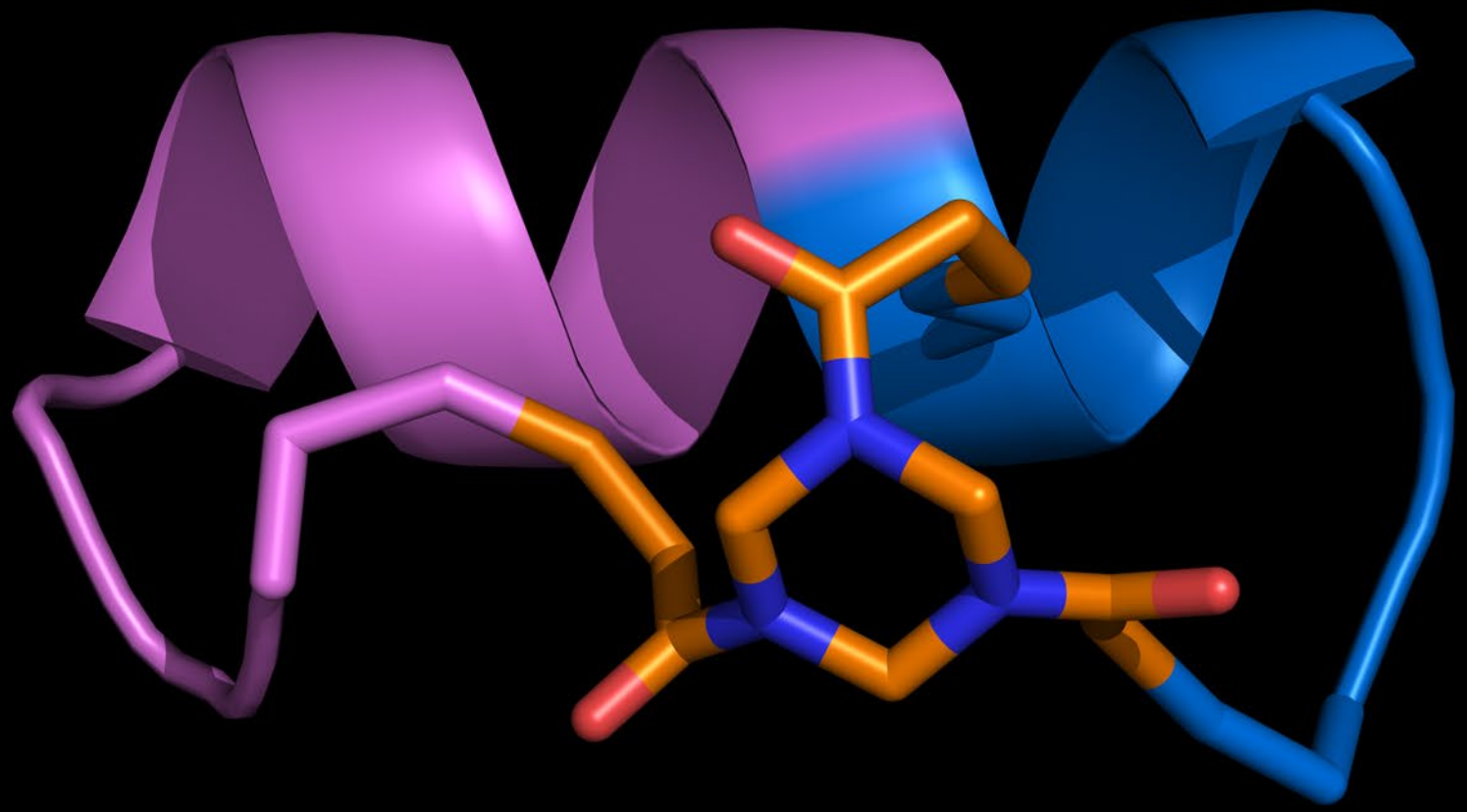
Extractables and Leachables potential concerns with high potency APIs

Dr Andrew Feilden



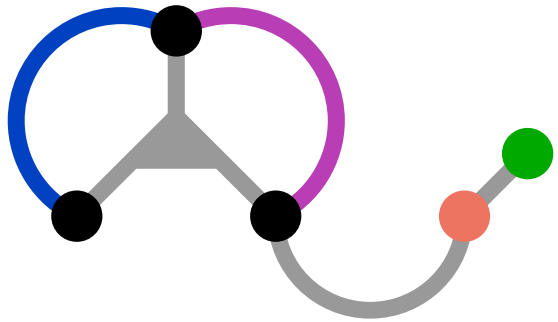
Bicycle®

Outline

- What are Bicycle Toxin Conjugates®?
- Potential regulations for E&L
- Challenges
- Conclusions

