PDA Training Course Extractables & Leachables

23-24 October 2025

Setting Up Leachable Studies - Do’s and Don’ts

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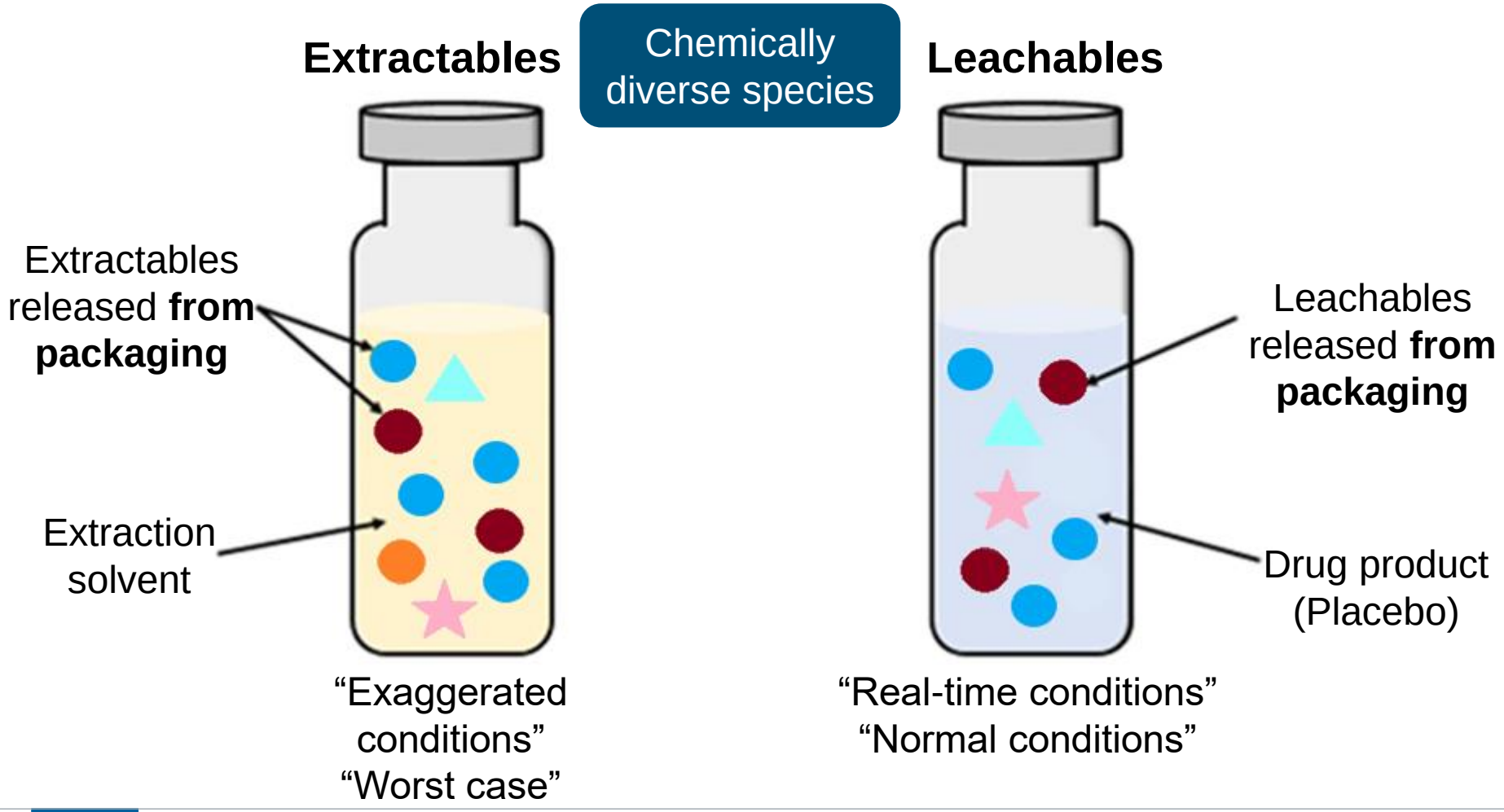
Extractables vs. leachables



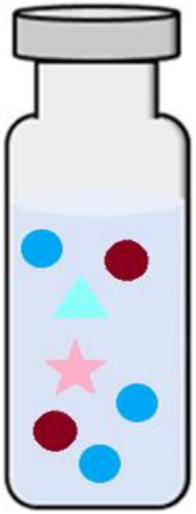
USP <1664> - **What?**

What?

"Lab investigation into the qualitative and quantitative nature of the leachables profile over the proposed shelf-life of a particular drug product"

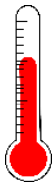
"discover, identify and quantify leachables"

Leachables



"Real-time/normal" conditions

- Pharmaceutical formulation as contact solution
- Conditions similar to stability studies
- Storage time / temperature / humidity



USP <1664> - **Why?**

Why?

"Assess the suitability for the use of a pharmaceutical packaging/delivery system"

- Assess the potential toxic consequences = **safety**
- Assess the impact on the **drug product quality, compatibility** and **stability**
- Provide an understanding of the **sources of leachables** and how to **evaluate** and **manage** them

- The focus is on **quantification** of **"target"** compounds
  - Known polymer additives
  - Validation package of container suppliers
  - **Extractables** study information
- Quantitative aspect: **validated methods** (ICH Q2 (R1))

Identities and levels of leachables should be known!

