

# Overview of International Harmonization through the Pharmacopeial Discussion Group

Catherine Sheehan, M.S., M.S.  
Veterinary Stakeholder Forum  
February 19-20, 2014

- Introduction to PDG and its Working Procedures
- PDG Workplan Status Update
- Challenges to Harmonization and Ongoing Improvements
- Summary

- ▶ PDG was formed in 1989 in response to proposals from industry.
- ▶ PDG is an informal body and consists of representatives from:
  - European Pharmacopoeia (EDQM)
  - Japanese Pharmacopoeia (MHLW)
  - United States Pharmacopeia (non-governmental)
  - WHO, an observer since 2001
- ▶ PDG meets twice yearly to work on pharmacopeial harmonization topics
- ▶ PDG processes are fully described on USP's website at <http://www.usp.org/usp-nf/harmonization>

Spring 2012 - FDA and USP form a U.S. Delegation to PDG

Benefits:

- Additional cooperative mechanism to strengthen working relationships between FDA and USP
  - PDG prep meeting discussions provide an opportunity for FDA to be up-to-speed on issues being discussed by PDG (first-time early awareness of PDG member issues/positions being discussed) -- all PDG regional parties on equal footing.
    - Gelatin - meeting discussions with FDA resulted in change to Gelatin monograph prior to sign-off to reflect FDA's need to establish chromium testing
- As a participant of the U.S. Delegation to PDG, FDA has direct input into the pharmacopeial harmonization process to:
  - Ensure that PDG output is reflective of FDA concerns in a more timely manner
  - Any necessary inclusion of 'local text' is in place at the time of Stage 6 harmonization
  - Proactive rather than reactive – savings for all
  - Removes a potential delay in PDG harmonization

## Benefits to stakeholders

- ▶ Elimination of redundant testing
- ▶ Multi-compendial compliance

## Benefits to the pharmacopeias

- ▶ Stronger monographs with a global set of experts setting and reviewing standards
- ▶ Specifications (test methods) are representative of the global supply chain
- ▶ Minimizes duplication of testing requirements, eliminating inconsistent standards internationally.

**Harmonized:** A pharmacopeial general chapter or other pharmacopeial document is harmonized when a pharmaceutical substance or product tested by the document's harmonized procedure as published in EP, JP and USP yields the same results, and the same accept/reject decision is reached.

- ▶ Text does NOT have to be identical.
- ▶ Each Pharmacopeia can adapt the text to local style, and take into consideration local reference standards and reagents.

# Harmonization by Attribute

- ▶ Applied retrospectively when agreement was unable to be reached on specific tests in a monograph, or parts of a General Chapter.
- ▶ Instituted as a means to move items forward where there was agreement on the main attributes (i.e. assay, identification) as opposed to delaying entire monograph or chapter.
- ▶ Attributes may have been determined to be non-harmonized by PDG for the following reasons
  - (1) Differing regulatory or legal requirements
  - (2) Non-harmonized methodology for procedures
  - (3) Differences in scientific expert opinions
- ▶ PDG have committed to work transparently in clearly identifying which specific attributes in a monograph or chapter are harmonized.
- ▶ PDG have committed to working on eliminating non-harmonized attributes where possible.

# Stages of PDG harmonization

The Pharmacopeial Discussion Group harmonization process consists of 7 stages. This process is followed for harmonization of general chapters and monographs on the PDG work plan.

Stage 1	Identification
Stage 2	Investigation
Stage 3	Expert Committee Review
Stage 4	Official Inquiry (public)
Stage 5	
Stage 5A	Consensus (Provisional)
Stage 5B	Sign-off
Stage 6	
Stage 6A	Regional Adoption
Stage 6B	Regional Implementation
Stage 6C	Indication of Harmonization
Stage 7	Inter-regional Acceptance

Catherine Sheehan, August 16, 2013

[http://www.usp.org/sites/default/files/usp\\_pdf/EN/2010-06\\_working\\_procedure\\_of\\_the\\_pdg\\_sign-off\\_document.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/2010-06_working_procedure_of_the_pdg_sign-off_document.pdf)



# Stages of PDG Harmonization (1-2)

- Stage 1: Identification
  - PDG **identifies subjects** to be harmonized among PDG pharmacopeias (originating from an inquiry among its users), and **nominates** a coordinating pharmacopeia for each subject.
- Stage 2: Investigation
  - The **coordinating pharmacopeia** prepares a draft monograph or chapter, accompanied by a report giving the rationale for the proposal with validation data.

