



Joint Position Paper on Pharmaceutical Excipient Testing and Control Strategies

This article presents collaborative positions among excipient manufacturers, drug product manufacturers, and members of the US Pharmacopeia on key issues pertaining to the control of pharmaceutical excipients stemming from a recent Pharmaceutical Quality Research Institute workshop.

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Pharmaceutical Technology

The Product Quality Research Institute (PQRI) Workshop on Excipient Testing and Control Strategies was held Oct. 11–12, 2006 in Bethesda, Maryland. The workshop was designed to provide industry, the US Food and Drug Administration, and the US Pharmacopeia an opportunity to interact on topics related to the testing and release of pharmaceutical excipients. Results of a recent PQRI industrywide survey on the control of pharmaceutical excipients were discussed in detail (1). Roundtable discussions about the impact of FDA regulations, guidances, and the Federal Food, Drug, and Cosmetic Act (FD&C Act) on excipient control strategies were held, and stakeholder concerns were identified (2–4). Ideas were discussed for potential changes in compendia, guidances, and regulations to mitigate or remove redundant, duplicative, or unnecessary testing on excipient batches that do not add value. Topics covered in this article apply to pharmaceutical excipients that have compendial monographs in *United States Pharmacopeia–National Formulary (USP–NF)*, *European Pharmacopoeia (PhEur)*, or *Japanese Pharmacopoeia (JP)*.

Commonly used ways to control and communicate the quality attributes of excipients manufactured using a continuous flow process were discussed in a roundtable format. Some current practices for skip testing of excipients were examined. Ways to improve pharmaceutical product quality by characterization and control of physical and chemical properties of critical excipients were explored. Advantages of using independent third-party audits to effectively assess and ensure quality of excipients were described. The issue of excipient manufacturers producing pharmaceutical-grade excipients that are not tested according to *USP–NF* was discussed. The workshop assessed the status of compendial harmonization and its expected reduction of overall testing requirements.

Each attendee had an opportunity to participate in five discussion topics in a roundtable format. The workshop concluded with a presentation of summaries of roundtable discussions about each topic to the entire assembly. Each presentation was followed by a question-and-answer session. This article presents the highlights and recommended action items for each of the five topics.

Continuous-flow manufacturing and skip-lot testing used for excipients in the context of 21 CFR Part 211.84 regulations

The workshop topic description was as follows:

The definition of 'continuous process' as currently used by excipient manufacturers does not clearly define a lot. This workshop will arrive at a commonly agreed definition of a 'lot' or 'batch' in a continuous-flow process and a commonly agreed way to control quality of excipients manufactured using a continuous-flow process. Skip-lot testing is not currently used effectively and efficiently by stakeholders, and this workshop will help identify and discuss best practices for use of skip-lot testing.

Survey results noted that less than 20% of drug-product manufacturers accept material based on excipient manufacturer's process controls and in-process tests not mentioned on a certificate of analysis (CoA) but providing assurance of USP–NF requirements. This is an area where opportunities exist for excipient manufacturers and drug-product manufacturers to research and subsequently use information and knowledge that lie in the manufacturing process-controls and in-process test-result domains of an excipient manufacturer. Assessment of such information also could confirm or otherwise indicate certain physicochemical quality aspects of an excipient batch or qualities of an excipient produced under continuous manufacturing conditions.

Defining a batch and a lot for excipients produced by continuous manufacturing. It was recognized that the definitions for a batch [21 *CFR* 210.3(b)(2)] or a lot [21 *CFR* 210.3(b)(10)] applicable to the manufacture of drug products can be applied in principle to the manufacture of excipients. According to current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, a *batch* means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture [21 *CFR* 210.3(b)(2)]. Furthermore, a *lot* means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified limits [21 *CFR* 210.3(b)(10)].

Workshop participants determined that continuous flow processes can be compliant with the CGMP definitions of batches and lots. It was felt that for continuous flow processes used to manufacture excipients, a batch or lot can be defined by an agreement between the excipient supplier or excipient manufacturer and drug product manufacturer.

Testing excipient batches. The CGMP regulations for finished pharmaceuticals [21 *CFR* 211.84(d)(1) and 21 *CFR* 211.84(d)(2)] require that before using an excipient in the manufacture of a drug product, the drug-product manufacturer must perform at least one test to verify the excipient's identity and must demonstrate that the excipient conforms to appropriate written specifications for purity, strength, and quality. The CGMP regulations also specify that in lieu of such testing by the drug-product manufacturer for purity, strength, and quality, a report of analysis may be accepted from the supplier of a component (i.e., excipient), provided that at least one specific identity test is conducted on such component by the drug-product manufacturer and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

CGMP regulations for component identity testing, 21 *CFR* 211.84(d)(1), is intended to

ensure that a component is what it purports to be on the container labeling. CGMP regulations in 21 *CFR* 211.84(d)(2) are intended to provide sufficient flexibility to minimize, reduce, or avoid duplicative or repetitive testing of excipient attribute(s) when the drug-product manufacturer establishes the reliability of the excipient supplier's (or excipient manufacturer's) analyses.

Current industry practice for excipient manufacturers is to use in-process testing and manufacturing process controls to ensure batch uniformity. Such practices also are intended to ensure compendial compliance, and as such, not all compendial tests are routinely performed by the excipient manufacturer. The CoA received by the drug-product manufacturer for an excipient batch may not report compendial test result(s) but will state that "if tested will meet pharmacopeial requirements." When such a statement is based on process controls, the survey reported that the current practice is for the drug product manufacturer to perform the compendial test(s).

There are numerous scenarios where compendial tests are performed on a bulk excipient after all manufacturing processes are complete, but before final package filling. Where an in-process or bulk excipient test result is traceable to the finished excipient material, such a test result can be reported on the CoA.