- Known compounds
- Quantitative methods

USP <1664> - **Why?**

Leachables studies can be used to…

1. Facilitate **timely development/selection** of the C/C packaging systems (material selection)
2. Establish qualitative/quantitative **correlations** between **extractables & leachables data**
3. Establish **worst case DP leachables profiles**, allowing a safety evaluation on the leachable compounds
4. Identify **trends in leachable accumulation** levels in the drug product over the shelf-life
5. Facilitate the **change control process**
6. Facilitate **investigations into the origin of identified leachables** that potentially may cause OOS for a marketed drug product

USP <1664> - **Why?**

Formal leachables studies are especially relevant:

- With the **actual packaging/delivery system** that will be commercialized
  - Final materials of construction (incl. color!)
  - Not with a prototype
  - Preferably on the same lots from the EXT study

- **On the product**, manufactured under conditions that reflect **actual commercial processes of production**
  - Fill - finishing - sterilization
  - Distribution and storage
  - Clinical use

- During **late stage product development**
  - Simultaneous with the formal product stability assessment
  - Should be performed on the **final drug product**, not on simulations thereof

USP <1664> - **Why?**

- For **“high risk” dosage forms**
  - Pre-clinical stage: selection of packaging components (possible with placebo or simulant)
  - Leachables characterization is recommended for test article batches in **clinical studies** (phase III)

- **Post market, supports the change control**
  - Changes in formulation
  - Changes in the manufacturing process
  - Changes in primary & secondary packaging or changes in the MoC of components

USP <1664> - **Why?**

- Leachables testing needed? ➔ Will depend upon the drug product

Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	**Likelihood of Packaging Component-Dosage Form Interaction**		
	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 Solutions and Suspensions	—	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

Degree of concern depends on:
- **dosage form**
- **route of administration**

USP <1664> - Leachables study design

Each case is different!

All possible sources of potential leachables should be included

Primary packaging
Secondary packaging (semi-permeable containers)

Details of **manufacturing process**

Nature of **contact with formulation** (direct vs. indirect)

Migration mechanism

Characteristics of drug product: **physical state**?

solid or liquid

Migration mechanism

Nature of **contact with patient**?

Identity and **maximum levels** of potential leachables

Chemical **composition** of the **packaging** material

Time of contact (long term vs. transient)

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Compounds that may migrate from process materials, may persist through the mfg. process and end up in the final DP: should be treated as leachables!

Do's and don'ts

Do – Don't #1: Blank solution

What is a good blank solution for leachables testing?

YES, we want to test for....

Leachables from the **packaging system**

NO, we don't want to test for ....

- Drug impurities
- Degradation products
- Batch variation
- Filling line
- Manufacturing equipment

Most important for the **screening step** in a leachables study!

Do – Don't #1: Blank solution

What is a good blank solution for leachables testing?

DOs

Blank solution:

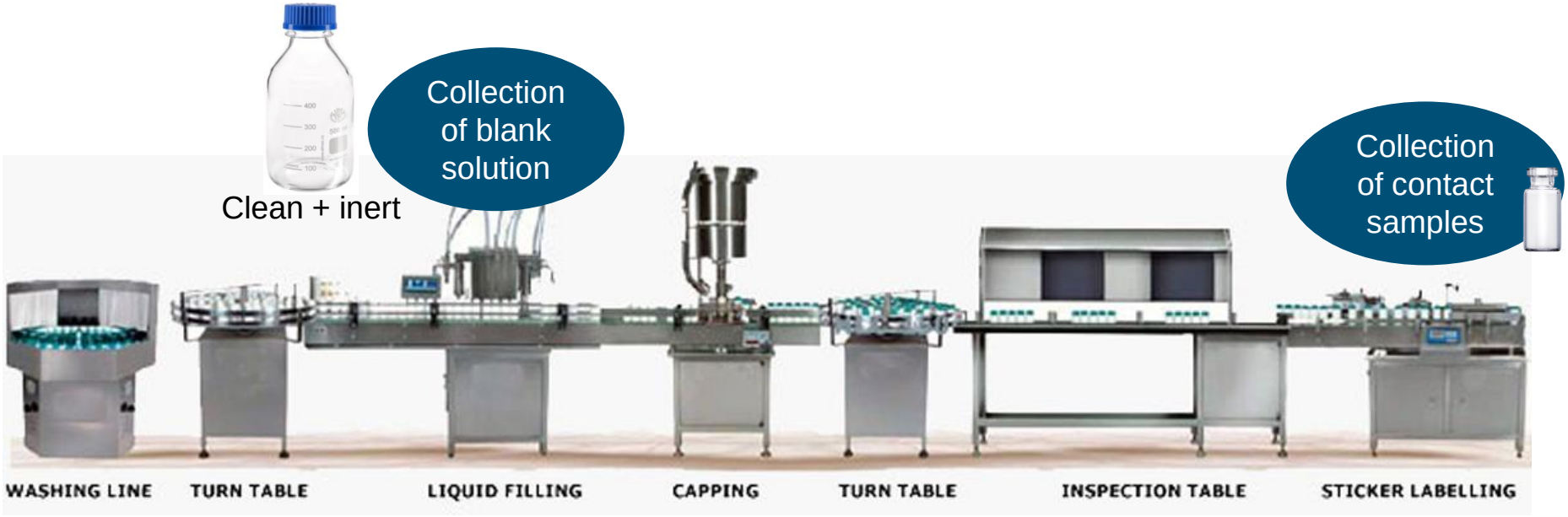
- **Leachables free real** drug product
- From the **same drug product batch** as the contact samples (if possible)
- **Aged** together with the **contact samples**

DON'Ts

But...

- Blank for a lyo product?
- Freshly prepared or frozen blank (non-aged)

