

# Leachables study: dos and don'ts

Dr. Dries Cardoen



# USP<1664> – WHY?

- Assess the potential toxic consequences = **safety**
- Assess impact on the **drug product quality**
- “Real-time” conditions
  - Storage time / temperature / humidity
  - Conditions similar to stability studies
  - Pharmaceutical formulation as contact solution
- 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))





## Leachables studies can be used to:

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

**Formal leachables** studies are especially relevant:

- With the actual C/C-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
- On registration batches of the drug product during overall stability assessments



# USP<1664> – WHEN?

- For “high risk” dosage forms
  - Pre-clinical stage: selection of packaging components (possible with placebo or simulant)
  - Leachable 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> – HOW?

- 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

# USP<1664> – HOW?

- Will depend upon the purpose and goals of a leachable study
- However, they require similar types of information
  - Chemical composition of packaging
  - Details of mfg. process
  - Extractables Assessment
  - ALL potential sources should be assessed
    - Primary packaging
    - Secondary packaging (important for semi-permeable containers)
- Nature of contact : direct versus indirect contact (migration mechanism)
- Time of contact: long term vs. transient
- Characteristics of the drug product formulation
  - E.g. solid or liquid? (migration mechanism)
- Compounds that may migrate from bulk packaging, may persist through the mfg. process and end up in the final DP: should be treated as leachables!!



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A good blank solution is the real drug product, but without leachables!!

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What do you want to test for?



Yes 	No 
Leachables from the container closure system	Drug impurities
	Filling line
	Manufacturing equipment
	Degradation products
	Batch variation

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Session on SUS 

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Session on SUS ←

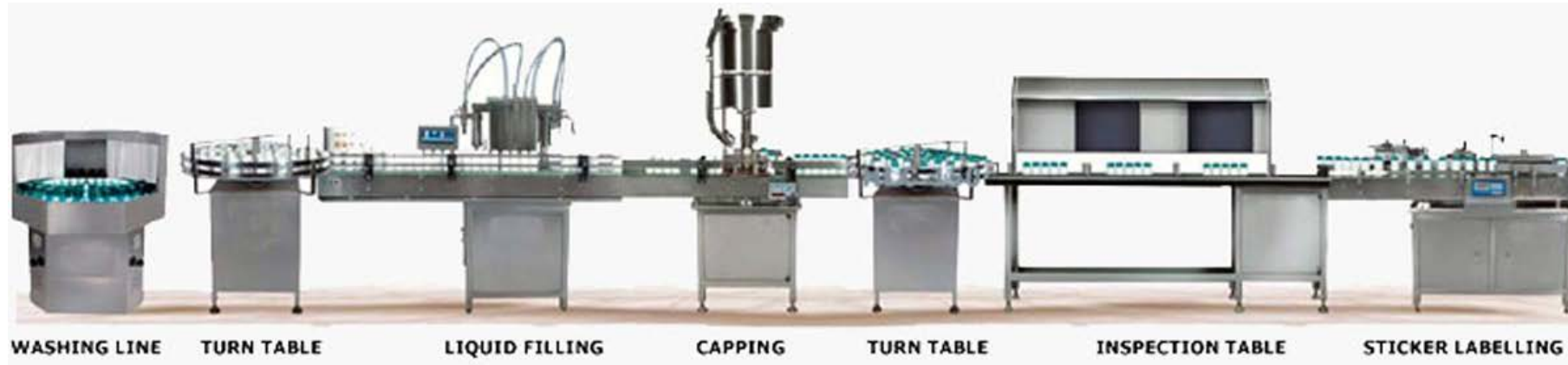
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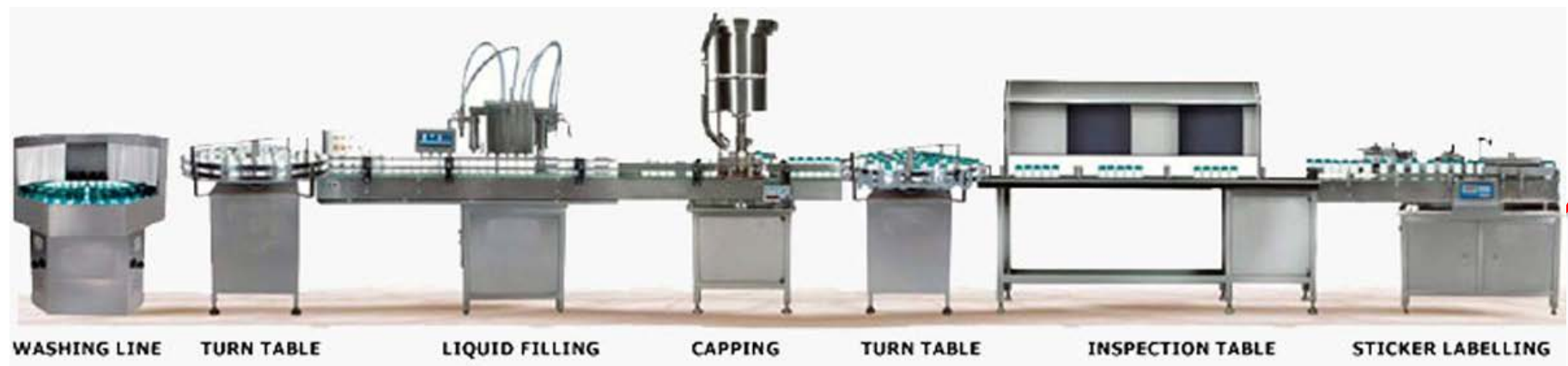