The determination of "critical" or "noncritical" attribute(s) of an excipient should be determined by the drug product manufacturer, depending on the excipient's use in a drug product with respect to its dose, dosage form, route of administration, and manufacturing process(es). When a drug-product manufacturer wants certain tests performed on its supply of an excipient, the manufacturer may need to set up a contract with the excipient manufacturer or supplier. In any case, as stated above, the CoA generated for each batch of excipient should indicate the compendial (or otherwise specified) tests performed, as well as those tests not performed.

Sampling for tests by a drug product manufacturer. Common sampling plans were discussed, and the assessment was that the practice of collecting $(n^{0.5} + 1)$ number of samples for a shipment of excipient batch received is justifiable, in which n is the number of containers received for an excipient lot. When compositing is appropriate, $(n^{0.5} + 1)$ can be a valid sampling plan.

An identity test is performed on excipient materials to determine whether the material is what it purports to be and to detect any mix-up or presence of foreign material before use of the excipient. Current practice in many companies is to perform the identity test on a composite sample. In contrast, workshop attendees recommended that the material sampled from each individual container not be composited before identity testing. In other words, the samples should be tested individually for identity. This practice increases the chance of detecting any incorrect or foreign material. In some situations, there can be a need for a modified approach, such as when excipients are shipped in bags on pallets, which results in a large number of bags per lot. A modified approach for sampling can be acceptable if a drug-product manufacturer has procedures in place to conduct a thorough inspection of the packaging and labeling, including auditing of excipient manufacturers facilities and procedures. Because each lot must at least be tested for identification, skip-lot testing should not be used by the drug product manufacturer for the identity test.

Workshop attendees from many drug-product manufacturers stated that they are using skip-test procedures based on CoA qualification and/or vendor qualification. This means that in

lieu of testing samples of each lot to show that an excipient material meets its specifications, a drug-product manufacturer relies on a CoA from its suppliers of excipient materials (which the drug product manufacturer has validated for reliability) to ensure that each lot meets its specifications. In effect, no test is actually being skipped, because the testing to show that each lot meets all of its specifications is being performed either by the excipient or drug-product manufacturer. Participants did not find any practice that must be changed or modified.

FDA's Guidance for Industry: Testing of Glycerin for Diethylene Glycol. As a specific exception to the previous discussion, on May 2, 2007 FDA issued *Guidance for Industry: Testing of Glycerin for Diethylene Glycol* in which FDA recommends that drug-product manufacturers perform a specific identity test that includes a limit test for diethylene glycol on all containers of all lots of glycerin before glycerin is used in the manufacture or preparation of drug products (5). This guidance was issued because of past incidences of diethylene glycol contamination in glycerin.

Excipient vendor qualification and periodic or skip testing of excipients. From the excipient survey answers on vendor qualification, 91% of drug-product manufacturers stated that their vendor qualification includes CoA qualification. International Pharmaceutical Excipients Council (IPEC) recommends vendor qualification as part of the CoA qualification. Vendor qualification begins with receipt of a completed questionnaire (e.g., the Excipient Information Program, IPEC-Americas) and generally followed by an on-site assessment of the excipient manufacturer by a trained auditor. For 78% of survey respondents, such qualification of CoA means a reduced frequency of complete monograph testing for their excipients. The reduced testing programs for 89% of drug-product manufacturers included at least five of their excipients. All five distributor respondents stated that a reduced testing program is applicable to some, most, or all of the products they distribute. This data suggest that many drug-product manufacturers and excipient distributors do not perform all monograph tests on their excipients after qualifying their vendors. Every 3rd lot of the excipient a drug product manufacturer receives is fully tested by 3% of them, every 5th lot by 7%, and every 10th lot by 29%, and the remaining 61% test their excipients according to "other" frequency. The workshop participants explored practices for skipping tests.

Workshop participants were confused by the terms *skip lot* and *skip test*. For this article, *skip test* or *skip testing* is the performance of specified tests at release on preselected batches and/or at predetermined intervals, rather than on a batch-by-batch basis, with the understanding that those batches not being tested still meet all acceptance criteria established for that product. The use of skip-test strategies should be identified on the CoA.

The International Conference on Harmonization (ICH) guidance Q6A and the World Health Organization (WHO) each have definitions for *periodic* or *skip testing* as well as *skip-lot* (*periodic*) testing (6, 7). These definitions apply to new drug substances and new drug products. The ICH and WHO definitions have the same approach yet use variations of the same terms. ICH guidance Q6A states periodic or skip testing is *the performance of specified tests at release on preselected batches and/or at predetermined intervals, rather than on a batch-by-batch basis, with the understanding that those batches not being tested still meet all acceptance criteria established for that product. This represents a less than full schedule of testing and should therefore be justified and presented to and approved by the regulatory authority prior to implementation.*

In a similar manner, WHO states skip-lot (periodic) testing is

the performance of specified tests at release on preselected batches and/or at predetermined intervals, rather than on a batch-to-batch basis, with the understanding that those batches not tested must still meet all the acceptance criteria established for that product.

This represents a less-than-full schedule of testing and should therefore be justified, presented to, and approved by the regulatory authority before implementation. When tested, any failure of a batch to meet the acceptance criteria established for the periodic (skip-lot) test should be handled by proper notification of the appropriate regulatory authority(ies). If the data demonstrate a need to restore routine testing, then batch-by-batch release testing should be reinstated.

For each excipient batch, it is important to demonstrate that it conforms to all of its specifications. This objective can be accomplished using in-process testing and appropriate in-process controls, and/or finished-product testing.