Do – Don't #1: Blank solution

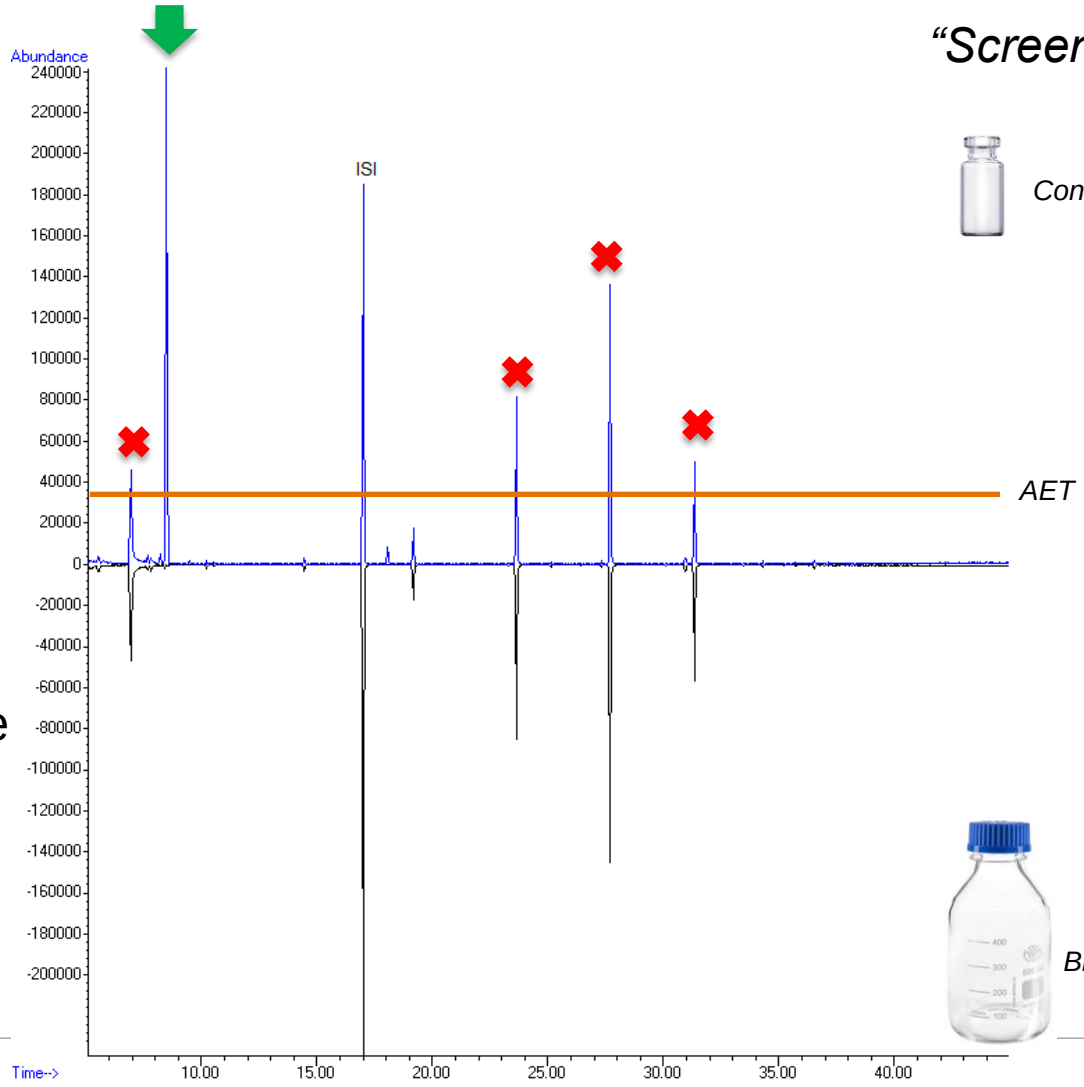


Blank solution:

- **Leachables free real** drug product (no placebo)
- From the **same drug product batch** as the contact samples (if possible)
- **Aged** (controlled storage) together with the **contact samples**

➔**Very important in screening leachables studies**

Do – Don’t #1: Blank solution



“Screening leachables study”

