PQRI Workshop: Leachables and Extractables

Rockville, Maryland
December 5-6, 2005

Best Practices Recommendation: Regulatory Science Strategies

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Outline

- Definitions
- Sources/types of leachables/extractables
- Quality by design considerations for CCS
- Strategies for extractables studies and methods
- Leachables/extractables correlation
- Next steps-PQRI process
- Summary

Definitions

- **CCS:** The sum of packaging components that contain, protect, meter, and deliver the dosage form. It also includes
  - Primary and secondary packaging components if the latter are intended to provide additional protection, e.g., foil overwrap
  - Associated accessories (e.g., integrated spacer, dose counter)

Definitions

- **Critical Components of CCS:** Components that contact either the patient (i.e., mouth, nasal mucosa) or the formulation, components that affect the mechanics of the overall performance of the drug product, or any secondary protective packaging
- **Drug product:** The finished dosage form and the CCS intended for marketing

Definitions

- **Extractables:** Compounds that can be extracted from elastomeric and plastic components, coatings of, and residues on a CCS component when in the presence of appropriate solvent(s) and under stressed extraction conditions
- **Leachables:** Compounds that migrate into the formulation from elastomeric, plastic, or coating of a CCS component. Leachables also include contaminants from processing aids (e.g., lubricants, cleaning and washing agents) used during fabrication/processing of CCS components or manufacture of the drug product

Drug Products of Concern

- Inhalation drug products (e.g., MDIs, DPIs, Inhalation Sprays, Solutions, and Suspensions)
- Nasal drug products
- Parenteral drug products (e.g.,SVPs/LVPs/PBPs)
- Ophthalmic drug products
- Oral non-solid drug products

Sources of L&E

- CCS components: direct or indirect, e.g., containers, closures, valve components, blisters, delivery units, tubing, labels, inks, adhesives, lacquers, coatings on inner surface of containers/valves, overwraps, cardboard boxes
- Chemicals employed as additives to CCS components and base polymers
- Processing aids (CCS/DP) and CCS surface treatment and washing/cleaning materials
- Environment (for leachables)

Types of L&E

- Monomeric units, oligomeric fragments
- Chemicals used as primary additives in elastomers and plastic components (e.g., antioxidants, plasticizers, lubricants, vulcanization accelerators, catalysts, filler contaminants, retarders, UV stabilizers, pigments)
- Trace levels in additives, e.g., PNAs, N-nitrosamines, mercaptobenzothiazole
- Components of processing aids (e.g., lubricants, mould release, antistatic, and antislip agents) and cleaning and washing agents
- Environmental contaminants

Quality by Design Strategies (1)

- Having clear scientific rationales for choices of CCS materials and components
- Designing the components and being aware of related processes up front through use of
  - First principles
  - Prior knowledge of materials/components
  - Semi-empirical relationships for understanding
  - Sponsor-suppliers close collaboration

Quality by Design Strategies (2)

- Developing information on each material/component and assessing their significance (e.g., composition, types of additives, polymerization/fabrication processes, processing aids, cleaning and washing agents and associated processes)
- Having capability of predicting extractables/leachables
- Understanding the science (chem/physics) of the materials involved
- Identifying and verifying physico-chemical and mechanical properties

Quality by Design Strategies (3)

- Feed knowledge forward-backward
  - Parties should have the information they need when they need it- to avoid surprises
  - Optimize CCS materials/components (Q/Q) in collaboration with CCS suppliers to modify composition/processing and minimize Ls/Es
  - Transform data from all sources into knowledge for critical decisions
  - Consider steps to decrease/minimize variability
  - Establish relevant controls upstream

Quality by Design Strategies (4)

- Designing, developing, and conducting at early stages of drug development appropriate
  - Extraction and leachable studies
  - Reliable analytical methods
- Developing a systematic process through knowledge (composition, processes) for detection, identification, and quantification (D/I/Q) of potential extractables/leachables
- Assessing compatibility of the CCS components with formulation components and drug product manufacturing processes

Quality by Design Strategies (5)

- Scientific understanding at early drug development stage could facilitate
  - Leveraging available information (material, component, process)
    - Design of extraction/leachable studies
    - Selection of extraction techniques,
    - Development of appropriate analytical methods
  - Defining a framework for potential design space
  - Development/assessment toxicity (qualification approaches)

Quality by Design Strategies (6)

- Scientific understanding at early drug development stage could facilitate
  - Risk based regulatory decisions for materials and components-risk identification, analysis, assessment and management
  - Timely initiation of additional qualification studies or minor modifications of the CCS materials/components, if necessary, for timely submission of application
  - Continuous improvements of the CCS within the design space
  - Development of more flexible regulatory approaches

Extractables Studies Strategy (1)

