Pharmaceutical Manufacturer Perspective - GPhA

Residual Solvents—Implementation of USP Requirements

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Common Goal

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Safe and effective products!!!

"***Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements***"*

*"ICH Q3C – Impurities: Guideline for Residual Solvents"

Purpose of Guideline

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- Recommend acceptable Residual Solvent use for:
  - API's
  - Excipients
  - Dosage Forms

- Recommend Residual Solvent levels for:
  - Pharmaceutical Dosage Forms
    - PDE (permitted daily exposure)
    - Acceptable limit depends on solvent classification

Practical Approach

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- Residual solvents cannot be completely eliminated from products.
- Manufacturers need to ensure the benefits of our products outweigh the risks of having solvents present.
  - Risk Based Approach – cGMP's for 21st Century
- How can industry, FDA, and USP work together to accomplish this?

Remove Residual Solvent Requirement from Monographs

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- Patient receives final dosage form only.
- Interpretation by industry that if test exists in monograph, a laboratory result must be generated.
  - Overly burdensome testing may result
  - Additional methods/validation submitted to FDA
- Will suppliers comply or remove USP/NF labeling?

USP has retracted this requirement until further comment/review is completed.

Maintain Compliance via General Notices and General Chapter

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- Safe products.

- Responsibility of manufacturer to determine best way to comply.
  - No need to test if solvents are not “likely to be present”
  - Important for suppliers to disclose solvents
  - Quantitative or Limit test
  - Consistent with risk-based approach

Changes proposed to <467> in Sept/Oct 2006 Pharmacopeial Forum are consistent with this approach.

Exempt Material

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- Dosage Forms
  - Not all are ingested or injected
  - Total Daily Intake for Topicals
- Excipients
  - Compounds that have long standing safe and effective use outside of pharmaceutical industry
  - Dextrose, NaCl, Mannitol

Communication

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- Necessary to have clear understanding of all parties as to requirements and expectations.

- Recommend USP stress that testing is not needed if knowledge exists that solvents are not present.

Reality Check

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- Office of Generic Drugs states that residual solvents questions are one of the leading deficiency comments in ANDA's.

Informal survey of GPhA:

- ~50% of ANDA's received at least one deficiency letter including a comment regarding residual solvents.
- Nearly all of these products followed ICH guidance requirements at initial submission.
- Why the disparity?

Discussion Points

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- Are ICH levels acceptable “as is” or are they “a starting point”?
- Are Limit Tests acceptable or must every test be Quantitative?
- Is Loss on Drying acceptable for Class 3 solvents?
- How will FDA apply and implement USP requirements going forward?
  - Approved applications
  - Products in development

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Thank You

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