Manufacturers

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The results from a Product Quality Research Institute study provide insights about the decisions of excipient manufacturers and drug-product manufacturers regarding testing excipient quality and using excipients in pharmaceutical manufacturing.

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The Product Quality Research Institute (PQRI) conducted an open, publicly available, electronic survey of current excipient-control strategies among pharmaceutical excipient manufacturers, excipient distributors, and drug-product manufacturers (excipient users). Among the major findings are:

- the majority of respondents supply their products for global markets, and thus must meet substantially different test requirements for different regions;
- the majority of respondents use reduced-testing strategies employing equivalent methods;
- a large majority of respondents perform tests on the excipients beyond those given in pharmacopeias to determine physical and chemical properties necessary for their intended use;
- drug-product manufacturers typically follow their own company procedures to qualify excipient manufacturers and suppliers.

The survey results provide insights about the decisions of excipient manufacturers and drug-product manufacturers regarding testing excipient quality and using excipients in pharmaceutical manufacturing.

Background

When the European Agency for the Evaluation of Medicinal Products (1) and US Food and Drug Administration (2) issued excipients guidances in 2003, industry predicted that they would have the unintended result of causing additional paperwork and excessive testing for excipient control strategies, without adding benefits. In addition, industry believed the guidances effectively eliminated generally accepted and common excipient control strategies.

FDA's interpretation of International Conference on Harmonization (ICH) common technical document (CTD) language used in section P.4, "Control of Excipients" required

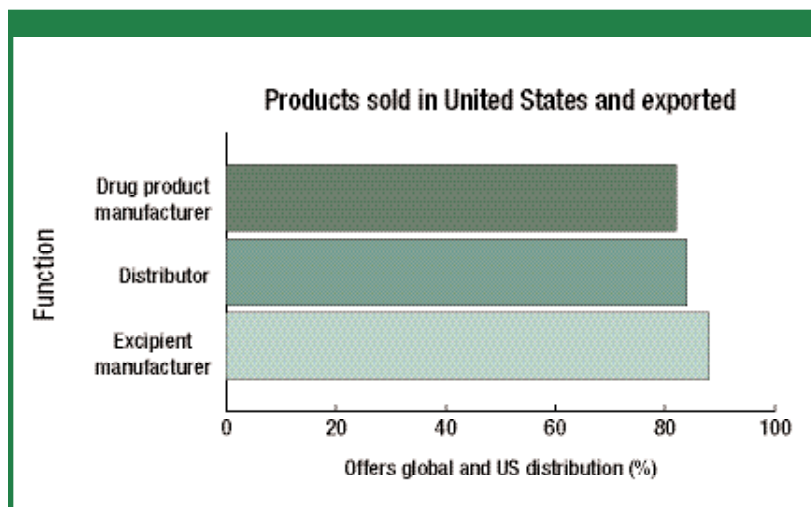


Figure 1: Respondents selling products both in the United States and abroad.

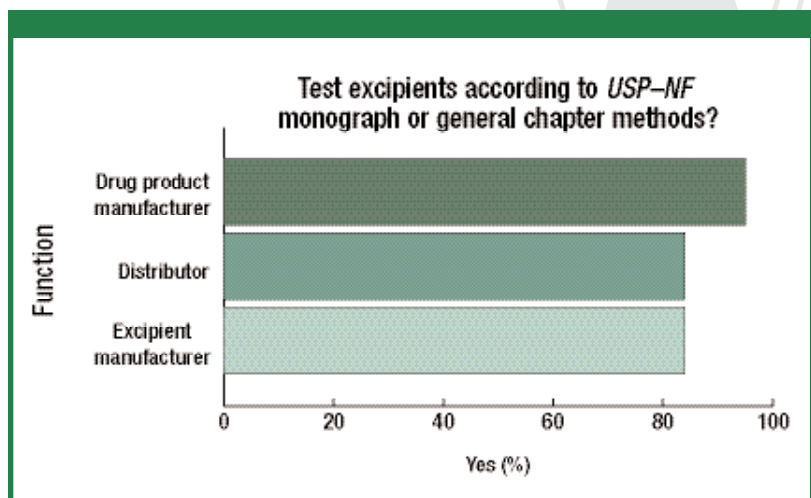


Figure 2: Respondents testing excipient according to USP—NF monograph/general chapter methods

