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Residual Solvents USP History

USP/PDA Joint Conference: Residual Solvents

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Outline

- **OVI**s
- **ICH**
 - Q6A
 - Q3A, Q3B
 - Q3C
- **Residual Solvents**
 - Sources
 - Implementation History
- **Basics**
 - Three components
 - ◆ General Notices, Monograph, General Chapter
 - The “Twos”
 - ◆ Procedures
 - ◆ Options
 - ◆ Solubilities (water-soluble, not water-soluble)
 - One approach for all monographs

Organic Volatile Impurities

- **Proposed in PF 14(2)(1988)**
- **Solvents found in a final dosage form**
- **Limits to 7 solvents**
 - Benzene
 - 1,4-Dioxane
 - Chloroform
 - Methylene Chloride
 - Ethylene Oxide
 - Tetrahydrofuran
 - Trichloroethylene
- **Acceptance criteria based on relative toxicity**
- **Applied only to Drug Substances and some excipients**

ICH Revolution

- **Q6A – Impurities – Universal test**
- **Q3A and Q3B**
 - Organic impurities
 - Inorganic impurities
 - Residual solvents
- **Q3C**
 - Acceptance criteria based on risk
 - Testing options
 - Compliance in final dosage form only

Residual Solvents Testing – c. 2002

- **ICH provides**
 - Excellent risk-based acceptance criteria
 - Innovative and insightful calculation methods
 - Decision trees
- **ICH excludes**
 - Procedures
 - Older products
- **Ph. Eur. provides**
 - Standard analytical procedures
 - Model of application to products
- **Ph. Eur. excludes**
 - Application in monograph
 - Class 3 procedures

Residual Solvents <467>

- **Primary criteria**
 - Includes ICH concepts and acceptance criteria
 - Provides clear procedures
 - In harmony with existing standards
 - Slow, deliberate implementation
- **Implementation strategy**
 - General Chapters <467> change
 - Eliminate old “Methods”
 - General Notices requirement
 - Eliminate monograph specific references
 - Ensure broad understanding
 - ♦ Training
 - ♦ Call to <467> in all articles

USP Documentary Standards

- **Three critical components**
 - Monograph for each article
 - General Chapter for common tests
 - General Notices for default conditions and expectations

- **Residual solvents application**
 - General Chapter – common approach – 2 procedures – one decision tree
 - General Notices – application to all articles

Residual Solvents Timeline

- **Chapter and General Notices Change**
 - Proposed in 29(4)
- **Chapter Revision to <467>**
 - *USP 28* - official in January 2005
- **General Notices Revision**
 - Added to *2nd Supplement of USP 28*
 - Delayed-implementation date - *Jan 2007*
- **Monograph Changes**
 - Notice of Retraction included in USP 29

Subsequent Activity

- **Request by GPHA**
 - Supportive of General Notices requirement
 - Requested extension of implementation date
- **Presentation at NJPQCA**
 - Many Questions, Most Technical
- **Increasing number of clarification contacts**
- **Implementation date Extended from 1-1-2007 to 7-1-2007**
 - Appeared in PF 32(4) as immediate IRA

USP 28-NF 23 General Notices text

- **Residual solvents** – The requirements are stated in *Organic Volatile Impurities* <467> together with information in *Impurities in Official Articles* <1086>. **Thus all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual monograph.** The requirements have been aligned with the ICH guideline on this topic. If solvents are used during production, they are of suitable quality. In addition, the toxicity and residual level of each solvent are taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in *Organic Volatile Impurities* <467>, using the general methods presented therein or other suitable methods. (Official January 1, 2007)
(Official July 1, 2007)

Chapter <467> Highlights

- **Two Procedures**
 - Procedure A – GC
 - Procedure B – GC
 - Orthogonal procedures
 - Co-elution known
 - Procedure C = Procedure A or B (Quantitatively)
- **Two Options**
 - Option 1 – Final dosage form sampling
 - Option 2 – Summation
- **Water Soluble and Insoluble**



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Thank You