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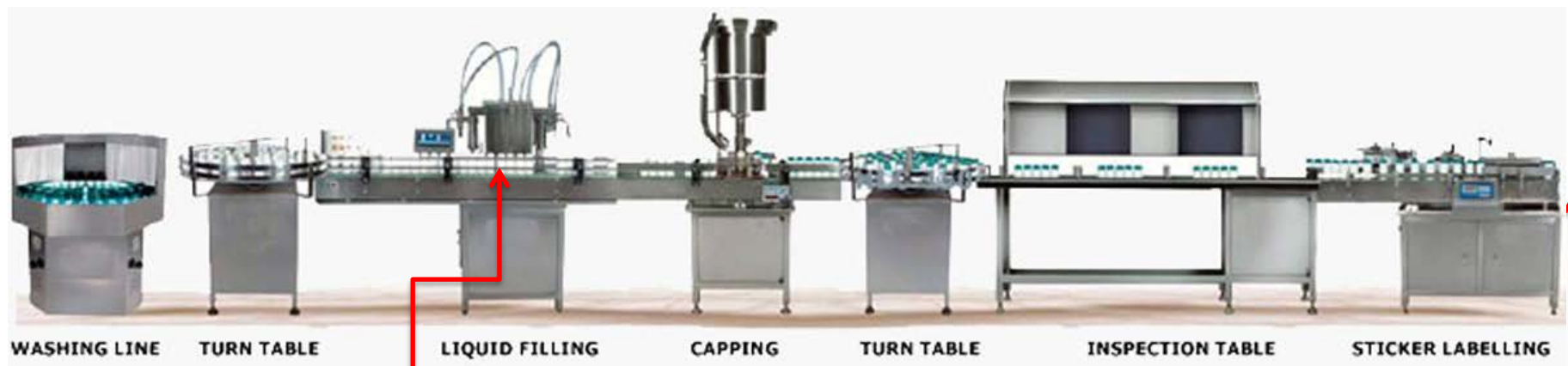


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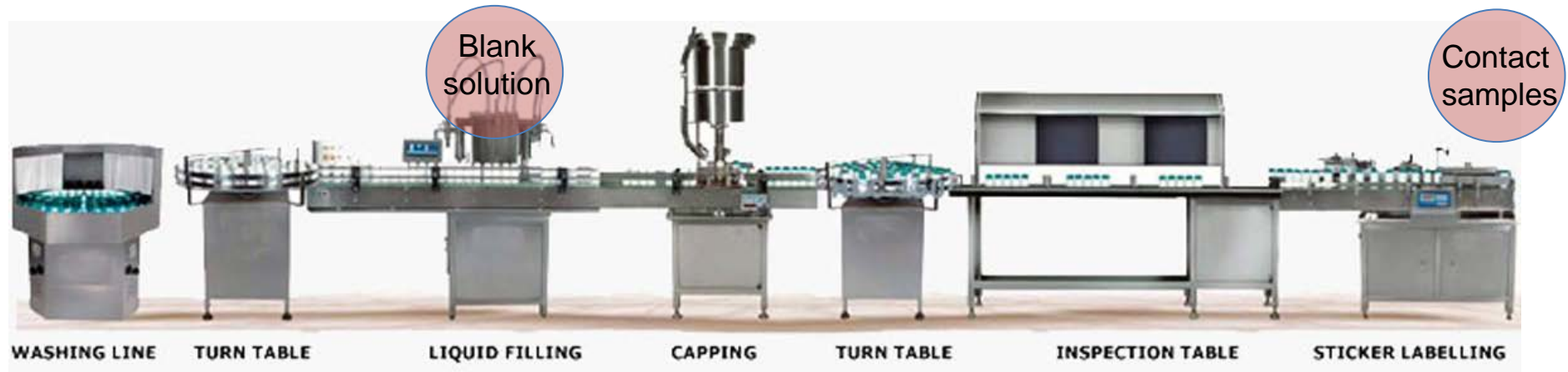