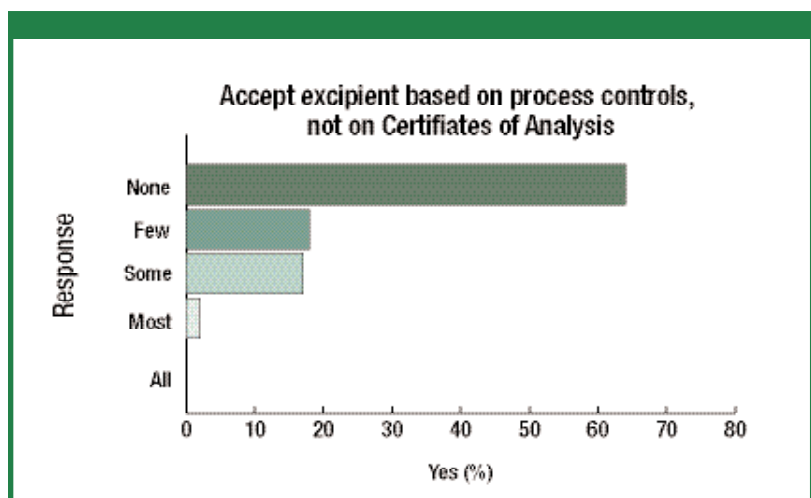


Figure 3: Respondents' frequency of accepting excipient based on process controls, not on Certificate of Analysis.

that manufacturers specify each method used for routine excipients testing, unless the method is exactly that of the pharmacopeia and full monograph testing is performed.

Often, a drug-product manufacturer has methods used internally that are shown to produce equivalent results to those in a pharmacopeia. In addition, many manufacturers with global markets seek to eliminate redundant testing of the same property by selecting a single method shown to be capable of ensuring compliance with requirements of many pharmacopeias. The United States Pharmacopeia (USP) has been clear that alternate methods are acceptable to demonstrate compliance with *USP-National Formulary (NF)* requirements (3).

FDA recently announced its *Guidance for Industry on Chemistry, Manufacturing, and Controls Information; Withdrawal and Revision of Seven Guidances* (4). By focusing on the *Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century (CGMP Initiative)* and ICH Guidelines, FDA has strategically reduced industry's regulatory and paperwork concerns, and changed the regulatory focus to concentrate on those aspects of manufacturing that pose the greatest risk to product quality. Although excipients constitute a large portion of most drug products, they have been viewed as a low-risk aspect of drug-product safety. They are, however, a key aspect of product Quality by Design (QbD).

Survey results

The PQRI Excipient Working Group developed three surveys to gather responses from each of three respondent groups: excipient manufacturers, excipient distributors, and drug-product manufacturers. The surveys gathered information about excipient-control strategies used by companies that manufacture, distribute, and sell prescription-only and over-the-counter drug products for US-only or US-and-world markets. The anonymous surveys could be completed electronically by individuals belonging to the PQRI member organizations (<http://www.pqri.org>) and other interested persons. The survey period was from June 13, 2005 to Oct.14, 2005.

PQRI received responses from 180 drug-product manufacturers, 26 excipient man-

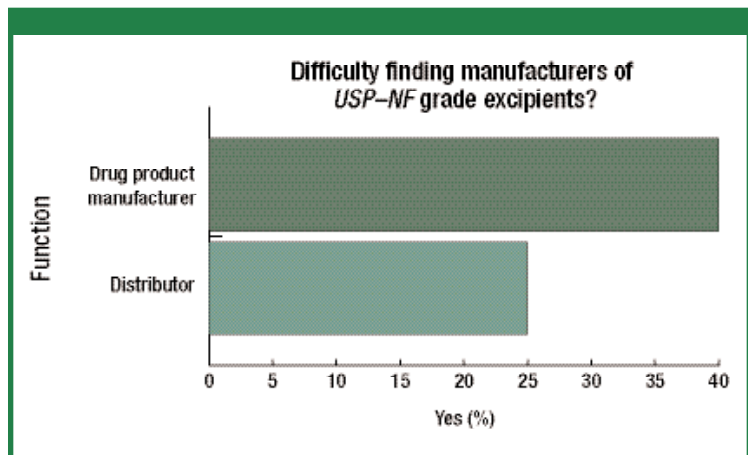


Figure 4: Respondents reporting difficulty finding manufacturer of USP—NF grade excipients.

