JOINT POSITION PAPER FROM EXCIPIENT MANUFACTURERS, DRUG PRODUCT MANUFACTURERS AND USP ON PHARMACEUTICAL EXCIPIENT TESTING AND CONTROL STRATEGIES; BASED ON A PQRI SURVEY AND WORKSHOP

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The PQRI[1] Workshop on Excipient Testing and Control Strategies was held October 11-12, 2006 in Bethesda, MD. The workshop was designed to provide industry, FDA[2] and USP[3] an opportunity to interact on topics related to the testing and release of pharmaceutical excipients. The results of a recently conducted PQRI industry-wide survey[4] on the control of pharmaceutical excipients were discussed in detail. Round table discussions on the impact of FDA regulations[5], guidances[6], and the Federal Food, Drug and Cosmetic Act (FD&C Act)[7] on excipient control strategies were held and stakeholder concerns identified. Ideas were discussed for potential changes in compendia, guidances and regulations to mitigate or remove redundant, duplicative, or unnecessary testing on excipient batches that does 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 (Ph.Eur.) 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 round table 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.

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[1] PQRI, Product Quality Research Institute, www.pqri.org
[2] FDA, U.S. Food and Drug Administration, http://www.fda.gov/default.htm
[3] USP, United States Pharmacopeia, www.usp.org
[4] PQRI Survey of Pharmaceutical Excipient Testing and Control Strategies Used by Excipient Manufacturers, Excipient Distributors, and Drug-Product Manufacturers, Pharmaceutical Technology Sep 2, 2006, Gregory Larner, David R. Schoneker, Catherine Sheehan, Rajendra Uppoor, Phyllis Walsh, Robert Wiens.
[5] 21 CFR Regulations, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (then, type Part and Section # in search, e.g. 211.84).
[6] Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, http://www.fda.gov/cder/guidance/6419fnl.htm .
[7] Federal FD&C Act, http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm.

Each of the attendees had an opportunity to participate in all of the below mentioned five discussion topics in a round table format. The workshop concluded with presentation of summaries of round-table discussions on each topic to the entire assembly. Each presentation was followed by a question and answer session. This paper will present the highlights and recommended action items for each of the five topics.

(1) "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:
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> 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 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 utilize information and knowledge that lies in the "manufacturing process-controls" and "in-process test results" domain of an excipient manufacturer. 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.

Definition of a "Batch" and "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 manufacturing of drug products can be applied in principle to the manufacturing of excipients. According to the 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 assures 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 of Excipient Batches

The cGMP regulations[8] for finished pharmaceuticals 21 CFR 211.84(d)(1) and 21 CFR 211.84(d)(2) require that prior to using an excipient in the manufacture of a drug product, the drug product manufacturer (i) must perform at least one test to verify the excipient's identity, and (ii) 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."

The cGMP regulations for component identity testing 21 CFR 211.84(d)(1) is intended to assure that the component is what it purports to be on the container labeling. The 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 assure batch uniformity. Such practices also are intended to assure 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), as required in 21 CFR 211.84(d)(1).

There are numerous scenarios where compendial tests are performed on a bulk excipient after all manufacturing processes are complete, but prior to 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 "non-critical" 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.

[8] Appendix – Definitions and Regulations

Sampling for Tests by a Drug Product Manufacturer

Common sampling plans were discussed, and the assessment was that the practice of collecting $\sqrt{n} + 1$ number of samples for a shipment of excipient batch received is justifiable, where 'n' is the number of containers received for an excipient lot. When compositing is appropriate, $\sqrt{n} + 1$ can be a valid sampling plan.

An identity test is performed on excipient materials to determine if the material is what it purports to be and to detect any mix-up or presence of foreign material prior to 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 prior to identity testing. In other words, the samples should be tested individually for identity. This practice increases the chance of detecting incorrect or foreign material, if any present. 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 the drug product manufacturer has procedures in place to conduct a thorough inspection of the packaging and labeling, including auditing of excipient manufactures facilities and procedures. Since 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 the excipient material meets its specifications, the drug product manufacturer relies on a CoA from its suppliers of excipient materials (which the drug product manufacturer has validated for reliability) to assure 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 needs to be changed or modified.

FDA's Guidance for Industry, Testing of Glycerin for Diethylene Glycol

As a specific exception to the above discussion, on May 2, 2007 FDA issued a "Guidance for Industry: Testing of Glycerin for Diethylene Glycol"[9] in which the 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. This guidance was issued due to 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 Certificate of Analysis (CoA) qualification.