# Stages of PDG Harmonization (3-4)

- Stage 3: Expert Committee Review
  - The three pharmacopeias forward the Stage 3 draft proposal to their **expert committee** for comments.
- Stage 4: Official Inquiry
  - The Stage 4 draft and the commentary are published in the revision document of **each pharmacopeia** in a section entitled International Harmonization.

- **Stage 5A: Consensus (Provisional)**
  - The **Stage 5A** draft is reviewed and commented upon
- **Stage 5B: Consensus (Sign-Off)**
  - The Stage 5B draft is sent by the coordinating pharmacopeia to the other pharmacopeias ideally no later than 4 weeks before a PDG meeting for final confirmation.
  - The document is presented for sign-off at the PDG meeting.

## Stages of PDG Harmonization (6)

- **Stage 6A: Regional Adoption.**
  - The document is submitted for adoption to the organization responsible for each pharmacopeia. Each pharmacopeia incorporates the harmonized draft according to its own procedures.
- **Stage 6B: Regional Implementation.**
  - The pharmacopeias will inform each other of the date of implementation in their particular region.
- **Stage 6C: Indication of Harmonization.**
  - The point at which the PDG process for harmonization has been completed.

- Stage 7: Inter-Regional Acceptance.
  - When a harmonized text has become official in **all three pharmacopeias**, EP and USP publish a statement indicating the harmonization status of the text; JP publishes a statement to the same effect at Stage 6B.
  - The date of Stage 7 will be common to all three Pharmacopoeias and will be assigned after receiving **formal notification of regulatory acceptance from Q4B**.
  - These efforts will be beneficial for users of the pharmacopoeias and facilitate the work of the Q4B Expert Working Group (EWG).

# Revisions to Harmonized Items

- ▶ Once reaching Stage 6, no pharmacopeia can unilaterally change harmonized text.
- ▶ Revisions are initiated by means of a formal request to PDG prior to upcoming meeting (at least 2 months in advance).
- ▶ PDG approves or rejects the revision.
  - If approved, a coordinating pharmacopeia (CP) is nominated (does not necessarily have to be the original CP for the item).
- ▶ The new CP prepares the revised draft.
  - Major revisions are introduced at Stage 3.
  - Minor revisions can be introduced by rapid revision at Stage 5A.
  - Decision on major or minor status must be agreed upon by PDG.

# Pharmacopeial Discussion Group (PDG) updates

- ▶ At present, 28 of the 35 General Chapters and 45 of the 62 excipient monographs on the current work program have been harmonized
- ▶ PDG meetings
  - June 2013
    - Sign off's:
    - New: Isomalt and Hydroxypropyl cellulose
    - Revisions: Saccharin and Sodium starch glycolate
  - November 2013
    - Sign off's:
    - Revisions: Bulk Density and Tapped Density, Sodium Chloride and Starch, Rice monographs
- ▶ Next PDG meeting Rockville 24-25,2014
- ▶ Omission of <1196> Pharmacopeial harmonization PF 39(6)
- ▶ PDG webpage: detailed information can be found on
  - <http://www.usp.org/usp-nf/harmonization>
  - S6 monographs are now under Official text
  - <http://www.usp.org/usp-nf/official-text/stage-6>

