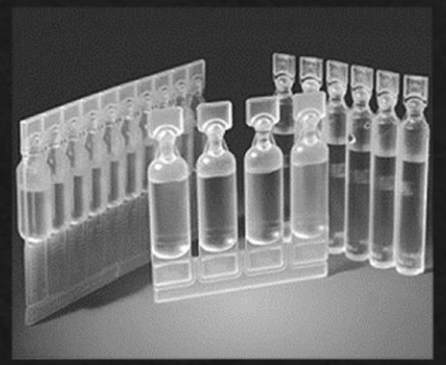


A Structured Approach to Selection of Container Closure Materials for Small Volume Parenterals

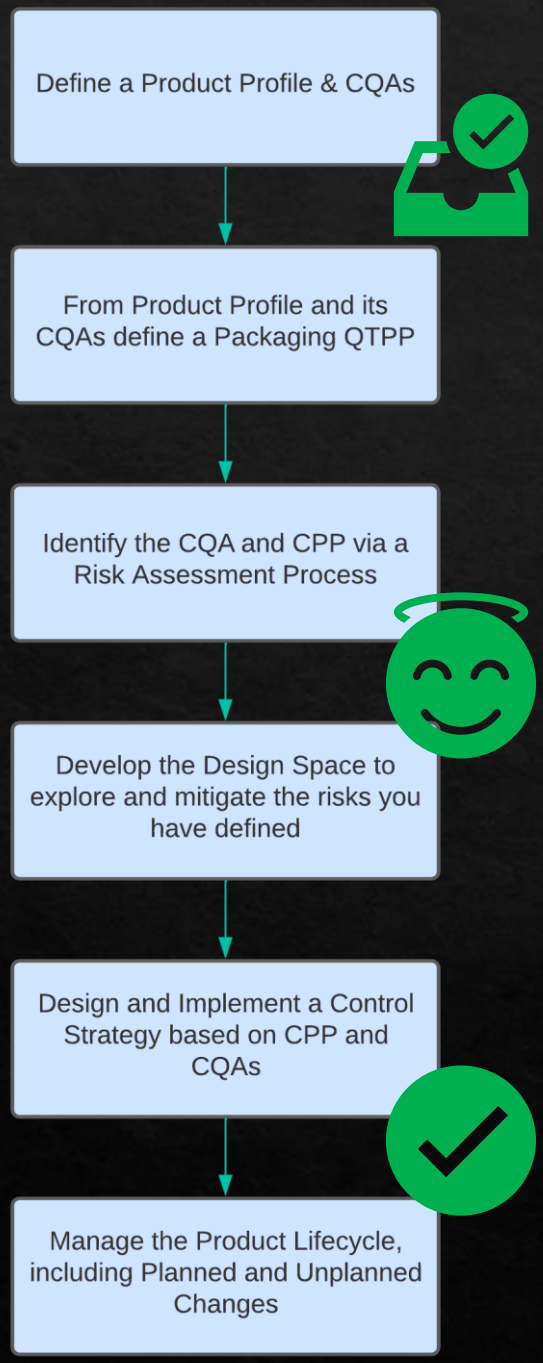
“Pipe Dream” or Necessity?