The workshop participants found that confusion exists because most excipient manufacturers do not conduct all compendial tests because their controls give assurance that a compendial quality material is produced. It was asserted that if an excipient manufacturer does not provide the result for a specification test, it must be clearly indicated on the CoA, and the drug-product manufacturer will need to perform that test (21 *CFR* 211.84).

The confusion exists because in today's environment of process analytical technology (PAT), one question raised is whether all tests really must be run if excipient manufacturers have the systems under control. This topic was felt important enough to have further discussion with FDA.

FDA comments on skip testing and Type 4 drug master files for excipients. The workshop attendees discussed that opportunities exist for skip testing of excipient batches by excipient manufacturers. Several conference participants suggested that the justification for performing skip testing may be submitted to regulatory authorities (e.g., FDA) in a Type 4 drug master file (DMF)—for an excipient—as allowed by 21 *CFR* 314.420(a)(4).

In post-workshop discussions, FDA representatives stated that normally, DMFs should not be submitted to the agency for standard compendial excipients unless the material is to be used in new and different ways where there may be a need for additional safety or technical data about the excipient. Normally, the excipient control strategy and test justification should be provided to the drug-product manufacturer. The justification can then be assessed by FDA during CGMP inspections of the drug-product manufacturer or the excipient manufacturer.

In a post-workshop meeting, FDA representatives stated that it considers the practice of skip-testing not to be compliant with CGMPs because for those lots that are not sampled and tested, there is a lack of assurance that the finished excipient material will meet all of its specifications. FDA believes that if an attribute for a finished raw material has required criteria, there must be some measurement or test of the material in each lot to ensure that the criteria are met. This may be a measurement from a surrogate test, from in-process control data, or from testing or measurement of the finished material in each lot. Conversely, FDA representatives believe that an approach, which allows for skip testing based on a satisfactory product quality history alone, is not acceptable from a CGMP standpoint because such an approach does not adequately verify that each lot meets all of its specifications.

FDA representatives stated that not all testing or measurements conducted to verify that a finished lot of excipient material complies with its required properties must be performed on samples taken from the finished lot. The representatives do not believe that testing or measurement of in-process materials to verify product quality constitutes skip testing. To ensure that a lot of excipient material complies with its required properties, it is acceptable to rely on tests or measurements conducted on samples of material taken at an in-process stage of production, provided that the in-process material will not be affected by subsequent processing or holding with respect to the attributes being verified. There should be justification that test results or measurements, or product performance characteristics, do not change from the in-process stage to the finished product.

According to FDA representatives, an appropriate determination to ensure that each lot conforms to appropriate specifications could involve some combination of the following approaches:

- End-product testing
- In-process testing
- Continuous monitoring of an attribute with statistical process controls
- Documented rationale that, based on the method of manufacture, the test attribute cannot be present and therefore the test is not applicable (e.g., residual solvents).

Using end-product testing alone requires testing each lot of excipient material for conformance to all specifications. In-process testing might involve the use of an on-line test to determine whether a product attribute meets an appropriate acceptance criterion, provided that the attribute does not change during the subsequent processing steps until the finished excipient is produced. Continuous process monitoring with statistical process controls involves comprehensive testing of an attribute using on-line monitoring and corresponding process and/or product adjustments to prevent lot-to-lot variation in the product. Depending on the product and specification, any of the above approaches might be appropriate for conducting a determination to ensure that each batch of the product conforms to the specification.

The term *skip testing* does not actually characterize how FDA perceives testing practices in the excipient industry, and FDA recommends that this term not be used. The term *skip testing* implies that certain required testing is not being done. Rather than skip testing, FDA representatives recommend that the excipient industry emphasize the development and use of sound sampling and testing plans for process parameters and product-quality attributes. The sampling plans should provide for appropriate frequency of material sampling and testing, accounting for the risks identified and assurance of quality to address them, including process control imperatives and intended use of the material.

The representatives stated for clarity, FDA prefers the term *measurement* instead of *test* as it relates to product quality, because measurement conveys the correct idea of analytical testing of material quality using either nondestructive in-line or on-line analytical techniques as well as off-line destructive analysis commonly used today. This approach gives excipient manufacturers more latitude to use various options to verify a given product attribute.

PAT for excipient manufacturing. PAT uses appropriate design, analysis, and control of manufacturing processes, including in-process testing and controls to ensure that a finished drug product is manufactured under appropriate controls. A benefit of using PAT is that finished-product testing can be minimized by a drug-product manufacturer on their final dosage forms. One meeting participant asked, "Why can't these same concepts be applied to

excipient testing when the excipient manufacturer applies similar control strategies?" Additional guidance or clarification is needed from the regulatory agency(ies) on these topics.

ICH Q6A applies to drug products, and an official clarification by FDA with a specific guidance for excipients is needed. Alternatively, an industry group such as IPEC-Americas may wish to present industry guidance suitable for self-regulation. Documents in this area are currently being developed by IPEC-Americas.

How characterization of excipient physical and chemical properties helps build quality into the drug product

This topic was described to the participants as follows:

Following the spirit of FDA's 21st Century Pharmaceutical CGMP and Quality by Design (QbD) initiatives, the workshop will explore ways to improve product quality by characterization and control of physical and chemical properties of critical excipients in a given product (8-10).

For the excipient survey question, approximately 74% of drug-product manufacturers answered few or none for testing excipient suitability using experimental-scale (laboratory scale) drug-product batches or pilot-scale manufacturing batches. This result is not encouraging. Even though the excipient is of compendial quality, not testing the suitability of an excipient(s) procured from new vendors through laboratory- or pilot-scale experiments may be contributing to difficulties currently encountered by drug-product manufacturers during production-batch scale-up operations or when an excipient is procured from different vendor(s).

