The Necessity of Extractable and Leachable Qualifications for Lyophilized Drug Products: Some Fallacies Addressed

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1. Lyo Containers and Administration Devices: what are we taking about?

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1. Lyo Containers and Administration Devices: what are we taking about?

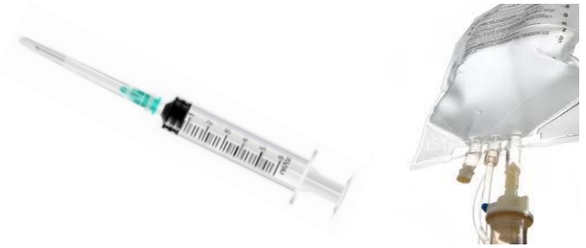
Primary Packaging
(Long term storage of LYO-Cake)

Low residual moisture

Low water vapor transmission

Reconstitution Solution Container

Drug Administration Sets
(Not discussed in this presentation)



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2. Lyo Primary Containers: What do the US & EU Guidelines tell us?

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Lyo Primary Containers: What do the US & EU Guidelines tell us?

Ranking the packaging concerns

LIQUID SVP's

Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	**Likelihood of Packaging Components – Dosage Form Interactions**		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	**Injections and Injectable Suspensions;** Inhalation Solutions	***Sterile Powders and Powders for Injection;*** *Inhalation Powders*
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	-
Low	Topical Solutions and Suspensions, Topical and Lingual Aerosols, Oral Suspensions and Solutions	-	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

LYO

Revision of "Table 1" in USP <1664>,
Originally Included into the FDA Guidance for Industry (1999):
"Container/Closure systems for Packaging Human Drugs and Biologics"

LIQUID SVP's

Examples of Packaging Concerns for Common Classes of Drug Products			
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High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	-
Low	Topical Solutions and Suspensions, Topical and Lingual Aerosols, Oral Suspensions and Solutions	-	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

LYO

The "Low" *Likelihood of Packaging - DP Interaction* for LYO SVP's: based upon the observation that:

1. the *interaction* between a solid (Lyo cake) a material (eg rubber) *is limited*
2. AND, there is *limited direct contact* between Lyo cake and Rubber closure

– **However the Interaction Mechanism between LYO Cake and Components may not need direct contact (see later)**

– **BE CAREFUL when "rationalizing" a LYO application as being Non Critical!!!**

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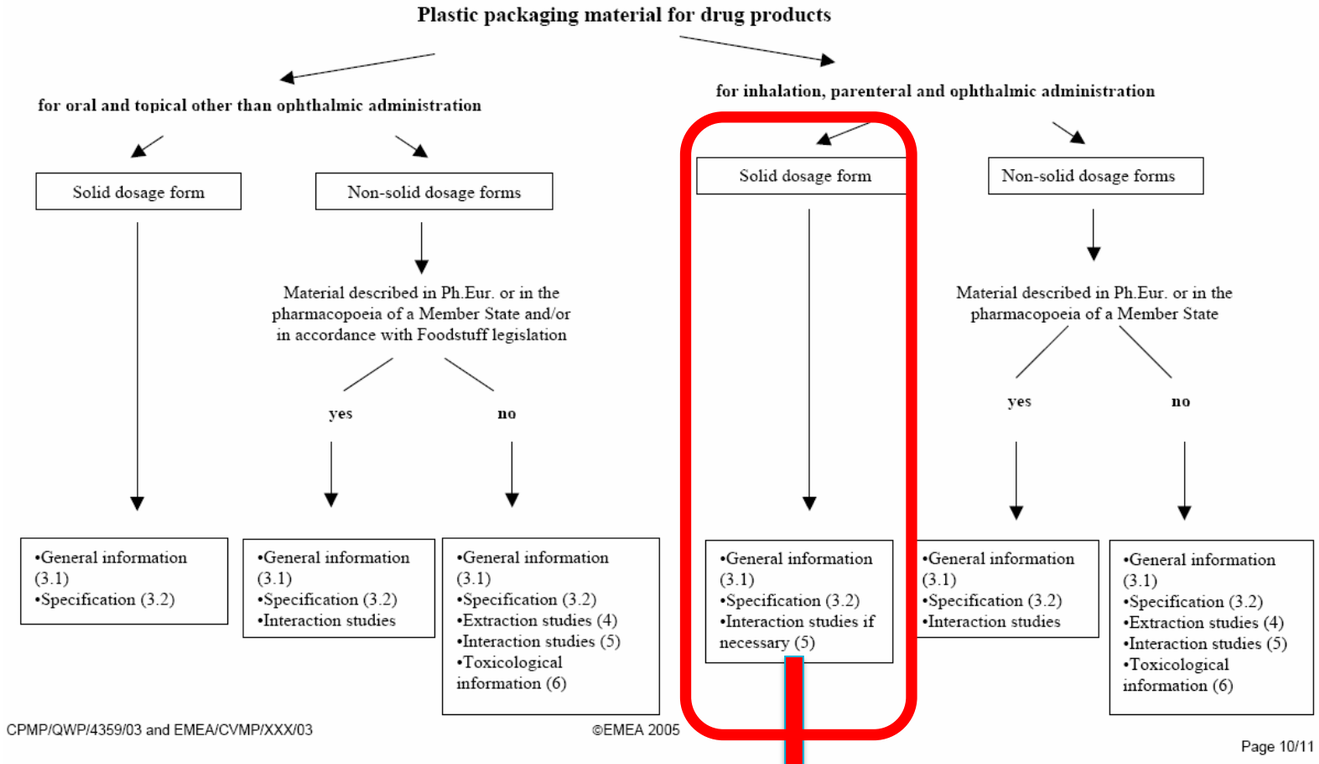
Lyo Primary Containers: What do the US & EU Guidelines tell us?

