

Quality Standards for Medicines, Supplements, and Food Ingredients throughout the World

Overview of the Pharmacopeial Discussion Group: Harmonization from a Compendial Perspective

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The Standard of QualitySM

Pharmacoepial Discussion Group (PDG)

- In response to proposals from industry
- PDG was formed in 1989
- PDG is an **informal body** and consists of representatives from
 - United States Pharmacopeia (non-governmental)
 - European Pharmacopoeia, (European Directorate for the Quality of Medicines in the Council of Europe)
 - Japanese Pharmacopoeia (Ministry of Health, Labour and Welfare)



Pharmacopeial Discussion Group (PDG)

- PDG meets twice yearly to work on pharmacopeial harmonization topics.
 - June 2009, Yokohama, Japan
 - October 2009, St. Louis, MO, USA
- In May 2001, PDG welcomed the World Health Organization as an observer.
- While not part of the International Conference on Harmonization (ICH), PDG usually meets in conjunction with ICH and provides the ICH Steering Committee with reports of its progress.



Definition of Harmonization

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.

Harmonized by Attributes: If a monograph or general chapter is not completely harmonized with the corresponding texts of the *Japanese Pharmacopoeia* and the *European Pharmacopoeia*, it is considered to be harmonized by attributes.



Stages of PDG Harmonization

- ◆ Stage 1 Identification
- ◆ Stage 2 Investigation
- ◆ Stage 3 Proposal for Expert Committee Review
- ◆ Stage 4 Official Inquiry
- ◆ Stage 5A Provisional Consensus
- ◆ Stage 5B Sign-off

- ◆ Stage 6
- ◆ Stage 6A Regional Adoption
- ◆ Stage 6B Implementation (in each Pharmacopoeia)
- ◆ Stage 6C Indication of Harmonization
- ◆ Stage 7 Inter-Regional Acceptance



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.



Stages of PDG Harmonization (5)

- **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.



PDG Stages 1-5



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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.



Stages of PDG Harmonization (7)

- 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 EWG.



PDG Stages 6-7



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Carboxymethylcellulose Calcium (Case study)

<u>USP Monograph</u>	<u>JP Monograph</u>	<u>EP Monograph</u>	<u>Harmonized Monograph</u>
Total Tests = 13	Total Tests = 13	Total Tests = 11	Total Tests = 10
Identification A	Identification A	Identification A	Identification A
Identification B	Identification B	Identification B	Identification B
Identification C	Identification C	Identification C	Identification C
Identification D	Identification D	Identification D	Identification D
Alkalinity	Alkali	Alkalinity	Alkalinity
Chloride	Chloride	Chlorides	Chloride
Sulfate	Sulfate	Sulphates	Sulfate
Silicate	Silicate	Silica	
Heavy Metals	Heavy Metals	Heavy Metals	Heavy Metals
	Arsenic		
Starch	Starch		
Loss on Drying	Loss on Drying	Loss on Drying	Loss on Drying
Residue on Ignition	Residue on Ignition	Sulphated Ash	Residue on Ignition
Organic Volatile Impurities			

GLOBAL Marketing test requirements = 37 without harmonization ; 10 with harmonization.



Carboxymethylcellulose Calcium (Case study)

<u>Test</u>	<u>USP Monograph</u>	<u>JP Monograph</u>	<u>EP Monograph</u>	<u>Harmonized Monograph</u>
Identification	Identical	Identical	Identical	Identical
Alkalinity	Identical	Identical	Identical	Identical
Loss on drying	105C	105C	100 - 105C	105C
Residue on ignition	450 - 550C	450 to 550C	600 +/- 50C	450 - 550C
Chloride	0.36%	0.36%	0.5%	0.36%
Sulfate	0.96%	0.96%	1%	1.0%
Heavy Metals	Non-Harmonized	Non-Harmonized	Non-Harmonized	Non-Harmonized



Signed Off Monographs (40 out of 63 as of Yokohama, June 2009)

- Alcohol
- Alcohol Dehydrated
- Benzyl Alcohol
- Calcium Disodium Edetate
- Calcium Phosphate Dibasic
- Calcium Phosphate Dibasic (Anhydrous)
- Carboxymethylcellulose
- Carboxymethylcellulose Calcium
- Croscarmellose Sodium
- Cellulose, Microcrystalline
- Cellulose, Powdered
- Cellulose Acetate
- Cellulose Acetate Phthalate
- Citric Acid, Anhydrous
- Citric Acid, Monohydrate
- Ethylcellulose
- Hypromellose
- Hypromellose Phthalate
- Lactose, Anhydrous
- Lactose Monohydrate
- Magnesium Stearate
- 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



Signed Off General Chapters (26 out of 34 as of Yokohama, June 2009)

- Analytical Sieving
- Bulk Density and Tapped Density
- Gas Pycnometric Density of Solids
- Powder Flow
- Tablet Friability
- Optical Microscopy
- Powder Fineness
- Specific Surface Area
- Porosimetry by Mercury Intrusion
- X-Ray powder diffraction
- Amino acid determination
- Capillary electrophoresis
- Isoelectric focusing
- Protein determination
- Peptide mapping
- Polyacrylamide Gel Electrophoresis
- Extractable Volume
- Residue on Ignition
- Particulate Matter
- Sterility
- Dissolution
- Disintegration
- Uniformity of Content/Mass
- Microbial Contamination
- Laser Diffraction
- Measurement of Particle Size
- Bacterial Endotoxins