Contact solution

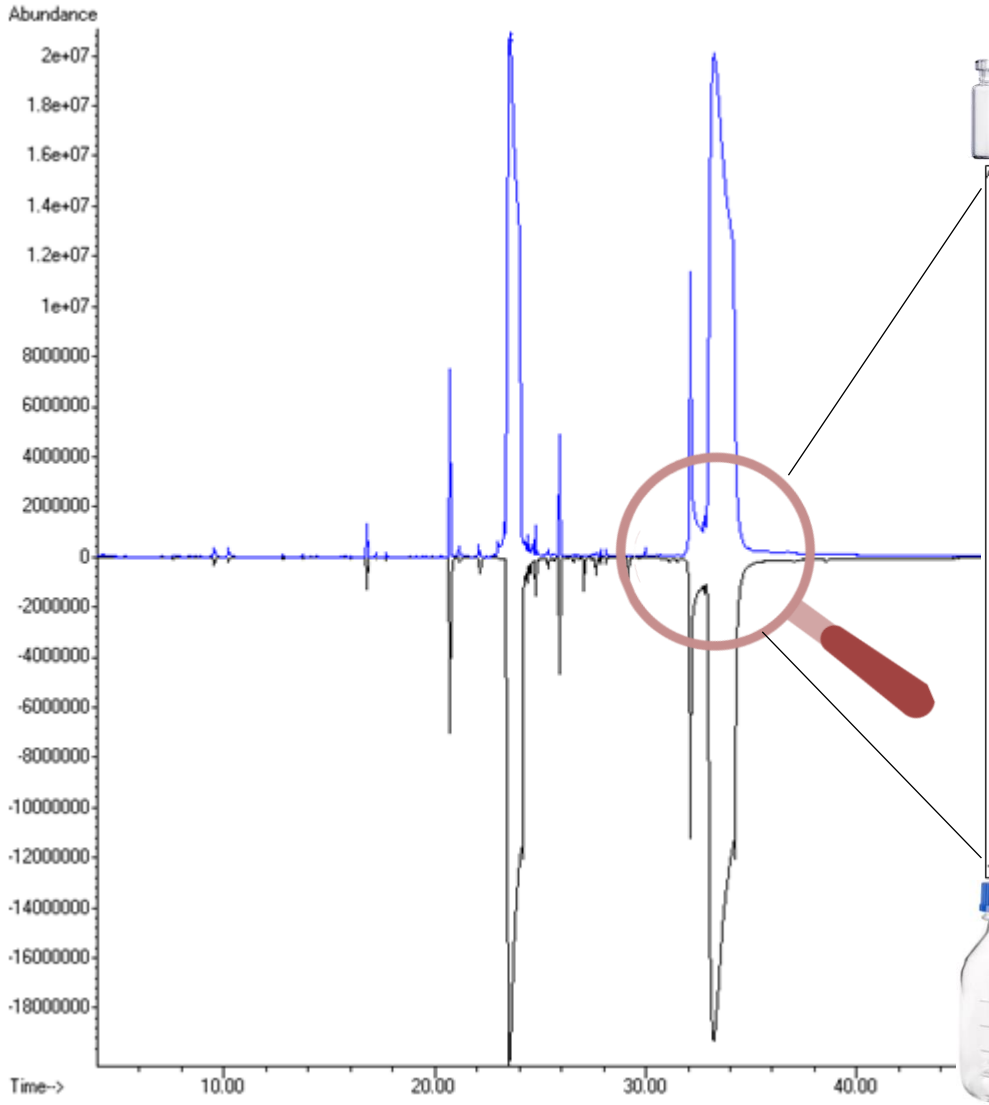
AET

Blank solution

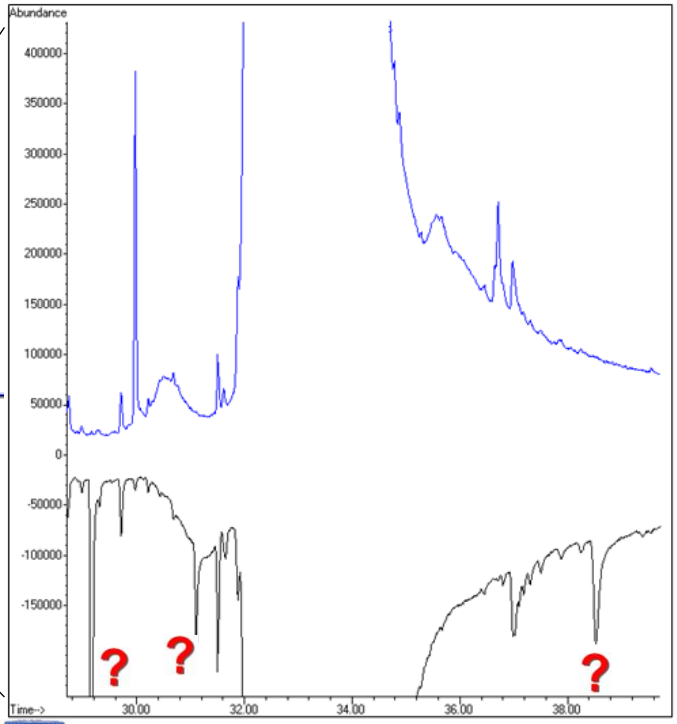
Most important in the **screening step** in a leachables study!

Do – Don't #1: Blank solution

"Screening leachables study"



Contact solution



Blank solution

Do – Don't #2: Batches?

- What the FDA wants....
  - Test multiple (3) batches

- What is a batch?
  - DP batch?
  - Batch of a CCS?
  - Batch of component of a CCS?
  - Batch of the raw material of a component of a CCS?

What is a batch?

- Contact your supplier!

DOs

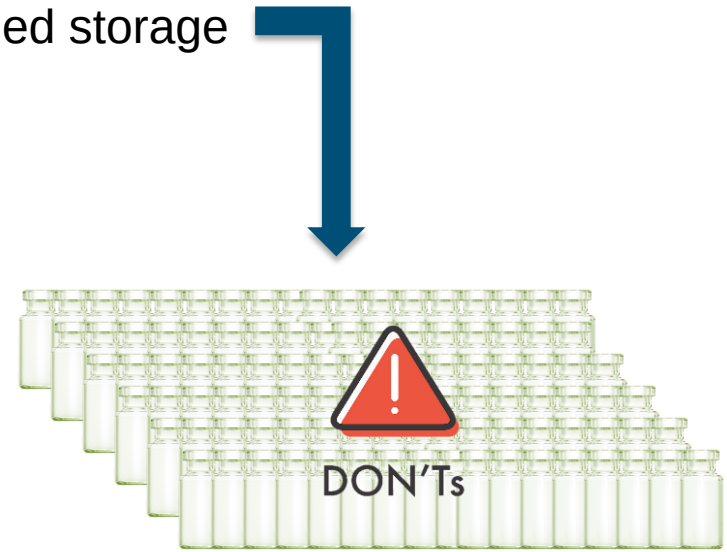
DON'Ts

- Ideally, 3 batches of drug product in 3 different batches of packaging
- Pooling of different batches?!

Do – Don't #3: Samples

- Sample requirements:
  - Provide sufficient amount of samples
    - Lab work has a large human factor ➔ something can go wrong!
    - Spare samples can save the day!
  - Please don't overkill!
    - We optimize our capacity for controlled storage

Spare samples!



DOs

Sufficient sample amount (contact samples and blank)

Analytical set-up and analytical limits (AET)