Survey responses showed that, for *USP–NF* excipients, 88% of excipient manufacturers, 75% of distributors, and 68% of drug-product manufacturers perform additional functionality or processability testing that is not part of any compendial monograph (e.g., *USP–NF*, *PhEur*, *JP*). About three-fourths (76%) of drug-product manufacturer respondents perform such tests to determine excipient suitability for their intended use.

FDA's QbD and CGMPs for the 21st Century initiatives and their anticipated impact on improving pharmaceutical product quality were discussed at the workshop. Workshop participants recognized the value in understanding the physicochemical properties of excipients that impart their functionality in the drug product, as well as their contribution to the successful manufacturing of the product. It was noted that there must be early interaction between the drug-product manufacturer and FDA for QbD-based applications to be successful.

Functionality-related characteristics. Workshop participants noted that IPEC and USP plan to question the need for *PhEur* to include the tests for functionality-related characteristics (FRCs) in monographs whether nonmandatory or not. Listing nonmandatory FRCs in the monograph may provide misleading guidance and could result in drug-product manufacturers not performing the studies they should to identify the FRCs that matter most in connection with their use of an excipient. It also may increase the possibility of non-value added testing in the supply chain. Recently *Pharmeuropa* published a proposed General Chapter 5.15, "Functionality-Related Characteristics of Excipients," which explains the use of FRCs in *PhEur* and how tests may be included in monographs (11). Workshop participants agreed that a general information chapter approach is preferred that does not include the listing of FRCs in monographs.

USP–NF informational chapter <1059> "Excipient Performance" provides an overview of the key functional categories of excipients identified in *USP–NF* along with tests that relate to excipient performance. Careful consideration of the function of the excipient in the dosage form and the critical attributes that relate to excipient performance will determine the need for additional tests on the excipient. The draft of <1059> "Excipient Performance" is projected for publication as a Stimuli Article in *Pharmacopeial Forum* Sept.–Oct. 2007 (PF 33.5). USP's goal is to have the draft available for discussion and feedback. USP emphasizes a distinction in the <1059> information chapter tests (focus on performance testing) and those in a monograph (focus on identity, strength, purity, quality). The following text from the most current draft of <1059> includes such a statement:

This Informational Chapter provides an overview of the key functional categories of excipients identified in USP–NF along with tests that may relate to excipient performance. This chapter focuses primarily on those tests that are not included as required tests in compendial monographs (e.g., strength, purity, identity). Careful consideration of excipient function, manufacturing process, and dosage form performance will allow for the selection of appropriate tests to assure that critical excipient attributes relating to performance are adequately monitored and controlled.

IPEC foresees a need to continue developing our knowledge and understanding of materials and processes and how they interact to produce medicines that consistently meet the public's expectations (12). The industry should continue to work with compendia to establish a harmonized approach for incorporating physical and chemical tests and analytical procedures in the General Chapters of the pharmacopeias. IPEC does not support the inclusion of these tests into monographs unless they may be needed to fulfill an identification requirement, (e.g., test for viscosity of a polymer). IPEC believes that the selection of appropriate performance-related tests be done by appropriate scientific investigation of the excipients used in a specific formulation in a specific process using specific equipment.

Control strategies concerning excipient functionality and/or performance-related tests should be based on excipient manufacturer's process capabilities and be negotiated between the excipient user and excipient maker. The test parameters and control strategies that are mutually agreed to should be included in contracts between the excipient maker and user. Workshop participants generally agreed with this approach.

IPEC also is supporting the development of educational programs in formulation science. Only through education will the industry have the formulation scientists required by the QbD approach for pharmaceuticals.

Significant change in excipient properties. Communication to excipient users about a significant change in excipient physical and chemical property(ies) should occur in a timely manner, even when the excipient would otherwise continue to meet all of its compendial specifications. IPEC has defined *significant change* as "any change by the manufacturer of an excipient that alters an excipient physical or chemical property outside the limits of normal variability, or that is likely to alter the excipient performance in the dosage form."

Such changes may necessitate notifying the local regulatory authority if required (as in Europe). Regardless of whether there is a regulatory requirement, the excipient manufacturer has an obligation to notify its customers of a significant change so that the customer can evaluate the effect of the change on the customers' products. Examples of significant change include differences in the methoxylated content of hydroxypropylcellulose, particle-size distribution profile, and change in polymorph or

crystalline properties. The issue of change control should be part of the quality agreement between an excipient user and the supplier.

Within a company, a drug-product manufacturer should ensure strong oversight of supply chain management decisions by research and development and other quality assurance and technical groups. There must be improved communication between supply chain management and technical functions as well as improved communication between excipient user and excipient supplier. In particular, it is very important to define and evaluate significant changes to the excipient. Changes to site, scale, equipment, process, packaging and labeling, and specification are considered in the IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients (13). To assess, evaluate, and agree upon such details, audits of excipient suppliers should be a team effort by members such as CGMP compliance auditors and technical personnel. In addition, education programs should be developed with a focus on formulation science and QbD collaboratively between academia and industry.

The closing session of the workshop also identified the need to define significant change in quality agreements as a key issue.

Highlight advantages of increased use of third-party audits

This topic was described to the participants as follows:

Third-party audits of excipient manufacturers, especially outside the United States, are critical to a control strategy for the global excipient supply chain. The use of independent third party audits may provide a cost effective way to accomplish control and ensure quality of excipients, especially for smaller pharmaceutical manufacturers. The concepts and advantages of independent third party audits will be described.