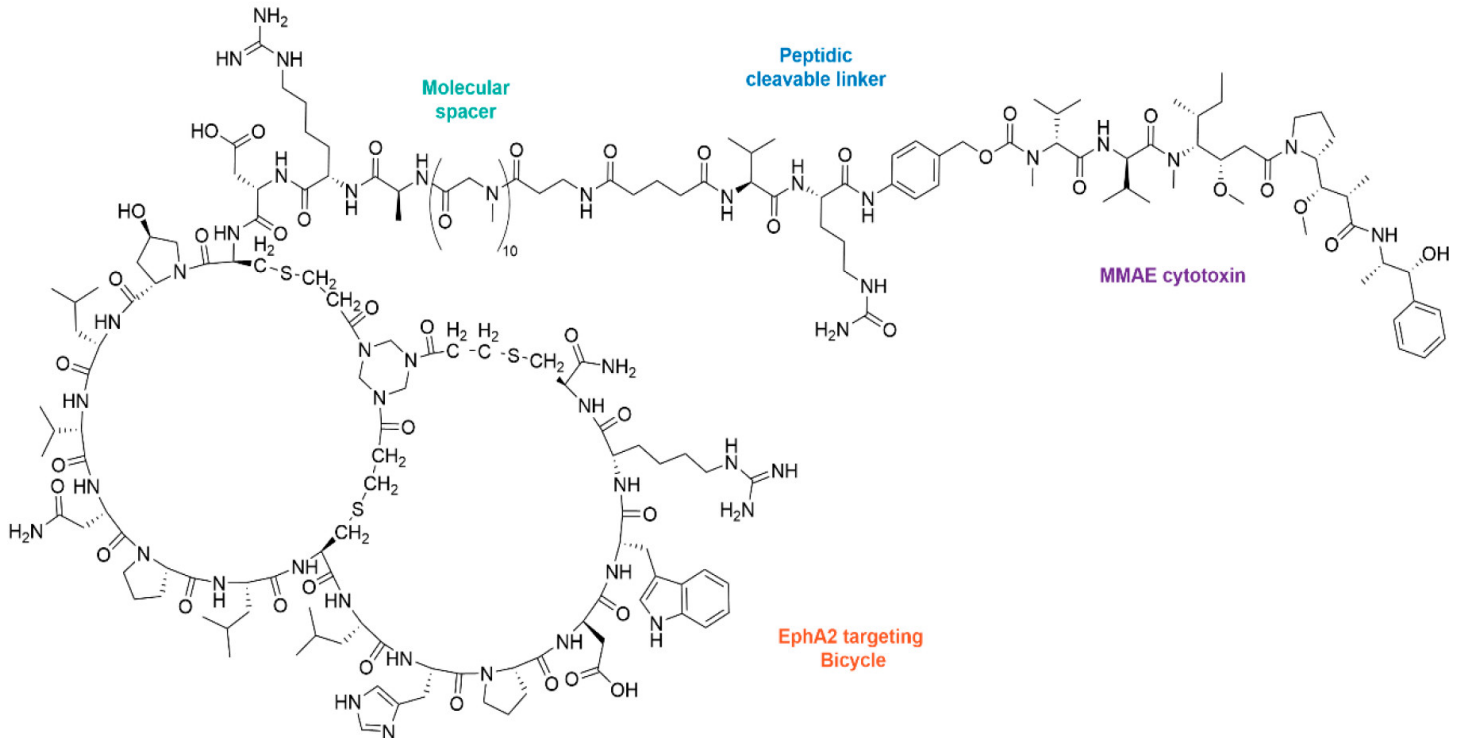
What are Bicycle Toxin Conjugates® (BTCs)

- They consist of a highly constrained, tumor-targeting synthetic bicyclic peptide that is conjugated to a cytotoxic payload via a cleavable linker, which allows payload release in the tumor microenvironment.
- BTCs aim to address the shortcomings of antibody drug conjugates (ADCs) in several ways.
- First, the small size of BTCs (~4 kDa) compared to large biologic entities such as monoclonal antibody (mAb)-based conjugates (~150 kDa) allows rapid distribution to tissues and extensive tumor penetration, which enables rapid delivery of payload into the tumor.
- Second, the peptidic nature of BTCs results in a short duration of systemic exposure (~1 h) and liver-sparing renal elimination. These properties limit the body's exposure to payload and should therefore minimize damage to normal tissue



