IPEC Europe Excipients Forum
“Changing times, Changing practices?
Focus on excipient quality
and functionality”
5th February 2015, The Negresco Hotel - Nice (FR)

Updates on USP’s proposed General Information Chapter, Good Distribution Practices <1083> - an Overarching Chapter

Catherine Sheehan, Sr. Director - Excipients
U.S. Pharmacopeial Convention (USP)
• Overview of the U.S. Pharmacopeial Convention (USP)
• How USP Standards are Established through a Public Process and Types of USP Standards
• USP-NF and Role of USP Quality Standards in US Law
• Currently official Good Distribution Practices Information Chapters in USP-NF
• Background and Current Status of the Proposed Information Chapter Good Distribution Practices <1083>
• Next Steps
US Pharmacopeial Convention (USP) founded in 1820. USP is a scientific, nonprofit, nongovernmental, private, independent, and self-funded organization.

Headquartered in Rockville, MD; 700 employees; facilities in India, China, Switzerland, Brazil.
The first edition of the National Formulary (NF) originally named “The National Formulary of Unofficial Preparations” was first published in 1888 by the American Pharmaceutical Association.

1975: USP purchased the NF, combining the two publications under one cover to create the United States Pharmacopeia– National Formulary (USP–NF).

1977: USP and NF scope was redefined: USP standards for drug substances and dosage forms and compounded preparations; NF standards for excipients.

USP sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide.

A drug product in the U.S. market must conform to the standards in USP–NF to avoid possible charges of adulteration and misbranding.
USP – An Overview

- USP’s drug standards are enforceable in the United States by the Food and Drug Administration (FDA), and these standards are used in more than 140 countries.

- USP today works with scientists, practitioners, and regulators of many nations to develop and revise standards that help protect public health worldwide.

- 2000-2010- Creation of Global sites
  - In 2005, USP opened an office in Basel, Switzerland. Helped build collaborative relationships, provide training programs on USP standards outside of the United States.
  - USP opened three new international state-of-the-art laboratories and office sites: Hyderabad, India (2006); Shanghai, China (2007); and São Paulo, Brazil (2008).
    - Help to cultivate strong relationships and support USP's collaborative laboratory testing efforts, provide technical assistance, and offer training and education opportunities in their respective regions.
USP is cited in United States Law…

- **1848**: Drug Import Act
- **1906**: Pure Food and Drug Act
- **1938**: Federal Food, Drug and Cosmetic Act (FFD&C Act)
  - Definition of a drug
  - Adulteration
  - Misbranding
  - Drug product name
- **1994**: Dietary Supplement Health and Education Act
- **2003**: Model Guidelines for Medicare Formularies

- In the FFD&C Act, both *United States Pharmacopeia (USP)* and the *National Formulary (NF)* are recognized as official compendia for drugs marketed in the United States. Legally, the *USP-NF* is two separate books published in the same volumes.
USP’s Compendia

- The *United States Pharmacopeia*
- *National Formulary (USP–NF)*
- *Food Chemicals Codex (FCC)*
- *USP Dietary Supplements Compendium (DSC)*
- *USP on Compounding*
- *Herbal Medicines Compendium (HMC)*

**Other Resources**
- *Pharmacopeial Forum (PF)*
- *FCC Forum (FCCF)*
- *USP Dictionary*
- *Chromatographic Columns*
USP creates and continuously revises *USP–NF* standards through a unique public–private collaborative process.

This involves pharmaceutical scientists in industry, academia, and government as well as other interested parties from anywhere in the world.

Public input and interaction are vital to the development of these standards.

The standards generally originate from sponsors who provide draft standards and supporting data to either create new or revise (*modernization*) existing monographs and general chapters.
USP's scientific staff and volunteer experts review this input, conduct laboratory tests (if necessary), and forward the new or revised monograph or general chapter to *Pharmacopeial Forum (PF)* for public review and comment. *PF* is free, online only resource.

The public process helps to refine USP standards for publication as official text in the *USP–NF*.

Prior to publication as official text, all monograph and general chapter proposals must be approved by a *USP Expert Committee*.

Comprised of volunteer scientists, academicians, practitioners, and other professionals elected on the basis of their knowledge and expertise.

USP-NF contains standards that must be applied to drug substances, excipients and drug products.

These two books are divided in several sections; the important ones for the purposes of this presentation are:

- General Notices
- General Chapters
- Monographs
General Notices contain requirements applicable throughout *USP−NF* unless superseded by a chapter or monograph.

General Chapters contain requirements applicable to monographs to which they apply.
- General Chapter requirements supersede General Notice requirements in case of conflict.