An on-site visit by a drug-product manufacturer's company auditor is the most common practice in auditing an excipient manufacturer. Survey results indicated that 87% of drug-product manufacturers have performed auditing of their excipient manufacturers for some to all of their excipients. Most drug-product manufacturers do not audit every one of their excipient manufacturers but instead have some type of risk prioritization process for selecting the ones to audit. Only 29% of the audits were performed by a third party. This is an opportunity to have third-party auditors provide an alternate view of the excipient supplier and reduce the number of independent audits of excipient suppliers. Of the 17 excipient manufacturers' responses, 1 stated that, on average, they have an on-site visit by their customers every week. Of the remaining responses, 5 are visited by at least one customer once in 2 weeks; 2 manufacturers are visited by their customers every 4 weeks and 8 weeks, respectively, and 7 stated that they have a customer at their site less often than every 8 weeks. The advantages of using independent third-party audits were discussed.

Third-party audits. Workshop participants described the expectations of a third-party audit program as including standard operating procedures that describe program operation, a preaudit questionnaire for the excipient manufacturer, an established audit standard, clearly identified report content, and a policy for confidentiality of audits. The audit standard must be based on applicable GMPs. Nicholas Buhay, deputy director, Division of Manufacturing and Product Quality Office of Compliance, Center for Drug Evaluation and Research, FDA, noted that "FDA is supportive of the Joint IPEC-PQG GMP Guide for Bulk Pharmaceutical Excipients." It should be noted that USP General Information Chapter <1078> "Good Manufacturing Practices for Bulk Pharmaceutical Excipients" is based on the IPEC-PQG GMP Guide for pharmaceutical excipients.

The third party should be an independent and unbiased organization of auditors, with strong qualifications and a good reputation. Auditors must be trained in excipient audits and should not audit the site as if it were a facility for the manufacture of active pharmaceutical ingredients (APIs) or drug products. The third-party audit firm should provide a mock or sample audit report. Users can qualify a third-party audit program by comparing audit reports for the same excipient with internal audits.

The firm conducting the third-party audit should not consult on the correction of identified issues. There must be a mechanism to confirm the veracity of the findings, including a review of the excipient manufacturer audit report by the drug-product manufacturer.

During the meeting, excipient manufacturers expressed that widespread use of third-party audit reports may reduce the number of site audits by customers. Third-party audits would reduce the number of questionnaires from their customers. The pharmaceutical manufacturers expressed that third-party audits would result in more excipient manufacturers audited thoroughly and completely because of the additional time that the third party would spend on each audit. This can augment a drug-product manufacturer's risk management strategy for deciding on which excipient manufacturer to audit, when needed.

The qualifications of the third-party auditor should include training and a general audit background. Qualifications should include formal recognition such as ASQ certified quality auditor, ISO 9001 certified lead auditor, or other recognized auditor training course certification. Familiarity with IPEC excipient GMPs is essential along with appropriate audit experience and background. The qualifications may include experience in API audits and an understanding of the regulatory environment. The auditor should be knowledgeable about differences between 21 *CFR* Part 211 and USP General Information Chapter <1078>. The auditor should set priorities or categorize audit observations, know what is important to audit, and know what findings are important. In summary, the auditor must demonstrate audit competency.

The benefits of third-party audits to small drug-product manufacturers include that the audit has more credibility than a questionnaire alone. Many small drug manufacturers do not have the resources to audit many of their excipient manufacturers other than the ones they may consider absolutely critical. Because these companies are not able to routinely audit their excipient manufacturers, they currently only use questionnaires. A concern with solely relying on a questionnaire is not knowing for certain whether the answers are truthful. Third-party audits may offer a good alternative. With third-party audits, a small drug-product manufacturer can avoid a staff of auditors, reduce the number of audits (especially outside the United States), and at the same time have more confidence in their excipient manufacturer. This strategy allows small drug-product manufacturers to assess more excipient producers more reliably. A small drug-product manufacturer would use the audit to help ensure that their supplier qualification program is adequate.

Workshop attendees identified International Pharmaceutical Excipients Auditing, Inc. (IPEA) and the USP Pharmaceutical Ingredient Verification Program as examples of organizations and programs that perform qualified third-party audits.

Strategies to increase the number of excipients labeled USP–NF

This topic was described to the participants as the following:

There is an increasing danger of excipient manufacturers not producing pharmaceutical-grade excipients that meet USP–NF criteria, which creates an enormous problem for the

drug manufacturing industry. This concern is exacerbated by the fact that, USP–NF is missing monographs for some commonly used excipients. The workshop will assess these issues, and propose solutions to preempt the issue of reduced numbers of excipients labeled USP–NF.

Approximately 40% of drug-product manufacturers and one out of four distributors reported that they had difficulty finding a manufacturer of a USP–NF grade excipient. The survey findings indicated that most of the excipient manufacturers and distributors who responded label their excipients as compendial grade. However, it is noteworthy that 11% of excipient manufacturers and one out of five excipient distributors are not choosing to label their products as compendial grade. The reason(s) for not labeling their excipients as compendial grade could not be accurately determined from the responses to this survey. The authors have experienced a growing number of situations in which excipient manufacturers are dropping the compendial-grade label suffix (i.e., USP, NF, PhEur, JP), either because of the increasing CGMP expectations and/or low volumes sold to the pharmaceutical market, combined with efforts required to meet pharmaceutical manufacturers' expectations. The current situation was explored by the workshop participants.

Compendia and compliance. Currently, FDA's *Compliance Policy Guide* (CPG) Section 420.400 "Performance of Tests for Compendial Requirements on Compendial Products" states, "Compendial methods need only be applied, as a batch release test, where a firm has made specific commitments to do so (as in a new drug application [NDA]), or where the official method is the only appropriate test. It should be noted that neither *USP–NF* nor the CGMP regulations necessarily require a firm to utilize, as a batch-release test, the methods and procedures stated in the official compendia." Scientifically sound alternate tests (including in-process analyses) can therefore be used in lieu of USP tests. However, in the event of a dispute as to whether a compendial article meets the standard, the pharmacopeial method and analytical procedures will be applied as the referee test (14).

