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

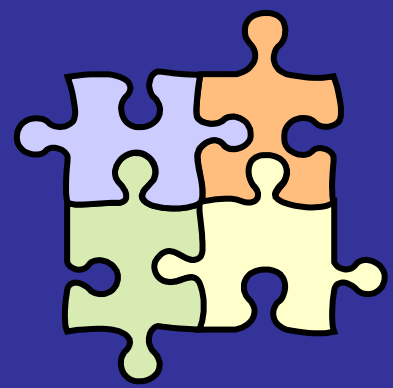
CHALLENGES

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

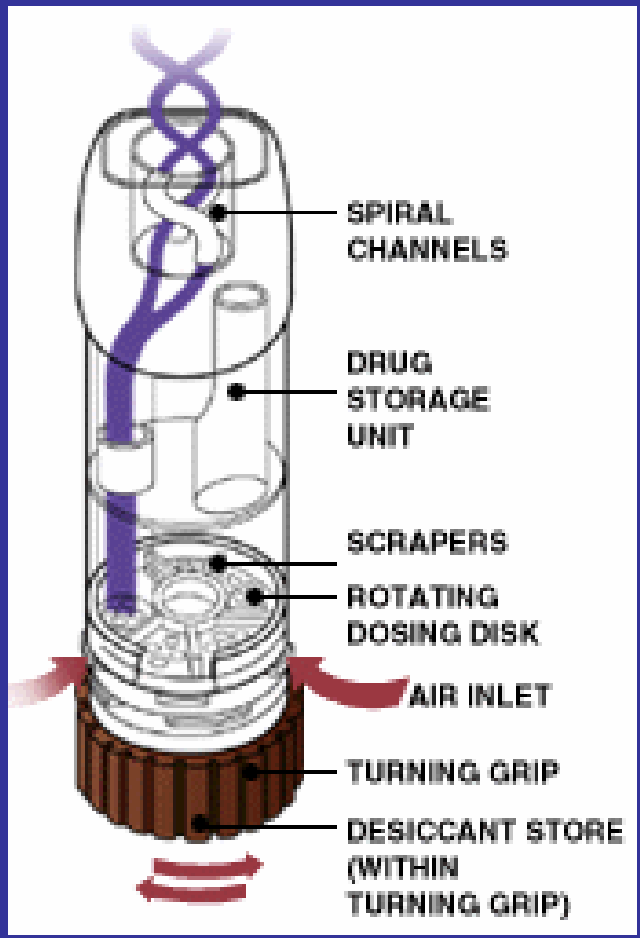
Challenges of L&E Testing in OINDP

- 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

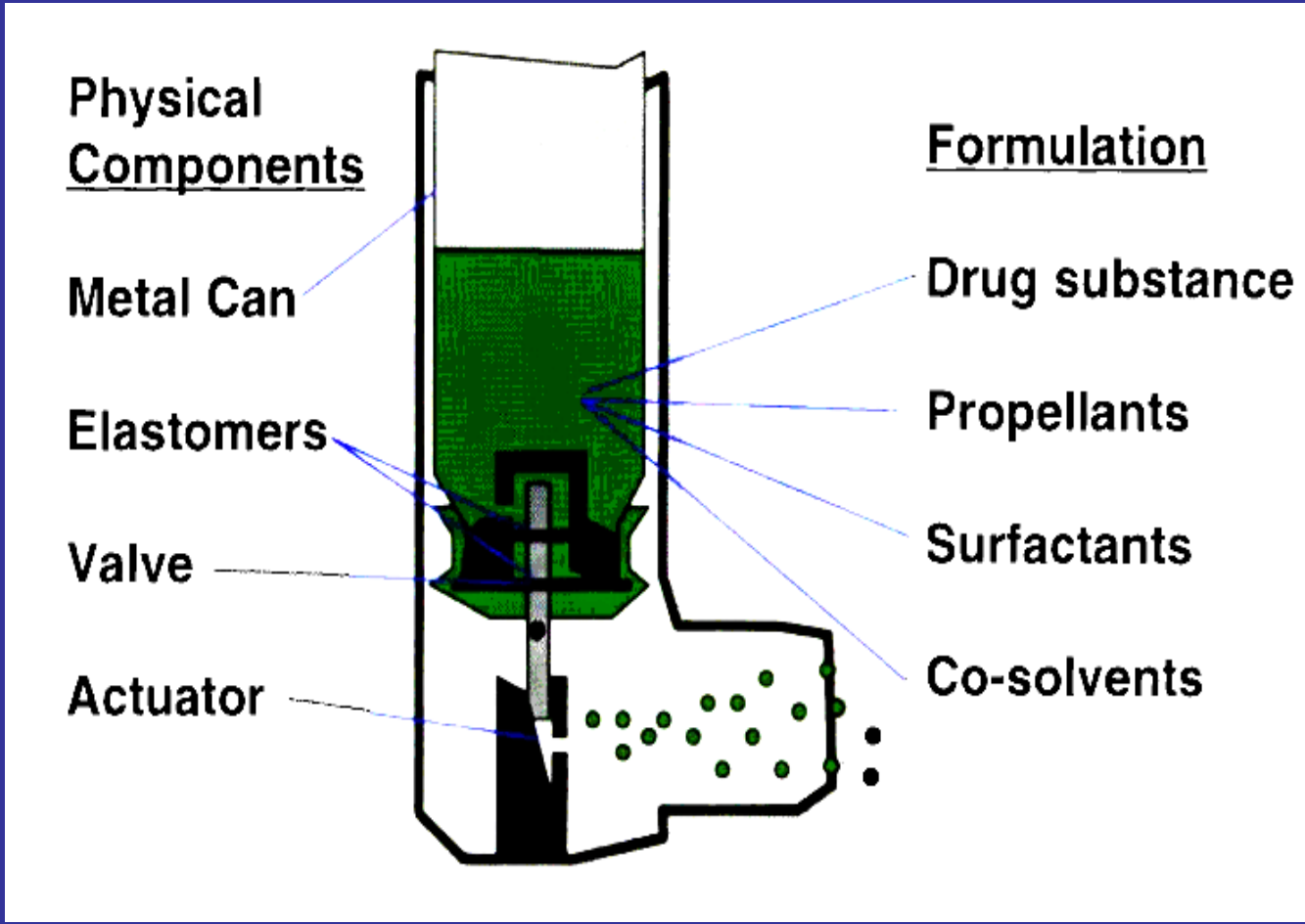
Challenges of L&E Testing in OINDP

- 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)

