Regulatory Perspectives on Extractables and Leachables

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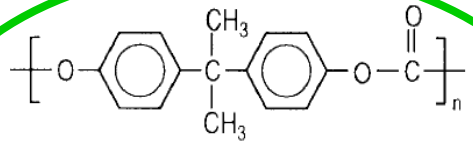
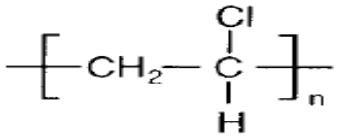
PQRI Workshop on Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products (PODP)

Bethesda, MD.

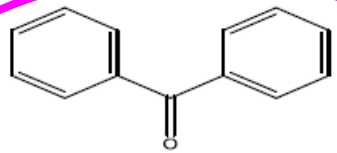
Structures of potential leachables



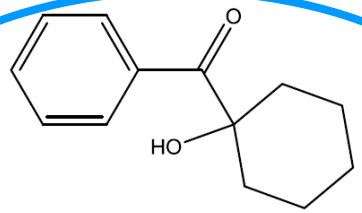
Bisphenol A
(known teratogen)



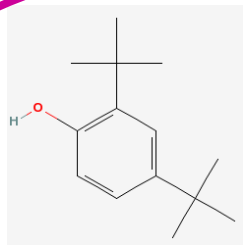
PVC monomers



Benzophenone
Known photo initiator



(1-hydroxycyclohexyl)phenyl-
Methanon, suspected leachable



2 2,4,-bis(1,1-dimethylethyl)
-phenol (DTBP)
Leachable,
toxicity to be determined

Would you want these in your drug products?

Definitions

- Extractables
  - Compounds that can be extracted from the container closure system (CCS) when in the presence of a solvent
- Leachables
  - Compounds that leach into the dosage form from the container closure as a result of direct contact with the formulation

Definitions

- Extractables
  - Compounds that [illegible] extracted from the container cl[illegible]stem (CCS) when in the pres[illegible] solvent
- Leachables
  - Compounds that l[illegible] the dosage form from the conta[illegible]ure as a result of direct co[illegible] the formulation

Proactive

Reactive

Outline

- Regulatory Background/Importance
- Recommendations
- Current Status
- QbD Approaches to Extractables and Leachables
- Conclusion

Background

- How did the importance of extractables/leachables come to FDA's attention?
- In the early 1990s.
  - Nitrosamines in metered-dosed inhalers elastomers (MDIs)
  - 2-Mercaptobenzothiazole in elastomers
  - Other classes of E/L's
  - Processing aid residues
  - Vanillin in inhalation solution
  - Aluminum in large volume parenterals