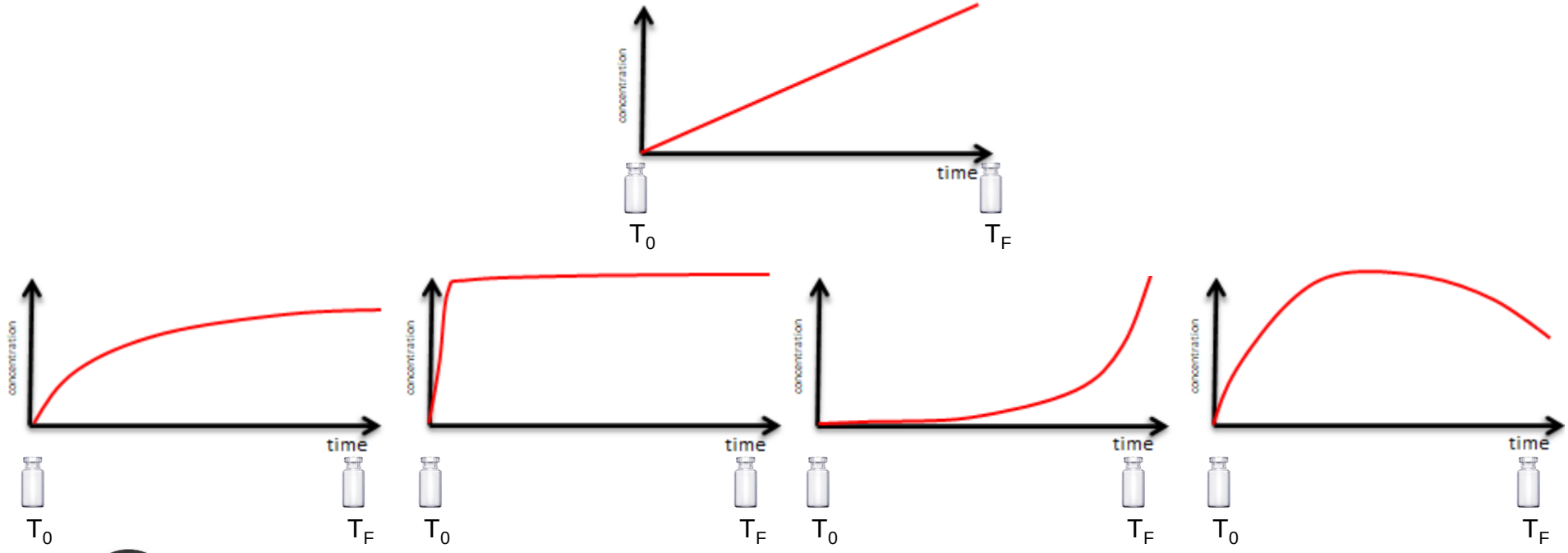
AET: analytical evaluation threshold

Do – Don’t #4: Ageing program

Which time points should be tested?

Do – Don't #4: Ageing program

- **Don't test your drug product only at the end of the shelf-life**
  - Not only because PQRI and USP<1664> say so...



DOs

Testing multiple time points

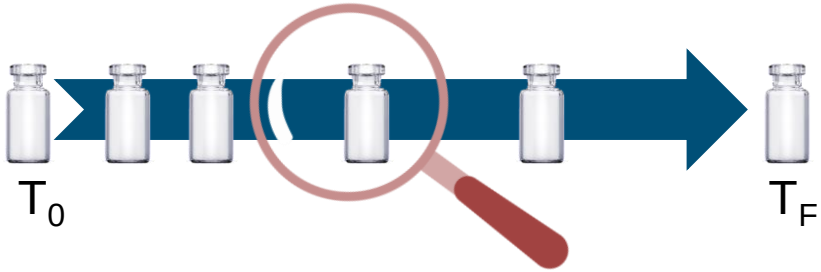
Testing only at the end of the shelf-life

DON'Ts

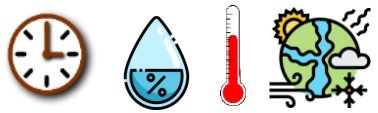
T_0 : initial time point
T_F : end of shelf-life

Do – Don't #4: Ageing program

- **Don't test your drug product only at the end of the shelf-life**
  - Not only because PQRI and USP<1664> say so...



- **Design an ageing program specific for your drug product:**
  - What is the shelf-life?
  - What are the recommended storage conditions?
  - What is the climatic zone of your market?
  - Are there specific in-use instructions for the patient?



DOs

- Real-time conditions
- May include accelerated conditions

Only accelerated conditions

DON'Ts

T_0 : initial time point
T_F : end of shelf-life

Do – Don’t #4: Ageing program

In summary

- Multiple time points
- Drug product specific
- Are there specific in-use instructions for the patient?
- Real-time conditions
- May include accelerated conditions
- Position of test item during ageing?

Worst case leachables profile!

Do – Don't #4: Ageing program

Example 1:

– Product for the Belgian market, shelf-life = 36 months, storage at ambient temperature

	Ageing time (months)								
	0	1	3	6	12	18	24	30	36
25 °C / 60% RH	X	-	-	X	X	(X)	X	-	X
30 °C / 65% RH	-	-	-	-	-	-	-	-	-
40 °C / 75% RH	-*	-	X	X	-	-	-	-	-

**real-time and accelerated aged samples are identical for time point zero*
(X): optional time point

DOs

- Multiple time points
- Real-time & accelerated conditions
- More sampling points in initial phase

Do – Don't #4: Ageing program

Example 2:

– Product for the Brazilian market, shelf-life = 24 months, storage at ambient temperature

	Ageing time (months)								
	0	1	3	6	12	18	24	30	36
25 °C / 60% RH	-	-	-	-	-	-	-	-	-
30 °C / 65% RH	X	-	-	X	X	X	X	-	-
40 °C / 75% RH	-*	-	X	X	-	-	-	-	-

**real-time and accelerated aged samples are identical for time point zero*
(X): optional time point

DOs

- Multiple time points
- Real-time & accelerated conditions
- More sampling points in initial phase

Do – Don't #4: Ageing program

Example 3:

– Product for the Italian market, shelf-life = 24 months, storage at 5 °C, in-use period for max. 3 months at ambient temperature

	Ageing time (months)								
	0	1	3	6	12	18	24	30	36
5 °C	X	-	X	(X)	X	X	X	-	-
25 °C / 60% RH	-*	-	(X)	X	-	-	-	-	-

After x months ageing at 5°C, transfer the samples to 25 °C / 60% RH to simulate the in-use period

**real-time and accelerated aged samples are identical for time point zero*

(X): optional time point

DOs

- Multiple time points
- Real-time & accelerated conditions
- More sampling points in initial phase

Do – Don't #5: Quantitative methods

- How quantitative should the methods to measure the leachables be?
- Is it always necessary to have fully validated, fully quantitative methods in place?

NO!

ICH Q2 guideline

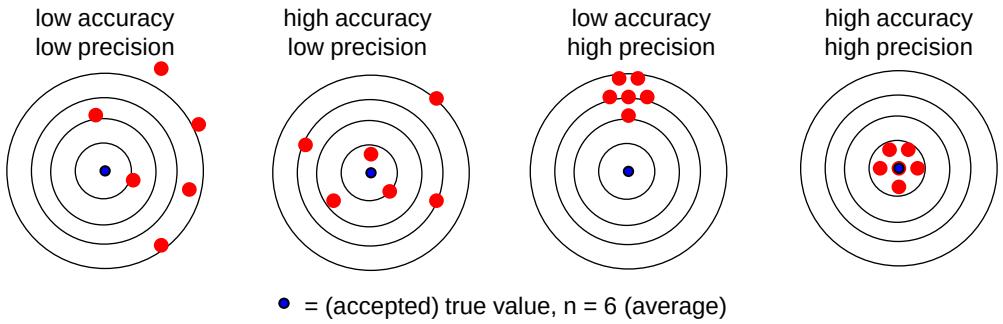
(Part I, chapter 1)