BTC™

BT5528: EphA2 targeting BTC

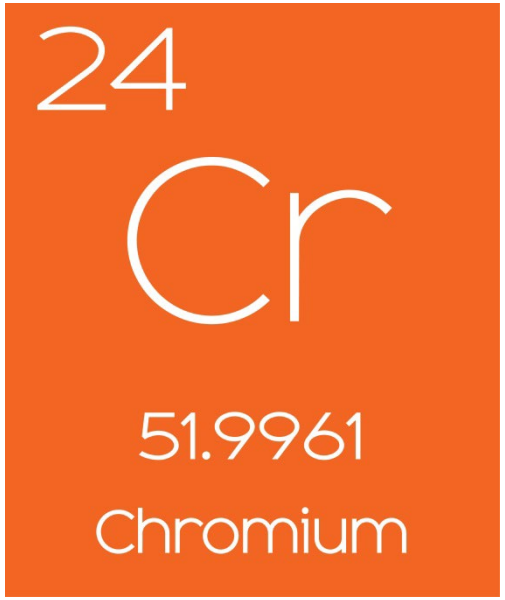


- The compound being a synthetic peptide is being filed as an NDA and NOT a BLA but has the challenges of both a small molecule and biological

What is E&L testing for?

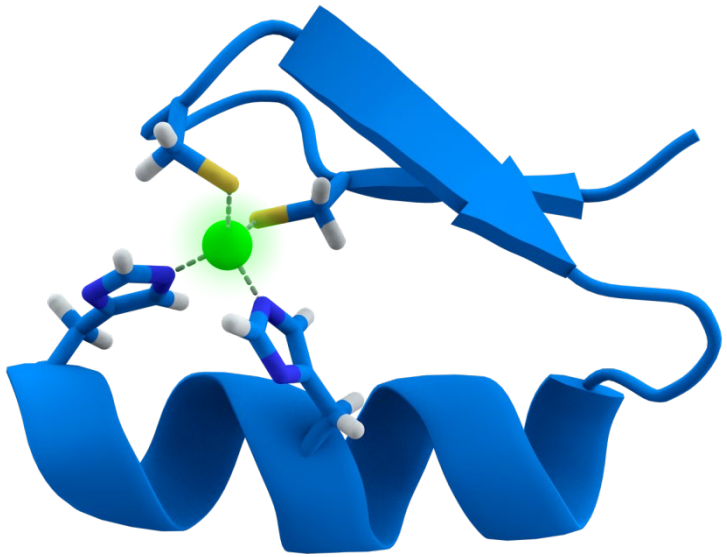
Extractable and leachable testing

CONTAMINANT TOXICICITY



Is there risk of harm to the patient?

DRUG EFFICACY



Is there impact on drug potency?

MMAE MSDS

Reduced Labeling (<= 125 ml)

Pictogram

Signal word	Danger
Hazard statement(s)	
H340	May cause genetic defects.
H370	Causes damage to organs.
H372	Causes damage to organs through prolonged or repeated exposure.
H412	Harmful to aquatic life with long lasting effects.
H360FD	May damage fertility. May damage the unborn child.
H300 + H330	Fatal if swallowed or if inhaled.

SECTION 3: Composition/information on ingredients

3.1 Substances

Synonyms : Monomethylauristatin norephedrine

Formula : C39H67N5O7
Molecular weight : 717.99 g/mol
CAS-No. : 474645-27-7

Component	Classification	Concentration
Monomethyl Auristatin E		
CAS-No. 474645-27-7	Acute Tox. 1; Muta. 1B; Repr. 1B; STOT SE 1; STOT RE 1; Aquatic Chronic 3; H300, H330, H340, H360FD, H370, H372, H412	<= 100 %

For the full text of the H-Statements mentioned in this Section, see Section 16.

Information from Merck MSDS

Regulations

- USP 1663-Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
- USP 1664 - Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
- USP 1665 - Characterization and Qualification of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products
- USP 665 - Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceuticals Drug Substances and Products (May 2026)
- USP 800 - Hazardous Drugs—Handling in Healthcare Settings
- USP 1661 - Evaluation of Plastic Packaging Systems for Pharmaceutical Use and Their Materials of Construction
- USP 661 - Plastic Packaging Systems and Their Materials Of Construction
- USP 381 - Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems
- USP 661.1 - Plastic Materials of Construction (Dec 2025)
- USP 661.2 - Plastic Packaging Systems For Pharmaceutical Use (Dec 2025)
- ISO 10993-18:2020 Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process

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USP 665 - Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceuticals Drug Substances and Products (May 2026)

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USP 800

- Despite being<1000 is not compendially applicable unless otherwise specified by regulators and enforcement bodies.
- Purpose
  - To promote patient safety, worker safety, and environmental protection.
  - Handling HDs includes, but is not limited to, the receipt, storage, compounding, dispensing, administration, and disposal of sterile and nonsterile products and preparations.