## **(28 out of 35 as of November 2013)**

- ▶ Amino Acid Determination
- ▶ Analytical Sieving
- ▶ Bacterial Endotoxins
- ▶ Bulk Density and Tapped Density
- ▶ Capillary Electrophoresis
- ▶ Disintegration
- ▶ Dissolution
- ▶ Extractable Volume
- ▶ Gas Pycnometric Density of Solids
- ▶ Isoelectric Focusing
- ▶ Laser Diffraction Measurement of Particle Size
- ▶ Microbial Contamination
- ▶ Microcalorimetry
- ▶ Optical Microscopy
- ▶ Particulate Matter
- ▶ Peptide Mapping
- ▶ Polyacrylamide Gel Electrophoresis
- ▶ Porosimetry by Mercury Intrusion
- ▶ Powder Fineness
- ▶ Powder Flow
- ▶ Protein Determination
- ▶ Residue on Ignition
- ▶ Specific Surface Area
- ▶ Sterility
- ▶ Tablet Friability
- ▶ Uniformity of Content/Mass
- ▶ Water-Solid Interactions
- ▶ X-ray Powder Diffraction



## (45 out of 62 as of November 2013)

- ▶ Alcohol
- ▶ Alcohol Dehydrated
- ▶ Benzyl Alcohol
- ▶ Calcium Disodium Edetate
- ▶ Calcium Phosphate Dibasic
- ▶ Calcium Phosphate Dibasic (Anhydrous)
- ▶ Carboxymethylcellulose
- ▶ Carboxymethylcellulose Calcium
- ▶ Cellulose, Microcrystalline
- ▶ Cellulose, Powdered
- ▶ Cellulose Acetate
- ▶ Cellulose Acetate Phthalate
- ▶ Citric Acid, Anhydrous
- ▶ Citric Acid, Monohydrate
- ▶ Croscarmellose Sodium
- ▶ Crospovidone
- ▶ Ethylcellulose
- ▶ Gelatin (gelling and non-gelling)
- ▶ Hydroxypropylcellulose
- ▶ Hypromellose
- ▶ Hypromellose Phthalate
- ▶ Isomalt
- ▶ Lactose, Anhydrous
- ▶ Lactose Monohydrate
- ▶ Magnesium Stearate
- ▶ Mannitol
- ▶ Methylcellulose
- ▶ Butyl, Ethyl, Methyl, Propyl Paraben
- ▶ Polysorbate 80
- ▶ Povidone
- ▶ Saccharin
- ▶ Saccharin Calcium
- ▶ Saccharin Sodium
- ▶ Sodium Chloride
- ▶ Sodium Starch Glycolate
- ▶ Starch, Corn
- ▶ Starch, Potato
- ▶ Starch, Rice
- ▶ Starch, Wheat
- ▶ Stearic Acid
- ▶ Sucrose
- ▶ Talc

## Magnesium Stearate

Portions of the monograph text that are national *USP* text, and are not part of the harmonized text, are marked with symbol (✦) to specify this fact.

Octadecanoic acid, magnesium salt;  
Magnesium stearate [557-04-0].

### DEFINITION

Magnesium Stearate is a compound of magnesium with a mixture of solid organic acids, and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. The fatty acids are derived from edible sources. It contains NLT 4.0% and NMT 5.0% of Mg, calculated on the dried basis.

## 4 Magnesium

$r_T$  = sum of the peak areas of all the fatty acid esters  
Similarly, calculate the percentage of palmitic acid in the portion of Magnesium Stearate taken.

$$\text{Result} = (r_p/r_T) \times 100$$

$r_p$  = peak area due to methyl palmitate

$r_T$  = sum of the areas of all the fatty acid ester peaks

Acceptance criteria: NLT 40% for the stearate peak. The sum of the stearate and palmitate peaks is NLT 90% of the total peak areas of all the fatty acids.

### ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.

### Change to read:

- **✦LABELING:** Where the labeling states the specific surface area, it also indicates which method specified under *Specific Sur-*

face Area (846) is used. ▲Label to indicate the fatty acids are derived from edible sources.▲N

- **USP REFERENCE STANDARDS (11)**

USP Palmitic Acid RS  
USP Stearic Acid RS

# Challenges to Harmonization and On-Going Improvements

- Time required to bring harmonized monographs and chapters to official status is very long and burdensome for stakeholders.
  - PDG is now using monthly meetings, improved communication pathways, and use of face-to-face expert level meetings to move difficult topics forward.
- Pharmacopeias operate on different publishing schedules.
- Differences in legal and/or regulatory requirements in the different regions can be barriers to harmonization.
  - PDG continues to use harmonization by attribute to move forward items within a monograph or chapter which are not in dispute.
  - Commitment not to spend resources on topics where there are insurmountable differences to achieving harmonization.