[9] Testing of Glycerin for Diethylene Glycol,) issued 5/2/2007. http://www.fda.gov/cder/guidance/7654fnl.htm.

IPEC[10] recommends vendor qualification as part of the CoA qualification. Vendor qualification begins with receipt of a completed questionnaire[11], and generally followed by an on-site assessment of the excipient manufacturer by a trained auditor[12]. 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 paper, "skip test" or "skip testing" is the performance of specified tests at release on pre-selected 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 Certificate of Analysis.

The ICH guidance Q6A[13] and WHO[14] each have definitions for "Periodic or Skip Testing" and "Skip Lot (periodic) Testing. They are applicable 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 pre-selected 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 like manner, WHO states "Skip Lot (periodic) Testing" is "the performance of specified tests at release on pre-selected 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.

The issue for each excipient batch is nonetheless to demonstrate that it conforms to all of its specifications. This can be accomplished utilizing in-process testing and appropriate in-process controls, and/or finished product testing.

[10] International Pharmaceutical Excipients Council, http://www.ipec.org/
[11] For example, the Excipient Information Program (EIP), IPEC-Americas.
[12] International Pharmaceutical Excipients Auditing Inc. (IPEA) http://www.ipeainc.com
[13] ICH Q6A, section 2.1, http://www.ich.org/cache/compo/276-254-1.html
[14] Good Trade and Distribution Practices for Pharmaceutical Starting Materials, World Health Organization, WHO Technical Report Series, No. 917, 2003

The workshop participants found that confusion exists because most excipient manufacturers do not conduct all compendial tests since 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) the question raised is do all tests really need to 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., US FDA) in Type 4 Drug Master File (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 going to be used in new and different ways where there may be a need for additional safety or technical data on 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 assure 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 assure 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 finished product.

An appropriate determination to assure 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 non-destructive in-line or on-line analytical techniques as well as off-line destructive analysis commonly employed today. This approach gives excipient manufacturers more latitude to use various options to verify a given product attribute.

PAT for Excipient Manufacturing

PAT utilizes appropriate design, analysis and control of manufacturing processes, including in-process testing and controls to ensure that the finished drug product is manufactured under appropriate controls. A benefit of utilizing PAT is that finished product testing can be minimized by a drug product manufacturer on their final dosage forms. Therefore, the question was raised, "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.

The 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[10] may wish to present industry guidance suitable for self-regulation. Documents in this area are currently being developed by IPEC-Americas.

(2) How Characterization of Excipient Physical and Chemical Properties Helps Build Quality Into the Drug Product.

> This topic was described to the participants as:
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> Following the spirit of FDA's 21st Century Pharmaceutical cGMP[15] and Quality by Design (QbD)[6] 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.[16, 17]

For the excipient survey question, about 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 fact 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 also stated, for *USP-NF* excipients, 88% of excipient manufacturers, 75% of distributors, and 68% drug product manufacturers perform additional functionality or processability testing that is not part of any compendial monograph (*USP-NF*, Ph.Eur., JP). About three-fourths (76%) of drug product manufacturer respondents perform such tests to determine excipient suitability for their intended use.

FDA's Quality by Design (QbD) and cGMPs for the 21st Century initiatives[7] 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 needs to 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 Ph.Eur. to include the tests for Functionality Related Characteristics (FRCs) in monographs whether non-mandatory or not. Listing non-mandatory FRCs in the monograph may provide misleading guidance and

[15] http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#_Toc84065754
[16] Excipient Functionality, R. Christian Moreton, p. 98 Pharmaceutical Technology May 2004.
[17] Debating Excipient Functionality, Maribel Rios, Pharmaceutical Technology, Sep 2006, p. 50.

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 may also 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 FRC in Ph. Eur.[18] and how tests may be included in monographs. Workshop participants agreed that a general information chapter approach is preferred which does not include the listing of FRCs in monographs.

The *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 the additional tests on the excipient. The draft of <1059> "Excipient Performance" is projected for publication as a Stimuli Article in Pharmacopeial Forum September –October 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.[19] 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 which are mutually agreed to should be included in contracts between the maker and user. The workshop participants generally agreed with this approach.

[18] PHARMEUROPA, July 2006, volume 18.3, proposed General Chapter 5.15 Functionality- Related Characteristics of Excipients.

[19] Moreton C.,*Excipients Performance 2006, A Technology Primer,* Supplement to Pharmaceutical Technology, p. s4, 2006.