ufacturers, and 6 distributors of pharmaceutical excipients. It should be recognized that PQRI is a unique US-based organization and that the survey questions were developed in the United States. Some survey responses may, however, have come from companies that manufacture their products for distribution and sale outside, as well as within, the United States.

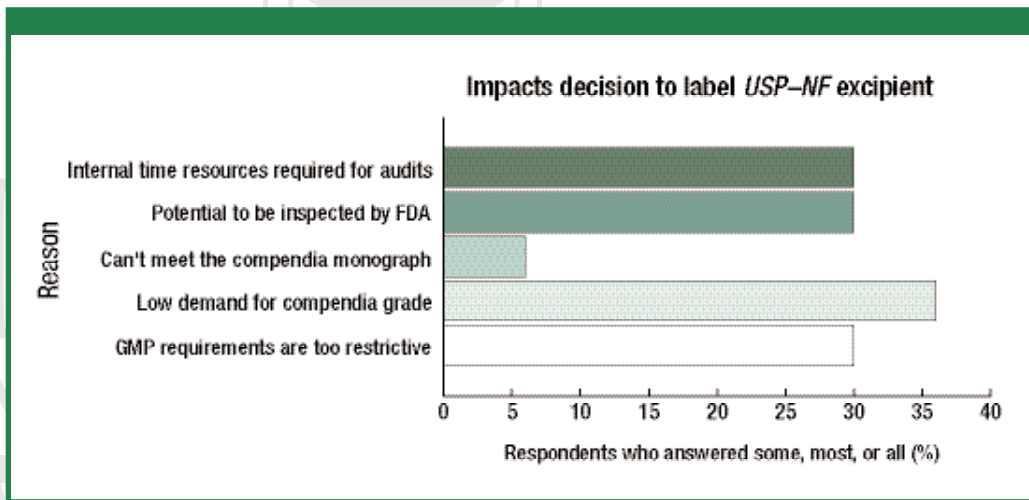


Figure 5: Obstacles to labeling excipients as USP—NF.

This report presents findings of the three surveys, and an analysis of survey responses. For the purposes of this report, the terms “excipient user” and “drug-product manufacturer”

mean the same, and are used interchangeably throughout the document.

The survey clearly indicates that the majority of excipient manufacturers, excipient distributors, and drug-product manufacturers make their products for global distribution (see Figure 1). They test their excipients according to USP—NF monographs and general chapter methods (see Fig. 2). Almost all (97%) drug-product manufacturers perform more than just the identification test when receiving excipients from their vendors along with Certificates of Analysis (C of A). The additional tests include analyses for desired physical and chemical properties.

Less than 20% of drug-product manufacturers accept some or most material based on the excip-

ient manufacturer’s process controls and on in-process tests. These controls and tests are not mentioned on C of A, but provide assurance of conformity with USP—NF requirements

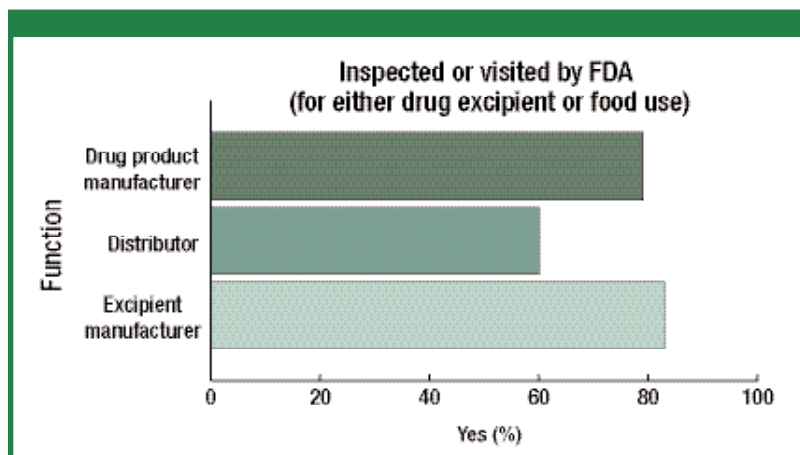


Figure 6: Respondents reporting inspections or visits by FDA (for either drug excipient or food use).

