Elastomers used in Pharmaceutical & Food Contact Applications

Jenny Cooper - Commercial Manager
Dr Martin Forrest – Principal Consultant
Smithers Group Overview

- **6** Unique Businesses
- **620** Worldwide Employees
- **13** Facilities
- **1925** Founded in Akron, OH
- **3** Countries with Operations
The Smithers Group

**SMITHERS**

Plastics, rubber and polymer materials, product and process expertise.

**SMITHERS RAPRA**

Materials and product knowledge focused on the packaging, paper & print supply chain.

**SMITHERS PIRA**

Development, analytical and bioanalytical services for the pharmaceutical & chemical industries.

**SMITHERS AVANZA**

Environmentals sciences supporting product registrations and risk assessments.

**SMITHERS VISCIENT**

Conformity assessments of quality and environmental management systems.

**SMITHERS QUALITY ASSESSMENTS**

Providing knowledge for niche, emerging and high-growth industries.

**SMITHERS APEX**
Smithers Rapra & Smithers Pira Services

• Consulting
• Chemical Analysis
• Lab-scale sample manufacture
• Material & Product Testing
• Distribution Testing
• Research
• Information
ISO/IEC 17025: 2005 General requirements for the competence of testing and calibration laboratories

Additional accreditation for the medical industry
FDA registered
Member of UK GLP compliance program

‘Quality is an essential component of the Smithers Rapra’s philosophy; our goal is to be number one in both real and perceived quality. This applies to all areas of our business and is central to our mission.’
Background

• Interaction of fluids with elastomers.

• As manufacturers of rubber parts:
  
  1. Introduction of testing requirements for single use systems (SUSs) for biopharmaceutical applications.

  2. Regulatory requirements for food contact
Diffusion is a function of:
- Solubility parameter
- Time & temperature
- Concentration
- Pressure

Effect
- Net change in volume (swelling or shrinkage)
- Chemical attack
- Extractable species
Examples of Extractable Species

- Oligomers
- Plasticisers
- Antioxidants
- Antiozonants
- Cure system species
- Breakdown products
- Reaction products

The analytical challenge is to identify the species.
Elastomers used in Pharmaceutical Applications

Jenny Cooper
Commercial Manager – Smithers Rapra and Smithers Pira
Compelling Event

In new or amended drug product applications, there is a legal obligation to demonstrate the product, and the materials used, are safe:

- Europe: Medicinal Products Directive 2001/83/EC
- USA: Title 21 Code of Federal Regulations (CFR)
  - Chapter 1 - Food and Drugs
    - 210 Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general
    - 211 Current good manufacturing practice for finished pharmaceuticals

The legal obligation is on the pharma company, not the supply chain.

SUSs offer biopharmaceutical manufacturers significant gains in process flexibility, speed and efficiency.

Their concerns are:
1. What is extracted into the drug?
2. Does the product still function?
How to determine that a material is safe for its intended use depends on:

- Route of administration
  - Inhalation, parenteral, ophthalmic, oral?
- Material(s) of construction
  - Rubber, Plastic (coated) metal, glass?
- Dosage form
  - Aqueous with or without cosolvent?
- Duration
- Patient population
- Toxicity classification
- Contact of materials
- Small or large volume parenteral

Once, twice, more?
Daily dose
Standardized Extractables Testing Protocol. 
Pharmaceutical Engineering 34 (2014)
Extractable & Leachable Studies

A lot of work already done with medical devices e.g. metered dose inhalers

Major sources of extractables
BPOG (BioPhorum Operations Group)
Collaboration of the major biopharmaceutical companies

(taken from BPOG website)
BPOG Opinion

• Most suppliers’ current extractables data packages were not technically adequate to undertake a risk assessment for component qualification and processes evaluation.
• Any extractable testing conducted was not consistent between suppliers therefore end users were unable to interpret and compare data from different SUS suppliers.
• Multiple testing of the same components resulting in increased overall costs and delays in applications of SUS in biomanufacturing.

http://www.biophorum.com/
Standardised Methods for Extractables Testing of SUS Components

• The biopharma industry is pushing testing back to the SUS component manufacturer.
• A supplier of SUS assemblies is not required to generate extractables data for SUS components not manufactured by them.
• Not necessary to test each product if it belongs to a family (e.g. tube of the same compound formulation / different sizes).
• Testing must be undertaken with the SUS component in the sterilisation condition of use; this may necessitate separate studies.
• At least two samples from different production lots should be tested.