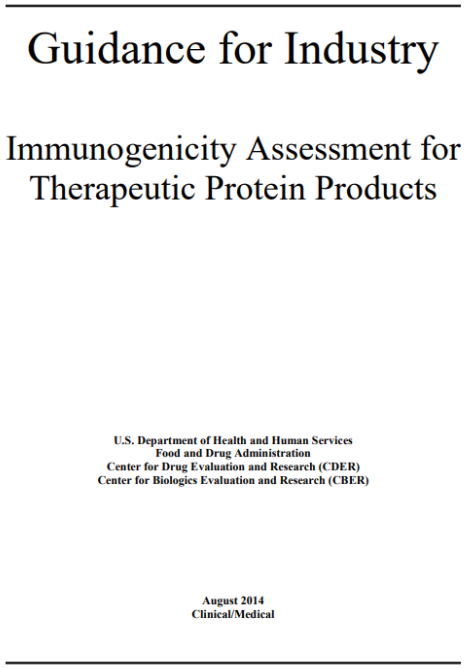
Guidances

- PQRI: Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular) (Feb 2022)
- Biophorum: Extractables testing of polymeric single-use components used in biopharmaceutical manufacturing (Apr 2020)
- FDA Guidance for Industry 2014 Immunogenicity assessment for Therapeutic Protein Products

FDA Guidance for Industry (2014) Immunogenicity assessment for Therapeutic Protein Products

8. Container Closure Considerations

- Leached materials from the container closure system may be a source of materials that enhance immunogenicity, either by chemically modifying the therapeutic protein product or by having direct immune adjuvant activity, including the following:
  - Organic compounds with immunomodulatory activity may be eluted from container closure materials by polysorbate-containing formulations: a leachable organic compound involved in vulcanization was found in a polysorbate formulated product when the stopper surfaces were not Teflon coated (Boven et al. 2005).


Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2014
Clinical/Medical

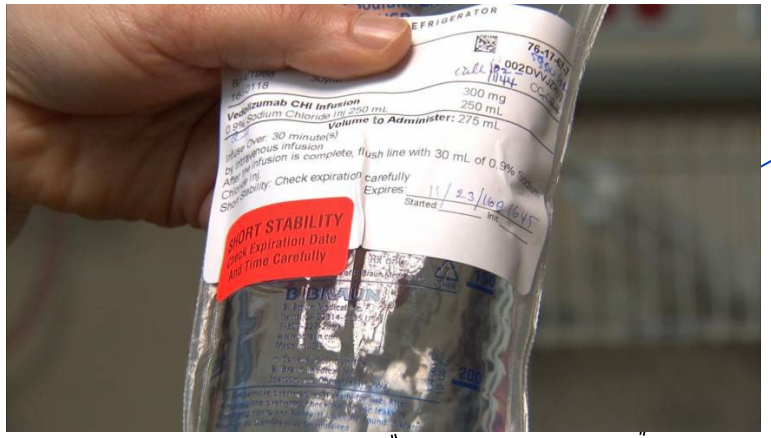
FDA Guidance for Industry (2014) Immunogenicity assessment for Therapeutic Protein Products

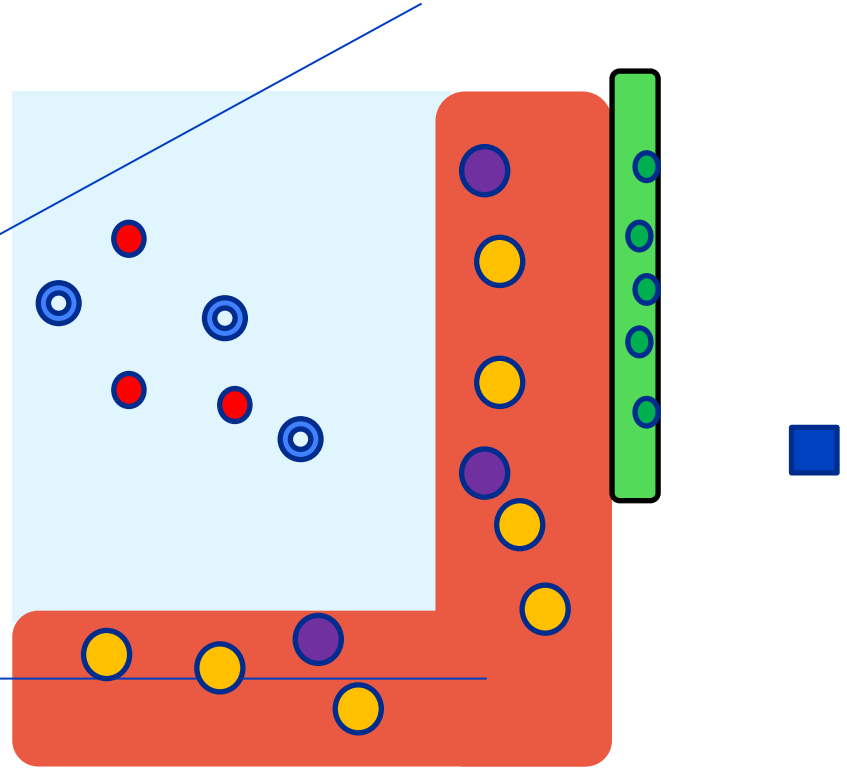
- Whenever possible, sponsors should obtain detailed information regarding a description of all raw materials used in the manufacture of the container closure systems for their products. Sponsors should conduct a comprehensive extractables and leachables laboratory assessment using multiple analytical techniques to assess the attributes of the container-closure system that could interact with and degrade protein therapeutic products.