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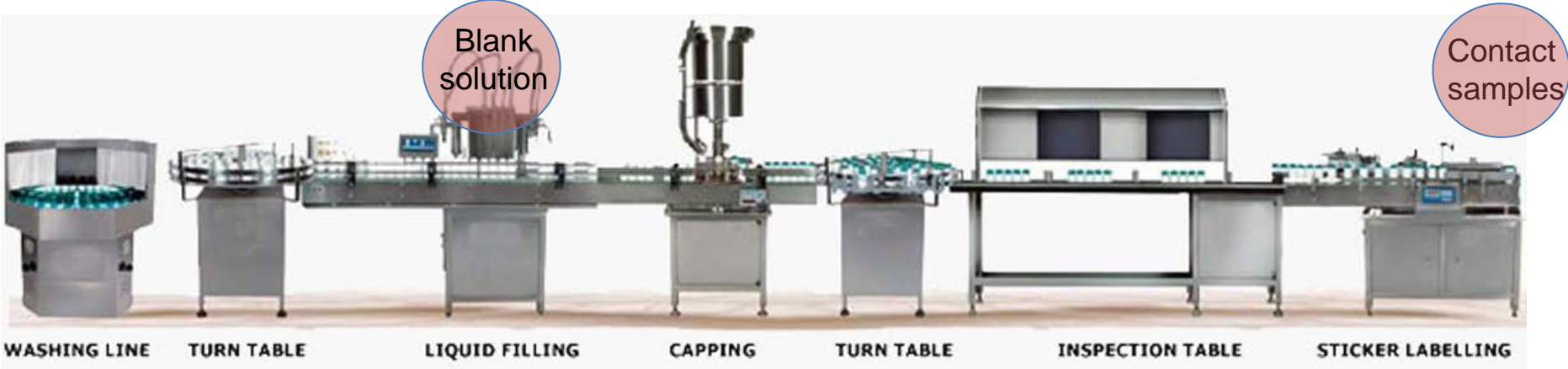
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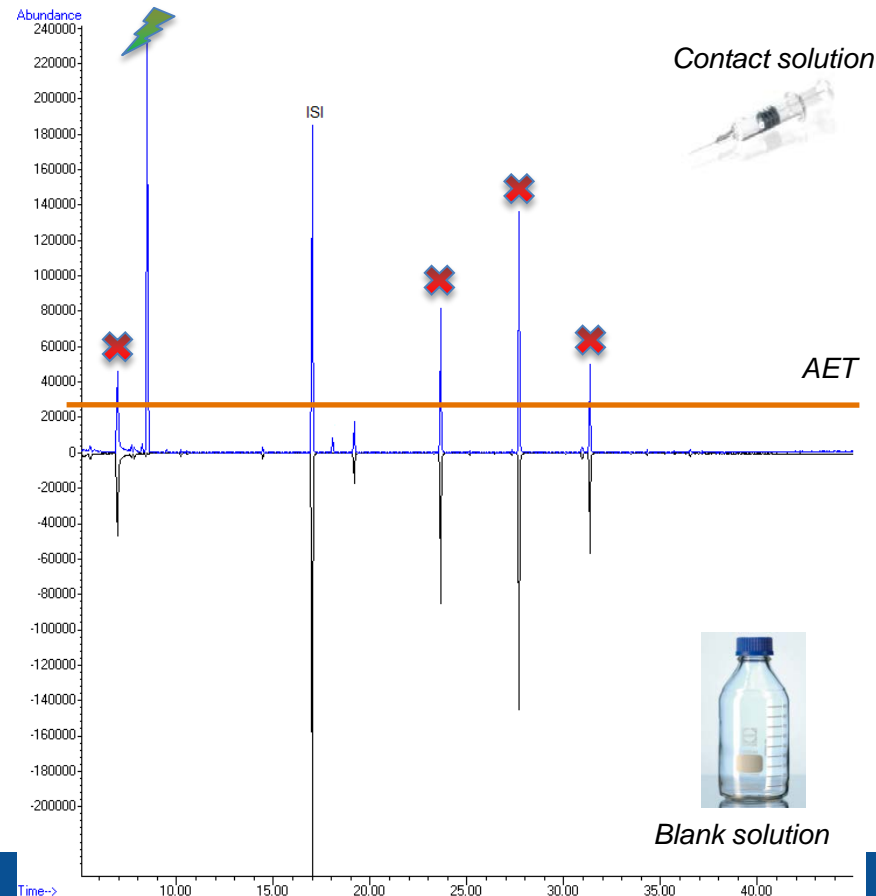
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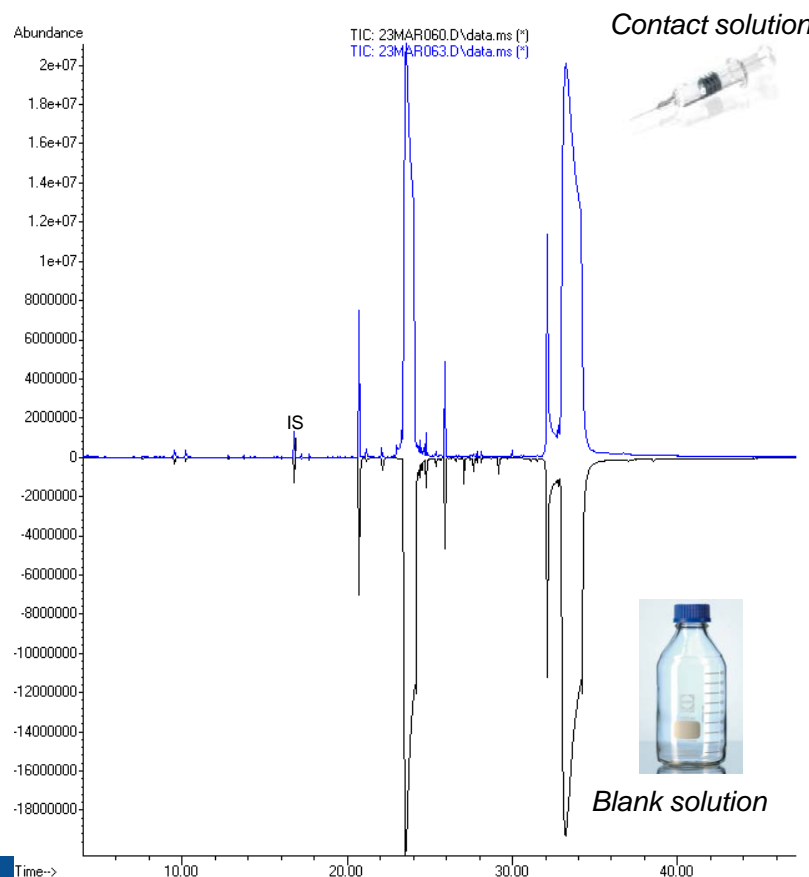
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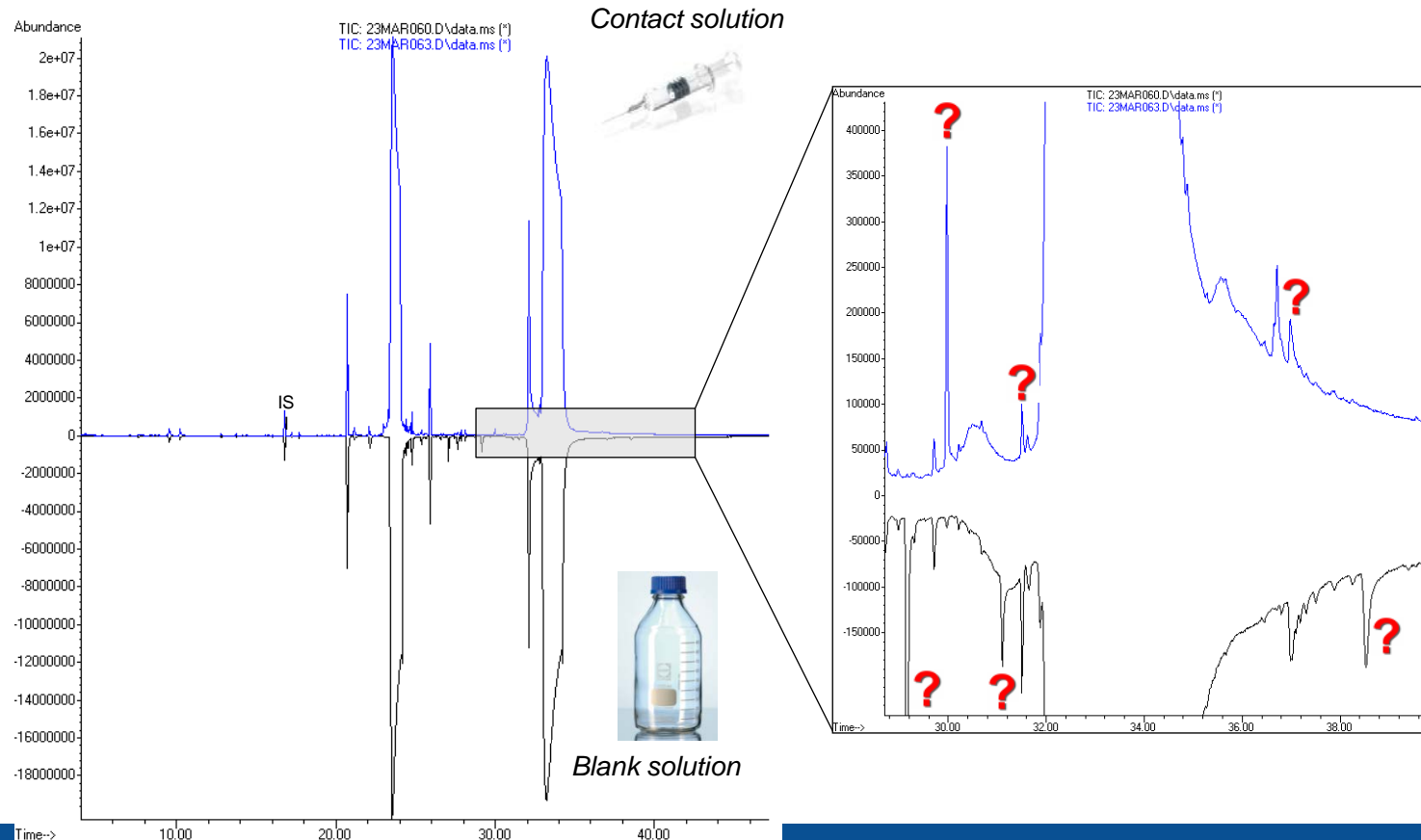
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# Do – Don't #2: Batches?

