Understanding and implementing the new standard for excipient GMP

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With the adoption in 2014 of a new standard governing excipients, IPEC-Americas has ramped up its program to educate and train excipient manufacturers, distributors, and users.

The year 2015 could prove a challenging one for makers, users, and distributors of excipients. Since mid-2012, when the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law, the FDA has held public meetings, developed guidance, and implemented plans to speed up reviews and access to safe and effective drug products. The Agency continues to seek more stakeholders to help improve the safety of the drug supply chain.

Now with a new standard—“NSF/IPEC/ANSI 363-2014 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients Standard” (NSF/IPEC/ANSI 363) —issued in December 2014, the industry is waiting to see how the FDA might use the standard to help ensure that drugs (components and drug products [1]) are manufactured in conformance with current GMP. Furthermore, in March 2015, the European Commission—acting under Article 46(f) of the European Falsified Medicines Directive (FMD) —issued a guideline “on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use” [2]. It describes how the holder of manufacturing authorization should use risk assessment to determine which GMP is required for each excipient in a drug formulation.
Historically, regulatory agencies and pharmaceutical manufacturers have focused almost exclusively on APIs and finished drug products. But as the number of incidents of counterfeiting and contamination of APIs and excipients has grown, their attention has turned to excipients. Realizing that excipients can comprise 90 percent or more of a drug product, especially in oral dosage forms, they understand that lapses in excipient quality or safety issues can have catastrophic consequences. For example, in 1996 almost 100 children in Haiti were poisoned by a cough syrup preparation that contained glycerin contaminated with diethylene glycol (DEG). In 2006, more than 100 people were confirmed dead in Panama from ingesting cough syrup that contained DEG misrepresented as 99.5 percent glycerin. While Glycerin USP is a common and safe excipient, DEG is a toxic component of antifreeze. When ingested, it causes renal failure and often death, especially in children, as was the case in these two incidents. Both contributed to the increased global regulatory scrutiny of excipient manufacture and distribution.

**Consequences of regulations on excipients**

Several sections of FDASIA could have an impact on excipients. For instance, under Title III, “Fees relating to generic drugs” (also known as the Generic Drug User Fee Amendments, GDUFA), the FDA is allowed to 1) charge fees when a generic drug application is submitted, 2) inspect sites where an active pharmaceutical ingredient (API) is manufactured, and 3) impose new requirements on Type II Drug Master Files.

The provision about inspecting API facilities can apply to manufacturers of excipients because some over-the-counter (OTC) drug products use an excipient to provide the therapeutic effect, that excipient is therefore labeled as the API. In these OTC products (e.g., glycerin in suppositories or isopropyl alcohol in rubbing alcohol), the excipients have been referred to as atypical APIs. Although they have been safely used this way for decades without explicit regulatory guidelines, the passage of FDASIA changed the regulatory environment. Now, even though the process used to manufacture these ingredients and the GMP expectations have not changed, if these substances are used to manufacture these ingredients and the GMP requirements found in EudraLex Volume 4 [4]. Furthermore, under the National Technology Transfer and Advancement Act of 1995, federal agencies are permitted to adopt private-sector standards, particularly those from standards-developing organizations, wherever possible, in lieu of creating proprietary, non-consensus standards [3]. Since NSF/IPEC/ANSI 363 is a consensus standard that was developed under the auspices of NSF International, a standards-writing organization accredited by ANSI, and since the FDA was a member of the NSF/IPEC/ANSI 363 working group (as required by Office of Management and Budget Circular A-119), we and most others in the industry expect the FDA to use the Standard to determine the requirements of quality management systems used in the manufacture of excipients.

While the FD&C Act has always required components of drugs to be manufactured under GMPs, historically, the only GMP specifically designed for use by excipient manufacturers was The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, first published by members of the International Pharmaceutical Excipients Council (IPEC). In December 2014, the NSF/IPEC/ANSI 363 standard was adopted. The Standard was developed with participation from pharmaceutical excipient manufacturers and distributors, drug-product manufacturers, and public health regulators. NSF/IPEC/ANSI 363 is based on the IPEC-PQG GMP guide but has provisions not included there, such as the requirement to conduct risk assessments. It provides a sound basis for drug-product manufacturers to establish that the excipients they use were produced under appropriate GMPs, as defined by FDASIA and the EU’s FMD guidelines.