- Testing for leachables should be performed on the product under stress conditions, 9 as well as under real-time storage conditions, because in some cases the amount of leachables increases dramatically over time and at elevated temperatures. Product compatibility testing should be performed to assess the effects of container closure system materials and all leachables on product quality.

- Because the United States Pharmacopeia elastomeric closures for injections tests do not adequately characterize the impact of leachables in storage containers on therapeutic protein products under real-time storage conditions, leachables must be evaluated for each therapeutic protein product in the context of its storage container under real-time storage conditions .

Possible Sources of Leachables





- Pack/Product interaction
- Label adhesive/ink migration
- Secondary Packaging
- In-process leachables

Manufacturing

- Steel/glass

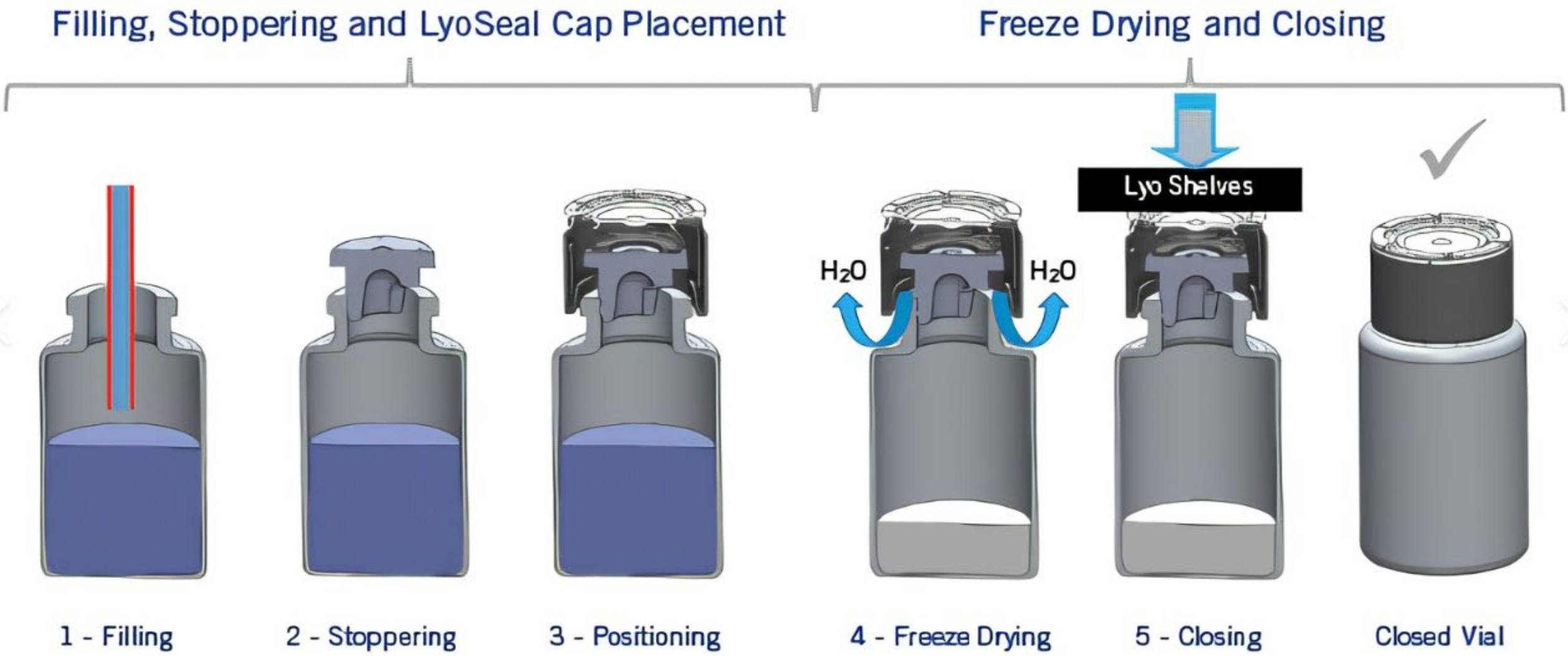
- Single Use plastics

Manufacturing

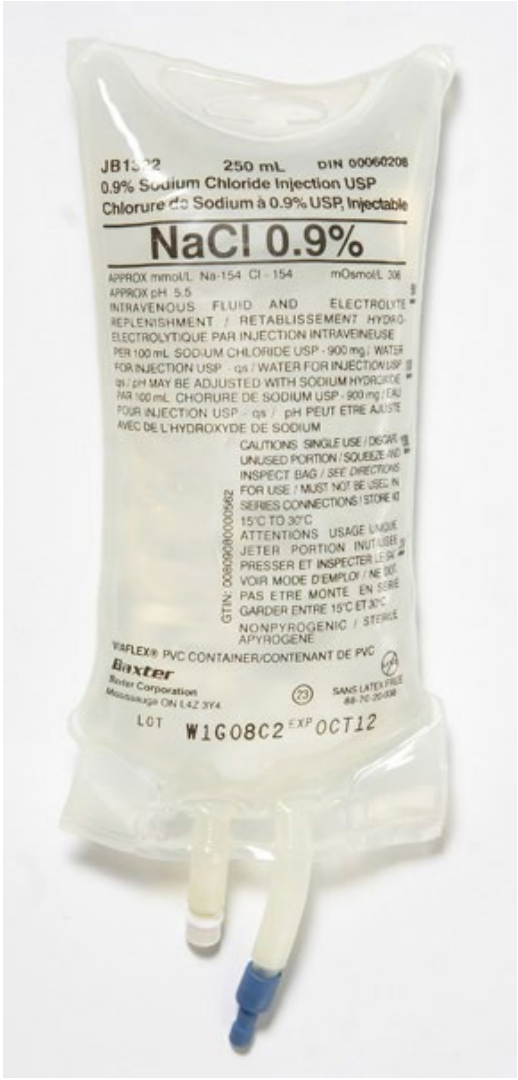
- Steel/glass

- Single Use plastics

Lyophilisation

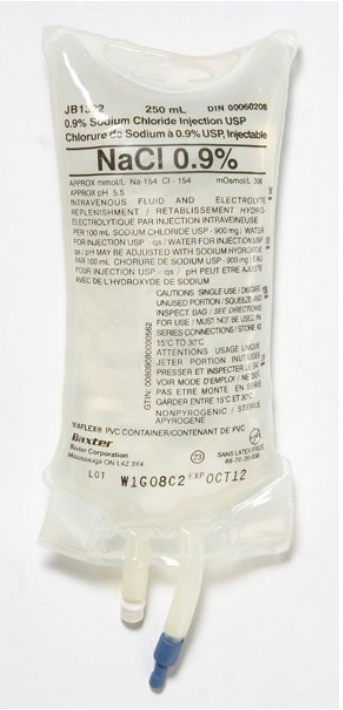


Drug Delivery:
Closed System Transfer Device & Saline Bag



Bicycle®

Drug Delivery:
Closed System Transfer Device & Saline Bag