Maven E&L

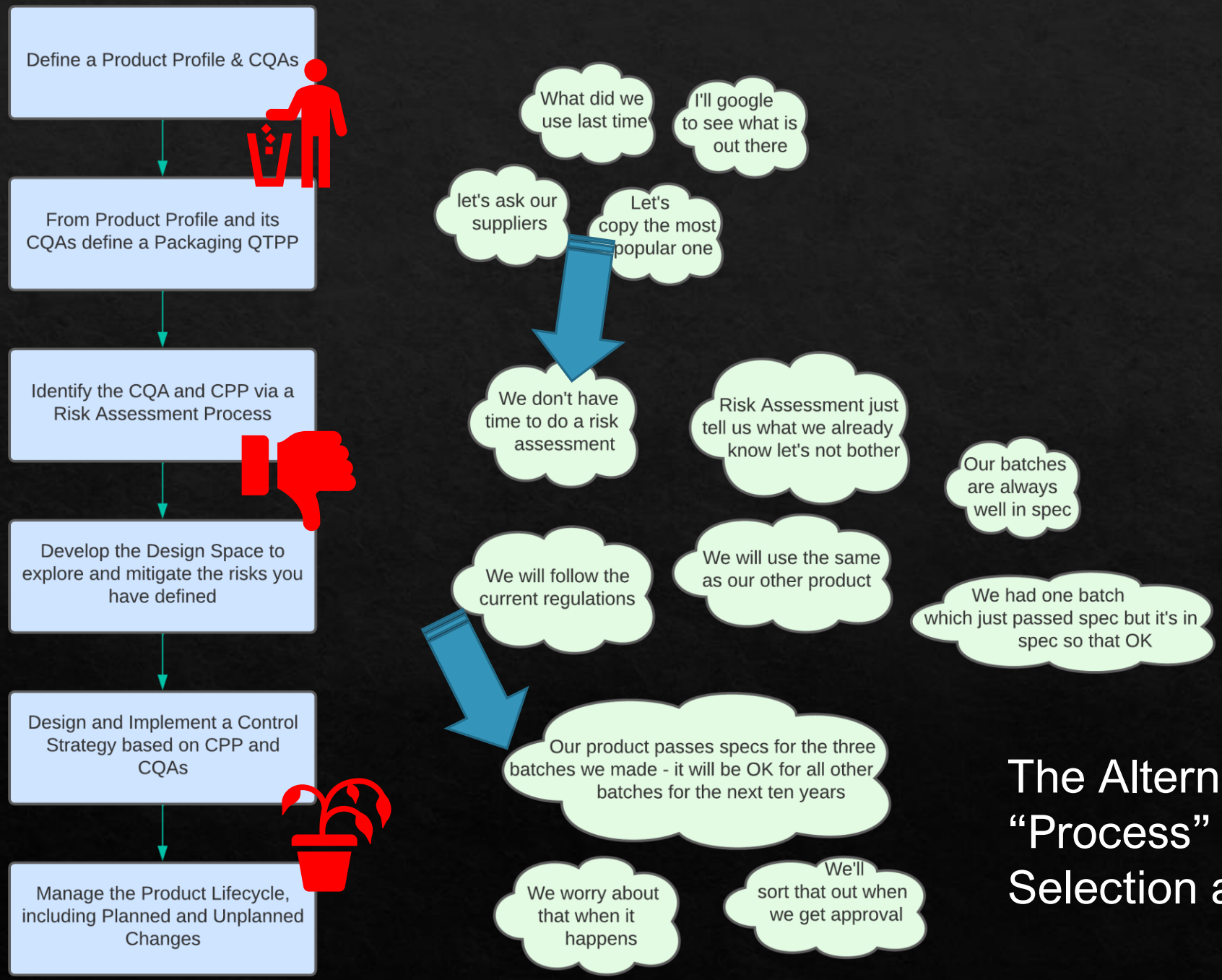
Expert Consultancy

Contents of Presentation

- What might be a structured approach?
- What is there to consider in selecting and qualifying a container closure system
- Examples of issues which might occur
- Key Recommendations