Current Status of PDG Harmonization (June 2009)

	Signed-off	Ongoing
Q6A General Chapters	9	1
General Chapters	11	7
Methods for Biotech Products	6	-
Excipients	40	23

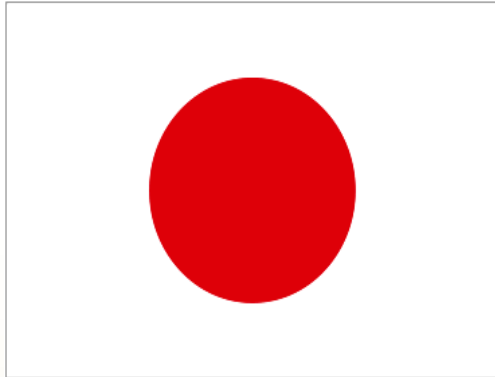


Interaction of PDG with ICH Q4B EWG

- November 2003: ICH SC established Q4 EWG to address **11 Compendial General Test Chapters** discussed during development of ICH Q6A Guideline
 - Harmonization of these 11 Chapters essential to obtain full utility of the ICH Q6A guideline.
- November 2008, ICH SC expanded the scope of Q4B EWG to address 5 additional Compendial General Test Chapters:
 - Analytical Sieving, Bulk and Tapped Density, Tablet Friability, Capillary Electrophoresis, Polyacrylamide Gel Electrophoresis.
- PDG has taken the responsibility to submit completed harmonized packages to ICH Q4B EWG



The Pharmacopoeias and the Regulators: Different Approaches for Moving Forward



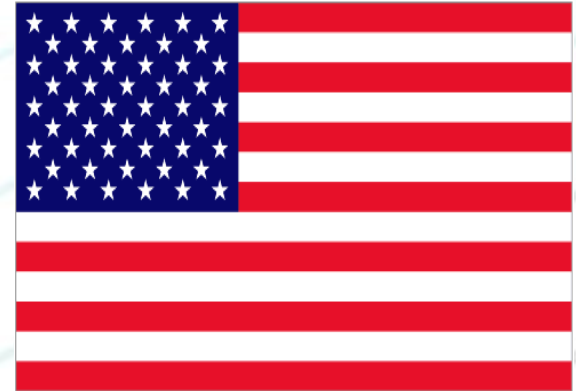
JP
(PMDA)

Governmental



Ph. Eur.
(EDQM)

Governmental



USP

Independent of
Government



QUALITY STANDARDS FOR MEDICINES, SUPPLEMENTS, AND FOOD INGREDIENTS THROUGHOUT THE WORLD

Q4B Process Steps

- PDG provides Q4B EWG:
 - PDG-harmonized text
 - JP/Ph. Eur./USP draft version of how harmonized text will be implemented in their compendia
 - Briefing note highlighting any local differences or potential issues
 - Anticipated timeline to move each pharmacopeia to official status
- Q4B members bring the documents back to their constituents for independent evaluation



Q4B Process (continued)

- Q4B EWG reviews the evaluations
- Conveyed back to and/or discussed with PDG
- Once issues are resolved, Q4B EWG recommends approval (ICH Step 2) to the ICH SC
- Start of Annex process



PDG vs. ICH Harmonization Processes

PDG

ICH Q4B

PDG Document Submission

Step 1: Q4B EWG assessment and annex development

Regional pharmacopeial implementation

Step 2: ICH Sign off on draft Q4B annex

Step 3: Regulatory Consultation on annex

Step 4: Annex adopted by ICH Steering Committee

Inter-regional Acceptance

Step 5: Regional regulatory implementation



Current Q4B Step of Harmonized General Chapters under Q4B Evaluation

Extractable Volume	Step 5
Residue on Ignition – Rev. 2	Step 5
Particulate Matter – Rev. 1	Step 5
Sterility	Step 4
Dissolution	Step 3
Disintegration	Step 4
Uniformity of Mass/Content	At PDG
Microbial Contamination	Step 5
Sterility- Rev.1	Step 4
Tablet Friability	Step 2
Polyacrylamide Gel Electrophoresis	Step 2
Capillary Electrophoresis	Step 1
Analytical Sieving	Step 1
Bacterial Endotoxins (Rev.1)	At PDG
Bulk and Tapped Density	At PDG
Color (instrumental measurement)*	At PDG

*Not yet been harmonized by PDG (Stage 3)



Future USP Compendial activities related to PDG

- Continue to add new items to the current Harmonization list of 63 excipient monographs and 34 General chapters related to Excipients (exclusive of General methods relevant to Q6A)
- Commitment within PDG to work on excipients and chapters already harmonized to determine Indication of Harmonization status (Stage 6C)
- Update and modernize PDG procedures to help perform harmonization activities with greater efficiency.



PDG Achievements from St. Louis (October 2009)

- Sign-Off on new chapter for Water-Solids Interaction and revisions to Polysorbate 80 and Ethylcellulose
- Review of Indication of Harmonization status for Sodium Chloride, Potato Starch, Wheat Starch, Saccharin, and Sodium Saccharin.
- Concept Paper for Viscosity Testing as it relates to mandatory ID testing was presented.
- Approaches to DEG/EG adulteration were presented.
- Discussion of harmonization of metal impurities through PDG and formation of a new ICH Expert Working Group





Thank You