Furthermore, under the EU FMD Guideline requires that drug-product manufacturers complete a risk assessment of excipients used in their formulation and to define the appropriate level of GMPs to apply to each excipient based on the requirements found in EudraLex Volume 4 [4]. Furthermore, the EU FMD makes it the responsibility of the “Qualified Person” at the “Manufacturing Authorisation Holder” (MAH) to assess the excipient risk in the drug product formulation. Based on the risk assigned, the MAH is to communicate the risk level to the excipient manufacturer to address the risk. For example, if an MAH notifies the excipient manufacturer that its excipient is used in a parenteral application and thus poses a high risk in the MAH formulation, the excipient manufacturer might be expected to use water of a quality that exceeds that of potable water to ensure the level of pyrogenic impurities in the excipient is low.

Members of IPEC-Americas believe that NSF/IPEC/ANSI 363 provides suitable GMPs for most excipients used in the majority of drug products.

Most people expect the FDA to use NSF/IPEC/ANSI 363 to determine the requirements of quality management systems used in the manufacture of excipients.
IPEC-Americas and its role in excipient regulation

The International Pharmaceutical Excipient Council of the Americas (IPEC-Americas) is a nonprofit trade association organized in 1991 with the goal of providing tools and other resources to help ensure that excipients are manufactured and distributed in a way that produces safe and effective drug products. These tools and resources address common excipient industry issues and include guides (e.g., Technically Unavoidable Particles Profile Guide), white papers, position papers, and training courses. Today, IPEC-Americas has 66 members who are excipient manufacturers, users, or distributors. [Editor’s note: Tablets & Capsules is an associate member of IPEC-Americas.] The group has a good working relationship with the FDA and is recognized as an important source of science-based facts that support the safe manufacture, distribution, and use of excipients.

IPEC-Americas provides collaborative solutions for excipient-industry stakeholders. It is also a reliable source of regulatory information and offers opportunities for members to discuss issues that affect makers, users, and distributors. Members can also discuss with regulators the implications and implementation of in-place and proposed regulations. This year, IPEC-Americas is developing a campaign to foster cooperation and keep members and other excipient stakeholders up to date about industry developments.

IPEC-Americas has seven committees of volunteers that meet quarterly to further its goals. To date, members have helped develop and issue 11 guides that support the association’s goals. Four of them have been adopted as USP General Chapters. Figure 1 provides a timeline of how these guides and USP General Chapters were issued and revised. Representatives from IPEC-Americas’ member companies frequently give presentations at trade meetings and lead workshops and webinars to educate the pharmaceutical industry about using the group’s guides.

Stakeholder participation is a hallmark of IPEC-Americas’ process for writing its guides, which offer both prescriptive and practical information to excipient makers, distributors, and users. The guides’ overriding objective, however, is to ensure the quality of excipients used in drug products. It is therefore paramount that each guide incorporate perspectives from all stakeholders, including, when applicable, regulatory authorities. Two recent guides that included review and comment by the FDA were IPEC’s Certificate of Analysis Guide for Pharmaceutical Excipients (2013) and its Significant Change Guide for Pharmaceutical Excipients (third revision, 2014). More such documents, including QbD Sampling Guide and Continuous Verification of Pharmaceutical Excipients, are expected to be issued later this year.

From 2002 through 2013, a subsidiary of IPEC-Americas, International Pharmaceutical Excipients Auditing (IPEA), provided workshops focused on the requirements of excipient GMPs as originally established in the 1995 IPEC-Americas guide Good Manufacturing Practices for Bulk Pharmaceutical Excipients. In January 2014, IPEC-Americas sold IPEA to NSF International. While the sale transferred ownership of the excipient GMP certification program and the excipient auditing program to NSF, it did not include the IPEA training program. Retention of that program demonstrates the commitment of IPEC-Americas members to continuing education and training, not only in the use of the IPEC guides and the NSF/IPEC/ANSI 363 standard, but in a variety of topics important to excipient makers, users, and distributors. In fact, IPEC-Americas plans to expand its training program.