The EM(E)A Guideline on "*Plastic Immediate Packaging Materials*" of 2005



For solid active substances and solid dosage forms: the risk of interaction is low and generally does not require a content/container interaction study. Solid dosage forms intended for inhalation or parenteral use, e.g. lyophilised products, may need interaction studies between the packaging material and the components of the formulation.

Lyo Primary Containers: What do the US & EU Guidelines tell us?

Conclusion wrt Regulatory Guidance (US, EU)

POTENTIAL AMBIGUITY
in the **NEED** and/or subsequent **DEPTH**
of E/L evaluations for Lyo-Containers

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3. The Interaction Mechanism between the Lyo Drug Product and its Primary Packaging: OUTGASSING

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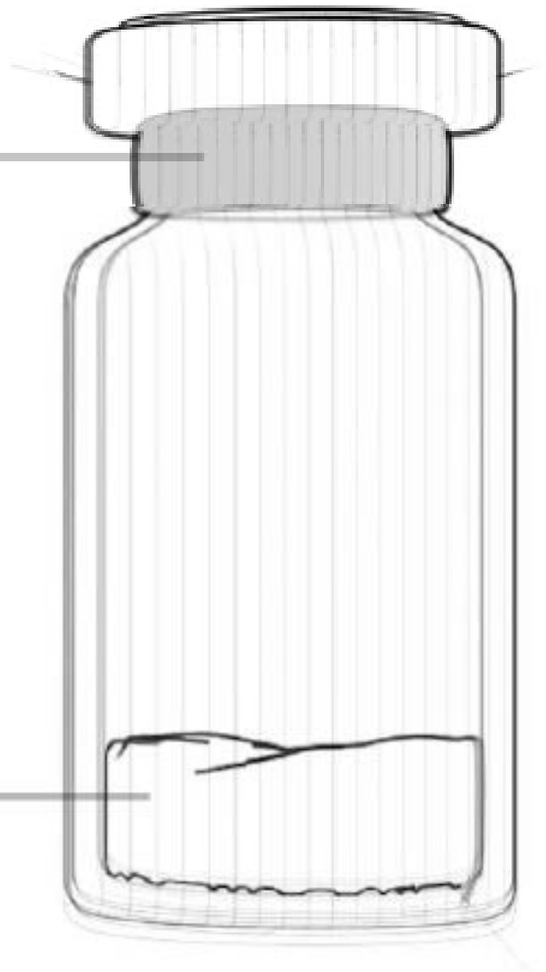
The Interaction Mechanism: During Long Term STORAGE of the LYO-Cake

RUBBER

OUTGASSING OF RUBBER STOPPER



LYO CAKE

Outgassing of rubbers is mainly an issue for:

- *Volatile Organic Compounds*
- *Semi-Volatile Organic Compounds*

LYO CAKE: EXTREMELY GOOD ADSORBENT

- *High Suface Area*
- *Extremely Dry*

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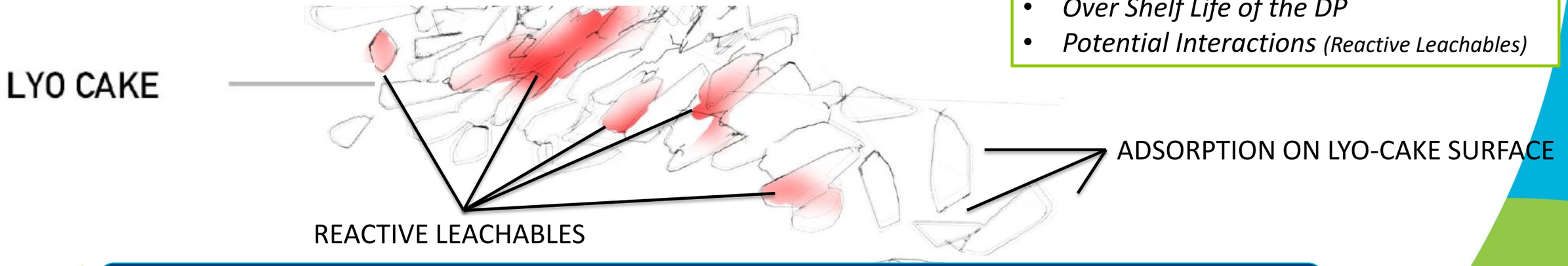
Rubber Stopper

OUTGASSING OF RUBBER STOPPER

Outgassing of rubbers is mainly an issue for:
- *Volatile Organic Compounds*
- *Semi-Volatile Organic Compounds*