"*The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose*"

Possibilities

- Fully validated method
  - *According to ICH Q2 R1 (part II): complete (linear) method range, known accuracy and precision*
- Limited method validation
  - *Less parameters of ICH Q2 R1 taken in account*
- Limit test
- Method Suitability Test (MST)

Do – Don't #5: Quantitative methods



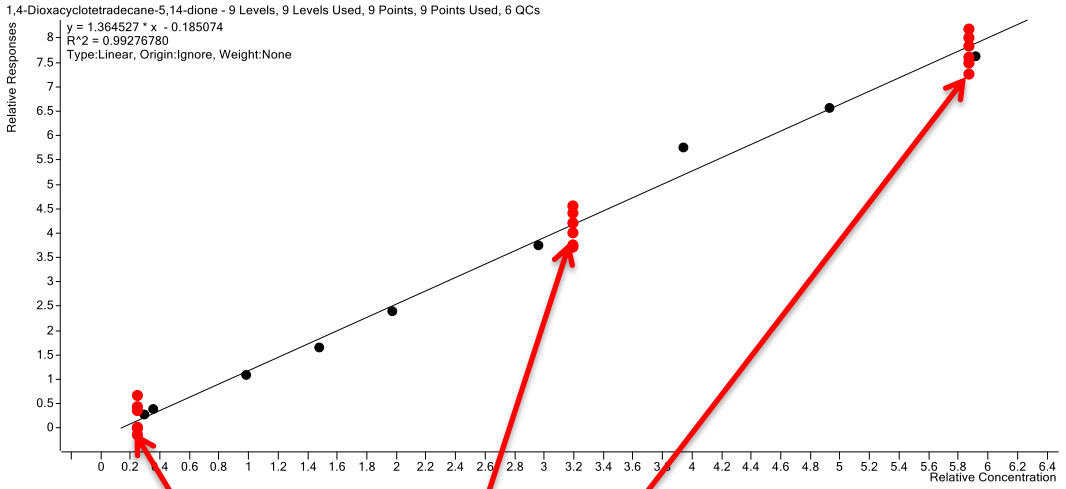
- The **accuracy** of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

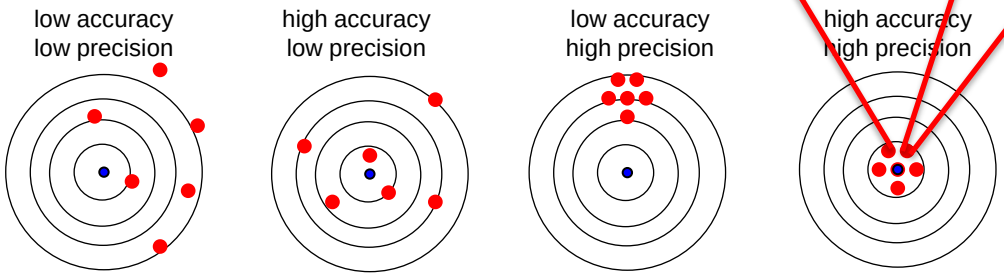
- The **precision** of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Source: ICH Q2 guideline

Do – Don't #5: Quantitative methods

Fully validated method

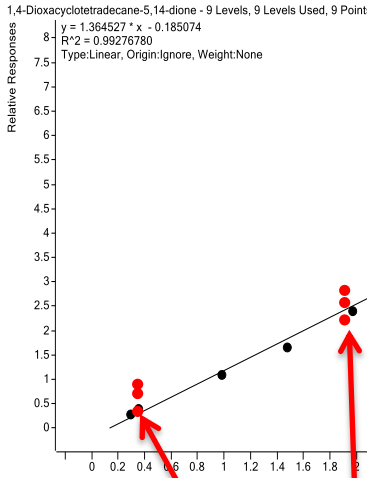


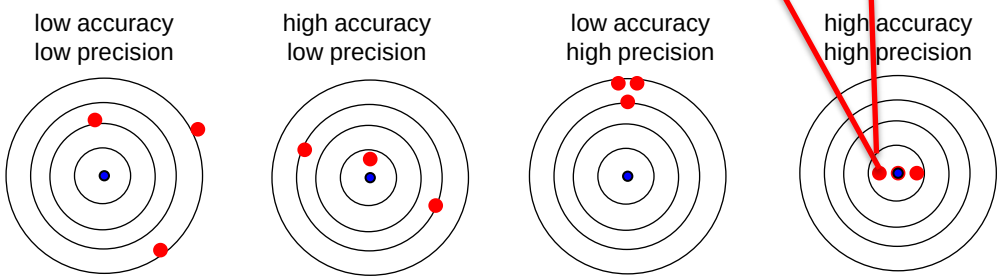


● = (accepted) true value, n = 6 (average)

Do – Don't #5: Quantitative methods

Limited validated method

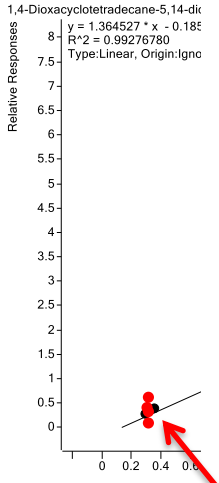


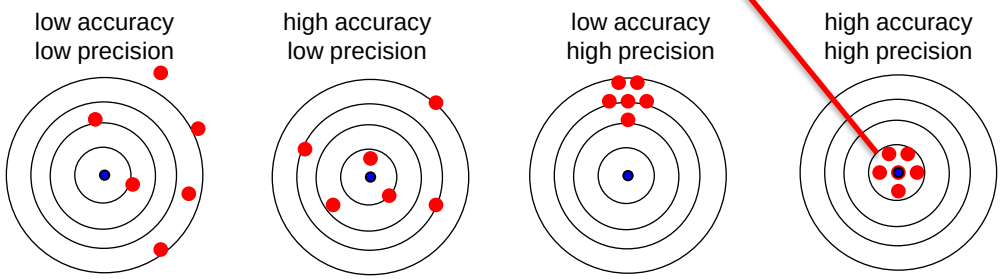


● = (accepted) true value, n = 3 (average)