- Are these medical devices or medicinal products- will depend on whether they are supplied with the product
- If devices ISO 10993-18:2020 comes into play

Potential Chemical species Partial list from PQRI PDP guidance

Dipropylene glycol, dibenzoate
Diisooctyl phthalate
Isobornyl propionate
4-Ethylguaiacol
Glycol monopropyl ether
(±)-4-Methyldecane
1-Octadecanethiol
Dioctyl azelate
Cyclooctane
Propylene glycol butyl ether
Cyclodecane
Cyclododecane
Cyclohexadecane
Cycloeicosane
3-Hydroxybutyric acid

Oleamide
Decanoic acid
Antioxidant 245 or Benzenepropanoic acid, 3-(1,1-dimethylethyl)-4-hydroxy-5-methyl-, 1,1′-[1,2-ethanediylbis(oxy-2,1-ethanediyl)] ester
Lauryl laurate
Norpristane
Tetracontane
Mono(2-ethylhexyl) phthalate
3,3-Dimethyl-2-butanol
2,4,6-Trimethylbenzaldehyde
γ-Stearolactone
2-Methyl-2-butene
Eicosanamide
2-Methylbenzaldehyde

Propane
Ethylamine
Acetaldehyde
Isobutane
2-Methyl-1-pentene
2-Ethylhexyl thioglycolate
2-Hexene
Isopentane
Isobutanol
Isobutyraldehyde
Methyl ethyl ketone
Propionic acid
2,3-Dimethylbutane
(±)-Camphene
4-tert-Pentylphenol

1-Undecene
1-Heptadecanol, 1-acetate

Octadecyl acetate
Diethyl phthalate
Diisobutyl phthalate
Dibutyl phthalate
Butyl octyl phthalate
Butyl 2-ethylhexyl phthalate
1-Decene
2-(1-Methylbutyl)phenol
Phthalic acid
cis-Cyclooctene
Cyclooctene