LYO CAKE: EXTREMELY GOOD ADSORBENT
- *High Suface Area*
- *Extremely Dry*

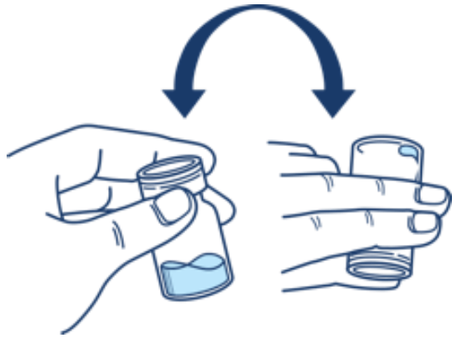
ACCUMULATION OF VOC/SVOC LEACHABLES
- *Over Shelf Life of the DP*
- *Potential Interactions (Reactive Leachables)*



The “Extent” of outgassing will also depend upon the Rubber Quality / Grade

The Interaction Mechanism: During RECONSTITUTION of the Lyophilized DP

RECONSTITUTION



SOLUBILIZATION
of adsorbed leachables in reconstitution solution

Reconstituted (Liquid) DP
Liquid Interaction with
Primary Packaging Components

Mainly Volatile & Semi-Volatile
Organic compounds
(OUTGASSING)

Although **SHORT TERM** Contact,
also Non-Volatile Compounds,
Metals and Ions may be released

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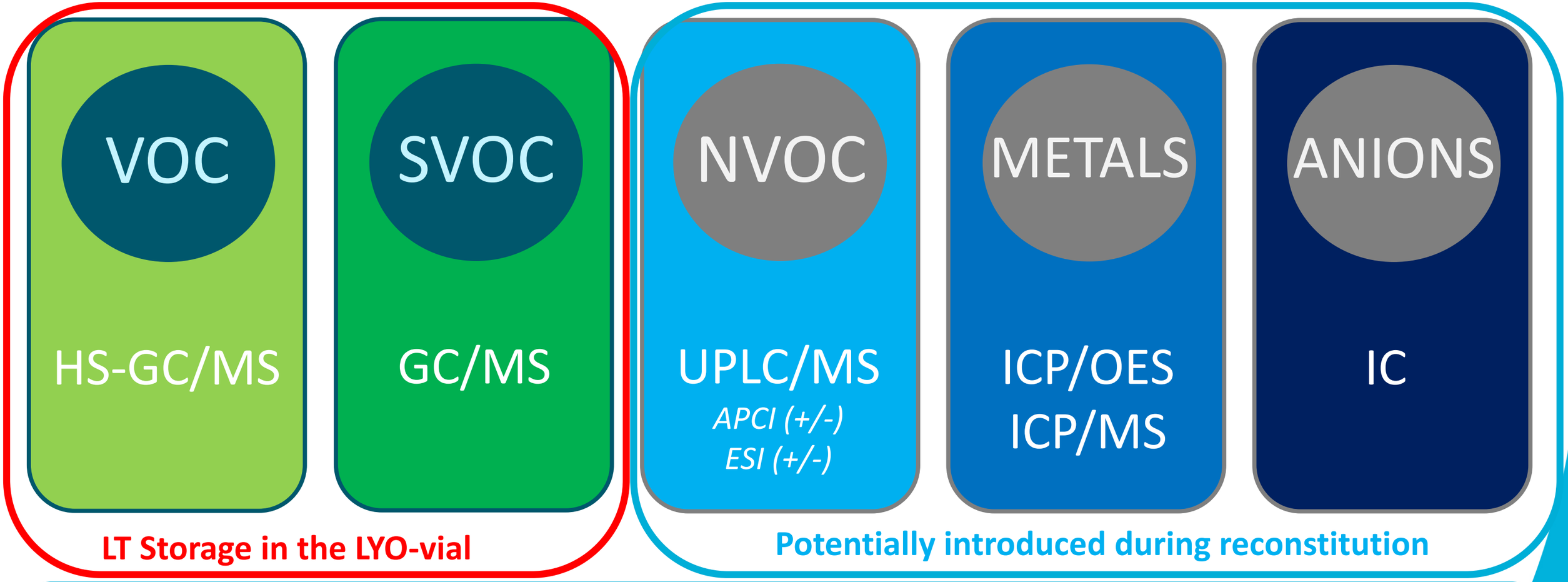
Basic Analytical Techniques



Approaches for EXT studies for LYO-vials and reconstitution solution containers are the same as for any other Small Volume Parenteral Application

(Long Term Outgassing and Short Term Contact during Reconstitution creates the need for Full EXT Characterization of the components)

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The Extractable Study

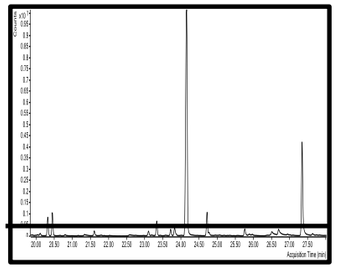
EXTRACTABLE STUDY

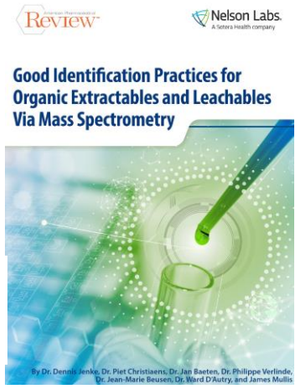
DISCOVER
ALL COMPOUNDS

ABOVE A TOX
THRESHOLD (AET)