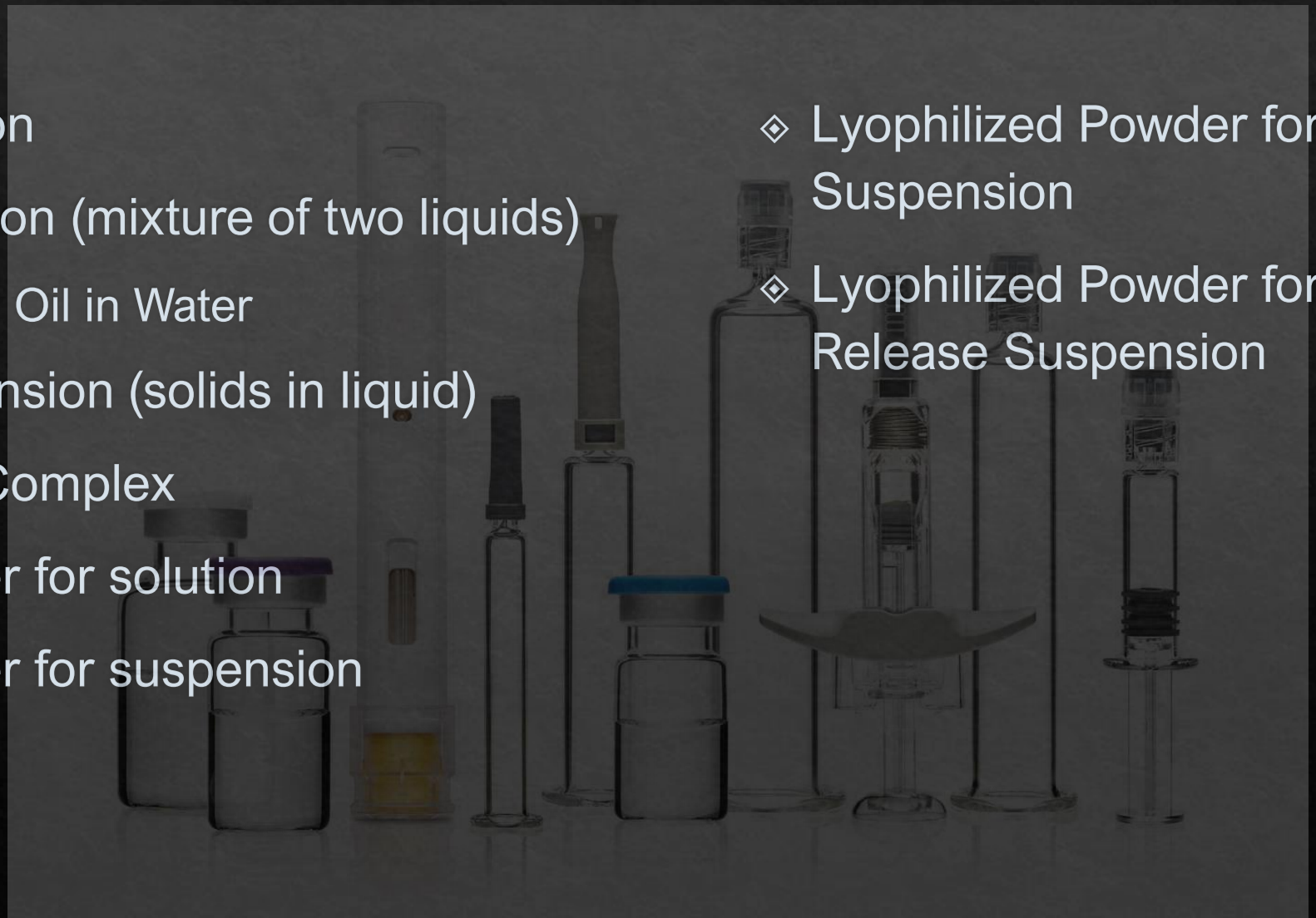


The Ideal Process for Container Closure Selection and Qualification?



The Alternative (sometime used?) “Process” for Container Closure Selection and Qualification.

Examples of Parenteral Dosage Forms

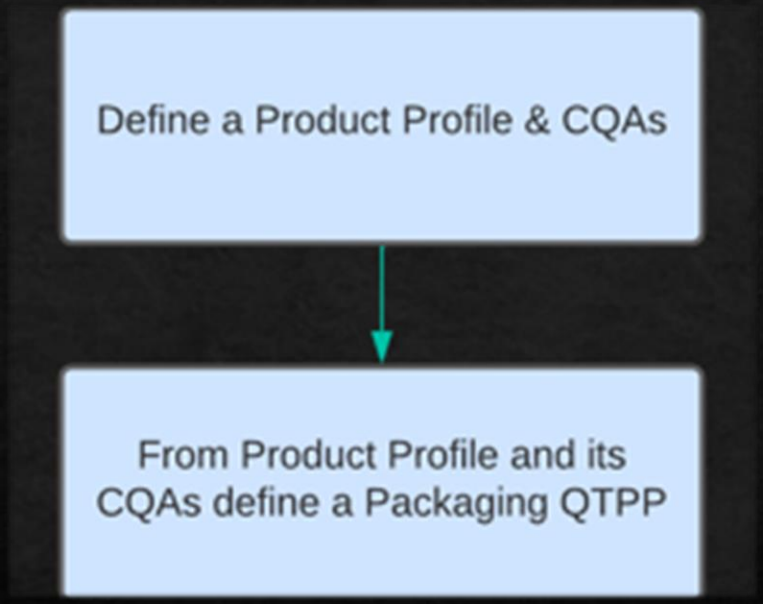


- Solution
- Emulsion (mixture of two liquids)
  - E.G. Oil in Water
- Suspension (solids in liquid)
- Lipid Complex
- Powder for solution
- Powder for suspension
- Lyophilized Powder for Suspension
- Lyophilized Powder for Extended Release Suspension

QTPP for Container Closure & Related Definitions

- QTPP (Quality Target Product Profile) is a prospective summary of the quality characteristics for a given system, that ideally will be achieved to ensure the desired quality (taking into account safety and efficacy).
- CQA – (Critical Quality Attribute) having impact on drug product quality
- CPP – (Critical Processing Parameter)
- Risk Assessment : A systemic evaluation to define understanding of risks which have an effect on CQAs or CPPs, determining relationships that link material attributes and processing parameters to product CQAs, identification through prior knowledge and experimentation risks to CPP and CQA which require risk reduction or can be accepted and/or controlled
- Control Strategy: Using the enhanced understanding gained from risk assessment and quality by design to maintain CQAs and CPPs both in short-term and during the product lifecycle

How the QTPP supports development of container closure packaging



For development and definition of a QTPP for the drug product, the relevant considerations might be:

- Intended use / Indication / Population
- Route of administration
- Expected dosage form and posology
- Targets for stability and other key attributes (in general these cover safety, efficacy, and quality – purity, identity etc)
- Delivery systems (if relevant)

- These will lead on to CQAs and CPP in order to achieve the Targets set out.

