Significance of Leachables and Extractables to Pharmaceutical Quality

Gordon Hansen, MS
Vice President Analytical Development
Ridgefield
Boehringer Ingelheim Pharmaceuticals, Inc.
Presentation Outline

• The early days of OINDP
  – Historical perspective from FDA
  – Industry/supplier uncertainty
• CFC replacement and IPAC
  – An opportunity for change
• Initial regulatory guidance
• IPAC-RS and PQRI
  – Removing uncertainty
  – Controlling the supply-chain
• Future possibilities
What are OINDP?

- Metered Dose Inhalers
- Dry Powder Inhalers
- Inhalation Solutions
- Inhalation Sprays
- Nasal Sprays

MDI Schematic Provided by Bespak Europe
What Mattered in the “Good Old Days”

• Container closure system component selection was based on:
  – Performance of the component relative to standard parameters (dose delivery, shot weight, etc.)
  – Price and availability ($$$$$$$$$$$$$$)
  – (Not necessarily in that order)
• “Off-the-shelf” components were typically selected and used.
• Supplier interactions were rudimentary.
• Change-control was not really a significant issue.
Risk or History – L&E in OINDP


• Evolutionary process for L/E
  – Problems observed in specific drug products
  – Increasing knowledge about materials and manufacturing processes
  – Data based
Risk or History – L&E in OINDP (continued)

- How did the importance of various Leachables/Extractables come to the attention of the FDA?
  - Reports of PNAs in elastomers
  - PNAs in MDIs
  - Nitrosamines in elastomers
  - 2-mercaptobenzothiazole (2-MBT) in elastomers
  - Other classes of L/Es
Leachables in a Metered Dose Inhaler Drug Product

canister
drug product formulation
dose metering valve

actuator/mouthpiece

drug product (and leachables) delivered to patient

aerosol plume
Industry/Supplier Uncertainty

• How should extractables/leachables be characterized?
• How low do you go with such characterizations?
• How should extractables/leachables be qualified?
• How should extractables/leachables be controlled?
• How should OINDP manufacturers interact with component suppliers to:
  – Minimize and control component extractables;
  – Remove bad actors (e.g., PAHs and nitrosamines);
  – Deal with change-control;
  – Secure the supply-chain?
Scientists have found that when CFCs get into the upper regions of the earth's atmosphere (stratosphere), they reduce the amount of ozone in the ozone layer that surrounds the earth, increasing the risk of potentially serious health problems, such as skin cancer and cataracts, as well as other health and environmental problems (http://www.ipacmdi.com/).

To lower the risk of health and environmental problems caused by ozone depletion and to help restore the ozone layer, most countries have agreed to stop using CFCs. The agreement was made in 1987 and is known as the Montreal Protocol (http://www.ipacmdi.com/).

The International Pharmaceutical Aerosol Consortium (IPAC) formed in 1989 to address regulatory consequences for MDIs of the Montreal Protocol, and to help manage the CFC transition to alternative propellants (i.e., HFAs) and other OINDP forms.
Note that the timing of the Montreal Protocol and the formation of IPAC coincided with the period of heightened concern regarding E/L.

Industry responses to both E/L concern and the CFC transition included:

- Initiation of research programs to characterize E/L related to MDIs under development.
- Consideration of strategies to create “cleaner” MDI container closure system components.
- Development of newer OINDP to minimize E/L and replace MDIs (e.g., DPIs).
- Begin to work more closely with component suppliers to engineer improved components and processes.
MDI Component Initial Improvements

• Prewashing (pre-extraction) of MDI valve rubber components.

• Improved degreasing processes for MDI aluminum and stainless steel canisters.

• “Custom-designed” MDI valve components (rubber/plastic/metal) with optimized curing processes and additive packages.
An Elastomeric Component Extractables Profile from “The Good Old Days”

Lot #79532/#78172 (12/90-4/91)

GC/MS “extractables profile” of an organic solvent extract
Rubber Quality – Then and Now

• Old Rubber:
  – Carbon black fillers (PAHs)
  – Sulfur cured (nitrosamines)
  – Curing processes and additive packages not optimized (excessive levels of additives and curing agents, etc.)
  – Unwashed prior to use

• Newer Rubber:
  – Alternate fillers (no PAHs/lower PAHs)
  – Peroxide cured (no nitrosamines)
  – Curing processes and additive packages optimized. (lower levels of extractables)
  – Washed prior to use
Change is Good!!!!!