# Challenges to Harmonization and On-Going Improvements

- Comments are often received too late in the PDG process.
  - USP publishes Stage 4 texts for public notice and comment in Pharmacopeial Forum (PF).
  - PF is now publically available free of charge at <http://www.usp.org/USPNF/pf/>.
- Need for global industry input at the early stages of monograph harmonization in order to prevent the need for repeat publications at Stage 4
- Early communication across different expert committees of the three pharmacopeias has proven to be helpful to move difficult items forward.
- Need for better understanding of purposes of specifications if based on safety or process capability

# Challenges to Harmonization and On-going Improvements

- Potential for harmonization often not realized by stakeholders until late in the process.
  - Education on PDG activities through on going workshops, conferences and development of Pharmacopeial Education courses related to PDG.
- Harmonized texts and changes are not always transparent to stakeholders.
  - PDG are in the process of performing Indication of Harmonization reviews to ensure that published texts are consistent with PDG harmonized agreements.

# Challenges to Harmonization and On-Going Improvements

- ▶ USP webpage devoted to Pharmacopeial Harmonization includes the following information
  - PDG Harmonization Working Procedures Process
  - PDG Press Release Statements
  - FAQ section
  - Official Stage 6 Text (link to official text webpage)
  - Sign-Off Cover Pages and official monograph
  - PDG Status Table for all items in Work plan
  - Information can be found at:

<http://www.usp.org/usp-nf/harmonization>



The screenshot shows the USP website's navigation structure for the Harmonization—Pharmacopeial Discussion Group. The top navigation bar includes links for About USP, USP-NF, Dietary Supplements, Food Ingredients, Reference Standards, and Around the World. A secondary bar contains Overview, Official Text, Pharmacopeial Forum, Key Issues, Development Process, Notices, and Harmonization (which is highlighted). Below this, a breadcrumb trail reads: You are here: Home > USP-NF > Harmonization—Pharmacopeial Discussion Group. The main content area is titled 'Harmonization—Pharmacopeial Discussion Group' and features a sidebar with links to General Chapters, Monographs, Calendar, and Links. The main text area includes a photo of scientists working and a paragraph stating: 'USP participates in the Pharmacopeial Discussion Group (PDG) to work on pharmacopeial harmonization topics. Visit the links below to learn more about PDG and also see the pages listed on the left sidebar for information about current PDG activities.' A list of links follows: PDG History, PDG Purpose, PDG Process, Notices of Stage 6 Harmonized Text, PDG Working Procedure, PDG Glossary, Interaction with ICH-Q4B, FAQs, Contacts, PDG State of Work (July 2013), and Implementation Timeline.



- ▶ Harmonization is important to pharmacopeias, regulators, and industry.
- ▶ PDG is the primary mechanism for harmonization and operates via a multi-step review and approval process.
- ▶ PDG remains linked to ICH-Q4B for revisions to standards previously deemed interchangeable by ICH-Q4B
- ▶ USP must always be cognizant of its responsibilities as a member of PDG.

## The USP staff involved in this process

- ▶ **Jon Clark**, Vice President , Chemical Medicines, head of USP delegation to the Pharmacopeial Discussion Group (PDG).
- ▶ **Catherine Sheehan**, part of the USP delegation to the PDG.
- ▶ **Kevin Moore**, Manager, Pharmacopeial Harmonization; primary contact and part of the USP delegation to PDG.
- ▶ **Jenny Liu**, Associate Scientific Liaison and Technical Support for PDG Harmonization.
- ▶ **Emily Meyer**, Executive Secretariat support for PDG activities and part of the USP delegation to PDG.



# Thank You