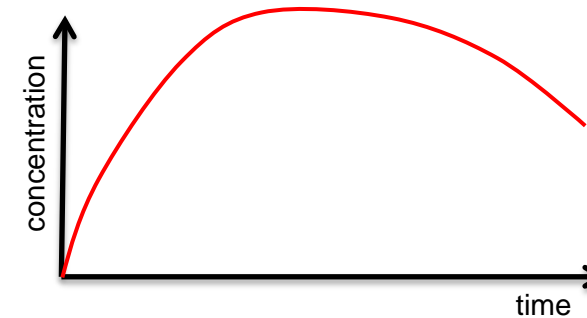
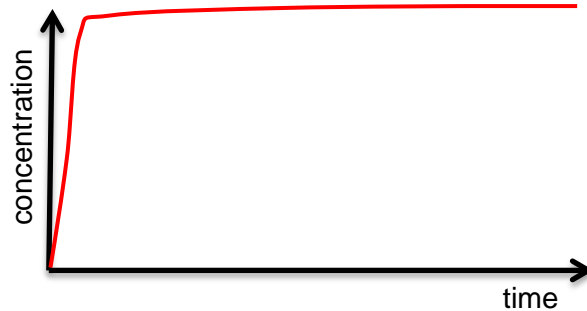
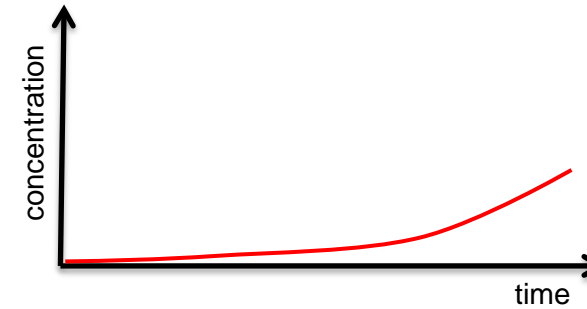
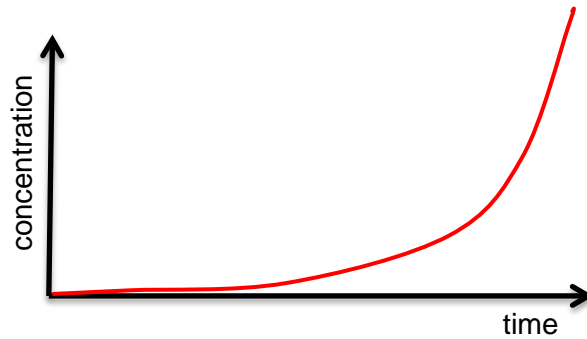
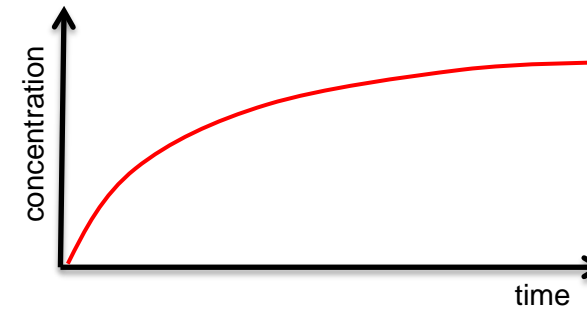
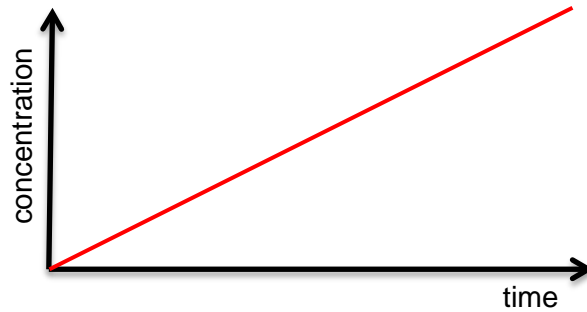
- What the FDA wants....
  - Test multiple batches (3) of critical drug products (e.g. inhaled drug products)
- What is a batch?
  - DP batch?
  - Batch of a CCS?
  - Batch of component of a CCS?
  - Batch of the raw material of a component of a CCS?
- Contact your supplier!