(see Figure 3). This area offers opportunities for excipient manufacturers and drug-product manufacturers to research and subsequently use information and knowledge that lies in the excipient-maker’s “manufacturing process-controls” and “in-process test results” domain. Assessment of such information could also confirm (or otherwise indicate) certain physicochemical quality aspects of an excipient batch, or qualities of an excipient produced under continuous manufacturing conditions.

Drug-product manufacturers qualify new sources of excipients by vendor audits and complete testing according to the compendial monograph. According to the survey, 40% of drug-product manufacturers had difficulty

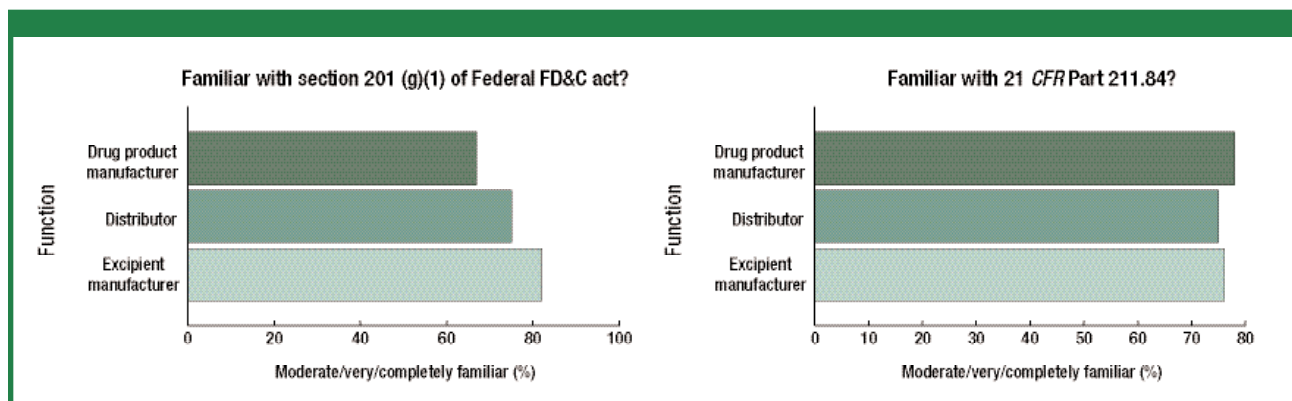


Figure 7: Respondents reporting familiarity with requirements of Food Drug and Cosmetic Act and 21 CFR Part 211.84.

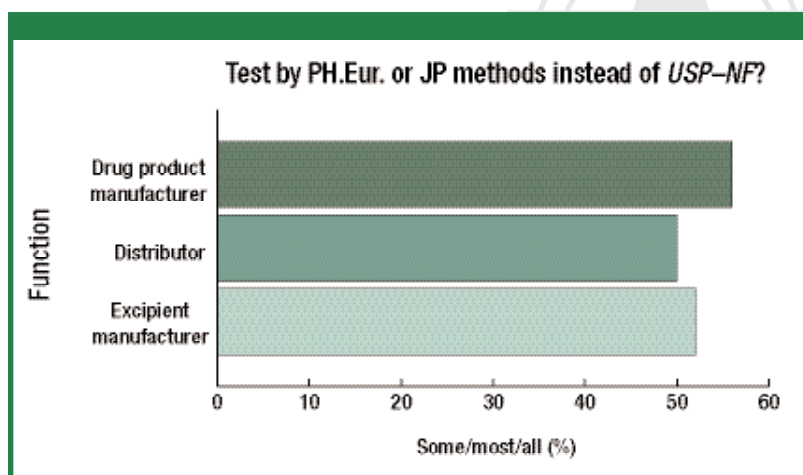


Figure 8: Respondents testing excipients by Ph.Eur. or JP methods instead of USP—NF