- Multiple/complementary and effective (vigorous) extraction techniques (e.g., reflux) without altering the qualitative and/or quantitative nature of the extractable profile
- Appropriate multiple solvent systems of varying properties for comprehensive extractable profile
- Representative lots of componentry (e.g., base polymer, component)

Extractables Studies Strategy(2)

- Multiple component surface area to solvent ratios
- Variable duration of extraction (profile)
- Technically justified and optimized extraction profile (Q/Q), preferably exceeding that of leachables profile (long-term/accelerated studies)
- Achievement of asymptotic levels

Extractables Studies Strategy(3)

- Multiple analytical techniques (D/I/Q) to ensure complete evaluation of extractables profile
- Comprehensive, systematic approach for identification of individual extractables
- Means of comparison with suppliers' reliable information
- Relationship between extractables data and supplier information
  - Strategy for discrepancy and appropriate actions

Analytical Method Considerations (1)

- Complex mixtures
- High efficiency separation techniques
- Capability of D/I/Q of expected extractables and leachables (based on knowledge, composition, processing)
- Sample preparation strategy for profile analysis (e.g., analytical technique, solvent selection, recovery/loss studies, interferences and obscuration of peaks)

Analytical Method Considerations (2)

- Qualitative and quantitative analysis approaches including:
  - Combination of appropriate/complementary methods, procedures
  - Compound specific detection and quantification
  - Scientific rationale for use of relevant response factors
  - Validated methods, ICH Q2A and Q2B

L&E Correlation (1)

- Valid correlation between L & E with established safety factors may obviate the need to monitor leachables in the drug product formulation in routine studies
  - Periodic testing of leachables may be appropriate
- Established acceptance criteria for leachables still should be included in the drug product specifications even if they are controlled as extractables in incoming materials/components

L&E Correlation Strategy (2)

- Extraction study conditions (ESC) should have the ability to generate an extractable profile that includes all compounds observed in the leachables profile obtained through shelf-life of the drug product at regular time points for analysis
- ESC should be demonstrated to appropriately achieve an equilibrium level (asymptotic) for each extractable and each extractable should exceed the level of compound leached into the drug product formulation during the proposed shelf-life

L&E Correlation Strategy(3)

- Extraction media, conditions, and procedures may need to be more effective than the formulation vehicle
- Extractables studies preferably should be performed with batches of CCS components used in the drug product leachables studies
- Validated multiple/complementary analytical techniques and procedures should be developed and utilized for leachables and in systematic stability studies

Pharmaceutical Quality Research Institute

PQRI Article I: Purpose

- Charitable, educational, and scientific
- A forum for academia, industry, and FDA to work cooperatively to conduct pharmaceutical quality research and to support development of public standards

Pharmaceutical Quality Research Institute

PQRI Article VIII: Recommendation to FDA (1)

- Once a project is completed by the WG*, the outcome will be presented by the TC* to the PQRI SC* for dissemination to FDA and the public
- If a vote is required FDA representative will not vote
- SC will forward recommendations and related research data to FDA

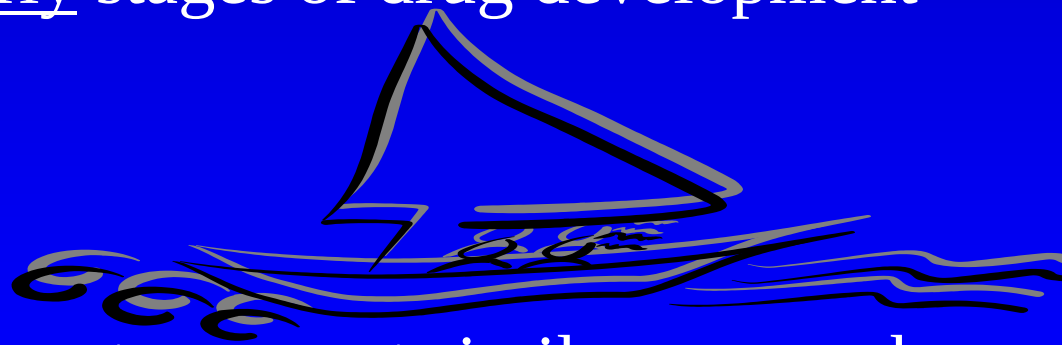
- *WG- Working Group; TC- Technical Committee; ST- Steering Committee

Pharmaceutical Quality Research Institute
PQRI Article VIII: Recommendation to FDA (2)

- FDA is not obligated to implement policy based on Institute information/recommendation (I/R) and may accept or reject any I/R at its discretion
- FDA has the sole statutory responsibilities for developing regulatory policy and guidance and may not delegate this responsibility

Summary

- Define expectations early
- Understand and apply the science involved
- Select appropriate CCS materials and components
- Apply appropriate upstream controls
- Communicate, collaborate, and feed knowledge forward backward starting in early stages of drug development
  - Within company
  - With suppliers
  - With regulatory bodies
- PQRI WG proposal seems to support similar approach



Thank You