IDENTIFY
ALL COMPOUNDS

(SEMI-)QUANTIFY
ALL COMPOUNDS





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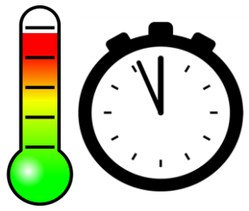
The Leachable Study

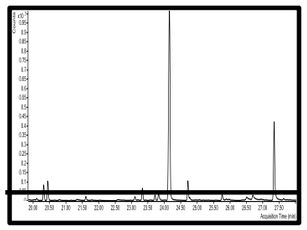
Primary Packaging
(Long term storage of LYO-Cake)

Reconstitution Solution
Container

LEACHABLE STUDY

LONG TERM & ACCELERATED | MONITORING **[LEA] > AET** | AT **DIFFERENT TIME POINTS** | USING **QUANTITATIVE** METHODS | **SCREENING** FOR **UNEXPECTED LEACHABLES**





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EXAMPLE OF FULL LEACHABLE STUDY

Type of Solution	Storage Time (Months)				
	0	3	6	12	24
Drug Product in Rubber Sealed Vials (Test Item) at 5 ± 3 ° C	×	×	×	×	×
Drug Product in Inert Containers (Blank) at 5 ± 3 ° C	×	×	×	×	×
Drug Product in Rubber Sealed Vials (Test Item) at 25 ± 3 ° C	-	×	×	-	-
Drug Product in Inert Containers (Blank) at 25 ± 3 ° C	-	×	×	-	-

× = sampling time point

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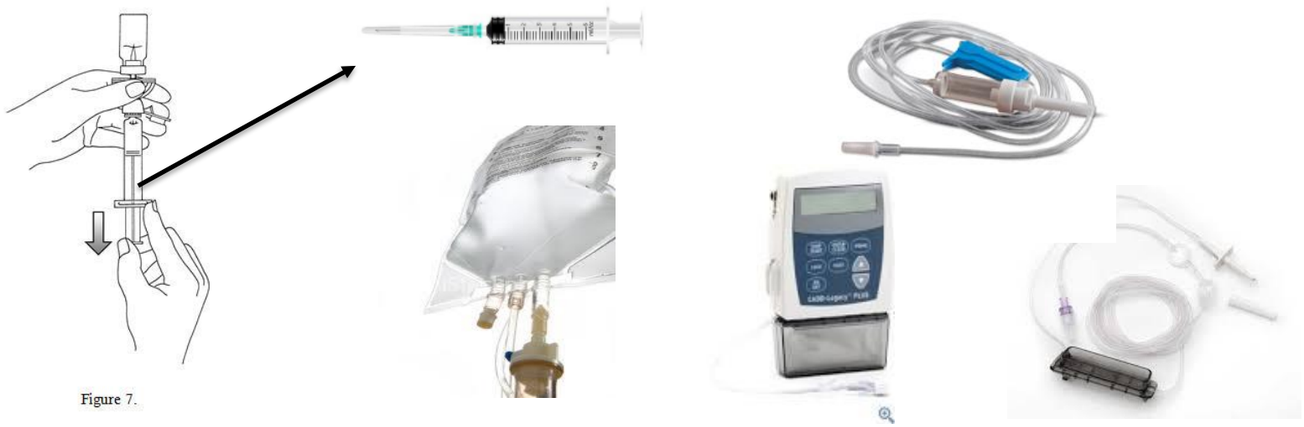
The Interaction Mechanism: During ADMINISTRATION of the RECONSTITUTED DP

ADMINISTRATION



TRANSIENT TO SHORT TERM CONTACT WITH DRUG ADMINISTRATION DEVICES

Transient or Short Term: No Long Term Accumulation
However: Potentially Increased Levels of VOC, SVOC, NVOC, Metals and Ions
Potentially: Include the Administration Step in the Leachable Procedures

IS IT A MEDICAL DEVICE, OR IS IT A COMBINATION PRODUCT
HOWEVER, THESE CONSIDERATIONS WILL NOT BE ADDRESSED IN THIS PRESENTATION

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4. The Challenges and Consequences of Leachables Profiling after Reconstitution