More specifically, official drug products are required to conform to the compendial standards and monograph requirements. This conformance must be ensured by suitable means, including adequate manufacturing process validation and control. Scientifically sound alternative test methods may be acceptable for the purpose of batch-release testing. This applies to official substances, official preparations (finished dosage forms), and excipients.

CPG Section 420.400 continues,

Where an official product purports to conform to the standards of USP–NF, the manufacturer must assure that each batch conforms to each monograph requirement. This assurance must be achieved by appropriate means, including process validation and controls and end product testing. However, the nature and extent of end-product testing which is needed will depend upon the circumstances. Factors to consider in determining the need to test each batch for a given monograph requirement include: the adequacy of the manufacturer's process validation, adequacy of in-process manufacturing controls, and the nature of the particular product characteristic which is the subject of the specification (e.g., potency, sterility, content uniformity). Therefore, in some cases it may not be necessary for a manufacturer to test each batch for each monograph requirement.

In postworkshop meetings, FDA representatives said that CPG Section 420.400 is under revision. The intent of this CPG is not to provide for a skip-test approach. There must be appropriate testing and measurement of in-process and/or finished-product samples from each batch to ensure that the finished material complies with all compendial requirements.

Federal Food, Drug, and Cosmetic Act and 21 CFR. During the workshop and at the closing session, it was noted that Section 501(b) of the FD&C Act applies to all articles recognized in an official compendium. Further, section 201(g) of the FD&C Act defines a drug in part as an article recognized in the official *USP* and *NF*, as well as an article intended for use as a component of a drug or drug product. Consequently, *USP–NF* excipients intended for the drug market must comply with *USP–NF* standards, regardless of whether the labeling on shipments of the excipient include the *USP–NF* designation.

Also Section 501(a)(2)(B) of the FD&C Act requires that drugs, including excipients meeting the definition of a drug in Section 201(g) of the Act, be manufactured in conformance with current good manufacturing practice. Hence, according to the Act, all excipients intended for use in the manufacture of a drug product, whether or not the excipient is listed in the official *USP–NF*, must be manufactured in conformance with current good manufacturing practice. However, FDA has not promulgated CGMP regulations for excipients. CGMP regulations in 21 *CFR* Parts 210 and 211 apply to the manufacture of finished drug products and not to the manufacturing of APIs or excipients. Therefore, GMP guidance for pharmaceutical excipients has been jointly published by IPEC and PQG (15).

Issue of excipient manufacturers removing USP or NF designation from the label.

During the workshop it was noted that some manufacturers of pharmaceutical excipients remove the USP or NF designation from labeling to avoid having to conform to CGMP and official *USP–NF* standards. FDA noted, however, that removing the USP or NF labeling does not obviate the requirement to meet applicable CGMP and official *USP–NF* standards.

Workshop participants highlighted several questions and answers. The first question was, What is industry's burden in supplying analytical methods validation data to regulatory agency for excipients no longer labeled USP or NF? This is an important topic, and there was no real answer at the conference. However, a drug-product manufacturer must find out the reason for the excipient manufacturer's removal of the USP or NF designation. Possible reasons include the manufacturer's inability to meet specification or GMP issues. If the reason is specification issues, excipient manufacturers can work with USP. For GMP issues, a drug-product manufacturer must carefully assess the suitability of its supplier's GMPs for the intended use. If the supplier stopped designating the excipient as USP or NF for GMP reasons, then the material from such a supplier should not be used, and a different acceptable supplier for that material should be found.

A second question was, If the drug manufacturer references the excipient manufacturer's DMF, does the drug manufacturer need to supply the analytical methods validation data? The answer was that no additional analytical methods validation data need to be supplied in an abbreviated new drug application (ANDA) or NDA if FDA determines the DMF to be adequate in support of an application.

After the workshop, the PQRI Excipient Working Group discussed the regulatory and implementation recommendations to address these two topics. These recommendations are summarized in the following paragraphs.

Analytical methods validation data for noncompendial analytical procedures used for testing noncompendial designated excipients. When an excipient manufacturer or drug-product manufacturer uses a noncompendial (or other FDA-recognized public standard) analytical procedure for testing a not-novel, noncompendial-designated component for which official *USP–NF* monograph exists, the analytical methods validation data for such

test procedures should be made available for review by the regulatory agency (e.g., FDA) at the site of excipient testing. If the excipient manufacturer were to submit the alternative analytical procedure and its analytical methods validation data in a Type 4 DMF, then the drug product manufacturers can reference it in their drug applications and need not submit the same information again for the agency's review (16, 17).

A not-novel or a new excipient can be a non-GRAS (referenced as substances Generally Recognized As Safe, according to 21 *CFR* Parts 182, 184, and 186) component used for the first time in a human drug product, or a previously used drug-product component proposed for use in higher quantity per dose or per daily human exposure, or by a new route of administration, or for a longer duration of human use than previously evaluated and allowed by FDA. Additional details on this subject can be found in FDA's Guidance for Industry (18, 19).

A noncompendial designated component is an article for which an official *NF* or *USP* monograph exists; and the article in all probability will meet *USP-NF* end-product test criteria if and when tested; and an article for which the excipient (article) manufacturer chooses "not to designate" on its label the *USP* or *NF* designation or suffix, even when each batch of the excipient would have passed the *USP-NF* end-product test criteria by a compendial analytical procedure or by an alternative analytical procedure.