For a packaging / container closure it is a similar list:

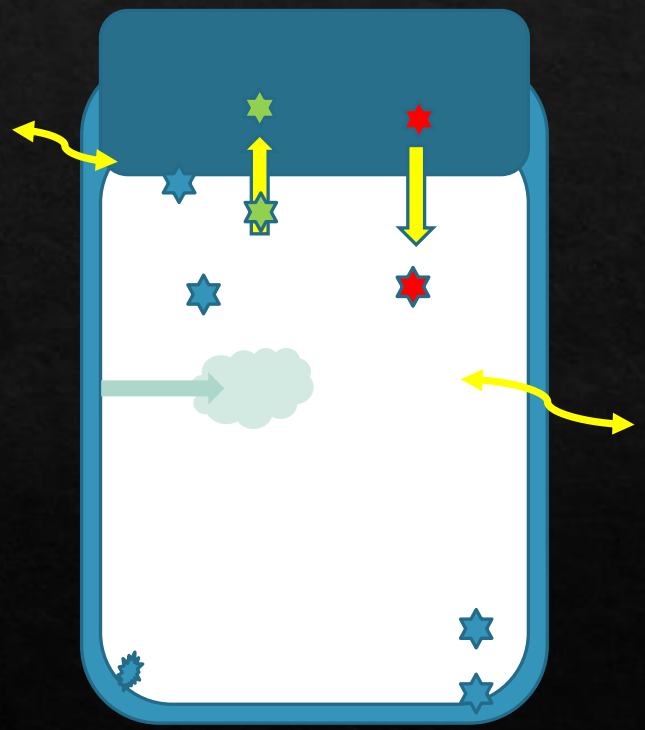
- What is the intended requirement for it?
  - How will it support administration
  - How will it support storage
  - What are the specific attributes for this product which will be critical

List of requirements

Requirements	
Light Transmission	Useability – Human Factors (age, tissue characteristics, strength, mobility, manual dexterity, other impairments among the user population)
Chemical Resistance (Glass)	Continuity of Supply
Permeation	Ability to Manufacture
Sterility	In-use conditions – environmental considerations (temperature, vibration, ambient lighting, pressure)

Factors to consider in container closure selection

- Seal integrity
- Identification and analysis of the effect of introduced particulates
- Corrosion from contact with DP
- Function over time and/or use
- Adsorption of formulation (API and excipients) into material of components
- Effect of leachables from the materials used in materials of construction on drug product safety



- Effect of leachables on drug product quality (more difficult?)
- Material biocompatibility
- Define mode of action
- Physical defects – control
- Ability to assemble
- Accuracy of delivered dose
- Shipping and transportation
- Labelling – can they be labelled, methods of labelling
- Warning and precautions

Risk Assessment

Risk = (Severity of Hazard x Probability of Hazard) x *Uncertainty*

Risk: "possibility of loss or injury; peril"
Uncertainty: "indefinite, indeterminate" and "not known beyond a doubt."

Risk is present when future events occur with measurable probability
Uncertainty is present when the likelihood of future events is indefinite or incalculable

Risk Identification - How the risk occurs

Cause - Risk Event – Effect
or
Because of.. there is a risk that.. resulting in..(safety, product performance, market acceptance

Cause: It started raining
Effect: I needed an umbrella

- Because the elastomeric stopper is in long term contact with the drug product formulation
- There is a risk that substances from the stopper will leach from the stopper into the drug product formulation
- Resulting in unknown substances from the stopper being dosed to a patient on a daily basis for the three months of treatment

Risk Identification - Where risk is

- This can take two format depending on whether your focus is a manufacturing process or a container closure system. Both are a form of process mapping to identify the materials present and the environment they are in contact with

Example of risk: Glass delamination

- Interaction between product and glass
- May take years to be detected as particles in vial (final stage)
- Associated with elevated levels of glass elements (sodium, potassium, boron, silicon etc)
- Common reason for product recalls (particles) Several drugs have been recalled due to this problem: epoetin alfa, methotrexate, hyaluronidase recombinant, and fluorouracil

- Factors which may drive delamination
  - pH of formulation >8
  - Vials subjected to sterilization, depyrogenation
  - Elevated temperature storage and longer storage periods
  - Vial created from tubing rather than moulded vials

FDA Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectables Drugs, March 25, 2011

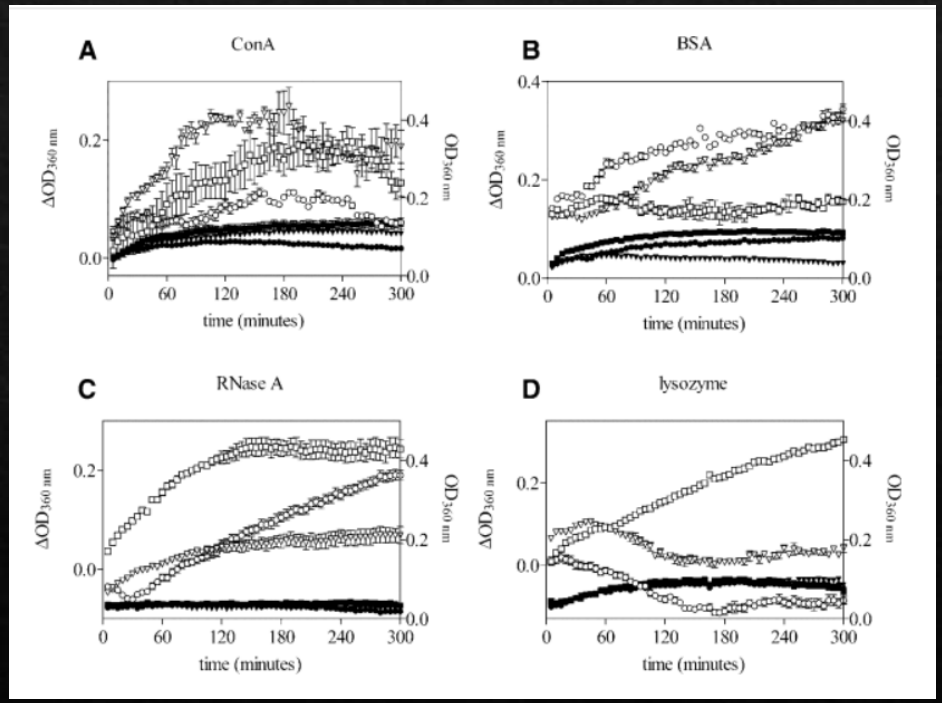
Example of risks: Barium Sulphate or similar (particulates in parenterals)

