USP E&L Initiatives: New General Chapters and Reference Materials

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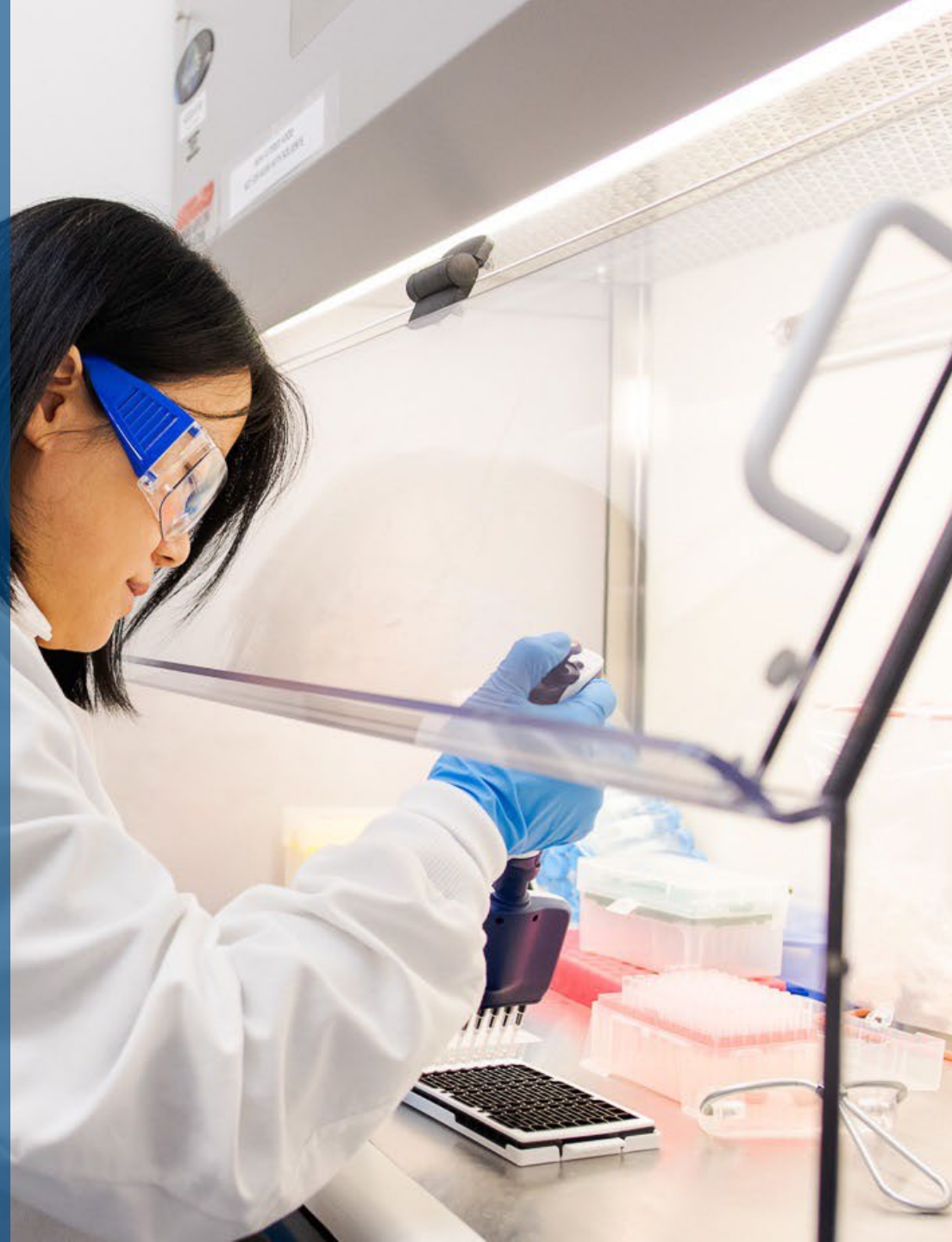