New MDI elastomeric valve component

Old MDI elastomeric valve component
Effects of Pre-washing “Process Optimized” MDI Valve Components

- Peroxide cured rubber
- Non-CFC MDI
Effects of Pre-washing “Process Optimized” MDI Valve Components (continued)

- Peroxide cured rubber
- Non-CFC MDI
Effects of Pre-washing “Process Optimized” MDI Valve Components (continued)

Representative GC/TEA Chromatogram of a 3 ng/canister Spiked MDI canister

Target N-nitrosamines

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>uV</th>
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<tbody>
<tr>
<td>0</td>
<td>5600</td>
</tr>
<tr>
<td>10</td>
<td>5600</td>
</tr>
<tr>
<td>20</td>
<td>5600</td>
</tr>
<tr>
<td>30</td>
<td>5600</td>
</tr>
<tr>
<td>40</td>
<td>5600</td>
</tr>
</tbody>
</table>
Effects of Pre-washing “Process Optimized” MDI Valve Components (continued)

Representative GC/TEA Chromatogram of an un-spiked MDI canister
Available FDA Guidances

• Container Closure Systems for Packaging Human Drugs and Biologics; Guidance for Industry; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER); Rockville, MD, May 1999.
  “Packaging Guidance”

• Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products; Draft Guidance for Industry; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Rockville, MD, October 1998.
  “MDI/DPI Guidance”

• Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation; Guidance for Industry; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Rockville, MD, July 2002.
  “Nasal Spray Guidance”
### Table 1. Examples of Packaging Concerns for Common Classes of Drug Products. (1)

<table>
<thead>
<tr>
<th>Degree of Concern Associated with the Route of Administration</th>
<th>Likelihood of Packaging Component-Dosage Form Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>Highest</td>
<td>High</td>
</tr>
<tr>
<td>Highest</td>
<td>Low</td>
</tr>
<tr>
<td>Inhalation Aerosols and Solutions; Injections and Injectable Suspensions&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sterile Powders and Powders for Injection; Inhalation Powders</td>
</tr>
<tr>
<td>Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays</td>
<td>Topical Powders; Oral powders</td>
</tr>
<tr>
<td>Oral Tablets and Oral (Hard and Soft Gelatin) Capsules</td>
<td>Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions</td>
</tr>
</tbody>
</table>

**Notes:**

<sup>a</sup> For the purpose of this table, the term suspension is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.
In 2001, the International Pharmaceutical Aerosol Consortium for Regulation and Science (IPAC-RS) was officially formed as a separate Consortium.

- **IPAC-RS Mission**: To advance consensus-based and scientifically driven standards and regulations for inhaled and nasal drug products (OINDP).

- **IPAC-RS Overall Goal**: Development of scientifically justified regulatory approaches for orally inhaled and nasal drug products.
IPAC/ITFG Collaboration (1999-2001)

STEERING COMMITTEE

TECHNICAL TEAMS

CMC TESTS AND METHODS
- CMC SPECIFICATIONS
  - DCU WG
  - PSD WG

CMC SUPPLIER QUALITY CONTROL

CMC LEACHABLES & EXTRACTABLES
- TOXICOLOGY WG

BA/BE IN VITRO AND IN VIVO TESTS

CMC Leachables and Extractables Technical Team
Team Overview of Draft CMC Guidances: (MDI/DPI and Nasal Spray)

- Team supported efforts of Agency in drafting guidance documents which address requirements for leachables and extractables for orally inhaled and nasal drug products.

- Team believed that current draft Guidances could be enhanced by clarification in specific areas.

- Team identified key areas of draft Guidances which would benefit from further investigation and dialogue with Agency.
Key Issues and Process:

• *What are appropriate reporting/identification/qualification thresholds for leachables & extractables?*

• *How is a correlation between leachables and extractables established?*

• *What are appropriate practices for establishing safety of leachables?*

• *Is extractables profiling appropriate for control of component composition?*

• *Which critical components should be subject to routine extractables testing?*

- Collected drug product specific leachables and extractables data in order to investigate the concept of correlation

- Formed toxicology WG to address toxicology issues for leachables

- Investigated current supplier practices for control of component composition and extractables profiles
Submitted *Points to Consider* (March 2001) technical paper to the Agency, which proposed:

- Alternate language for the draft Guidances, which clarifies the requirements for leachables and extractables studies
- Reporting and qualification thresholds for leachables
- A leachables qualification process
- Result: A PQRI proposal from IPAC-RS
What is PQRI?