IPEC is also supporting the development of educational programs in formulation science. Only through education the industry will 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 impact of the change on the customer's products. Examples of significant change would include differences in the methoxylated content of hydroxypropylcellulose, particle size distribution profile, change in polymorph or crystalline properties, etc. The issue of change control should be part of the quality agreement between an excipient user and the supplier.

Within a company, the drug product manufacturer should ensure strong oversight of supply chain management decisions by R&D and other QA/technical groups. There needs to be improved communication between supply chain management and technical functions, and 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.[20] In order 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.

Education programs should be developed with a focus on formulation science/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.

(3) Highlight Advantages of Increased Use of Third Party Audits.

This topic was described to the participants as:

[20] The IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients (First Revision, January 2005), IPEC-Americas®, 2005.

Third party audits of excipient manufacturers, especially outside the US, 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.

On-site visit by a drug product manufacturer's company auditor is the most common practice in auditing an excipient manufacturer. The 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 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 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: SOPs describing program operation, a Pre-Audit 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. Mr. Nicholas Buhay[21] 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 and auditors. There should be strong qualification and a good reputation for the organization and auditors. Auditors would be trained in excipient audits and not audit the site as if it was an Active Pharmaceutical Ingredient (API) and/or drug product manufacturing site. 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 doing the third party audit should not consult on 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.

The 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

[21] Mr. Nicholas Buhay, Deputy Director, Division of Manufacturing and Product Quality Office of Compliance, Center for Drug Evaluation and Research, FDA.

questionnaires from their customers. The pharmaceutical manufacturers expressed that third party audits would result in more excipient manufacturers audited thoroughly and completely, due to 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, or ISO 9001 Certified Lead Auditor, or other recognized Auditor Training Course. 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 regulated environment. The auditor should be knowledgeable on differences between 21 CFR Part 211 and USP General Information Chapter <1078>. They can prioritize/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. Since they are not able to routinely audit their excipient manufacturers, they currently only use questionnaires. A concern with just using a questionnaire is how do you know the answers are truthful? The use of third party audits may offer a good alternative. With third party audits, a small drug product manufacturer can avoid a staff of auditors, can reduce the number of audits (especially outside the US), 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 assure them that their supplier qualification program is adequate.

The workshop attendees identified International Pharmaceutical Excipients Auditing, Inc. (IPEA[22]) and the USP-Pharmaceutical Ingredient Verification Program[23] as examples of organizations and programs that perform qualified third party audits.

(4) Strategies to Increase Number of Excipients Labeled *USP–NF*

This topic was described to the participants as:

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*.

[22] WWW.IPEAINC.com
[23] http://www.usp.org/USPVerified/pharmaceuticalIngredients/

Approximately 40% of drug product manufacturers and 1 out of 4 distributors reported that they had difficulty in 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 1 out of 5 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 where excipient manufacturers are dropping the compendial grade label suffix, i.e. USP, NF, Ph.Eur., 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, the FDA 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), or where the official method is the only appropriate test. It should be noted that neither the *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. Alternate tests (including in-process analyses) can therefore be used in lieu of USP tests[24].

More specifically, official drug products are required to conform to the compendial standards and monograph requirements. This conformance must be assured 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. However, in the event of a dispute as to whether or not a compendial article meets the standard, the pharmacopeial method and analytical procedures will be applied as the referee test". 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 the *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 post workshop 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

[24] USP30 General Notices; Section Tests and Assays – Procedures.

appropriate testing and measurement of in-process and/or finished product samples from each batch to assure 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[25] applies to all articles recognized in an official compendium. Further, Section 201(g) of the 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, whether or not 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. The cGMP regulations in 21 CFR Parts 210 and 211[26] 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.[27]

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 current good manufacturing practice and official *USP– NF* standards. It was noted by FDA however, that removing the USP or NF labeling does not obviate the requirement to meet applicable current good manufacturing practice and official *USP– NF* standards.

Workshop participants highlighted several questions and answers. First, 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, the drug product manufacturer needs to find out the reasons why the excipient manufacturer is removing the USP or NF designation. Is it because they cannot meet the specification? Is it due to GMP issues? For specification issues, excipient manufacturers can work with the USP. For GMP issues, the drug product manufacturer must carefully assess the suitability of 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.

[25] See Appendix below.
[26] CFR Title 21-Food & Drugs Good Manufacturing Practice, Part 211.
[27] Joint IPEC – PQG Good Manufacturing Practice Guide For Pharmaceutical Excipients 2006. Available at http://www.ipecamericas.org/.