New requirements became effective 1st January 2017
SUS components

• Storage, mixing, or bioreactor bags and films
• Tubing
• Tubing connectors or disconnectors
• Aseptic connectors or disconnectors
• Sterilising-grade and process filters
• Tangential-flow filtration cassettes
• Sensors
• Valves
• Elastomeric parts (e.g. gaskets, O-rings, diaphragms, and septum)
• Wetted polymeric surfaces of positive displacement pumps.
• Chromatography columns
• Molded parts of mixers (e.g. impellers)
• Filling needles
Scope

1. Sample preparation - filling or soaking SUS components in model solvents (ratio of surface area to volume).

2. Extraction conditions – the exposure times and temperature ranges are extended to exaggerate the chemical conditions of actual use.

3. Recording test article sampling conditions.

4. Reporting data from analysis of extracts.
Model Solvents

1. 50% ethanol (represent organic solvents)
2. 1% Polysorbate, PS-80 (typical surfactant)
3. 5M NaCl (high salt concentrations)
4. 0.5N NaOH (high pH)
5. 0.1M Phosphoric acid (low pH)
6. Water for injection (WFI)

The six solvents effectively simulate protein solutions which typically involve high pH, low pH, salt, WFI, organic compound and surfactant.

When the recommended pH range is outside the SUS components product claim due to chemical compatibility issues, the compatible pH range should be used for testing.
## Extractables Test Programme

<table>
<thead>
<tr>
<th>Component Type</th>
<th>Solvents</th>
<th>Time</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50% Ethanol</td>
<td>1% PS-80</td>
<td>5M NaCl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5N NaCl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1M Phosphoric acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WFI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time 0 (≤30 min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 days</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70 days</td>
</tr>
<tr>
<td>Tubing</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Elastomeric Parts (O-rings,</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>gaskets, diaphragms)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Smithers Rapra Approach

<table>
<thead>
<tr>
<th>Species</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volatile extractables</td>
<td>Static headspace gas chromatography mass spectroscopy (HS-GC-MS)</td>
</tr>
<tr>
<td>Volatile / semi-volatile extractables</td>
<td>Direct injection gas chromatography mass spectroscopy (GC-MS)</td>
</tr>
<tr>
<td>Non-volatile extractables</td>
<td>Direct injection liquid chromatography mass spectroscopy and ultra violet detection (LC-MS/UV)</td>
</tr>
<tr>
<td>Elemental analysis</td>
<td>Inductively coupled plasma optical emission spectroscopy (ICP-OES)</td>
</tr>
</tbody>
</table>

Based on industry best practices based on Smithers Rapra expertise, current discussion at BPSA, ASTM, ASME and pharmaceutical E&L conferences.
Additional Tests

Additional tests can be used to supplement the required data:

- Total organic carbon (TOC)
- pH of extracts (when the test solvent doesn’t interfere).
- Non-volatile residue may be necessary when the test solvent is volatile
Summary

• The regulations have always been out there and methods continue to been developed.

• The pharmaceutical companies are responsible for the risk based assessment.

• The biopharmaceutical industry (BPOG) are placing new demands on the rubber manufacturers for SUS components.

• Smithers Rapra can support you to win new business.
Food Contact Regulations – Rubber Products

Dr Martin Forrest
Principal Consultant – Smithers Rapra and Smithers Pira
Contents

• Overview of Regulations
• European Regulations
• FDA Regulations
• Conclusion
Common Features – Food Contact Regulations

• All developed nations have food contact regulations

• Common features are:
  – Prohibit sale of products contacting food that:
    • Transfer chemicals at concentrations hazardous to health
    • Adversely affect sensory properties
  – GMP required for manufacture of products
General Consideration – Food Contact Work

1. Manufacturing
   – GMP (Quality system) needed
2. Composition
   – Monomer ratio’s, Positive lists of ingredients etc
3. Migration Testing
   – Overall and specific limits
4. Other Tests
   – Heavy metals, overall volatiles, taint of food etc
General Considerations – Steps to Take

- Determine what regulations apply to your product – European, FDA etc
  - Influenced by market & client requirements

- Regulations then provide detail on:
  - Manufacturing requirements
  - Compositional requirements
  - Migration Testing and Other Tests
    - What to do and how to do it

- Carry out an assessment to these defined requirements
European Regulations
EU Regulations - Background

• 1\textsuperscript{st} Tier – Apply to all Food Contact Materials

• 2\textsuperscript{nd} Tier – “Harmonised” regulations for specific food contact materials
  – e.g. Plastic Regulation

**Important:**
No harmonised EU regulation for rubber.
EU Regulations – 1st Tier

Two Regulations in 1st Tier

• Framework Regulation – (EC) 1935/2004

• Good Manufacturing Practice (GMP) Regulation – (EC) 2023/2006
Framework Regulation – (EC) 1935/2004