# Do – don't #3: Ageing program

- Don't test your drug product only at the end of the shelf life
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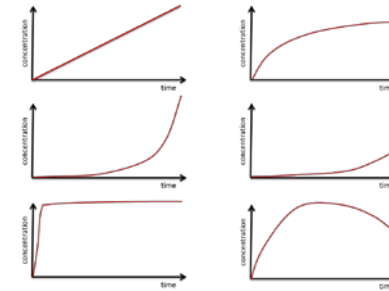
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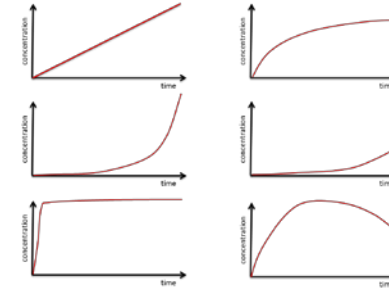
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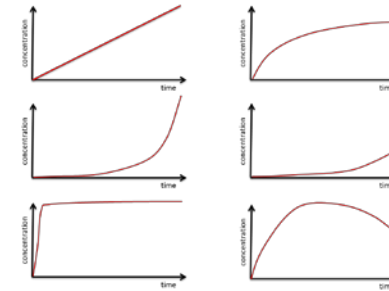
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- Example 1:
  - A product for Belgian market, shelf life = 36 months, storage at ambient temperature



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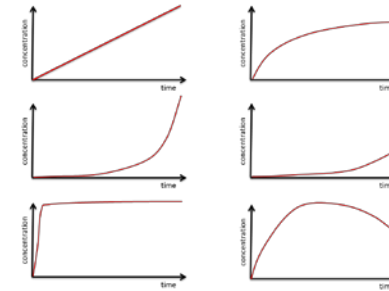
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	0 months	1 month	3 months	6 months	12 months	18 months	24 months	30 months	36 months	... months
25 °C / 60 % RH	X			X	X	(X)	X		X	
30 °C / 65 % RH										
40 °C / 75 % RH	(X)		X	X						

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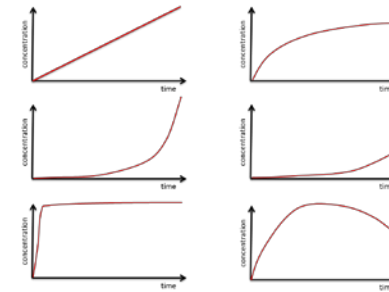


- Example 2:
  - A product for Brazilian market, shelflife = 24 months, storage at ambient temperature

	0 months	1 month	3 months	6 months	12 months	18 months	24 months	30 months	36 months	... months
25 °C / 60 % RH										
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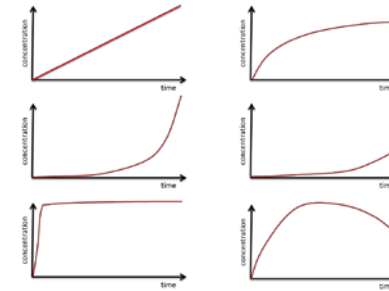
- Example 3:

- A product for Italian market, shelflife = 24 months, storage a 5 ° C, in-use for max. 3 months at ambient temperature

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5 °C	X			X	X	X	X			
25 °C / 60 % RH	(X)		(X)	X						

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    - ICH Q2 R1 (Part I, chapter 1):  
*“The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose”*

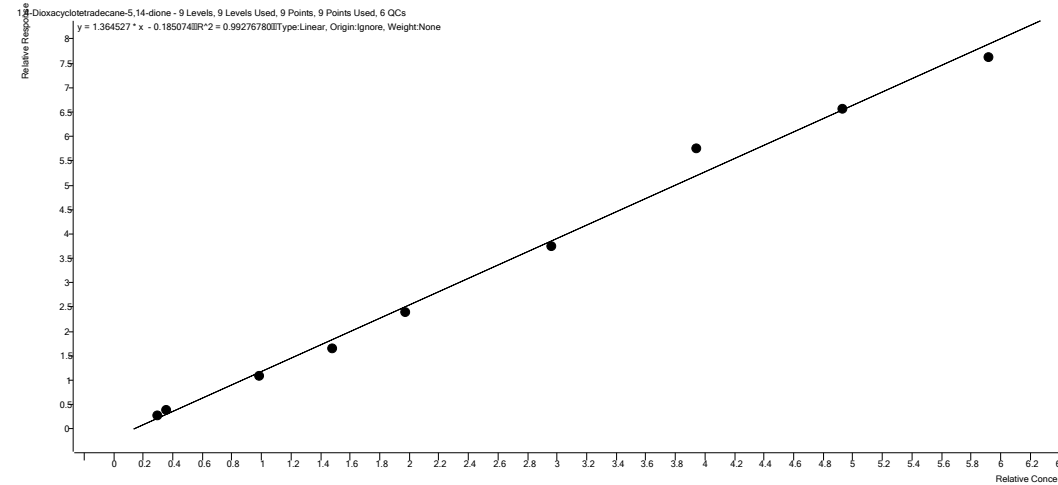


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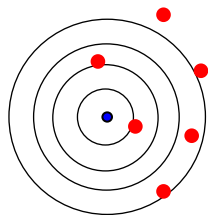
- How quantitative should the methods to measure the leachables be?
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    - ICH Q2 R1 (Part I, chapter 1):  
*“The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose”*
  - Possibilities:
    - Fully validated method according to ICH Q2 R1 (Part II)
      - Complete (linear) method range
      - Known accuracy and precision
    - Limited validation (less parameters of ICH Q2 R1 taken in account)
    - Limit test
    - Method Suitability Test

# Do – don't #4: Quantitative methods?

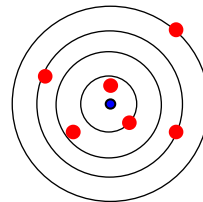
Quantitative validated methods:



low accuracy, low precision

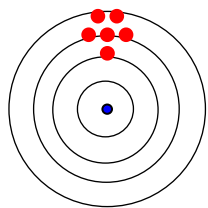


high accuracy, low precision

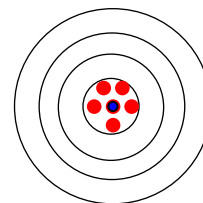


• = (accepted) true value, n = 6 (average)