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 or 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. Although the regulations do not directly apply, the following practices can apply.

Analytical Methods Validation Data for Non-Compendial Analytical Procedures Used for Testing Non-Compendial Designated Excipient

When an excipient manufacturer or drug product manufacturer uses a non-compendial (or other FDA recognized public standard) analytical procedure for testing a not novel[28], non-compendial 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[29], then, the drug product manufacturers can reference it in their drug applications, and need not submit the same information again for Agency's review.

A not-novel, or non-novel, or a new excipient can be a non-GRAS (Ref: substances Generally Recognized As Safe, 21 CFR Parts 182, 184, 186[30]) 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[31].

A "non-compendial 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 alternate analytical procedure.

[28] Guidance for Industry: M4Q: The CTD - Quality ICH CTD, Section 2.3.P.4.6., http://www.fda.gov/cder/guidance/4539Q.htm

[29] Guideline For Drug Master Files; http://www.fda.gov/cder/guidance/dmf.htm; Also see IPEC Excipient Master File Guideline, Available at http://www.ipecamericas.org/.

[30] substances Generally Recognized As Safe, 21 CFR Parts 182, 184, 186; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

[31] Guidance for Industry; Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients; http://www.fda.gov/cder/guidance/5544fnl.htm

A non-compendial analytical procedure is an end-product test procedure that is not described in a pharmacopeia. An alternate analytical procedure is other than a compendial analytical procedure or other FDA recognized public standard[32] procedure such as those published in FCC, AOAC International, ASTM[33] standard procedure, etc. For a compendial analytical procedure, the 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 non-compendial 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 non-compendial 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[27] or not.

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 are used by the pharmaceutical industry which 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[34] for an excipient monograph or revision to an existing monograph to the *USP– NF*.

Workshop participants agreed that FDA providing additional guidance to excipient manufacturers may alleviate some of these issues. USP has already published IPEC guidelines as a general information chapter, <1078> GMPs for Bulk Pharmaceutical Excipients. These guidelines also educate the drug manufacturer with regard to excipient GMP and other expectations.

(5) Reduced Testing Due to Use of Compendial Harmonization

This topic was described to the participants as:

[32] 21 CFR 211.194(a)(2); http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.194
[33] ASTM International; www.ASTM.org
[34] USP Submission Guide; Chapter 3 Excipients and addenda; http://www.usp.org/USPNF/submitMonograph/subGuide.html

> 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.

Over 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 only grow. 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), Ph.Eur., or JP monograph as part of the specifications in a drug application. This approach would aid the use of test methods where the analytical procedure and acceptance criteria in the BP, Ph.Eur., 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 – (i) harmonization (full) or (ii) 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 the 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[35].

The closing questions and comments of the workshop observed that one word in the CFR 211.84 that causes confusion is the use of the term – "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

[35] http://www.fda.gov/cder/guidance/7386dft.htm (also see 71 FR 45059, dated August 8, 2006)

testing and measurement to assure that each finished lot of excipient meets all of its quality requirements.

Use of a 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 to use 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 the FDA.

The issue of post approval compendial changes was also discussed at the workshop. A post-approval change submission to a 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 non-application 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 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. 21CFR 314.70 to clarify this issue.

Summary and Recommendations

(1) "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 $\sqrt{n} + 1$ 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 not use a composite sample.

(2) 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 Quality by Design, 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. Drug product manufacturer and 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.

(3) 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 due to the additional time spent by the third party. A small drug manufacturer would have a more credible assessment than by a questionnaire alone.

(4) Strategies to Increase Number of Excipients Labeled *USP–NF*

The FD&C Act required that official drug products and excipients that have pharmacopeial monographs must conform to compendial standards whether or not they are labeled as USP or NF. Conformance to compendial specifications may be assured 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.

The 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. This can be overcome by quality and risk assessments such as audits to verify GMP compliance and compendial testing. It was expressed that when an excipient source does not maintain GMP compliance, the drug product manufacturer needs to obtain a new source for that material.

Alternative test methods may be used for batch release testing, but if there is a dispute, the compendial test is applied as the standard. Use of alternative test methods like ACS, AOAC International, Ph.Eur., 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/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 may also educate the drug manufacturer regarding excipient GMP and specific ways the GMPs are applied to the excipient manufacturer.