- Barium is potential present in glass, and occasionally as part of an additive system (as filler) for plastics or elastomers
- Barium sulphate is classical known as insoluble in aqueous solution, so the obvious risk is that either through abrasion or chemical reaction barium sulphate particles find their way into parenteral solutions
- A quality by design approach therefore is to avoid / limit / control the use of barium and similar metals which may give rise to this risk

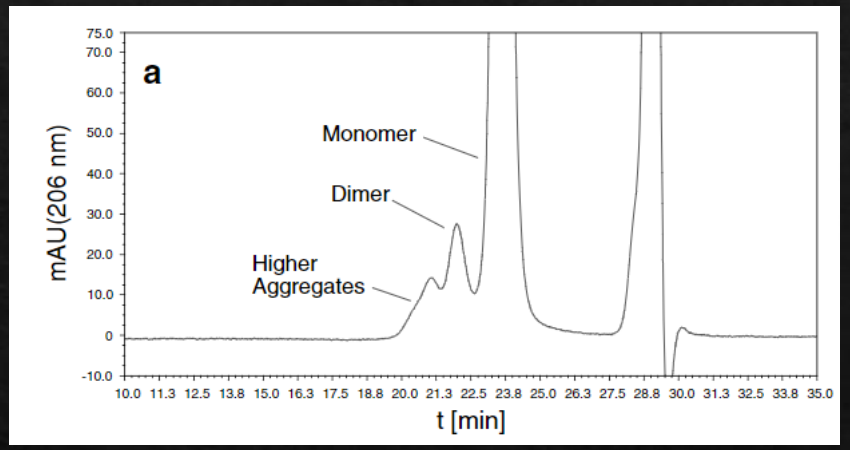
Bohrer, D., Morschbacher, V., Viana, C., do Nascimento, P. C. & de Carvalho, L. M. Barium in intravenous solutions for administration to neonates: Origins and levels of contamination. ESPEN. J. 9, e223–e227 (2014).

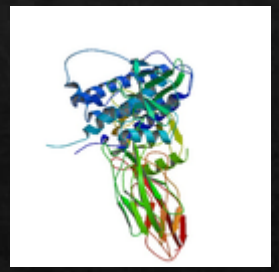
Example of risks: Silicone Oil (protein aggregates and visible and sub-visible particles)

- Silicone oil, has been implicated in the induction of protein aggregation.
- In one study a significant induction of aggregation in four proteins of various molecular weights and isoelectric points was found in the presence of 0.5% oil. (DOI:https://doi.org/10.1002/jps.20321)
  - ribonuclease A (RNase A), lysozyme, bovine serum albumin (BSA), and concanavalin A (ConA)