low accuracy, high precision

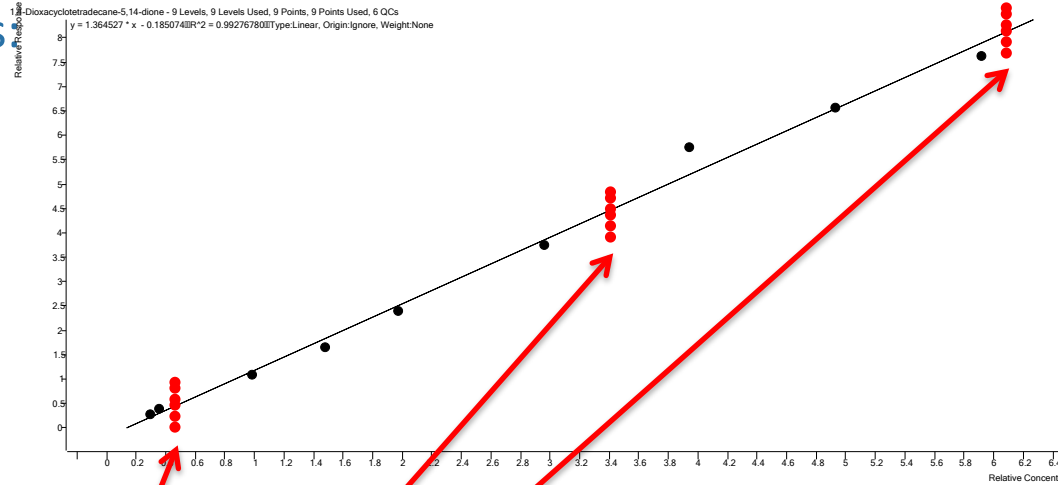


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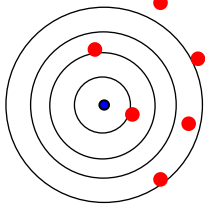


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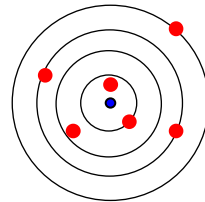
## Fully validated quantitative methods



low accuracy, low precision

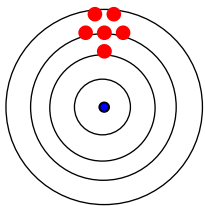


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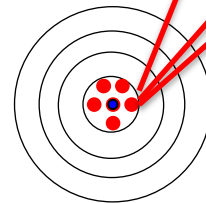


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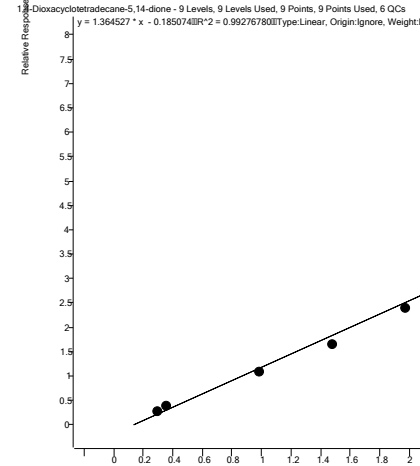


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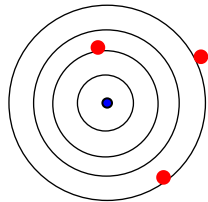


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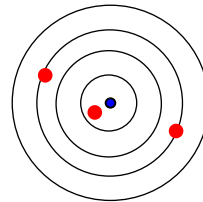
Limited validated methods:



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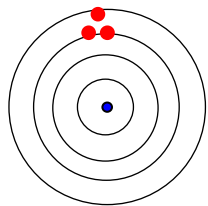


high accuracy, low precision

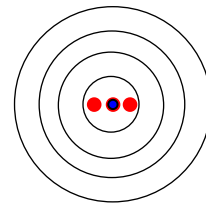


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low accuracy, high precision

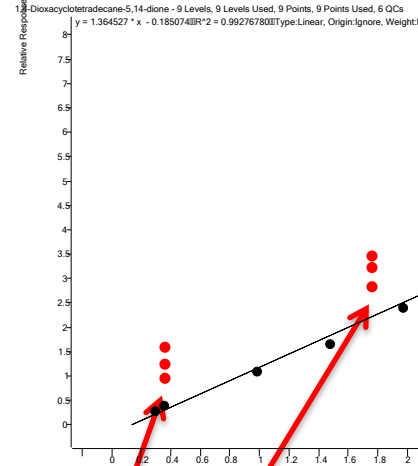


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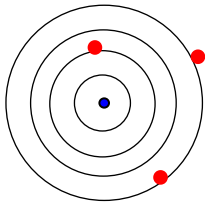


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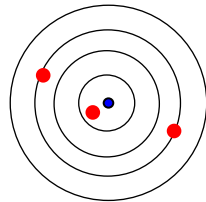
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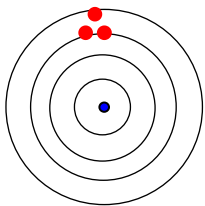


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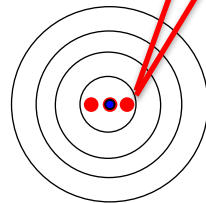


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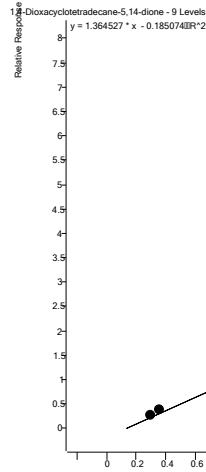


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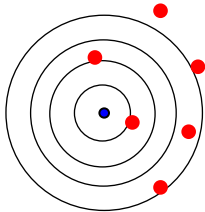


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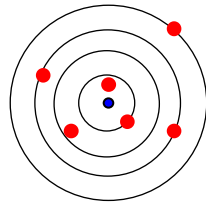
Validated limit test:



low accuracy, low precision

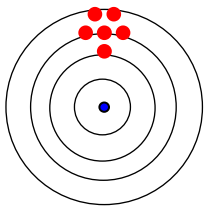


high accuracy, low precision

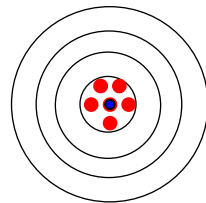


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low accuracy, high precision

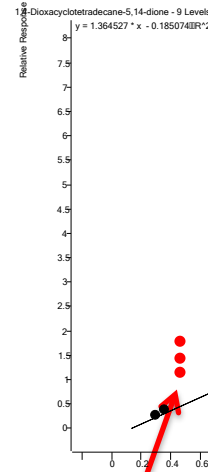


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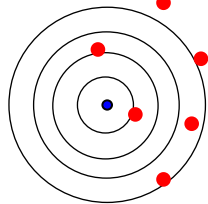