Propylidenecyclohexane
3,5-Di-tert-butyl-4-hydroxybenzyl alcohol
Polyethylene glycol nonylphenyl ether
1-Hydroxycyclohexyl phenyl ketone
5-Methoxyindole
4,4′-Bis(α,α-dimethylbenzyl)diphenylamine
Diphenyl ether
Diphenylguanidine
Dibenzylamine
N,N-Dimethylbenzylamine
5-Ethyl-2-methylpyridine
Caprolactam
α2-2-Furanyl-2,5-furandimethanol
2-(2-Hydroxypropoxy)-1-propanol
Trimethylsilanol
3-Dodecyl-1-(1,2,2,6,6-pentamethyl-4-piperidyl)pyrrolidine-2,5-dione
Octamethyltrisiloxane

1-Methoxy-2-propanol
1,3-Diphenylpropane
2,6-Lutidine
1-Methoxy-2-propyl acetate
Cyclohexylamine
Diethylamine
Tetrahydrofuran
2-Methyl-4,6-Bis[(octylthio)methyl]phenol
Morpholine
Bis(2-hydroxypropyl) ether
3-Vinylpyridine

Limits- Screening technique

- ICH Q3B 5µg TDI
- ICH Q3C –Various PDEs 200 µg/day
- ICH Q3D – metals range of PDEs depending on route of administration 0.1 µg/g
- E&L 0.15 µg/day- 120 µg/day

AET (Analytical Evaluation Threshold) Based on dose and a safety concern threshold down to 0.15 µg/day

AET (µg/mL) = (SCT/DBT (µg/day) × (A / (B × C × D))) / (UF × Number of sequential extractions)

A = number of components extracted

B = extract volume

C = number of components/device

D = dilution factor (D>1), if concentrated (D<1). If not diluted (D=1)

UF = uncertainty factor of analytical methods (UF >=1)

Limits- Screening technique

- Assumptions
  - Saline bag volume 1000 mL
  - Vial 10 mL
  - 1 device/day
  - Total Duration <30 days
  - Uncertainty factor 10

DBT/SCT	Vial (µg/mL)	Saline bag (µg/mL)
1.5	0.015	0.00015
5	0.05	0.0005
120	1.2	0.012

Limits- Screening technique

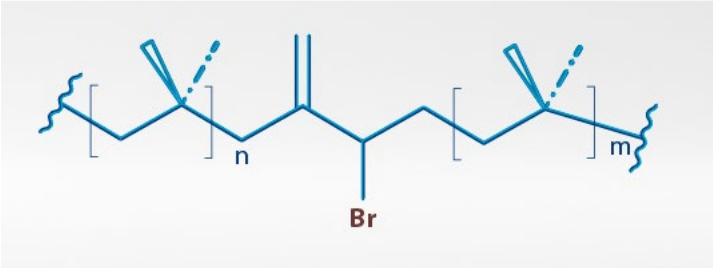
- Assumptions
  - Saline bag volume 1000 mL
  - Vial 10 mL
  - 1 device/day
  - Total Duration <30 days
  - Uncertainty factor 10

DBT/SCT	Vial (µg/mL)	Saline bag (µg/mL)
1.5	0.015	0.00015
5	0.05	0.0005
120	1.2	0.012
Impurities	2	0.02

Reactive Leachables

- These include
  - Alkylating agents
  - Michael reactive acceptors
  - Degradation products
- They can originate from a variety of sources
  - Additives
  - Processing aids
  - By products
- They are chemically Diverse

Rubber Stoppers



- Common material halobutyl rubber
- Common leachable $C_{13}H_{23}Br$
- Can react with Histidine via S_N2 reaction