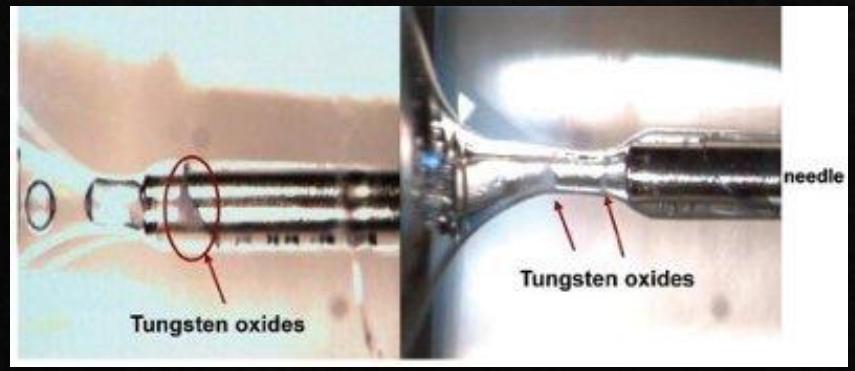


Example of risks: Tungsten in prefilled syringes





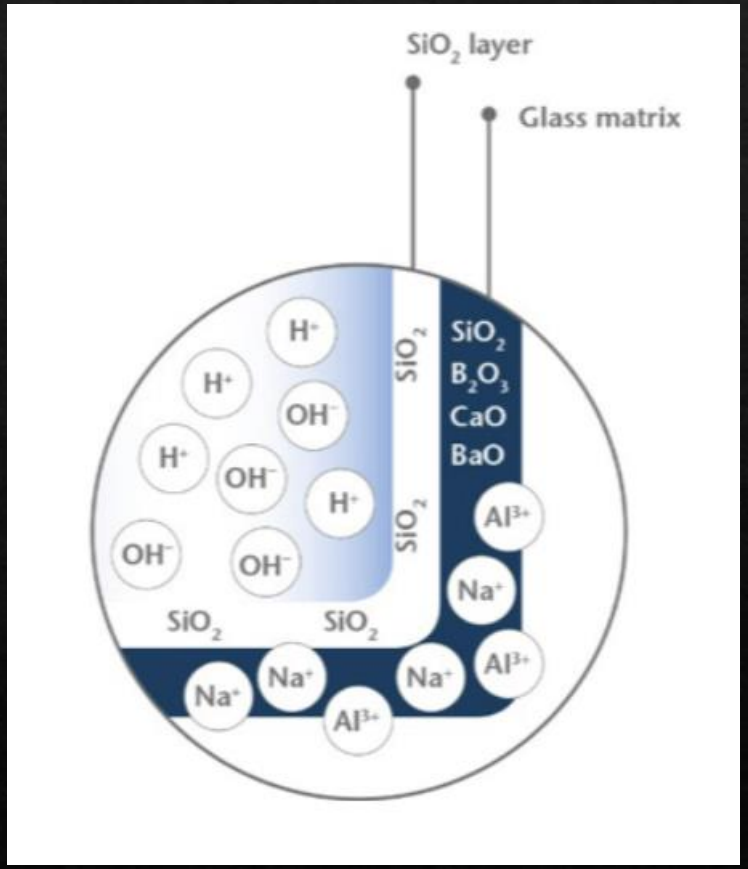
Epoetin alfa drug product illustration of polytungstate-induced aggregation



Pharm Res (2012) 29:1454–1467
DOI 10.1007/s11095-011-0621-4

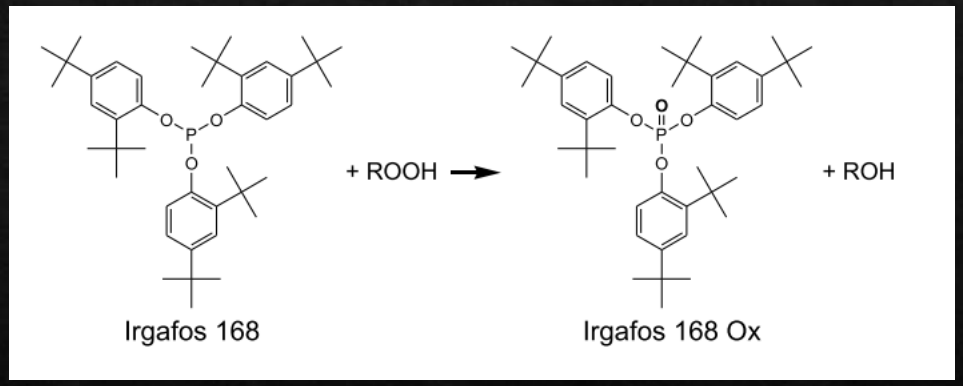
Example of risks: pH shifts from container closure choice

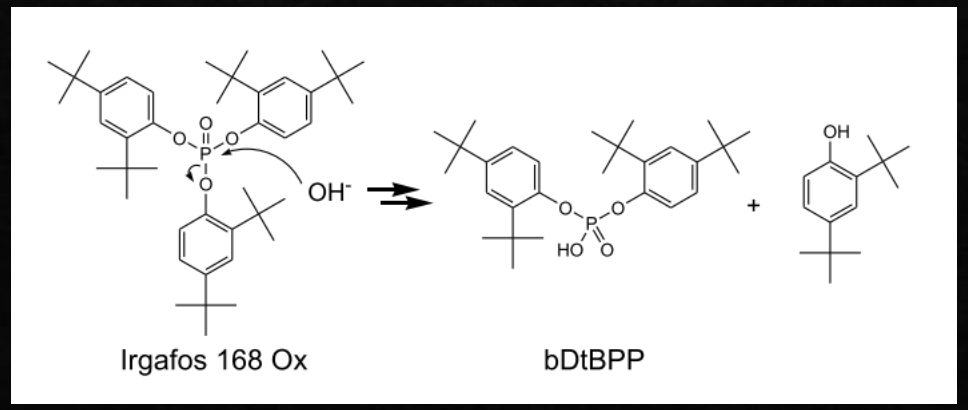
- There are a number of ways that container closure choice might affect the pH of the drug product, variation in pH can ultimately then affect the drug product quality
  - Glass can leach ionic species which affect pH
  - Plastic container can be semi-permeable and allow acidic gases such as CO2 to enter or leave changing the pH
  - Elastomeric seals can leach in-organic or organic substances which can also change the pH of the formulation