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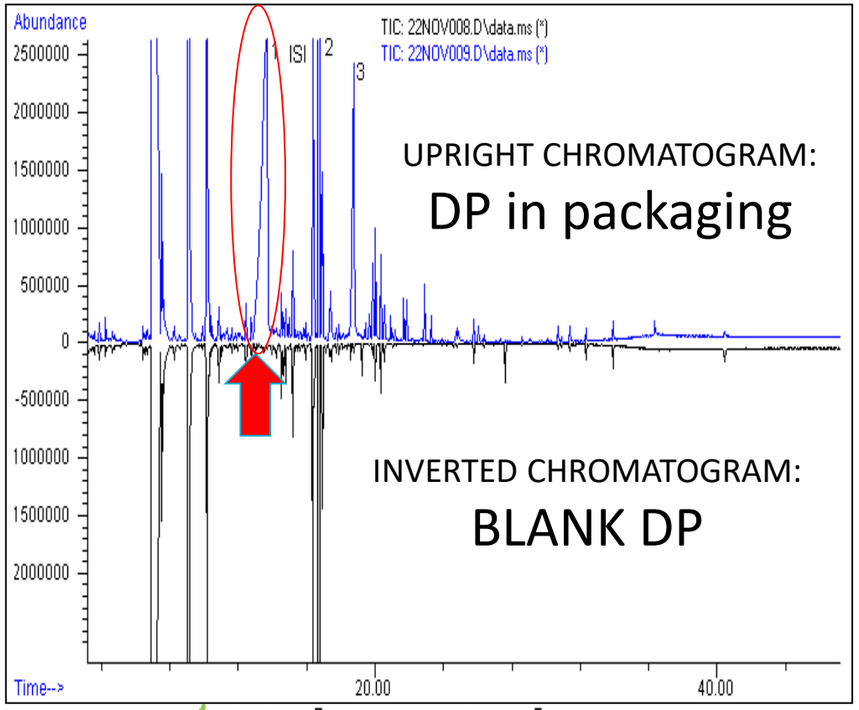
The Challenges and Consequences of Leachables Profiling after Reconstitution

LEACHABLE STUDY DESIGN



ASSESS ALL **DIFFERENTIAL PEAKS**

IN A **COMPARATIVE** ASSESSMENT

BETWEEN THE **AGED DRUG PRODUCT IN PRIMARY PACKAGING**

AND **AGED BLANK** DRUG PRODUCT (NO C/C EXPOSURE) **BASE LINE**

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Blank solution: What defines a good blank and what is the issue with LYO?

A good blank solution is a **leachables free drug product**!!

LYO DRUG PRODUCTS

The Liquid LYO drug product is freeze dried (low Temp vacuum sublimation) in the vial itself

A good blank solution is best from the **same drug product batch** as the contact samples

A good blank solution is **put on controlled storage together with the contact samples**

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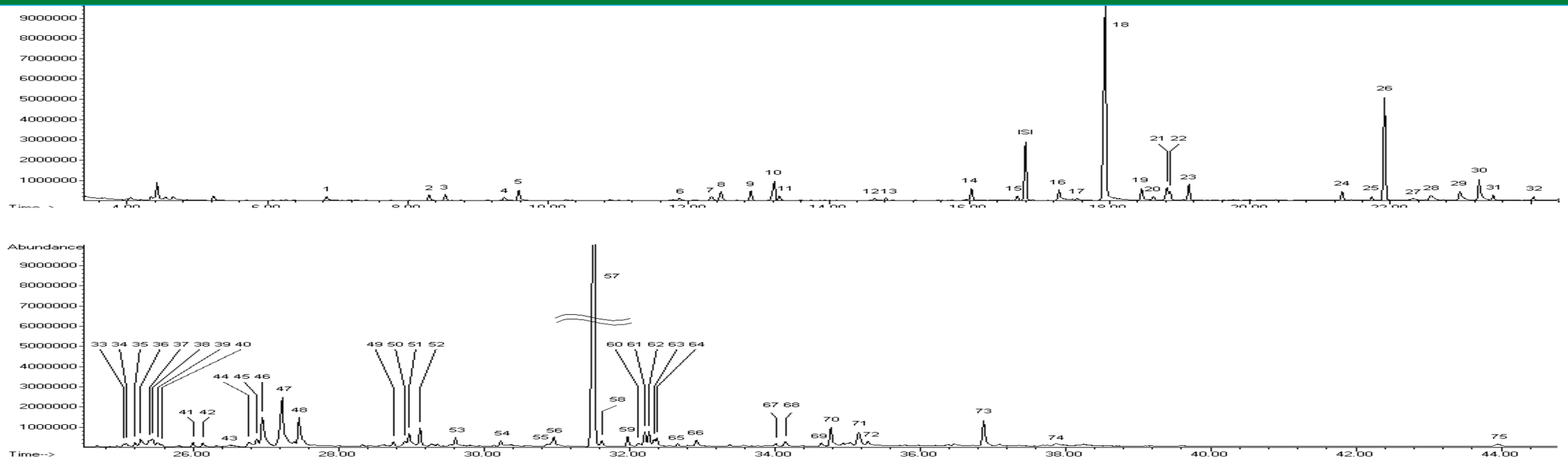
EXAMPLE: SCREENING LEACHABLE WITHOUT BLANK REFERENCE = IMPURITIES PROFILING

No Blank for LYO-product is available: *“you know what? I will screen without the Blank Baseline”*



75 Organic Impurities = More than only Leachables from the Primary Packaging!

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The Challenges and Consequences of Leachables Profiling after Reconstitution

THE CHALLENGE:

IN LYO-APPLICATIONS:
NO TRUE AGED BLANK DRUG PRODUCT IS AVAILABLE

POTENTIAL SOLUTIONS:

THERE IS NO "PERFECT" SOLUTION

Consider **t = 0 as blank baseline throughout the complete study**
Disadvantage:
- Some Compounds may already be present after a short term contact
- Stability / Degradation of DP is not accounted for

NOT THE PREFERRED OPTION

Use upright position as a "reference" for inverted position
Disadvantage:
- *Migration Mechanism* is not based upon material contact, rather base… release of VOC/S-VOC into headspace of vial with subsequent adsorptio…

NO OPTION AT ALL!!