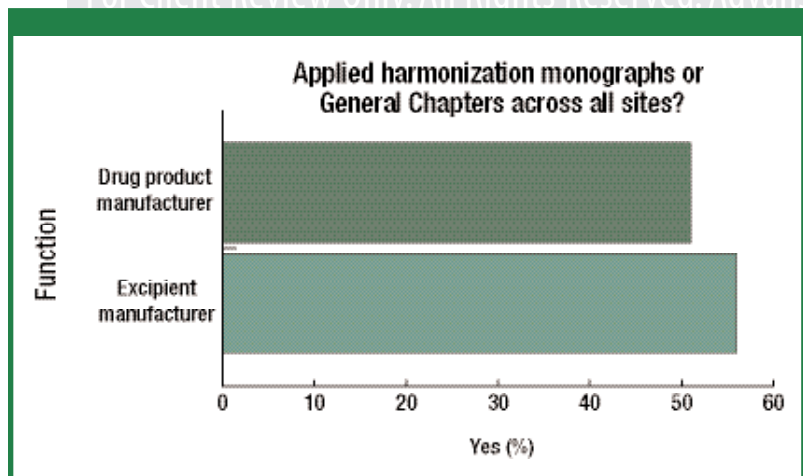


Figure 9: Respondents applying a) harmonized monographs or b) general chapters across all sites.

finding a manufacturer of at least one *USP-NF* grade excipient (see Figure 4). In such a situation, they would use the best grade available, test the excipient according to the compendial monograph, and conduct an audit of the excipient

manufacturer. Approximately 75% of drug-product manufacturers indicated they test and perform site audits to confirm compliance (for “a few” to “all” excipients) with compendial-grade standards. In 80% of the cases, respondents used validated test procedures to confirm the compliance of noncompendial grade excipients with compendial grade standards, or confirm that products conforming with one compendial grade also met standards from other compendia.

Only a minority of responding excipient manufacturers and distributors cited specific reasons for not labeling their products as *USP-NF* compendial grade. Approximately one-third cited low demand for compendial grade products; just under 30% cited restrictive GMP requirements, the prospect of FDA inspection, or the time and resources needed to perform required audits. Only a handful expressed doubts about being able to meet compendial monograph requirements (see Figure 5). Nearly 80% of excipient manufacturers and drug-product manufacturers, and 60% of distributors, have been inspected or visited by FDA for either drug excipient or food use (see Figure 6).

Among drug-product manufacturers, 89% have five or more excipients in reduced-testing programs, and do not perform complete monograph testing after vendor qualification and receipt of C of A.

Excipient manufacturers, distributors, and drug-product manufacturers all responded that they feel adequately familiar with the applicable FDA and compendial requirements

and recommendations related to testing of excipients used in a drug product (see Figure 7).

Among manufacturers, distributors, and users of *USP-NF* excipients, 70% or more perform additional functionality or

processability testing that is not part of any *USP–NF*, *European Pharmacopoeia* (*Ph.Eur.*), or *Japanese Pharmacopoeia* (*JP*) compendial monograph. Of these, 87% perform the tests because of processing concerns. Most additional testing was performed for solid oral dosage forms (87%), and 24% of drug-product manufacturers have products for which excipient variability is a problem in spite of such extra-compendial testing.

At least half of excipient manufacturers, distributors and drug-product manufacturers test some, most, or all of their excipients by alternate international (*Ph.Eur.*, *JP*) compendial methods instead of *USP–NF* (see Figure 8).

Nearly 60% of excipient and drug-product manufacturers conduct excipient testing per harmonized monographs, and reduce redundant testing by either demonstrating multiple compendial specification equivalence or using the most stringent method or specification for confirming compliance with more than one compendium. Approximately 50% of both excipient manufacturers and drug-product manufacturers have applied harmonized excipient monographs and harmonized general chapters across all their sites (see Figure 9).

The PQRI and its Excipient Working Group encourage active participation by stakeholders from excipient manufacturers, excipient distributors, drug-product manufacturers, compendia, and regulatory agencies in discussing the current issues and for developing possible solutions to problems faced by pharmaceutical excipient manufacturers, distributors, and drug-product manufacturers (5).