(5) Use of Reduced Testing Due to Use of Compendial Harmonization

Over half of excipient and drug product manufactures 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 pharmacopoeias by regulators.

Conference participants indicated that the term "test" in 21 CFR 211.84 creates confusion in the excipient industry. Post-workshop conversations with FDA remind 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 to 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.

Where 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, BLA), 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[10], September 10-11, in Alexandria, VA. In particular, this paper will be the basis for the section "Excipient Testing, Control and Communication: Findings of a PQRI Working Group". The stakeholders may further benefit by attending this conference.

Appendix – Definitions and Regulations

Federal Food, Drug, and Cosmetic Act

Chapter II – Definitions:

Section 201(g)(1) The term "drug" means; (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).

Section 201(j) -The term "official compendium" means the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them.

Chapter V - Adulteration sections:

A drug or device shall be deemed to be adulterated -- Section 501(a)(2)(B) If it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess or is represented to possess.

A drug or device shall be deemed adulterated -- Section 501(b) If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium. Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium, except that whenever tests or methods of assay have not been prescribed in such compendium, or such tests or methods of assay as are prescribed are, in the judgment of the Secretary, insufficient for the making of such determination, the Secretary shall bring such fact to the attention of the appropriate body charged with the revision of such compendium, and if such body fails within a reasonable time to prescribe tests or methods of assay which, in the judgment of the Secretary, are sufficient for purposes of this paragraph, then the Secretary shall promulgate regulations prescribing appropriate tests or methods of assay in accordance with which such determination as to strength, quality, or purity shall be made. No drug defined in an official compendium shall be deemed to be adulterated under this paragraph because it differs from the standard of strength,

quality, or purity therefore set forth in such compendium, if its difference in strength, quality, or purity from such standards is plainly stated on its label. Whenever a drug is recognized in both the United States Pharmacopeia and the Homeopathic Pharmacopeia of the United States it shall be subject to the requirements of the United States Pharmacopeia unless it is labeled and offered for sale as a homeopathic drug, in which case it shall be subject to the provisions of the Homeopathic Pharmacopeia of the United States and not to those of the United States Pharmacopeia.

Title 21 Code of Federal Regulations

Parts 210 and 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

211.84(d) Samples shall be examined and tested as follows:

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the 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.

21 CFR 211. 194 (a) (2) - A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability of the sample meet proper standards of accuracy and reliability as applied to the product as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, AOAC INTERNATIONAL, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.

21 CFR 314.70 Supplements and other changes to an approved application:

(d) Changes to be described in an annual report (minor changes): (1) Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product must be documented by the applicant in the next annual report in accordance with 314.81(b)(2). (2) These changes include, but are not limited to:

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements.

21 CFR 314.70 (c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).
(2) These changes include, but are not limited to:
(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

See also, FDA's Guidance to Industry, Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes, dated 11/19/2004 at http://www.fda.gov/cder/guidance/6451fnl.htm.

Compliance Policy Guides

Sub Chapter 420 - Compendial /Test Requirements
Sec. 420.100 - Adulteration of Drugs Under Section 501(b) and 501(c) of the Act. *Direct Reference Seizure Authority for Adulterated Drugs Under Section 501(b)* (CPG 7132a.03)

Any official drug which, when tested by compendial methods, fails to conform to compendial standards for quality, strength, or purity, is adulterated unless the differences from such standards are plainly stated on the drug's label.

Sec. 420.200 - Compendium Revisions and Deletions (CPG 7132.02)

All official articles shipped prior to the date that the current *USP– NF* became official should be in compliance with the official compendia in effect at the time of shipment.

Sec. 420.300 - Changes in Compendial Specifications and NDA Supplements (CPG 7132c.04)

Any change in the compendial specifications for an NDA drug will normally require the submission of an NDA supplement.

Sec. 420.400 - Performance of Tests for Compendial Requirements on Compendial Products (CPG 7132.05) [Section 420.400 presently is under revision by FDA]

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), or where the official method is the only appropriate test. Neither the *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. What is required is that official drug products conform to the appropriate compendial standards. The manufacturer's specifications for standards of strength, quality and purity may be less stringent in those cases in which the differences from the official standards are stated on the product label.

Where an official product purports to conform to the standards of the *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. Therefore, in some cases it may not be necessary for a manufacturer to test each batch for each monograph requirement.

Sec. 420.500 - Interference with Compendial Tests (CPG 7132a.01)

A compendial drug product containing an added substance which interferes with the compendial assay of the product would be adulterated under 501(b) of the Act.