Monograph requirements are specific to the monograph in which they appear.
- Monograph requirements supersede General Notice and General Chapter requirements in case of conflict.
Types of USP Standards

- **Monographs (Vertical Standards)**
  - Specifications for pharmaceutical articles in commerce
  - Specifications – Tests, assays and acceptance criteria needed to demonstrate the article meets required quality standards

- **General Chapters (Horizontal Standards)**
  - Required (numbered <1000)
  - Informational (numbered >1000)
  - Support monographs by centralizing methods and procedures

- **Physical Reference Materials**
  - Provide traceable standards to demonstrate broad-based acceptability of procedures
There are three types of General Chapters in the USP-NF:

- **General Chapters <1000**
  - These are mandatory when applicable.

- **General Information Chapter 1000 – 1999**
  - These are not mandatory unless they are specifically referenced in a monograph in which case they become mandatory for that monograph.

- **Dietary Supplement General Chapters ≥2000**
  - Only applicable to dietary supplements.
Under FD&C Act

- **21 U.S.C. § 351 Section 501 - Adulterated Drugs and Devices**
  - A drug with a name recognized in *USP-NF* must comply with compendial identity or be deemed adulterated, misbranded, or both (501(b) & 502(e)(3)(b)). *Cannot label away from identity!*
  - Must also comply with compendial standards for strength, quality, and purity, unless labeled to show all differences (501(b) & 21 CFR 299.5).
  - Removing the *USP-NF* designation from labeling does not obviate the requirement to conform to compendial requirements.
Under FD&C Act

- 21 U.S.C. § 321 Section 201(g)(1)
  - The term “drug” means:
    - intended to provide diagnosis, cure, mitigation, treatment, or prevention of disease
    - intended to affect the structure or any function of the body
    - intended for use as a COMPONENT of any article meeting the above criteria
21 CFR § 210.3 Definitions (under cGMP for Drugs; General)

- **a(4) Drug product** means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an **active drug ingredient** generally, but not necessarily, in association with **inactive ingredients**. The term also includes a finished dosage form that does not contain active ingredient, but is intended to be used as a placebo.

- **a(3) Component** means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such a drug product.

- **a(8) Inactive ingredient** means any component other than an active ingredient

(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.
Globalization of the supply chain has a direct impact on the sourcing and qualification of quality raw materials (Excipients and APIs) and regulated drug products intended for patient’s safe usage.

Global Expertise | Trusted Standards | Improved Health
FDA Detects High Levels of Peroxide in Crospovidone
Issuing a Drug Safety Advisory on 10/21/2010
http://www.fda.gov/drugs/drugsafety/ucm230492.htm

• Peroxide levels found (1700 ppm) were 30-40x typical levels in this excipient
• Peroxides can degrade APIs resulting in sub-potent drug
• Impurity levels were not being monitored by the manufacturer of Crospovidone
• USP revised monograph to add limit of peroxide
  (Second Supplement to USP 34–NF 29)
Are We Only Seeing the Tip of the Iceberg?
International Excipient Workshop
Excipient Quality Control, Testing, and
International Harmonization

USP Headquarters, Rockville, Maryland
July 20-21, 2009

Summary: Excipient Supply Chain Integrity
Excipient Workshop Outcomes

- Workshop concluded that recent events have shown that excipients are vulnerable to adulteration
- No one solution will fix the problem
- Approach through a series of measures:
  - Collaborate with industry and FDA to modernize monographs with more specific methods
  - World-wide, pharmacopeias are working; industry co-operation is necessary but not always forthcoming
  - Better understanding of our supply chains
  - Vigilance: Audits and Continuing assessment
- Create a General Chapter <1197> Good Distribution Practices For Bulk Pharmaceutical Excipients
- Proposed in PF 37(6) [Nov. – Dec. 2012];
- Published in USP 36 NF 31, Official May 1, 2013
The Joint Expert Panel on Good Distribution Practices for Bulk Pharmaceutical Excipients, formed in Nov. 2009 under the Excipient General Chapters and the Excipient Monograph Expert Committees

PF 37(6) [Nov. – Dec. 2012] Briefing:

- “The pharmaceutical excipient supply chain may comprise many participants, both domestically and globally, and may include manufacturers, distributors, brokers, suppliers, traders, transport companies, forwarding agents, and repackagers. The quality of pharmaceutical excipients can be affected by the lack of adequate control of activities including distribution, packaging, repackaging, labeling, and storage. Improper or inadequately controlled trading practices can pose a significant risk to the quality of pharmaceutical excipients and can increase the risk of contamination, cross-contamination, adulteration, mix-ups, degradation, or changes in physical or chemical properties.”

Because of the variety of ways in which users can source material, potential issues and misunderstandings can arise as to whether the sourced material quality is suitable for its intended use in pharmaceutical preparations.