References

1. European Agency for the Evaluation of Medicinal Product (EMA), *Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier for Application for Marketing Authorisation of a Medicinal Product (CPMP/QWP/419/03)* (EMA, London, UK, Feb. 20, 2003).
2. US Food and Drug Administration, *Guidance for Industry, Drug Product: Chemistry, Manufacturing, and Controls Information* (FDA, Rockville, MD, Jan. 2003), now withdrawn, *Fed. Reg.* 71 (105), 31194–31195 (June 1, 2006).
3. *United States Pharmacopeia VOLUME–National Formulary VOLUME*, General Notices, section Tests and Assays under Procedures (United States Pharmacopeia Convention, Rockville, MD, *YEAR*).
4. FDA, “Guidance for Industry on Chemistry, Manufacturing, and Controls Information; Withdrawal and Revision of Seven Guidelines,” *Fed. Reg.* 71 (105), 31194–31195 (June 1, 2006).
5. Details are posted online at <http://www.pqri.org/workshops/Excipient/Excipient06.asp>.
6. Product Quality Research Institute (PQRI) workshop on Excipient Testing and Control Strategies, Oct. 10–11, 2006, Marriott Bethesda North Conference Center in Maryland.

Appendix: Excipient Working Group Recommendations for a PQRI Workshop

The Product Quality Research Institute (PQRI) Excipient Working Group has identified key issues from the survey. The task of clarifying and discussing the issues is best done in a workshop with participation from excipient manufacturers and distributors, drug-product manufacturers, regulatory agencies, and compendia. Therefore, a PQRI workshop on Excipient Testing and Control Strategies has been scheduled for Oct. 10th and 11th, 2006 at the Marriott Bethesda North Conference Center in Maryland. (Details are posted online at <http://www.pqri.org/workshops/Excipient/Excipient06.asp>.)

The workshop has been designed to provide industry, FDA, and USP an opportunity to interact on topics related to the testing and release of excipients for use in drug-product manufacturing. It will consider in detail the results (summarized in this article) of the recently conducted PQRI industry-wide survey on the control of pharmaceutical excipients. The meeting will be the first time that survey participants will be able to meet face-to-face to discuss their concerns and experiences.

Through these discussions with FDA and USP, industry will become aware of and be encouraged to use the practices allowed by the regulations. Participants will gain confidence that any petitions for regulatory changes emerging from the survey and this workshop will be relevant to both public safety, and manufacturing efficiency. It is anticipated that the proceedings of the workshop will give the stakeholders a better understanding of how industry-wide tests for physical characterization of excipients help build quality into the drug product.

Expected outcomes of the workshop will be summaries of workshop discussions and possible solutions to issues currently faced by the stakeholders. In addition, the workshop will produce a position paper from excipient manufacturers, drug-product manufacturers, and USP on the following key excipient issues.

- The definition of “continuous-flow manufacturing process (or continuous process)” as currently used by excipient manufacturers does not clearly define a lot. The workshop will attempt to gather information about continuous manufacturing processes used by excipient manufacturers, and work towards arriving at a commonly agreed upon definition of a “lot” or “batch” of material produced using a continuous flow manufacturing process. The workshop will discuss commonly used ways to control and communicate the quality attributes of excipients manufactured using a continuous flow process.
- “Skip-lot” testing is not currently used effectively and efficiently by stakeholders, and this workshop will discuss and identify best practices for using skip-lot testing based on scientific rationale and risk analysis.
- Following the spirit of FDA’s Pharmaceutical CGMPs for the 21st Century and Quality by Design (QbD) initiatives, the workshop will explore ways to improve pharmaceutical product quality by characterization and control of physical and chemical properties of critical excipients used in a given product.
- Third-party audits of excipient manufacturers, particularly those located outside the United States, are critical to a control strategy for the global excipient supply chain. Using independent third-party audits may provide a cost-effective way to accomplish control and ensure quality of excipients, especially for smaller pharmaceutical manufacturers. The

Appendix (continued): Excipient Working Group Recommendations for a PQRI Workshop

concepts and advantages of independent, third-party audits will be described.