- **Product Quality Research Institute**
- Not-for-profit, non-stock, tax-exempt entity incorporated in Virginia
- Serves as a forum for academia, industry and FDA to work cooperatively
- PODP Leachables and Extractables Working Group currently in operation
Highlights of PQRI Process

• 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
History of PQRI OINDP Leachables and Extractables Working Group

- Proposal to develop thresholds and examine best practices for L&E in OINDP drafted by IPAC-RS and submitted to PQRI
- Working Group formed in 2001, consisting of chemists and toxicologists from FDA, industry and academia
- Working Group developed a hypothesis and step-wise plan to investigate per established PQRI process
- Workplan approved by PQRI DPTC and Steering Committee in 2002
- Toxicologists and chemists formed sub-groups
History of PQRI OINDP Leachables and Extractables Working Group

- Toxicologists: acquired data through extensive literature and database searches and analyses
- Chemists: acquired data by conducting extractions studies and placebo leachables study
- Submitted final to PQRI and FDA in summer 2006
  - Science and data-based recommendations to PQRI and FDA.  Not a policy/regulatory document
Why Produce L&E Recommendations?

- To reduce uncertainty in the pharmaceutical development process for OINDP
- To reduce or eliminate “Horror Stories”
- To support regulatory initiatives, such as Quality-by-Design and Risk Management
Recommendations - Best Practices Overview

- Application of safety thresholds
  - Safety Concern Threshold (SCT)
  - Qualification Threshold (QT)
- Integration of safety expertise into component selection, controlled extraction studies, leachables studies and routine extractables testing
- Analytical/chemistry
  - Selection of components
  - Controlled Extraction Studies
  - Leachables Studies and Routine Extractables Testing
  - The Analytical Evaluation Threshold (AET)
Other Accomplishments of the PQRI OINDP Leachables and Extractables Working Group

• Training courses in the United States, Europe and Canada.
• Peer reviewed publications:
  – Pharmaceutical Research
  – Toxicological Sciences
• A comprehensive book on leachables and extractables (in progress).
• Numerous public scientific presentations and short courses (e.g., EAS).
Additional Quality Challenges

• Working with OINDP container closure system component suppliers to:
  – Understand and secure the supply-chain
  – Ensure consistent component quality
  – Educate all suppliers about the issues faced by OINDP manufacturers, including E/L

• Accomplishing the above while accepting the fact that the OINDP industry represents only a small fraction of business for many suppliers (i.e., Exxon-Mobile, BASF)

• Thinking about the future (Quality-by-Design)
IPAC/ITFG Collaboration (1999-2001)

- STEERING COMMITTEE
- TECHNICAL TEAMS
  - CMC TESTS AND METHODS
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    - BA/BE IN VITRO AND IN VIVO TESTS

CMC Supplier Quality Control Technical Team
Supplier Quality Control Technical Team

- Conducted survey of suppliers to evaluate quality and compliance practices at all stages of component, excipient, raw materials, and active drug substance manufacture
- Received evaluations on 53 supplier companies
- Concluded that no generally accepted cGMP guidelines exist for component supply chains
- Endorsed IPEC guideline for control and cGMP compliance of excipients
- Proposed industry-wide initiative to develop cGMP guideline for component suppliers
Supplier Quality Control Technical Team (continued)

  – Quality Management System
  – Management Responsibility
  – Resource Management
  – Product Realisation
  – Measurement Analysis and Improvement
  – Contamination Control
Other IPAC-RS Initiatives to Address Quality Challenges

• Supplier outreach and education (IPAC-RS Materials Working Group)
  – Supplier forums and workshops
  – Publications
  – International outreach

• Quality-by-Design initiative related to E/L (IPAC-RS Development Paradigm Working Group)
  – Unit operations and laboratory investigations of injection moulding processes for MDI valve components
Conclusions

• The E/L issue was and is a complex and technically challenging one for OINDP manufacturers, component suppliers and regulators.

• Regulatory guidances, pharmaceutical industry initiatives, and industry/regulatory collaborations have served to:
  – Remove uncertainty from the pharmaceutical development process.
  – Educate container closure system suppliers and help secure the supply-chain.
  – Ensure the quality of OINDP.
The Future

• Quality-by-Design
  – Ensure OINDP quality while reducing product testing and facilitating change control processes.

• Safety database for leachables
  – ELSIE (The Extractables Leachables Safety Information Exchange).
  – Facilitate safety qualification of leachables.

• Additional regulatory guidances
  – Potential USP General Chapter on Extractables
Acknowledgements

• IPAC-RS and its various technical teams and working groups

• PQRI and the PQRI OINDP Leachables and Extractables Working Group

• BIPI Ridgefield and BIKG Ingelheim RDD staff

• PQRI PODP Leachables and Extractables Working Group