Do – Don't #5: Quantitative methods

Validated limit test



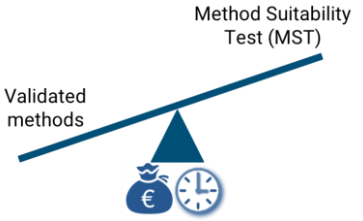


● = (accepted) true value, n = 6 (average)

Do – Don't #5: Quantitative methods

Method Suitability Test (MST)

- **Cost friendly** and **fast alternative** to method development and validation
- Performed in **drug product** (=drug product specific)



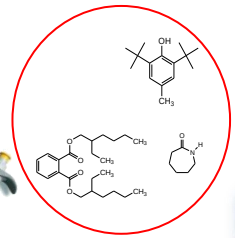
MST procedure

- Spike analytical standards of the target compounds to a portion blank (leachables free) solution
  - N = 1
  - Spike level = AET
- Spiked samples are treated as other samples
- MST can prove the **detectability of the targets with generic methods**

Do – Don't #5: Quantitative methods

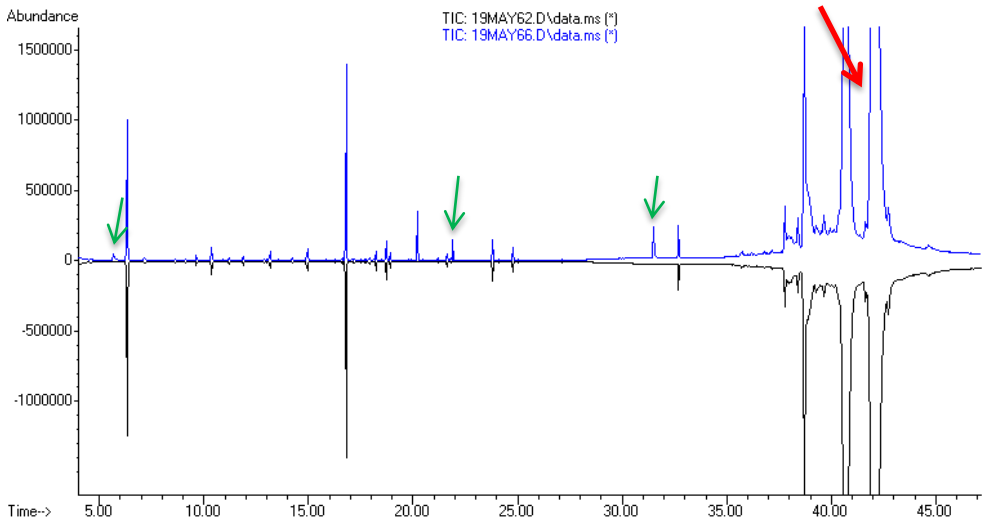
Method Suitability Test (MST)

Spike level = AET
N=1



Blank solution

Drug matrix



DOs

MSTs can prove the detectability of the targets with **generic methods** and thus the **suitability of the method to detect target**

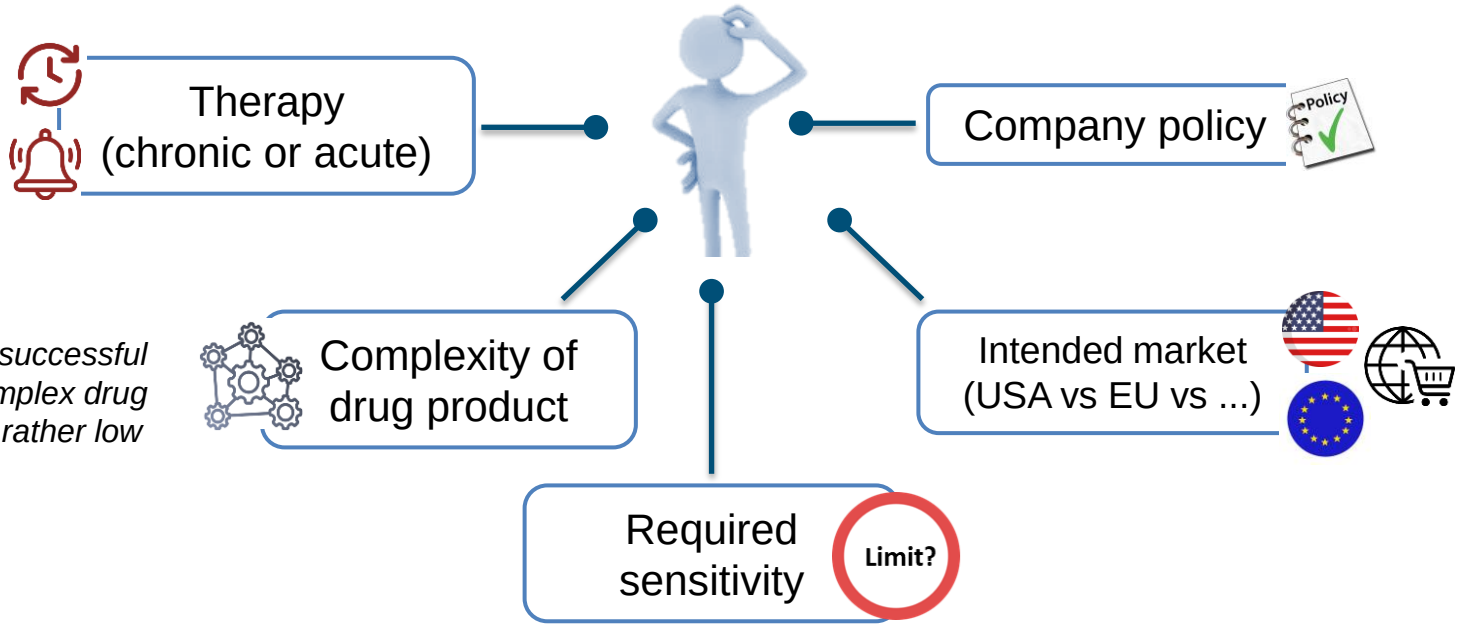
Do – Don't #5: Quantitative methods

Method Suitability Tests (MSTs)

- Drug product specific
- Less time and resource consuming

Validated methods

- Drug product specific
- Time and resource consuming



Chance on successful MST on complex drug matrices is rather low

The flow of an E&L study: don't forget the screening step!!