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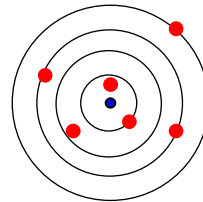
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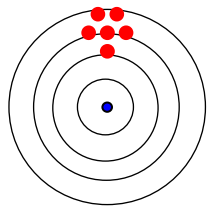


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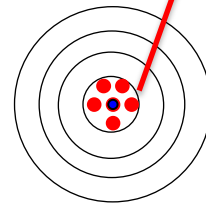


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high accuracy, high precision



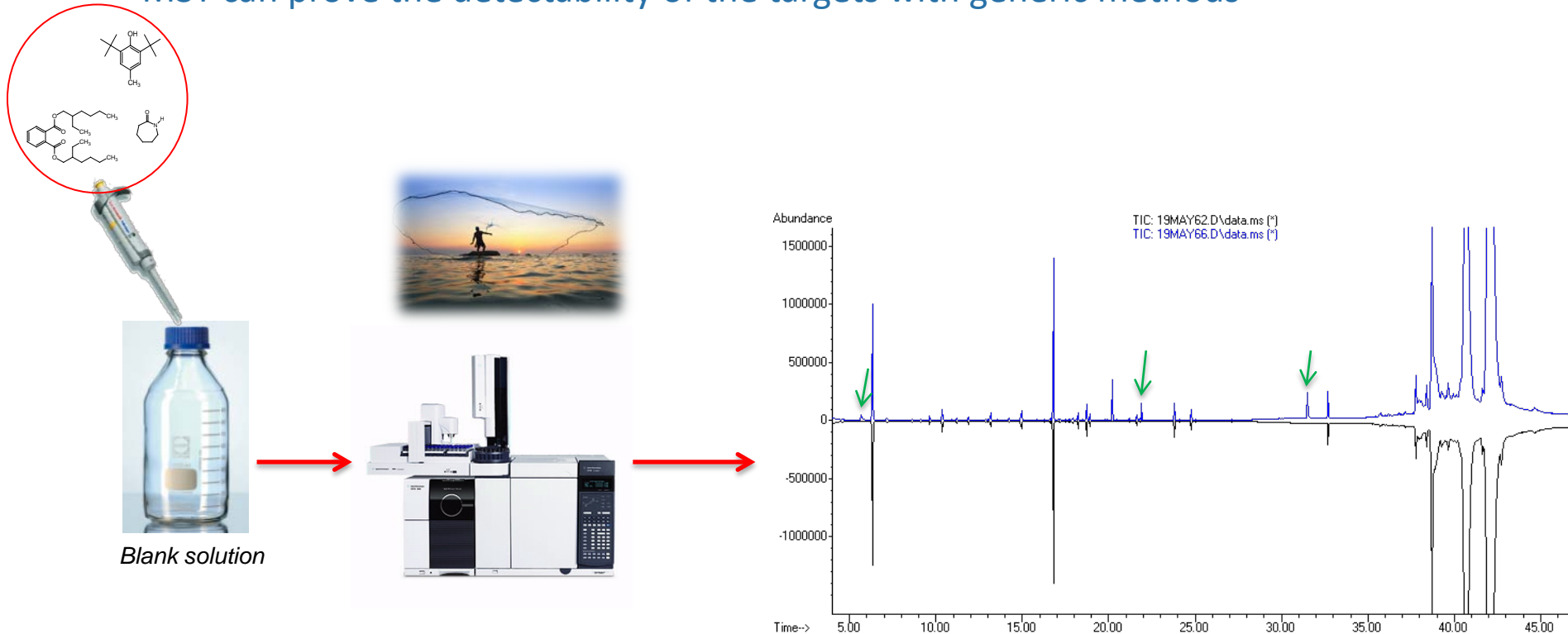
# Do – don't #4: Quantitative methods?

- Method Suitability Test (MST)? = Cheap and fast alternative to method development and validation
  - 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



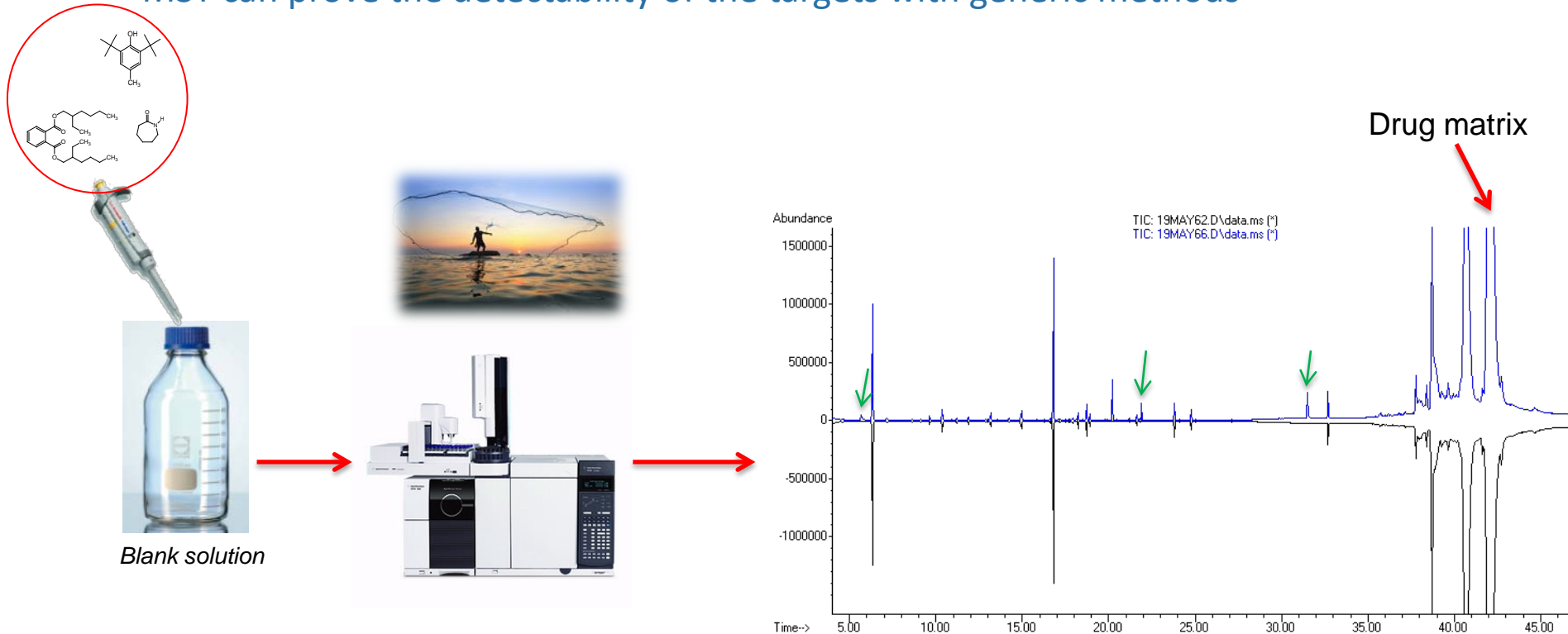
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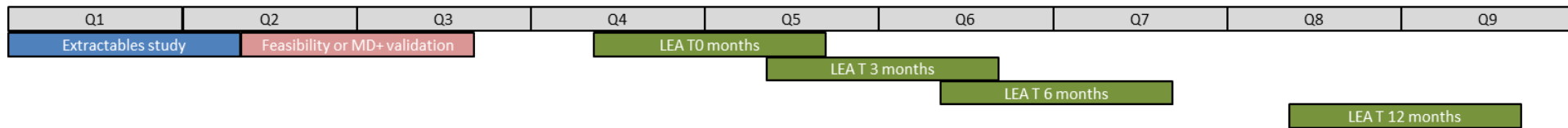