<1197> provides key information to help assure excipient quality and help prevent economically motivated adulteration.

The chapter outlines key strategies necessary in the qualification of starting materials of good quality, the maintenance of that quality throughout the distribution chain and the confirmation of the quality by the users of starting materials.
Proposal for new information chapter in *PF 38(2)* [March-April 2012]

Rationale:

Because there is no information in the *USP–NF* on this subject, a new general information chapter is being proposed. This new chapter will be a part of the series of information chapters describing various aspects of the pharmaceutical supply chain.

The current official chapter in this series is Good Storage and Shipping Practices <1079>, with a recent proposal for revision appearing in *PF 37(4)*.

Workshop held May 22-23 at USP in Rockville to discuss comments on Good Distribution Practices—Supply Chain Integrity <1083> that have been received from industry.
What did we learn?

• USP’s current approach to GDP has been piecemeal:
  – Individual components, e.g. Excipients; Drug Products
  – Individual topics, e.g. Storage & Shipping; Supply Chain Integrity

• A holistic approach to Good Distribution Practices (GDP) is preferred:
  – Acquisition of ingredients (drug substances, excipients)
  – Importation and Exportation
  – Maintaining quality of medicines to the end-users
  – Adherence to labeled storage conditions
    • Sub-set of GDP
What did we learn?

• Integrate individual components and topics under a single overarching GDP (umbrella) chapter

• Avoid separate USP chapters on GDP with non-sequential chapter numbers
  – End-user friendly chapters

• Technologies and their application change rapidly, so guidance should focus on best practices and principles
  – Not specific individual technological approaches
  – Non prescriptive
• Subcommittee Collaboration to develop USP overarching chapter on GDP
  – Four EC have ownership and responsibility for the chapters
    • Compounding
    • Monographs—Excipients
    • Packaging, Storage, and Distribution
    • Physical Analysis
      • The goal of the Subcommittee is to develop general informational chapters on the GDP topic that can apply across all USP products

• Identified all Compendial chapters that discuss GDP and determine overlap.
  – Identify GDP topics to include in a overarching chapters
  – Develop a strategy for the overarching chapters that would allow all relative chapters to be sequential in the USP
# 2010-2015 GDP and GMP related Official Information Chapters in *USP-NF*

<table>
<thead>
<tr>
<th>USP Information Chapter</th>
<th>Current Expert Committee *</th>
<th>Applicable to</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1079&gt; Good Storage and Shipping Practices</td>
<td>GC/PSD</td>
<td>API and DP</td>
</tr>
<tr>
<td>&lt;1177&gt; Good Packaging Practices</td>
<td>GC/PSD</td>
<td>API and DP</td>
</tr>
<tr>
<td>&lt;1178&gt; Good Repackaging Practices</td>
<td>GC/PSD</td>
<td>API and DP</td>
</tr>
<tr>
<td>&lt;1197&gt; Good Distribution Practices For Bulk Pharmaceutical Excipients</td>
<td>GCPA: EXC</td>
<td>Excipients</td>
</tr>
<tr>
<td>&lt;1080&gt; Bulk Pharmaceutical Excipients Certificate of Analysis</td>
<td>GCPA: EXC</td>
<td>Excipients</td>
</tr>
<tr>
<td>&lt;1195&gt; Significant Change Guide For Bulk Pharmaceutical Excipients</td>
<td>GCPA: EXC</td>
<td>Excipients</td>
</tr>
<tr>
<td>&lt;1078&gt; Good Manufacturing Practices For Bulk Pharmaceutical Excipients</td>
<td>GCPA: EXC</td>
<td>Excipients</td>
</tr>
</tbody>
</table>

* GC/PSD : General Chapters Packaging, Storage & Distribution  
GCPA:EXC : General Chapters Physical Analysis: EXC. (previously under Excipient General Chapters prior to 2010)
## Analysis of &<1079>&<1197>

<table>
<thead>
<tr>
<th>Requirements</th>
<th>&amp;&lt;1079&gt;</th>
<th>&amp;&lt;1197&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. General Good Distribution Practices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Quality Management Systems</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>B. Buildings and Facilities (Storage)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C. Transportation Vehicles (Shipping)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>2. Environmental Control Management</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. General Principles and Practices</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>B. Buildings and Facilities (Storage)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C. Transportation Vehicles (Shipping)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>3. Importation/Exportation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Audits and Supply Agreements</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>B. Container Seals, Cargo Inspection, Customs, and Brokers</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>C. Knowing the Product, Applicable Regulatory Requirements, and Trade Rules</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>D. Verifying Product and Firm Compliance with Regulations</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>E. Taking Corrective and Preventive Action</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>4. Supply Chain Integrity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Legal and Illegal Outlets</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>B. Packaging Technologies</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>C. Diversion and Theft</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>D. Product Recall Procedures</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
GDP Topics Identified