Agenda

- USP proposal for system suitability standards for E&L testing:
- Analytical reference materials:
  - Rubber Oligomers
  - Manufacturing & Packaging related standards
- New and revised documentary standards:
  - 1664.2 (new)
  - 1664.3 (new)
  - 1664.4 (new)
  - 1665.5 (new)
  - 1664.1 (revised)

USP E&L System Suitability Standards:

Stakeholder Feedback & Surveys

Qualitative (2021) and quantitative (2022) surveys

2024 online survey (n=86) indicated strong support for reference standards for system suitability testing

Need for universal standards in GC-MS and LC-MS methods

System Suitability Standard Proposal

Developing system suitability mixtures for common chromatographic methods: GC-MS (Headspace & Direct), LC-MS (ESI & APCI with positive and negative ionization)

Standards focus on instrument functionality, not leachable analysis

Criteria include anchor compounds, critical pairs, sensitivity markers, and linearity checks

Stimuli article published: USP-PF 49(4) July 2023

80% positive feedback on proposal

Round-Robin Study Results

15 participating labs tested proposed standards

Challenges identified:

- Anchor compounds sometimes eluted in void volume
- Peak crowding due to fast gradient
- DMSO stability issues (Methanol was better)
- Low detector sensitivity in some cases

Next steps: Re-optimized standards, will be released soon for industry use, publish a second stimuli article, and potentially integrate into USP ⟨1663⟩

To be launched soon, 4 sets of standard mixes

- GC-MS (Direct)
- GC-MS (Headspace)
- LC-MS (ESI with positive and negative ionization)
- LC-MS (APCI with positive and negative ionization)

USP E&L: Rubber Oligomers:

Possible genotoxic leachables

Present when there is an elastomeric / rubber component is present, such as:

- **Stoppered Vials**
- **Rubber Caps**
- **Prefilled Syringes**
- **Plungers / caps**

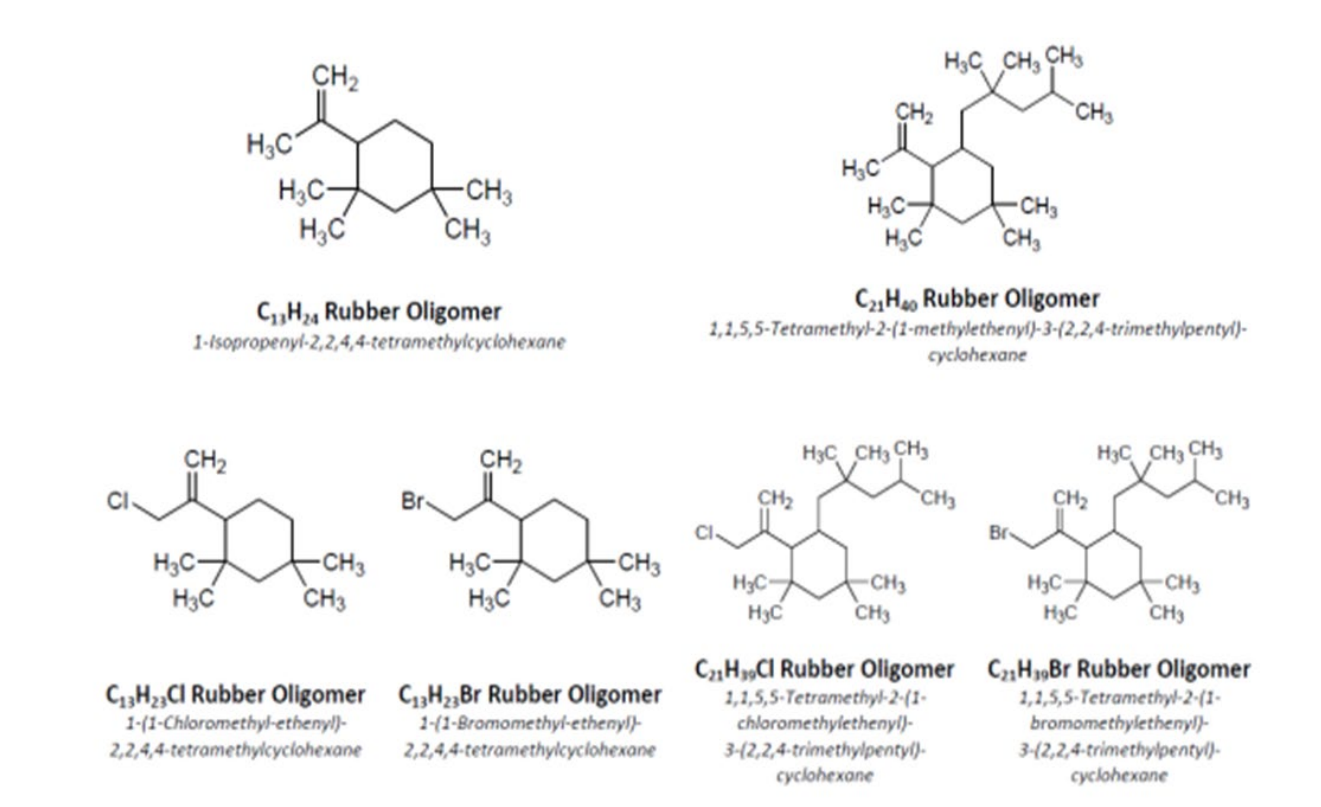
Limited suppliers – difficult to synthesize