Use "Lab Prepared & Freshly Prepd DP", containing all the ingredients
Disadvantage:
- Some volatile impurities may be present in "Prepared DP" but not in… material (lyophilization also removes a lot of VOC/S-VOC impurities)
- Degradation of DP may/will be different in solution compared to Lyop…

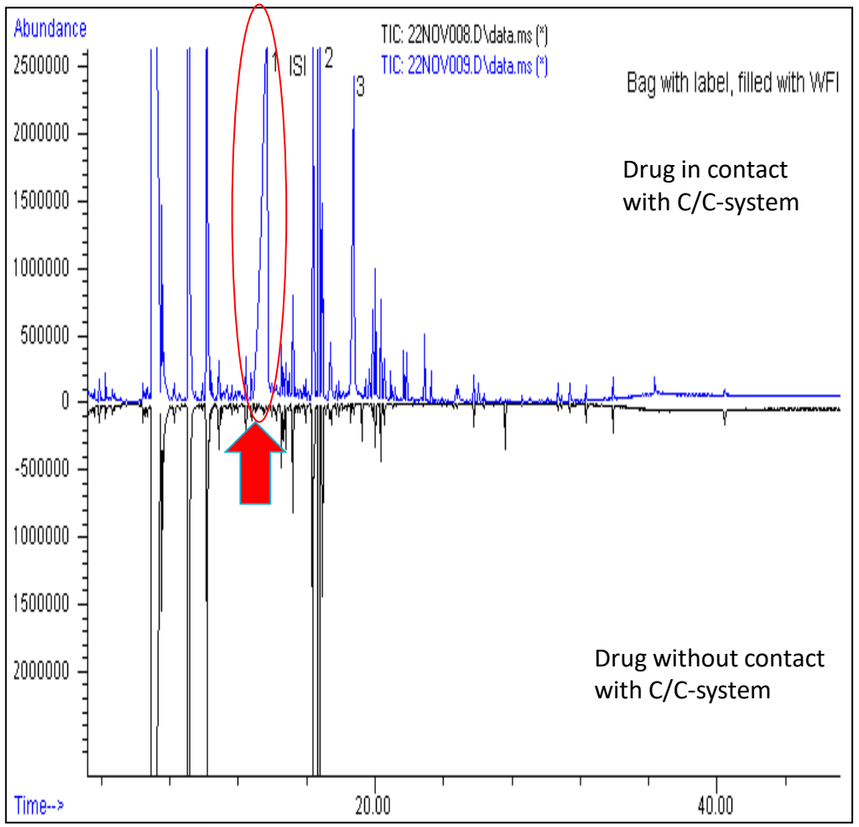
AN OPTION… WITH LIMITATIONS

Emptying Lyo-vial right after manufacturing and store the dry LYO-pr…
Disadvantage:
- Find the right container for long term storage?
- How to keep the LYO-DP dry over the shelf life?

AN OPTION… WITH LIMITATIONS

The Challenges and Consequences of Leachables Profiling after Reconstitution

LEACHABLE STUDY DESIGN



RELY MORE ON TARGET ANALYSIS OF LEACHABLES IN THE DRUG PRODUCT WITH QUANTITATIVE METHODS

ADD A SCREENING STEP:

TARGETED SCREENING FOR EXTRACTABLE COMPOUNDS

ALTERNATIVE: SCREENING WITH A WELL POPULATED DATABASE OF POTENTIAL RUBBER EXTRACTABLES

OR: REPORT ALL DIFFERENTIAL COMPOUNDS FROM BLANK

- **Advantage:** unexpected leachables, reactive leachables detected
- **Disadvantage:** potential reporting of DP degradation compounds

EVALUATE TRENDS (eg via t=0)

EVALUATE E & L CORRELATIONS

EVALUATE REACTIVITY

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5. Reactive Leachables – a Concern for LYO-DP Applications

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5. Reactive Leachables – a Concern for LYO-DP Applications

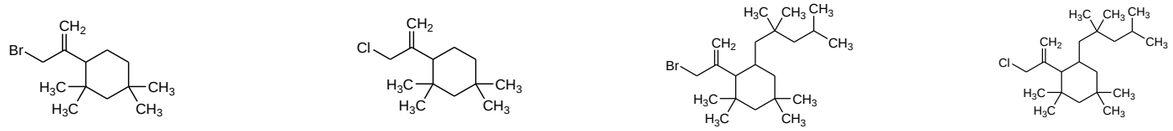
REACTIVITY

- WITH SMALL MOLECULE API'S
- WITH EXCIPIENTS AN OTHER INGREDIENTS
- WITH THERAPEUTIC PEPTIDES AND PROTEINS

ELECTROPHILIC LEACHABLES

REACTING WITH NUCLEOPHILIC FUNCTIONAL GROUPS OF PEPTIDES AND PROTEINS

MOST OCCURING REACTIVE LEACHABLES IN LYO:



Halogenated Rubber Oligomers (Alkylating Agents)