A noncompendial analytical procedure is an end-product test procedure that is not described in a pharmacopeia. An alternative analytical procedure is one other than a compendial analytical procedure or other FDA-recognized public standard procedure such as those published in *Food Chemical Codex*, *AOAC International*, American Society for Testing and Materials standard procedure, and so forth (20). For a compendial analytical procedure, FDA does not expect to receive analytical methods validation data in a drug-product application. A reference to the official compendial procedure or a FDA-recognized public standard analytical procedure would suffice. Validation data for noncompendial analytical procedures should be made available for inspection at the testing site and need not be submitted in an application.

If a drug-product manufacturer tests every batch of a noncompendial-designated excipient they receive using compendial analytical procedures, then it would amount to a practice of verifying their excipient quality by testing. A substantive issue in that case can be whether the excipient was manufactured under GMP conditions.

At the workshop, it was discussed that some extensively used excipients do not have monographs in *USP-NF*. On the other hand, there are *USP-NF* monographs without excipient manufacturers supplying *USP*- or *NF*-grade material.

The following excipients used by the pharmaceutical industry do not have current monographs in *USP-NF*: corn syrup, edetate calcium (calcium EDTA powder), propylene glycol stearate, propylene glycol diacetate, and gentisic acid ethanolamide. Diethyl phthalate, liquid glucose, and lecithin do not have excipient manufacturers producing *NF*-grade material. Additional supply problems occur with particular grades such as synthetic glycerin. For lecithin, some grades are available, but others are not. *USP* provides assistance in the form of submission guidelines for an excipient monograph or revision to an existing monograph to *USP-NF* (21).

Workshop participants agreed that additional guidance from FDA to excipient manufacturers may alleviate some of these issues. *USP* has already published IPEC

guidelines as General Information Chapter <1078> "GMPs for Bulk Pharmaceutical Excipients." These guidelines also educate the drug manufacturer with regard to excipient GMP and other expectations.

Reduced testing as a result of the use of compendial harmonization

This topic was described to the participants as:

By increasing the pace of global harmonization, industry stakeholders are expecting to reduce testing 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.

More than half of excipient manufacturers (59%) and of drug-product manufacturers (55%) reduce redundant testing by selecting the most stringent method or specification for confirming compliance with more than one compendium. About 53% of excipient manufacturers and 74% of drug-product manufacturers stated that redundant testing could be reduced by at least 20%. Only two respondents indicated redundant testing would not be reduced.

As more excipient and drug-product manufacturers operate globally, the use of harmonized monographs will increase. Presently, a majority of stakeholders use the most stringent test method, specification, or acceptance criteria for compliance, or may also test for the same attribute using another pharmacopeial analytical procedure, resulting in redundant testing of the same attribute. Drug-product manufacturers would like the option of using a specification (test for an attribute, analytical procedure, and acceptance criteria) for a drug substance or excipient from the current edition of the *British Pharmacopoeia (BP)*, *PhEur*, or *JP* monograph as part of the specifications in a drug application. This approach would facilitate the use of test methods where the analytical procedure and acceptance criteria in the *BP*, *PhEur*, or *JP* monograph are equivalent or superior to the analytical procedure and acceptance criteria in the corresponding *USP–NF* monograph. This option would be helpful for both drug substance and excipient monographs.

The workshop discussed the effective use of harmonized monographs. Excipient and drug-product manufacturers envisioned two ways going forward: full harmonization or mutual acceptance of the other pharmacopoeias by the regulators. As stated in USP General Information Chapter <1196> "Pharmacopeial Harmonization":

A pharmacopeial general chapter or other pharmacopeial document is harmonized when a pharmaceutical substance or product tested by the document's harmonized procedure yields the same results and the same accept–reject decision is reached.

Further details of ongoing effort and activities by the Pharmacopoeial Discussion Group (PDG) and ICH on this subject can be found in the ICH Step 2 document, "Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC)" available at FDA's website (22).

The closing questions and comments of the workshop observed that one word in *CFR* 211.84 that causes confusion is the use of *test* instead of a term such as *evaluate*. It was pointed out that excipient manufacturers are not going to perform every compendial test on samples of finished material if it is not necessary to perform such tests to demonstrate control of their processes and adequate product quality. Also, there is no requirement for excipient manufacturers to perform compendial tests on finished material as a release test. It apparently was not understood that the CGMP regulations in 21 *CFR* Parts 210 and 211

apply to manufacturers of finished dosage forms and not to the manufacturers of excipients. As such, the requirements in 21 *CFR* 211.84 do not apply to excipient manufacturers. Nevertheless, excipient manufacturers should have appropriate control processes in place along with sufficient testing and measurement to ensure that each finished lot of excipient meets all of its quality requirements.

Using ICH Q4B harmonized compendial procedure published in USP–NF or its supplement, with a future implementation date. When a new compendial procedure or a general chapter is published in *USP–NF* or its supplement with a future implementation date, an excipient manufacturer or a drug-product manufacturer may begin voluntarily use of such new procedure or general chapter before the published implementation date. In general, FDA has not objected to such a practice. In other words, before the implementation date of a published harmonized procedure, either the current official procedure or the new harmonized procedure may be used for testing. However, after the official implementation date of an ICH harmonized new procedure or a *USP–NF* general chapter (specifically, those numbered between <1> and <999>), the new procedure becomes effective and enforceable by FDA.

The issue of postapproval compendial changes also was discussed at the workshop. A postapproval change submission to an NDA or ANDA application should be relevant to the information originally contained in the application. In general, changes in an excipient specification to comply with compendial requirements would not require any notification to FDA for nonapplication drug products. For drug products approved by the agency through an application, FDA's *Guidance for Industry, Changes to an Approved NDA or ANDA; Specifications—Use of Enforcement Discretion for Compendial Changes*, published in November 2004, recommends filing an annual report for all excipient specification changes made to comply with the official compendium. FDA should revise regulations (e.g., 21 *CFR* 314.70) to clarify this issue.