• Contains Sixteen Articles (i.e. Laws)
  – Article 3 General requirements – very important, see below
  – Other Articles include:
    • Role of EFSA in food contact assessments (Article 7)
    • Labelling materials and articles (Article 15)
    • Product compliance declarations (Article 16)

• Article 3
  – Products must comply with GMP Regulation (EC) 2023/2006
  – Do not transfer constituents to food in quantities which could:
    – *Endanger human health*
    – *Bring about unacceptable change in composition of food*
    – *Bring about deterioration in organoleptic properties*
Article 3 of (EC) 1935/2004

Demonstrating compliance with Article 3

• Organoleptic tests on final product
• Composition that complies with “Positive List” in a National regulation (e.g. German BfR XXI)
• Show compliance with:
  – Overall migration limits
  – Specific migration limits of additives
  – Compositional limits (e.g. residual monomer)
  – Specific testing requirements, e.g. heavy metals, polyaromatic amines, volatiles etc
Good Manufacturing Practice Regulation (EC) 2023/2006

• Quality assurance system (e.g. ISO 9001) should be appropriate to size of business and not excessive burden

• Applies to all stages of manufacture, processing and distribution of materials and articles
  – e.g. polymer, additives, final product ……etc
  – But excludes production of starting substances, e.g. monomers used to product polymer
National Regulations in Europe

• National regulations used if no harmonised EU regulation available

• German BfR Recommendations
  – English translations available and widely accepted
  – Recommendation XXI (Natural & Synthetic Rubber)
  – Recommendation XV (Silicone Materials)

• Other national regulations
  – French, Italian, Dutch, Spanish etc
    • Getting translations can be very difficult
  – Sometimes required by clients, distributors etc
Council of Europe Resolutions

• Council of Europe
  – 47 states = EU states + Georgia, Turkey etc
• Resolutions not legally binding
• Nine CoE Resolutions to date – none since 2005
  – Resolution for Rubber – dated 2004
  – Resolution for Silicones (includes silicone rubbers) – dated 2004
• Can be useful guidance documents but losing importance with time
• Contain positive lists, migration testing protocols etc
Assessing EU Compliance of a Rubber Product

Final rubber product complies with Framework Regulation (EC) 1935/2004 if:

- Manufacturing of ingredients and final product meet GMP Regulation (EC) 2023/2006
- Composition of rubber compound complies with positive list in applicable regulation (e.g. BfR XXI)
- Final, cured product passes all applicable migration tests and other tests
- including organoleptic tests!
US FDA Regulations
US FDA Regulations

• US Food & Drug Administration (FDA) regulations are in the Code of Federal Regulations (CFR)
• CFR divided into Titles, Parts and sub-Parts
• Food contact regulations
  – Title 21 (Parts 170 to 190)
• No single reference for GMP
  – Part 174.5 and Part 110
• Part 177.2600 - Main regulations for rubber
  – But often need to consult other parts of CFR
CFR Title 21 Part 177.2600

• Positive list of polymers with specifications
  – e.g. monomer ratio’s, molecular weight etc
• Positive list of additives with restrictions
  – e.g. addition levels etc
• Extractable limits for final products using:
  – Hexane (fatty food simulant)
  – Distilled water (aqueous food simulant)
• Specific restrictions
  – e.g. acrylonitrile rubbers (refers to Part 180.22)
US FDA – Other Parts and Sources

• Consulting other parts of CFR to ensure full compliance, e.g.
  – Part 177.1210 (Sealing gaskets for food containers)
  – Part 182 Generally Regarded As Safe (GRAS)
    • Certain additives, e.g. zinc oxide, kaolin clay etc.

• Also other FDA sources, e.g. :
  – Food Contact Notification list
  – Threshold of Regulation statement
  – Prior Sanction list (e.g. Lehman list)

• Consult FDA web-site
Assessing FDA Compliance of a Rubber Product

• Does the polymer pass all the requirements?
  – Molecular weight, ratio of monomers, residual monomer etc

• Is each substance in the rubber permitted by any of the below?:
  – Part of CFR Title 21, e.g. 177.2600 (Rubbers)
  – Food Contact Notification (FCN)
  – Threshold of Regulation (TOR) statement
  – A Prior Sanction

• Does the final rubber product pass the food migration tests?
  – e.g. Distilled water and hexane
Conclusions

• Regulations for rubber products exist throughout the world.

• They share common overall objectives.

• But have differences in requirements, approach and methodology.

• Smithers Rapra can provide expert assistance and guidance.
Thank You

More support available:

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