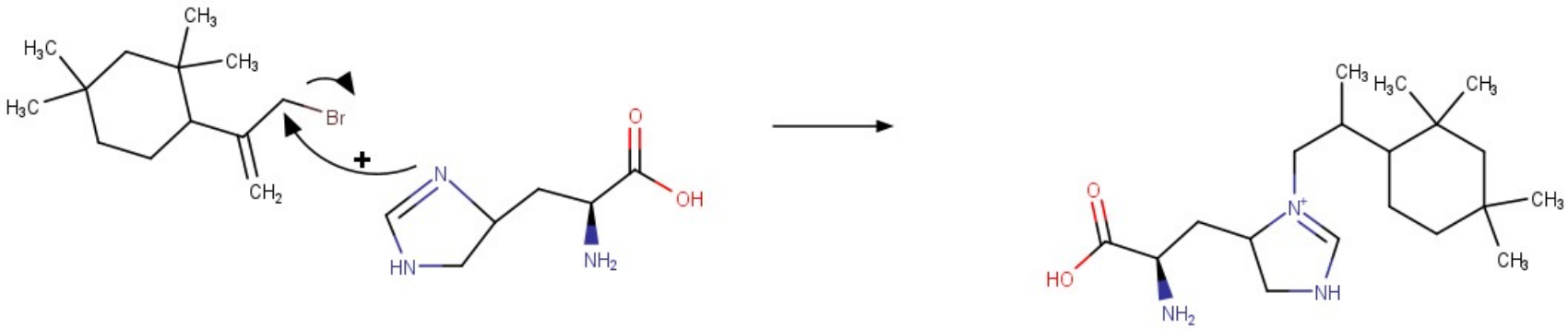
Performance and benefits

Low permeability
to better keep air, gasses and moisture in or out depending on application needs

Vibration damping
to mitigate uneven vibration causing potential damage

Aging resistance
Resistance to aging and to weathering from atmospheric exposure for a long lasting quality product

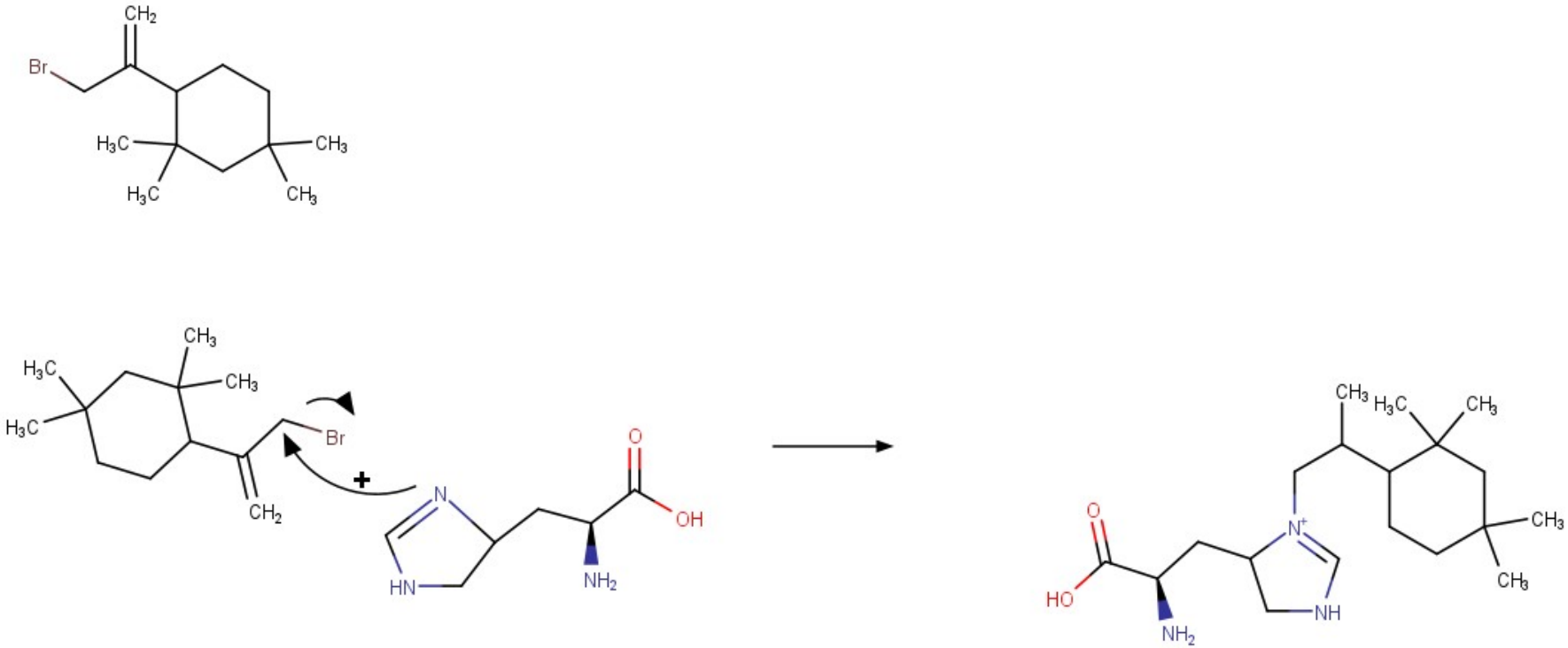
Low glass transition temperature
to fit low temperature applications



Rubber Stoppers

Potential Reaction pathways

With Glycine (excipient and common bulking agent for lyophilised drug products)



Conclusions

- Biological Compounds are challenging
- High Hazard compounds are even more challenging!!
- Knowledge and understanding can minimise risks

Thank you

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