Extractables and Leachables: Challenges in Orally Inhaled and Nasal Drug Products

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Overview

- Importance of L&E testing
- Challenges of L&E testing in OINDP
- Industry initiatives leading up to PQRI effort
- PQRI L&E effort
- Looking Ahead
IMPORTANCE
Importance of a Rationalized Approach to L&E Testing

• Both industry and regulators have long known the importance of extraction studies and leachables testing for consumer products

• Example: nitrosamines in baby bottle nipples. FDA action limit of 10 ppb
Importance of a Rationalized Approach to L&E Testing in OINDP

- Potential consequences for patient safety
  - Sensitive target delivery site
    - Lung and nasal mucosa
- Large and diverse body of suppliers that provide a variety of materials and components to the industry
CHALLENGES
Challenges of L&E Testing in OINDP

- Numerous potential sources of leachables
  - Primary packaging
  - Secondary packaging
  - Labels and adhesives
  - Inks and colorings
  - Etc!!
Challenges of L&E Testing in OINDP

• Variety of plastic, elastomer, etc. components in contact with formulation
  – Container
  – Valve
  – O-rings
  – Gasket
Challenges of L&E Testing in OINDP

• Great variety of OINDP
  – Testing approaches must take into account material contact with variety of environments
Challenges of L&E Testing in OINDP

• Depending on drug product, potential for several hundreds of extractable and leachable compounds at trace levels

• Supply of a variety of materials from variety of suppliers must be controlled for quality
Challenges of L&E Testing in OINDP

• Potential for observation of leachables depends on drug product type
  – Relatively strong solvents (CFC, HFC, some alcohol, e.g., MDIs)
  – Weak solvents (water, e.g., nasal sprays, inhaled insulin)
  – No solvents (powders, e.g., DPIs)
Example: Elements of a DPI
Example: Elements of an MDI

Physical Components
- Metal Can
- Elastomers
- Valve
- Actuator

Formulation
- Drug substance
- Propellants
- Surfactants
- Co-solvents
Potential for Large Number of Compounds at Trace Levels

GC/MS extractables profile of elastomer
INDUSTRY INITIATIVES
PRE-PQRI
Impetus for a Collaborative Effort

• Given these challenges, industry and regulators can benefit greatly from a rationalized approach to L&E testing in OINDP, incorporating:

  – Thresholds
  – Understanding of best practices
  – Clear process for L&E testing in pharmaceutical development
Impetus for a Collaborative Effort

- Issuance of 1998 FDA draft guidances for OINDP provided forum for discussion among industry
  - Industry commented collectively on guidances
  - Industry collaborated to produce Points to Consider document on OINDP
Points to Consider

• IPAC-RS in collaboration with AAPS/ITFG:
  – Conducted confidential surveys of pharma industry and suppliers
  – Developed and submitted to FDA

Leachables and Extractables Testing: Points to Consider in 2001

• Points to Consider provided basis for proposal to PQRI
Points to Consider

• Noted that constant improvement of detection/characterization technology leads to detection of compounds at increasingly low levels

• Proposed a rationale for safety and analytical thresholds for leachables and extractables in OINDP
  – Safety qualification threshold of 5 µg total daily intake
  – “Reporting” threshold of 0.2 µg total daily intake
Points to Consider

• Outlined industry practices for conducting leachables and extractables studies
• Publicly available
PQRI L&E
Proposal to PQRI

• IPAC-RS developed and submitted L&E proposal to PQRI
  – Investigate development of analytical and safety thresholds for leachables and extractables in OINDP
  – Investigate and determine approaches to leachables and extractables testing in the pharmaceutical development process for OINDP
"...serve as a forum for academia, industry and FDA to work cooperatively to conduct pharmaceutical product quality research and to support development of public standards..."
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Formation of L&E Working Group

- L&E Project accepted into PQRI in 2001
- Working Group formed and work commenced in late 2001
- Working Group members include scientists from FDA, industry and academia
Highlights of PQRI Processes

• Opportunity to collect raw data through independent experiments/studies, or through data-mining

• Scrutiny of data by scientists from diverse backgrounds

• Discussion of data outside of NDA process
Looking Ahead

• FDA and industry are entering a new phase which will apply principles such as “Quality by Design” and “Risk Management”

• The L&E effort supports these approaches

• PQRI looks forward to supporting FDA in its new initiatives
Thank You

Questions??