Summary and recommendations

Continuous-flow manufacturing and skip-lot testing used for excipients. Discussions with FDA resolved several issues beginning with definitions of *batch* and *lot* as applied to continuous-flow manufacturing. A *batch* means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits. A *lot* means a batch, or a specific identified portion of a batch. The continuous-flow manufacturing process may have a batch or lot defined by agreement between the supplier or manufacturer and customer.

The term *skip-lot testing* does not correctly reflect current practice. Wherever an in-process or bulk-excipient test result is traceable to the final package, that test result can be reported in the CoA.

A sampling plan based on $(n + 1)^{0.5}$ containers sampled is appropriate for creating a composite sample. Common practice is to perform the identity test on the composite sample. It was suggested that identity tests should be performed on samples collected from individual containers and should not use a composite sample.

Characterization of excipient physical and chemical properties to help build quality into the drug product. Additional functionality or processability testing beyond the compendial monograph testing is performed by a great majority of excipient manufacturers,

distributors, and drug-product manufacturers. This approach is consistent with FDA's QbD and CGMPs for the 21st Century initiatives. As proposed by USP–NF, compendial support of functionality testing should be presented in a General Chapter with references to tests appropriate to the desired function. The drug-product manufacturer and the excipient manufacturer should mutually agree to the correct control strategy.

Communication to excipient users about a significant change in excipient physical and chemical property(ies) should occur in a timely manner, even when the excipient would otherwise continue to meet all of its compendial specifications. The issue of change control should be part of the quality agreement between an excipient user and the supplier.

Advantages of third-party audits. Audits are a key part of supply chain management, and are commonly performed by the auditors of the drug-product manufacturer. Audits should be based on a uniform standard such as the USP General Information Chapter <1078>, which is based on the *IPEC GMP Guide for Bulk Pharmaceutical Excipients*. The benefit to excipient manufacturers is a reduction in site audits and questionnaires from their customers. The benefit to drug-product manufacturers is a more thorough and complete audit as a result of the additional time spent by the third party. A small drug manufacturer would have a more credible assessment than by a questionnaire alone.

Strategies to increase the number of excipients labeled USP–NF. The FD&C Act requires that official drug products and excipients that have pharmacopeial monographs must conform to compendial standards regardless of whether they are labeled as USP or NF. Conformance to compendial specifications may be ensured by adequate manufacturing process validation, in-process controls, and through in-process tests or measurements of excipient quality.

About 40% of drug-product manufacturers experience the loss of an NF label for an excipient. When a compendial excipient is not labeled USP or NF, the reason for not designating the component as USP or NF by the excipient manufacturer should be determined.

Reasons an excipient manufacturer drops the USP or NF designation include low volumes sold to the pharmaceutical industry and the perceived cost of maintaining GMP compliance. These challenges can be overcome by quality and risk assessments such as audits to verify GMP compliance and compendial testing. During the workshop, attendees expressed that when an excipient source does not maintain GMP compliance, the drug-product manufacturer must obtain a new source for that material.

Alternative test methods may be used for batch-release testing, but if there is a dispute, then the compendial test is applied as the standard. Using alternative test methods such as those of the American Chemical Society, AOAC International, *PhEur*, or *JP* will generally require verification but not validation. Analytical test method validation data in support of alternative analytical procedures should be kept for inspection at the excipient testing site. When a DMF is referenced in an NDA or ANDA, the drug-product manufacturer does not need to submit additional analytical test method validation data unless FDA determines the DMF to be inadequate.

When an excipient monograph is not found in *USP–NF*, contact USP for resources to create the monograph. The workshop found that additional FDA guidance to excipient manufacturers may alleviate some of these issues. USP has published the *Joint IPEC–PQG GMP Guide*, and this guideline also may educate drug manufacturers regarding excipient

GMP and specific ways GMPs apply to excipient manufacturers.

Use of reduced testing as a result of the use of compendial harmonization. More than half of excipient and drug-product manufacturers reduce redundant testing by selecting the most stringent method or specification for confirming compliance with more than one compendium. The addition of more harmonized monographs is very helpful to industry, but further success depends on either full harmonization or mutual acceptance of the other pharmacopeias by regulators.

Conference participants indicated that the term *test* in 21 *CFR* 211.84 creates confusion in the excipient industry. Postworkshop conversations with FDA reminded us that 21 *CFR* 211.84 applies to drug products. Especially for continuous manufacturing processes, the excipient industry should apply "tests and measurements" in the control strategies of excipients. These control strategies are viewed as good examples of PAT concepts in practice. The tests and online measurements can give assurance of compliance to compendial standards. Assurance of compliance is demonstrated if test and measurement methods are validated, compared with compendial test method results, and linked to the excipient in the final package. Such documentation justifies the reporting content of the excipient CoA and should be available at the excipient manufacturing or testing site.

When USP publishes a harmonization chapter with delayed implementation dates, FDA will not enforce the new chapter until the implementation date. Either the current official procedure or the new published procedure may be voluntarily used between publishing a change and the implementation date.

Workshop participants stated that in general, changes in excipient specifications to comply with compendial requirements would not require any notification to FDA for non-application (e.g., over-the-counter) drug products. For drug products approved by the agency through an application (e.g., NDA, ANDA, biologics license application), FDA's *Guidance for Industry: Changes to an Approved NDA or ANDA; Specifications—Use of Enforcement Discretion for Compendial Changes* recommends filing an annual report for all excipient specification changes made to comply with the official compendium.

Further discussions are scheduled at the 2007 IPEC-Americas Regulatory Affairs Conference, Sept. 10–11, in Alexandria, Virginia. In particular, this article will be the basis for the section "Excipient Testing, Control and Communication: Findings of a PQRI Working Group." Stakeholders may further benefit by attending this conference.

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