Example of risk: Cell growth Inhibition – Potential effects from leachates

- Irgafos 168 is a common antioxidant

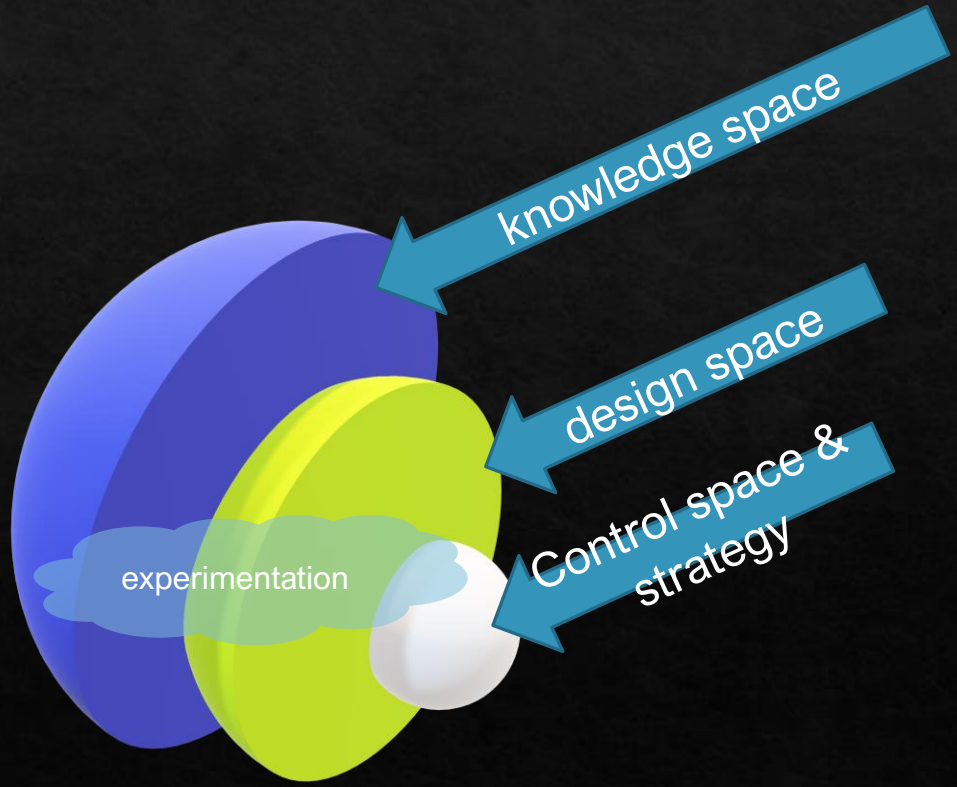




Shah, R. R., Linville, T. W., Whynot, A. D. & Brazel, C. S. Evaluating the toxicity of bDtBPP on CHO-K1 cells for testing of single-use bioprocessing systems considering media selection, cell culture volume, mixing, and exposure duration. Biotechnol. Prog. 32, (2016).

Risk Control

- Elements of Risk Control
  - from the risk assessment you have a list of scenarios – test these with experimental design and knowledge gathering, find the limits
  - Outputs are acceptance criteria and specification for CPP & CQAs