![Figure 1: Timeline of IPEC-Americas' guidelines](image-url)
Training initiative

With its history of offering expertise in excipient GMPs, regulations, and safety, IPEC-Americas is already recognized as a premier provider of training and education to excipients stakeholders. In fact, IPEC-Americas' membership comprises a large—perhaps the world's largest—group of excipient quality and safety experts uniquely qualified to teach and train people in a variety of areas, including excipient GMP auditing, Quality by Design, and “technically unavoidable particles." In 2014, IPEC-Americas integrated IPEA’s “Excipient GMP Auditing Workshop” (offered since 2005) with IPEC-Americas’ webinars and formed a training committee to develop and deliver additional webinars and face-to-face workshops. It is also evaluating other training needs and opportunities. Training sessions in 2015 will address:

- The NSF/IPEC/ANSI 363 standard,
- Risk assessment,
- Significant change,
- The Technically Unavoidable Particle Profile (TUPP) Guide,
- Total excipient control (TEC), and
- Elemental impurities/USP <232>/ICH Q3D.

These topics will be addressed in webinars that focus on a specific topic and more broadly in classroom settings, where participants can question the instructor, participate in discussions with other attendees, and test their understanding through exercises, quizzes, brainstorming, and other evaluation methods. The classroom training sessions are offered to the public—open to all for a fee—and on-site to companies seeking to train a large number of employees. The advantages of attending a public workshop include networking with suppliers to share problems and solutions and interacting with customers to understand their requirements. Interaction between makers and users at public workshops provides insight into the needs of excipient users and how excipient makers can meet them. One benefit of on-site private workshops is the freedom to speak openly and without concern about disclosing confidential information.

While current IPEC-Americas’ webinars are largely presentation-based, the group is developing instructor-led online training modules that allow real-time interaction between the presenter-trainer and participants so they can practice and evaluate what they learned.

All the training that IPEC-Americas offers in excipient GMP conformance, quality, and safety is reviewed by other subject matter experts to ensure the content is correct, current, and pertinent. Members of its training committee also evaluate the delivery of the presentation to ensure it meets established training industry guidelines and will offer suggestions for improvement as needed.

IPEC-Americas is offering several public workshops in 2015 and 2016.

Excipient GMP auditing for NSF/IPEC/ANSI 363. The key objective of this 3-day event is to educate attendees about the principles of conducting and documenting an audit and to discuss the audit expectations associated with NSF/IPEC/ANSI 363. There are also opportunities to practice audit skills.

Qualification and validation. This workshop provides training in the qualification of equipment and the principles of validation of processes, cleaning methods, computer systems, and test methods. Attendees learn various qualification and validation techniques and apply what they learn to meeting the requirements of NSF/IPEC/ANSI 363.

Risk assessment for excipients. Participants learn the fundamentals of assessing risk under a quality risk-management program. Various risk-assessment tools are discussed and practiced. Attendees learn the many risk assessments that NSF/IPEC/ANSI 363 requires and how to determine the extent of assessment expected.

Significant change. This workshop provides an understanding of IPEC’s Significant Change Guide for Pharmaceutical Excipients, illustrates the application of the guide to manage change (“change control”), and emphasizes evaluating changes to the manufacture of excipients to ascertain the potential that a change could affect the drug product.

Since it is expected that the pharmaceutical industry will adopt NSF/IPEC/ANSI 363 as the GMP standard for assessing and auditing excipient suppliers, IPEC-Americas dedicated a two-part webinar to the standard’s new requirements and the resources available from IPEC in March and June. It will be offered again in early 2016.

By adopting the practices outlined in NSF/IPEC/ANSI 363, excipient suppliers and distributors will be better able to serve pharmaceutical customers in the USA and Europe expecting compliance. IPEC is developing several guidelines that support the requirements of the Standard. It is also offering education and training to help excipient industry stakeholders address new requirements from the FDA and the EU. We encourage industry stakeholders to turn to IPEC-Americas for excipients training as it expands the program.

References

1. Food, Drug and Cosmetic (FD&C) Act, Section 501(a)(2)(B)

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