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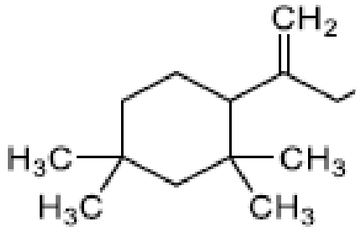
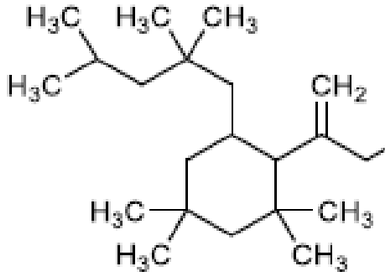
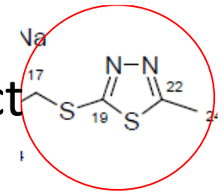
Reactive Leachables – a Concern for LYO-DP Applications

WITH SMALL MOLECULE API'S

Adduct Formation of an API with the $C_{13}H_{23}Br$ and $C_{21}H_{39}Br$ oligomers





Drug Product 

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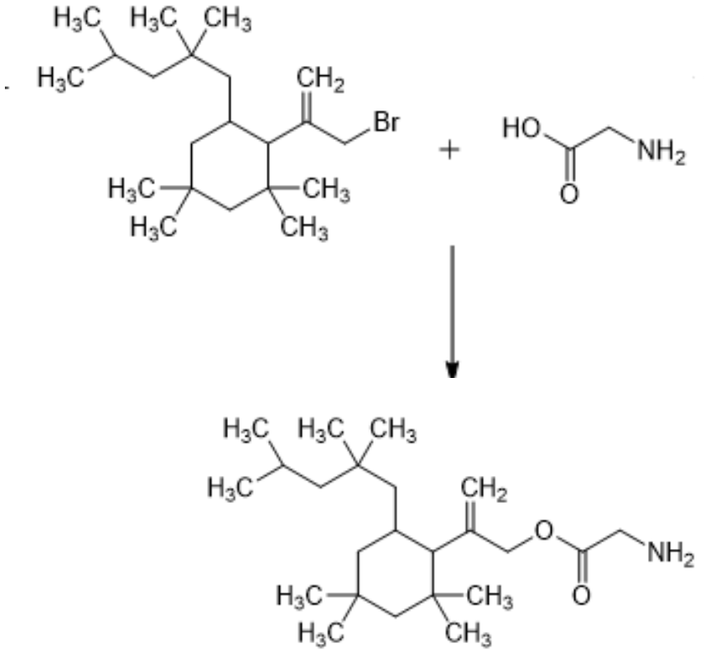
Reactive Leachables – a Concern for LYO-DP Applications

WITH EXCIPIENTS AN OTHER INGREDIENTS

Lyophilized Drug Product in a glass vial with a rubber stopper (without coating):

Excipients a.o.: Glycine

C21H39Br rubber oligomer source - leachable from a rubber stopper



Glycine (excipient, bulking agent)

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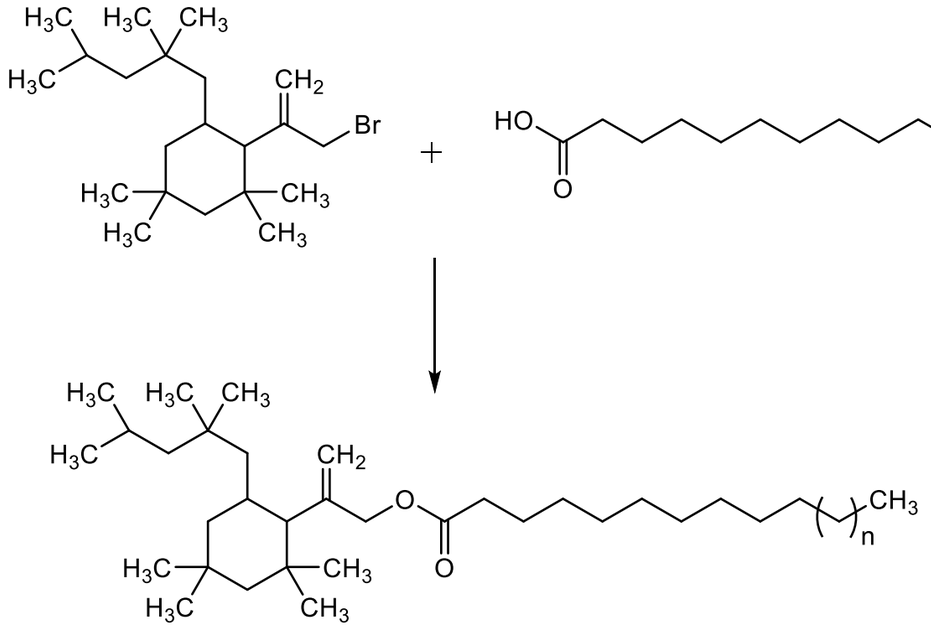
Reactive Leachables – a Concern for LYO-DP Applications

WITH EXCIPIENTS AN OTHER INGREDIENTS

Lyophilized Drug Product in a glass vial with a rubber stopper (without coating):

Excipients a.o.: Polysorbate 20

C21H39Br rubber oligomer source - leachable from a rubber stopper



Fatty acids source – Polysorbate 20

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Reactive Leachables – a Concern for LYO-DP Applications

