

Elastomers used in Pharmaceutical Applications

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Compelling Event

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

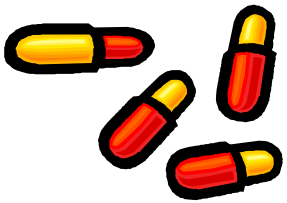
- Europe: Medicinal Products Directive 2001/83/EC
- USA: Title 21 Code of Federal Regulations (CFR)
    - Chapter 1 - Food and Drugs
        - 210 Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general
        - 211 Current good manufacturing practice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

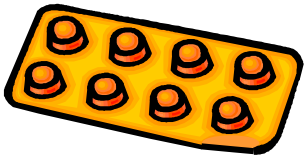
Their concerns are:

1. What is extracted into the drug?
2. Does the product still function?





Inhalation, parenteral, ophthalmic, oral?



Once, twice, more?

Route of administration



Toxicity classification

Daily dose

How to determine that a material is safe for its intended use depends on

Rubber, Plastic (coated) metal, glass?

Material(s) of construction

Contact of materials

Small or large volume parenteral





Duration



Patient population

Dosage form

Aqueous with or without cosolvent?

Regulatory Landscape

National Regulators

Methods & Advisory Bodies



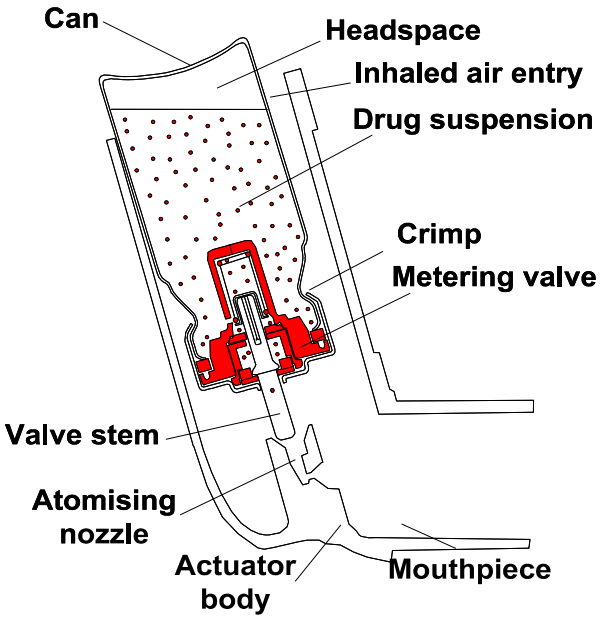
USP 1663 & 1664

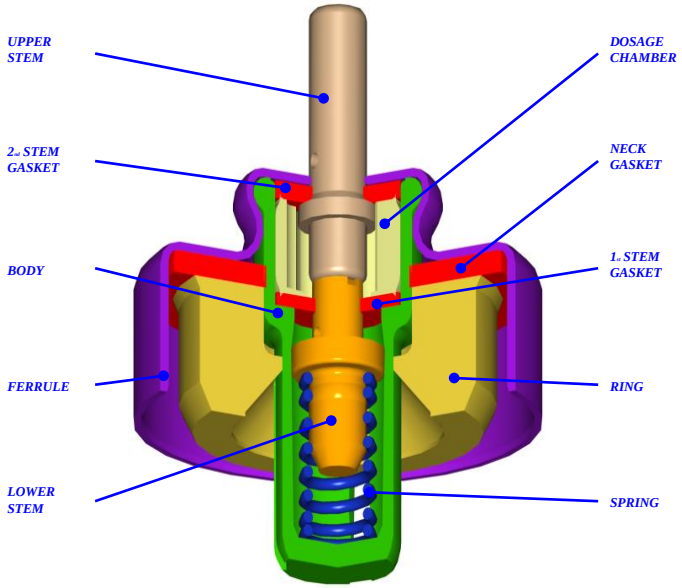
Industry Groups

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

Component Type	Solvents						Time				
	50% Ethanol	1% PS-80	5M NaCl	0.5N NaCl	0.1M Phosporic acid	WFI	Time 0 (≤30 min)	24 hours	7 days	21 days	70 days
							Temperature				
							Ambient (25°C)	40°C			
Tubing	X	X	X	X	X	X	X	X		X	X
Elastomeric Parts (O-rings, gaskets, diaphragms)	X	X	X	X	X	X	X	X			

70-day data point is necessary to support long-term storage of up to 3-years shelf life at 0°C storage conditions based on ASTM F1980 (the tube is typically integrated to the bag)

Smithers Rapra Approach

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

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.

Thank You