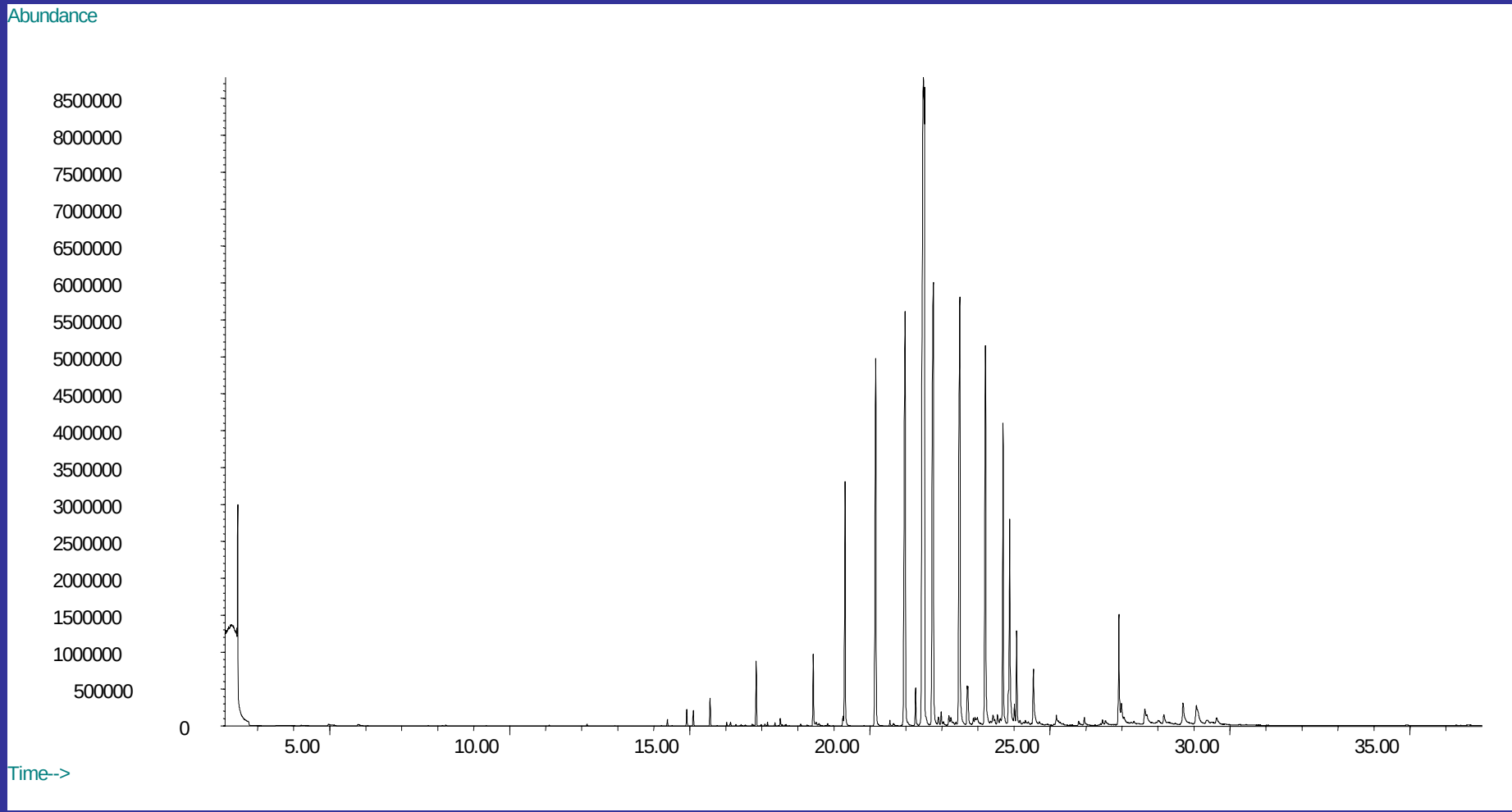
Example: Elements of a DPI



Example: Elements of an MDI



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

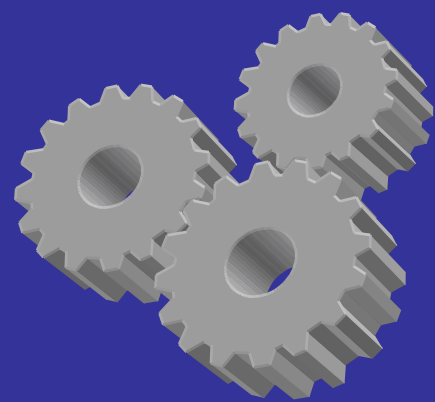
PQRI L&E

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

PQRI

"…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..."



PQRI Membership

- AAPS
- BIO
- CHPA
- FDA
- GPhA
- IPAC-RS
- IPEC
- ISPE
- PDA
- PhRMA
- USP

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??