- There is increasing danger that excipient manufacturers will stop producing pharmaceutical-grade excipients that meet United States Pharmacopia (USP)—National Formulary (NF) criteria, which would create an enormous problem for the drug-product manufacturers. This could, for example, lead to withdrawal of the compendial standard from

USP—NF because of lack of availability of compendial grade material. The workshop will assess these issues, and propose solutions to the problem of declining numbers of USP—NF-labeled excipients.

- By increasing the pace of global harmonization, industry stakeholders expect to reduce overall testing requirements significantly. The workshop will assess the status of harmonization and will recommend

how to effectively use harmonized monographs, and reduce the testing burden of pharmaceutical excipients.

To facilitate the development of a position paper, PQRI Excipient Working Group recommends the following topics and questions be discussed in the PQRI workshop.

1. Clarify “continuous-flow manufacturing” and “skip-lot testing” used for excipients in the context of 21 CFR Part 211.84 regulations.
 - How are “batch” or “lot” defined in the context of continuous manufacturing of an excipient?
 - Is skip-lot testing routinely used by the excipient industry for obtaining test results for the Certificate of Analysis? What are the current regulatory expectations? Could skip-lot testing apply to excipients? What should be the criteria for skip-lot testing of excipients?
2. Discuss how characterization of excipient physical and chemical properties helps build quality into the drug product.
 - How is Quality by Design built into a drug product by understanding critical properties of excipients used?
 - What are processability issues when excipients are procured from multiple vendors and sources?
 - Should these properties be addressed in compendial monographs or registration filings?
3. Highlight advantages of increased use of third-party audits.
 - How are third-party audits viewed? Is this a part of building a qualified excipient? Can third-party be used to develop a good qualification program for excipient suppliers? How should third-party audit programs be qualified? How might small manufacturers benefit from a third-party audit?
 - What qualifications should a third-party auditor have?
4. Discuss strategies to increase the number of excipients labeled USP—NF.
 - What are the barriers to labeling an excipient as USP—NF grade? How can the barriers be reduced?
 - What excipients are no longer available as USP—NF grade?

Appendix (continued): Excipient Working Group Recommendations for a PQRI Workshop

- What are the implications when an excipient user moves from a compendial grade excipient to noncompendial grade (i.e., not designated through labeling suffix, namely USP–NF, European Pharmacopoeia [Ph.Eur.], or Japanese Pharmacopoeia [JP])?
- What is industry’s burden in supplying analytical-method validation data to regulatory agency for excipients no longer labeled USP–NF?

- What test methods are used when an excipient user must replace a compendial grade excipient with a noncompendial grade?
- What are the ongoing initiatives at the USP to address these problems?

5. Discuss when reduced testing is appropriate.

- How should industry resolve problems with ICH Q4B interchangeability?
- When can industry start implementing a new

signed-off general chapter—once it is published in USP–NF, wait until the delayed implementation date, or when ICH Q4B has been completed?

- How many tests should be performed to assure an excipient’s quality for global drug products when there are a number of nonharmonized tests in the global (e.g., USP–NF, Ph.Eur., JP) compendia?
- What are the regulatory approaches when industry uses Ph.Eur. or JP test results to meet the USP–NF requirements?
- How are companies currently filing changes to USP–NF excipient monographs and general chapters to a previous submission to the FDA? FDA’s 21 CFR 314.70 regulations apply, but the Agency’s Nov. 19, 2004 Guidance to Industry, Changes to an Approved NDA or ANDA; Specifications—Use of Enforcement Discretion for Compendial Changes allows discretionary enforcement, so industry uncertainty remains. What are current company policies and practices under 21 CFR 314.70 and the Guidance on Enforcement Discretion?
- How should industry make effective use of Pharmacopeial Discussion Group (USP, Ph.Eur., JP) harmonization in light of the resulting changed excipient monographs?

The PQRI and its Excipient Working Group encourage active participation by stakeholders from excipient manufacturers, excipient distributors, drug-product manufacturers, compendia and regulatory agencies in discussing the current issues and for developing possible solutions to problems faced by pharmaceutical excipient manufacturers, distributors and drug-product manufacturers (6).