Quality Management Systems

Supply Chain Integrity & Security

Environmental Control Management

Good Importation/Exportation Practices
Chapter Development

• These four key topics serve as the foundation for the overarching chapter
  – Covering material flow beginning with initial procurement and continuing throughout the supply chain to delivery to the end-user
Chapter Development

• Two levels of chapters
  • Level 1
    – Address the four main GDP topics—Quality Management System; Environmental Control; Good Importation and Exportation Practices; and Supply Chain Integrity—highlighting best practices and principles.
    – Written in a non-specific way so as to apply across all Compendial products.
  • Level 2
    • Address special GDP consideration for five specific products/materials—Finished Drug Products, API’s, Excipients, Packaging Materials and Clinical Trial Materials
    • Written to focus specifically on the products/materials
Chapter Development: Outline

<1083>
GOOD DISTRIBUTION PRACTICES

Level 1

<1083.1> QUALITY MANAGEMENT SYSTEM
<1083.2> ENVIRONMENTAL CONDITIONS MANAGEMENT
<1083.3> IMPORTATION & EXPORTATION MANAGEMENT
<1083.4> SUPPLY CHAIN INTEGRITY & SECURITY

Level 2

<1083.5> Finished Drug Products
<1083.6> Excipients
<1083.7> API’s
<1083.8> Clinical Trial Materials
<1083.9> Packaging
A Quality Management System (QMS) is defined as a set of interrelated or interacting elements, such as policies, objectives, procedures, processes, resources which individually or collectively, established to guide an organization.
Environmental Control Management

- Environmental Conditions Management
  - Environmental Controlled Facilities, Equipment and Vehicles
  - Packaging for Shipping
  - Performance Qualification
  - Data Monitoring
  - Short-Term Excursions
Importation and Exportation Management (IEM) is a set of basic principles that should be followed in order to ensure the quality, safety and security of imported and exported materials and products.

- Organizations involved in the importation and exportation of materials and/or products should be aware of local, national, and international regulations, risks associated with material and/or product handling and have controls in place to mitigate the likelihood that the material or product quality, safety or security is compromised.
Supply Chain Integrity and Security (SCIS) is defined as a set of policies, procedures and technologies used to provide visibility and traceability of products within the supply chain. This is done to minimize the end-user’s exposure to adulterated, economically motivated adulteration, counterfeit, falsified or misbranded products or materials, or those which have been stolen or diverted. This is minimized by implementing procedures to control both the forward and the reverse supply chains.
<1083> Good Distribution Practices – Next Steps

• Publish the information chapter, target *Pharmacopeial Forum* 41(5) [Sept. – Oct.] 2015
  – <1083> Good Distribution Practices
    – 1.<1083.1> Good Distribution Practices—Quality Management System
    – 2.<1083.2> Good Distribution Practices—Environmental Conditions Management
    – 3.<1083.3> Good Distribution Practices—Good Importation and Exportation Practices
    – 4.<1083.4> Good Distribution Practices—Supply Chain Integrity and Security
    – 5.<1083.5> Good Distribution Practices—Finished Drug Products

• In development
  – 1.<1083.6> Good Distribution Practices—Excipients
  – 2.<1083.7> Good Distribution Practices—API’s
  – 3.<1083.8> Good Distribution Practices—Clinical Trial Materials
  – 4.<1083.9> Good Distribution Practices—Packaging

• Submit comments on <1083> to:
  – Contact Liaison: Dr. Desmond Hunt at dgh@usp.org
  – Contact Liaison (excipients): Dr. Galina Holloway at gh@usp.org
Why not just use cGMPs & GDPs from regulators or other sources?

- USP must cover all stakeholders
  - May seem redundant to a few, but needed by smaller companies, virtual firms or new business entities
  - Compendial Standard – as such is translated into multiple languages; not every country has a standard QMS expectation
  - Does not supersede or supplant national requirements

- Above 1000 means guidance; agencies may choose to use
Seeking experts in pharmaceutical, biological, and food sciences; pharmacy; medicine; and related disciplines to volunteer for USP’s Council of Experts and Expert Committees for the 2015-2020 cycle

Application deadlines:

- January 1, 2015: Council of Experts (Expert Committee Chairs)
- May 15, 2015: Expert Committee members
- End of May 2015: CoE Orientation and Election of Expert Committee members
- July 2015: 2015-2020 Council of Experts and Expert Committees begin their work

Visit [www.usp.org](http://www.usp.org) and click the Call for Candidates banner to access information and to create an application account.
2015–2020 Council of Experts
Expert Committees and Collaborative Groups

- Similar number of Expert Committees
- Retain Expert Panels in advisory capacity