WITH THERAPEUTIC PEPTIDES AND PROTEINS

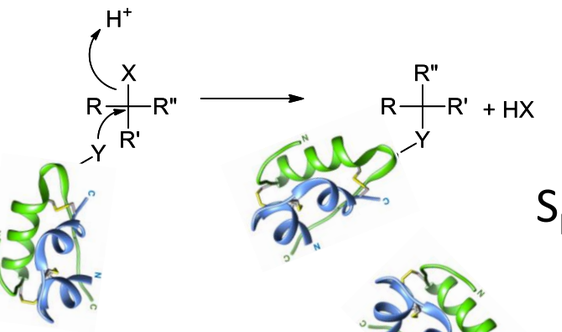
PDA Journal of Pharmaceutical Science and Technology

Creating a Holistic Extractables and Leachables (E&L) Program for Biotechnology Products

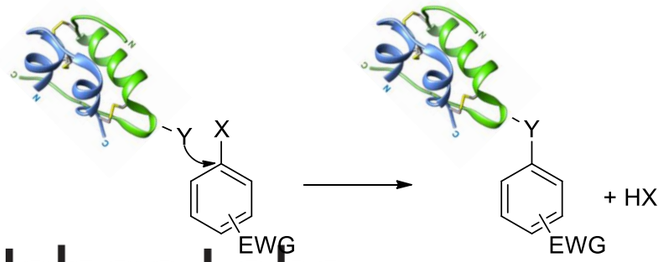
Kim Li, Gary Rogers, Yasser Nashed-Samuel, et al.

PDA J Pharm Sci and Tech 2015, *69* 590-619
Access the most recent version at doi:10.5731/pdajpst.2015.01073

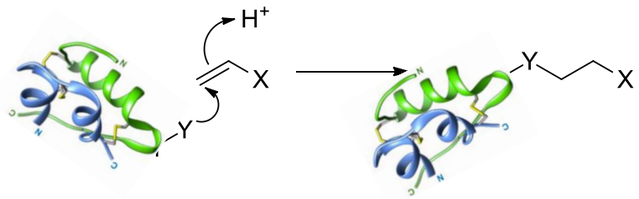
S_N2 reaction



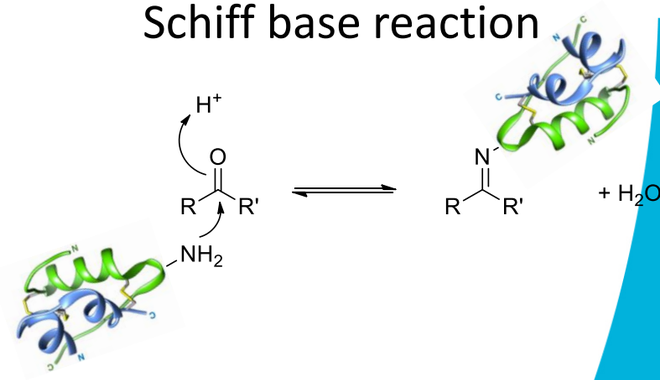
S_NAr reaction



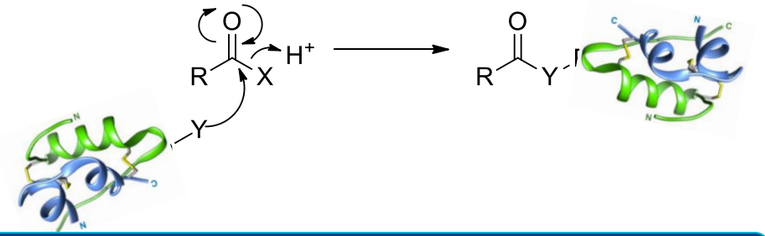
Michael addition



Schiff base reaction



acylation



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Electrophilic Leachables may react with **Nucleophilic Functional groups** of a **protein**

Reactive Leachables – a Concern for LYO-DP Applications

WITH THERAPEUTIC PEPTIDES AND PROTEINS

Leachable	Reacted with Lyophilized Glargine (Insulin Peptide)?
cis-9,10-epoxystearic acid	✓
$C_{13}H_{23}Br$ rubber oligomer	✓
2-Chloroacetophenone	✓
Isophorone diisocyanate	✓
2,6-di-tert-butyl-p-benzoquinone	✓
7,9-di-tert-butyl-1-oxaspiro [4.5]deca-6,9-diene-2,8-dione	✓

Experimental R&D work, performed by Nelson Labs on Lyophilized Glargine

See presentation of Paulo Forte on Reactive Leachables and the R&D work we did and why it is relevant for Imunogenicity assessment for Therapeutic Protein

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6. Key Learnings

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Key Learnings

- The (regulatory) need or depth of performing an E/L-qualification is ambiguous
- The interaction mechanism between the LYO DP and the rubber stopper is NOT based upon a direct contact mechanism but goes through the mechanism of OUTGASSING
- This may lead to accumulation of leachables, adsorbed onto the Lyo cake
- In addition adsorbed Leachables may be reactive and may lead to DP degradation
- Adding a screening step in your formal leachable studies can evaluate the occurrence of leachable reactivity
- This can assist in mitigating the risk of the occurrence of immunogenicity through chemical modification of the Therapeutic Protein
- Consider the right rubber quality for your Lyophilized C/C-system – consult supplier

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Thank you

Questions?

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