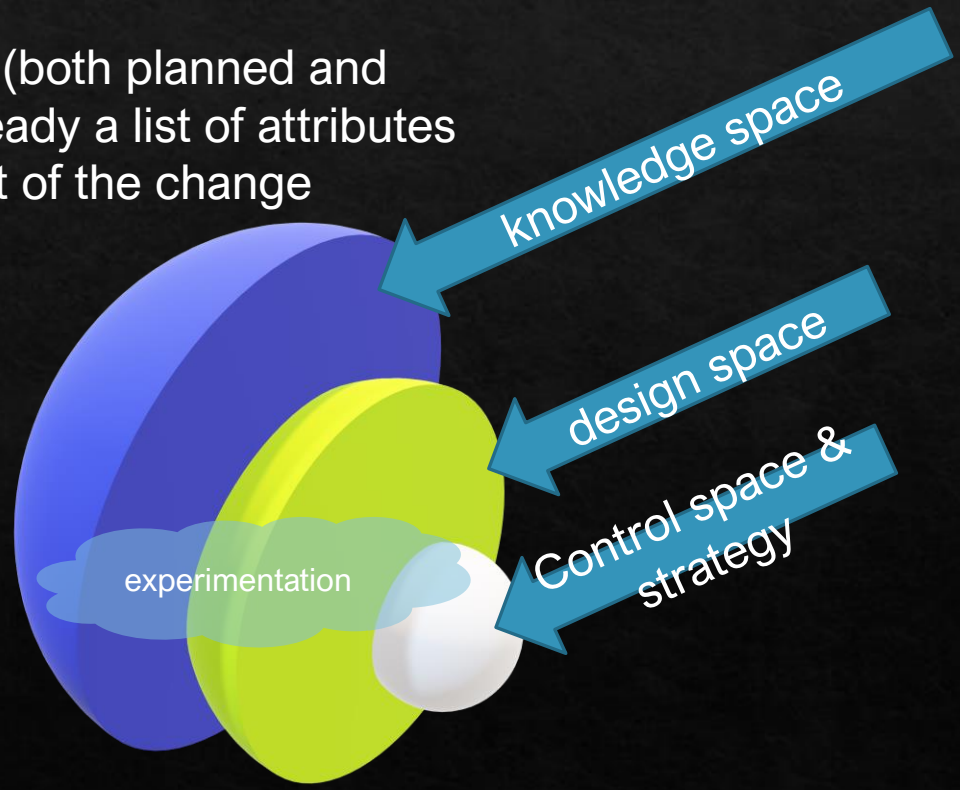


List of some of the experimental activities

- Functional evaluations assess sterilizability, puncture-reseal capability, and system integrity.
- Physicochemical screening tests for closures and plastic formulations as 1st pass suitability tests
- Biological screening (including biocompatibility) tests are used to assess toxicity.
- Specific extractable testing or leachable studies to explore either general screening or specific targeted substances
- Stability testing of storage drug product in container closure system to address a variety of attributes including
  - pH change (and associated effects on drug product parameters such as impurities or solubility)
  - Particles in formulation
  - Loss of drug content to container closure system
  - Effect of processing conditions such as sterilization

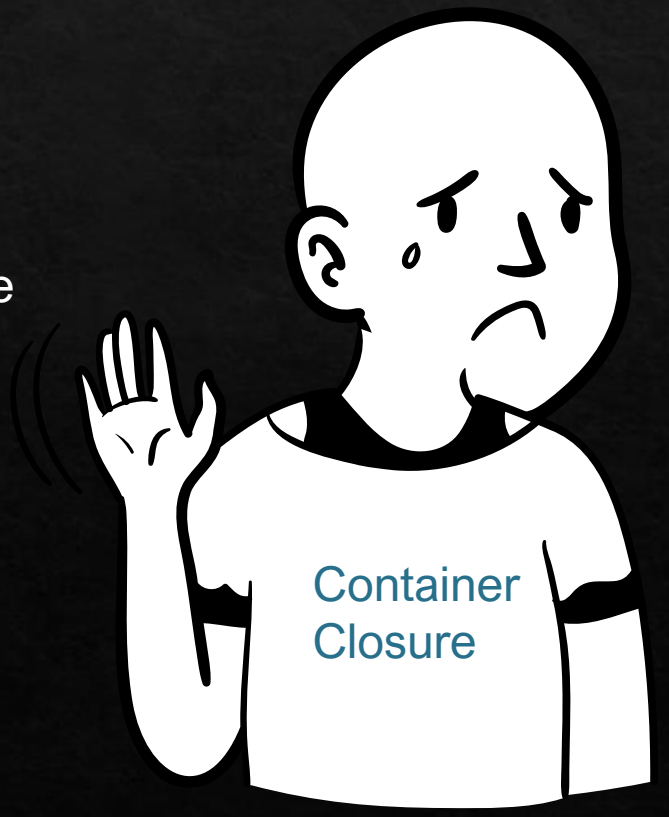
Risk Review - Lifecycle

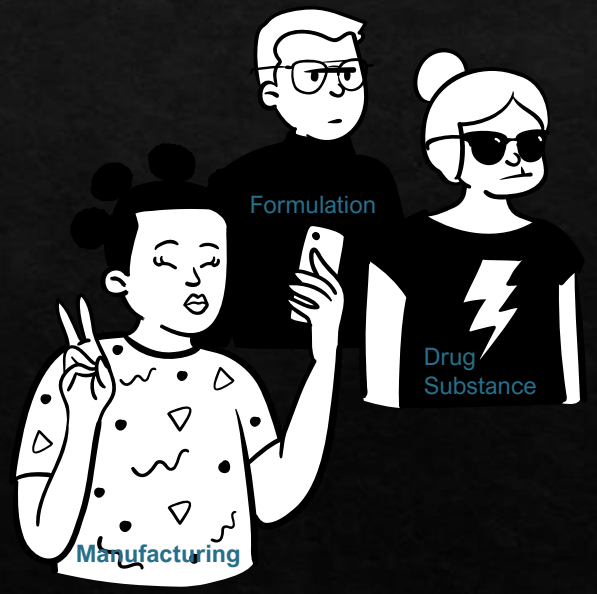
- Think for the long term – the risk assessment will define and differentiate between low and high risks
- When change happened (both planned and unplanned) you have already a list of attributes to consider in the context of the change



Recommendations

1. Don’t let container closure be the forgotten member of the team!
2. A structured approach to selection of container closure can follow the same principles as drug product development
3. Plan and execute a risk assessment to support selection and qualification
4. Align risk control to factors determined to be significant
5. Plan for lifecycle changes early using the learning from the risk assessment





Questions?