# Do – don't #4: Quantitative methods?

- 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 R1 (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 validation (less parameters of ICH Q2 R1 taken in account)
    - Limit test
    - Method Suitability Test
- What should you choose? It depends on
  - Therapy (chronic vs short)
  - Drug product complexity
    - Chance on successful MST on complex drug matrices is rather low
  - Required sensitivity
  - Intended market (USA vs EU vs ...)
  - Company policy
  - ...

# Do – don't #5: Planning

- Plan ahead!
  - A leachables study design depends on
    - Extractables data
    - Target selection
    - Method development and validation



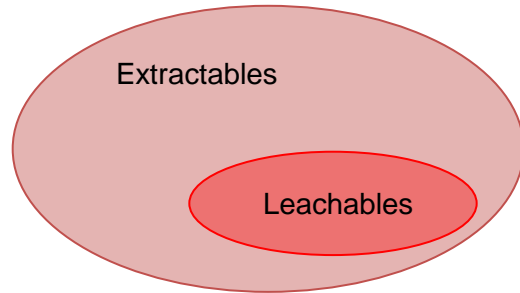
- There are possibilities to deviate from this sequence of events, however
  - Unexpected results?
  - Anticipation?
  - Estimate sample quantity?
  - ...

# Do – don't #6: Simulation study vs. Leachables study

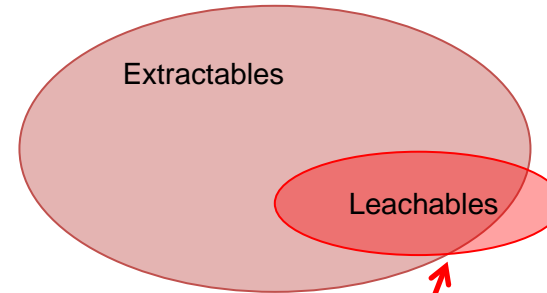
- Differences with a leachables studies
  - The drug product is replaced with a simulating solvent
  - The ageing conditions have been accelerated
  - The test article can be the complete packaging system or a partial packaging system
- Purpose according to USP<1663>
  - Find + identify extractables which are probable leachables
  - Establish which extractables must be targeted in a migration study
    - Screening
    - 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 #6: Simulation study vs. Leachables study

Theory



Reality



The gap can be closed with a simulation study

Dedicated session on 'closing the gap'

# Do – don't #6: Simulation study vs. Leachables study

How to select a simulating solvent?

1. Aqueous based solutions with organic solvent added to mimic the extraction propensity of the actual DP
  - Mix of alcohol in water
    - Nelson Labs Whitepaper ([www.nelsonlabs.com](http://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 the DPV is not substantially different from the DP
3. The Drug Product itself (see “Closing the gap” presentation)
  - “Screening leachable study”

# Do – don't #6: 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

Example Novo Nordisk (Carsten Worsoe, PDA Pre-Filled Syringes Conference)

- exaggerated exposure: 10x increase of exposed surface area + accelerated ageing
- 3 months at 40 ° C using the drug product



Only for visualisation – rubber plunger surface area to solution >> 10  
novonordisk

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



# Do – don't #6: Simulation study vs. Leachables study

- Regulatory acceptance of a simulation study – **think as a regulator**
- **Example 1:** use a simulant of 20 % ethanol in water
  - Justifications will need to be provided to prove the predictive character of a simulation study.
  - Secondary leachables – reaction products of leachables with DP – are not covered
- **CONCLUSION: Risky!**
  - The approach can be taken if a drug formulation is extremely complex and no trace analysis is possible. However, the failed attempts should be documented to help justifying the alternative approach



# Do – don't #6: Simulation study vs. Leachables study

- Regulatory acceptance of a simulation study – **think as a regulator**
- **Example 2:** use the drug product as simulant
  - Justifications will need to be provided to prove the predictive character of a simulation study compared to a formal leachables study.
  - Only the end point is tested, no trend analysis possible
- **CONCLUSION:** contributes to the E&L assessment, but this is not sufficient!



# Do – don't #7: What if the formulation is too complex

What if the DP is so complex and challenging in its formulation that a normal analytical approach cannot be taken?

- Try to prove and document the analytical difficulties
- Narrow down the analytics
  - Very targeted, specific compound detection
  - No screening possible
- Consider a simulation study
  - Justify a simulation study by proving the difficulties in the regular leachable study approach

# Questions?



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