EXT → TOX → LEA → TOX

Which chemical impurities are migrating into the drug product?

Targeted

Screening

DOs

Target compounds
Quantitative
Compound-specific tresholds

Unexpected leachables
Semi-Quantitative
Safety Concern Threshold / Qualification Threshold

All leachables in the DP at >5 µg/day need to be identified (D. Mellon, FDA).
➔This implicitly calls for a screening step in a leachable evaluation.

The flow of an E&L study: don't forget the screening step!!

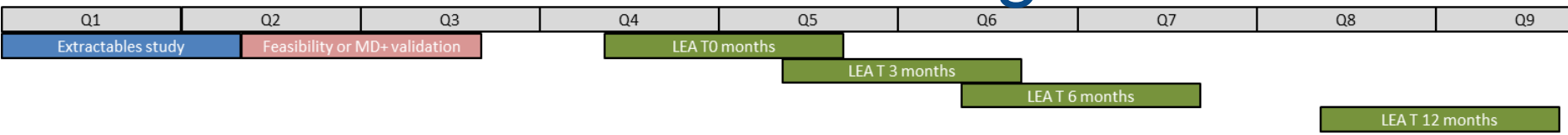
- Screening for **unexpected leachables** is considered to be necessary – when (technically) possible*

- Sources of *"unexpected leachables"*
  - **Degradation of materials and additives** over shelf-life, not always accounted in an EXT study
  - **Degradation, hydrolysis, oxidation of leachables** when present in the DP
  - **Reactive leachables** (reacting with DP ingredients or API)
  - ...

- May address inaccuracies in the study design.

**Technically possible means: some DP are too complex in their composition to allow screening at final AET levels.*

Do – Don't #6: Planning



… is **time** consuming

- Multiple time points
- Real-time (& accelerated) conditions

Leachables testing...

… depends on **extractables data**

…depends on **target** selection

… depends on drug **product manufacturing** schedule

...depends on **method development** and **validation**

DOs

- Think upfront and plan ahead!
- Be aware of submission deadlines!

Do – Don't #7: Simulation study vs. leachables study

What if...

… the discovery and identification of all actual leachables in a leachables study is analytically not feasible?

Simulation study

Differences with leachables studies

- The drug product is replaced with a **simulating solvent**
- The ageing conditions have been **accelerated**
- The test article can be the complete packaging system or a partial packaging system

Find and **identify** extractables which are **probable leachables**

According to USP<1663>

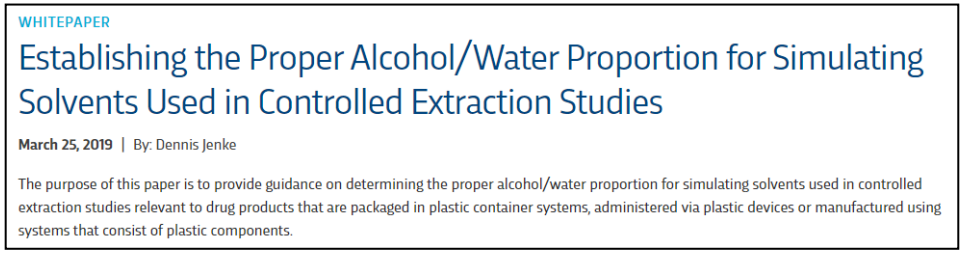
Establish which extractables must be targeted in a migration study

- Screening approach
- Mimic circumstances of final drug product: acceleration, moderate exaggeration
- Worst case: sufficient amounts to identify
- Safety/ toxicological risk assessment to define target leachables

Do – Don't #7: Simulation study vs. leachables study

How to select a simulating solvent?

1. **Aqueous based solution with organic solvent** added to mimic the extraction propensity of the actual DP
   ➔Mix of alcohol in water (Nelson Labs Whitepaper, www.nelsonlabs.com)


WHITEPAPER

Establishing the Proper Alcohol/Water Proportion for Simulating Solvents Used in Controlled Extraction Studies

March 25, 2019 | By: Dennis Jenke

The purpose of this paper is to provide guidance on determining the proper alcohol/water proportion for simulating solvents used in controlled extraction studies relevant to drug products that are packaged in plastic container systems, administered via plastic devices or manufactured using systems that consist of plastic components.

2. The **drug product vehicle** when it is not substantially different from the DP

3. The **drug product itself** → "Screening leachables study"

Do – Don't #7: Simulation study vs. leachables study

How to select the conditions of a simulation study?

1. **Exaggerated and accelerated** conditions
   - Exaggerated:
     - Composition of the simulant
     - Increased surface area
     - Underfilling (bags)
   - Accelerated: temperature of storage – accelerated ageing

2. Study the **complete packaging system**, not only the individual parts

3. Or **study some parts of the packaging system** which are of particular interest

Remark: *beware of solubility of the extractables in the extraction medium when "back extrapolating" to original ratios*

Do – Don't #7: Simulation study vs. leachables study

PROS

- **Usable data** when leachables cannot be measured (e.g. complex drug formulation)
- Recognized by USP 1664 and PDP recommendations

CONS

Think as a regulator

- Regulatory acceptance

- Only end point is tested (no trends)
- Secondary leachables* not covered

**Reaction products of leachables with DP*

- **Risky**! Contributes to the E&L assessment, but is not sufficient
- **Justifications** to prove the predictive character of simulation study compared to formal leachables study
- **Documentation** with failed attempts to help justifying use of simulation study

Do – Don't #8: What if the formulation is too complex?

What if...

… the drug product is so complex and challenging in its formulation that a normal analytical approach cannot be taken?

DOs

- Try to **prove** and **document** the analytical difficulties
- Narrow down the analytics: focus on **known compounds** (targeted approach, no screening possible)
- Consider a simulation study*?!

**Justify a simulation study by proving the difficulties in the regular leachable study approach*

Questions?