Most common rubber oligomers

- **C13 and C21, and their chloro and butyl compounds**
- **Now available from USP store**

Application Note

- **Mechanism of Formation**
- **Analytical methods with chromatograms**



Rubber Oligomer Application Note:

BACKGROUND

In the Pharmaceutical and Biological industry, the function of a packaging material is to adequately preserve the integrity of a drug product. However, sometimes the packaging of pharmaceutical dosages forms can invalidate the most stable formulation. Hence, the potential adulteration of drug products by Extractable and Leachable (E&L) compounds that enter a drug product from a container, closure system, disposable or device is an area of increasing concern. The primary U.S.FDA

MECHANISM OF OLIGOMERS FORMATION AND ITS CHEMISTRY

Oligomers (i.e., short chains of butyl and halo butyl) are inherent to the raw rubber before and after manufacture of the elastomeric closures. Once the raw rubber is manufactured into the final component the chemistry becomes more complex because of additives, fillers, vulcanization agents, processing aids, by-products of the curing reaction and other residuals.

USP E&L: Standards for Material Types:

- Develop set of standards for manufacturing & packaging material types.
  - Tubing
  - Filters
  - Rubber Stoppers
  - Gaskets
  - IV Bags
  - Single use systems (SUS)
- Around 200 known possible compounds identified.
  - ~40 available
- These compounds will be added later to their appropriate informational USP E&L chapters.

Complex Products have a higher risk for E&Ls:

	Likelihood of interaction between packaging component and dosage form		
Degree of concern associated with Route of Administration	**High**	**Medium**	**Low**
Highest	Inhalation aerosols and solution Injections and injectable suspensions	Sterile powders Injection powders Inhalation powders	
High	Ophthalmic solutions and suspensions Transdermal ointments and patches Nasal aerosols and sprays		
Low	Topical solutions and suspensions Topical and lingual aerosols Oral solutions and suspensions	Topical powders Oral powders	Oral tablets Oral hard capsules Oral soft gelatin capsules

USP new and revised leachable chapters:

- **<1664.2> Assessment of leachables in parenteral drug products (IM, IV and SC)**
  - New chapter published in PF 51 (2)
  - Small molecules and biologics included
  - Extensive comments received
- **<1664.5> Assessment of leachables in oral drug products**
  - New chapter, Published in PF 51 (5), 1 Sep 2025, comments are due until 1 Dec 2025
- **<1664.3> Assessment of leachables in topical ophthalmic drug products**
  - New chapter, will be published in PF 51 (6), Publication date: 1 Nov 2025
- **<1664.4> Assessment of leachables in topical and transdermal drug products**
  - New chapter, will be published in PF 51 (6), Publication date: 1 Nov 2025
- **<1664.1> Assessment of leachables in orally inhaled and nasal drug products (OINDP)**
  - Revised chapter, will be published in 51 (6), Publication date: 1 Nov 2025

Thank You

The standard of trust