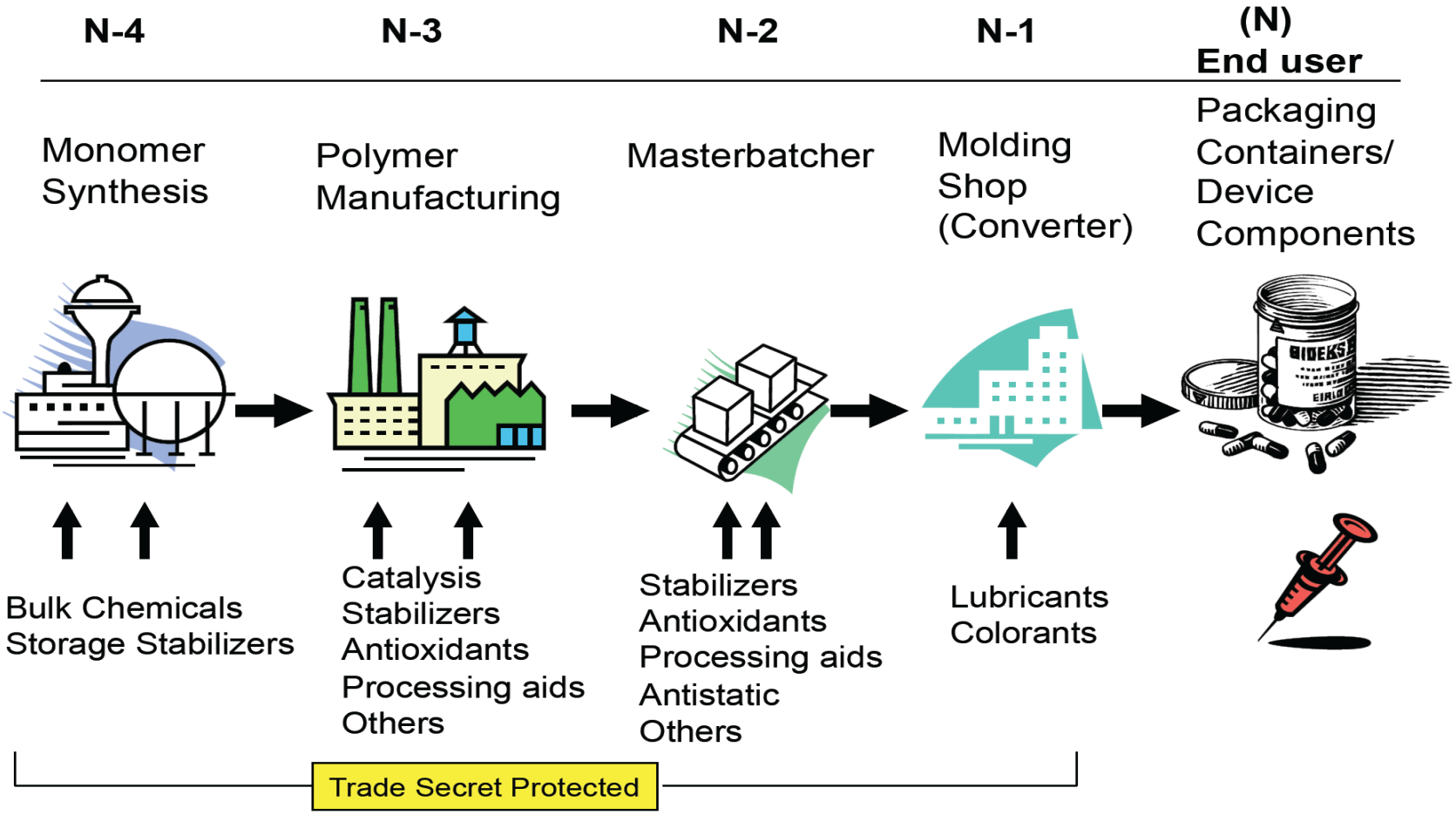
Why the Concern?

- Safety concerns
  - MDIs
    - Sensitive, compromised patient populations
    - Paradoxical bronchospasm
    - Long-term safety for chronic use
  - Parenterals
    - Direct exposure to leachables
- Quality concerns
  - Lack of knowledge/control of source materials
  - Lack of understanding of potential risks from extractables and leachable
  - Lack of control of extractables and leachables

Relevant Recent Meetings/Courses

- PDA Extractables and Leachables Nov 6-8, 2007, Bethesda, MD.
- PharmaEd's Extractables and Leachables 2010, May 2010, San Francisco
- Extractables and Leachables for Pharmaceuticals Products, 14-15 Sept 2010 (London).
- PDA/FDA Joint Regulatory Conference, 13-16 Sept 2010, Washington DC.
- Leachables and Extractables Testing and Assessment, Nov. 2010, Prague Czech Republic.
- IPAC RS Workshop on Extractables and Leachables 2011 March.
- Extractables-Leachables Forum 2011, May 17-18, 2011 in Goettingen, Germany

Potential for Extractables and Leachables



Cindy Zweiben, Characterization of Extractables and Leachables in Parenteral Drug Products, Sept 2010

Present and Future

- Only in the past 15 years have attempts been made to proactively design materials fit for use based on increased knowledge about container closure system (CCS) materials and manufacturing processes.
- There is room for a *risk-based approach* for ophthalmic and *some* parenteral drug products regarding E/L studies
    - Likelihood of CCS – formulation interaction
    - Potential risk to the patient based on the route of administration.
    - If risks not known, can use conservative approaches (e.g., MDI/DPI)

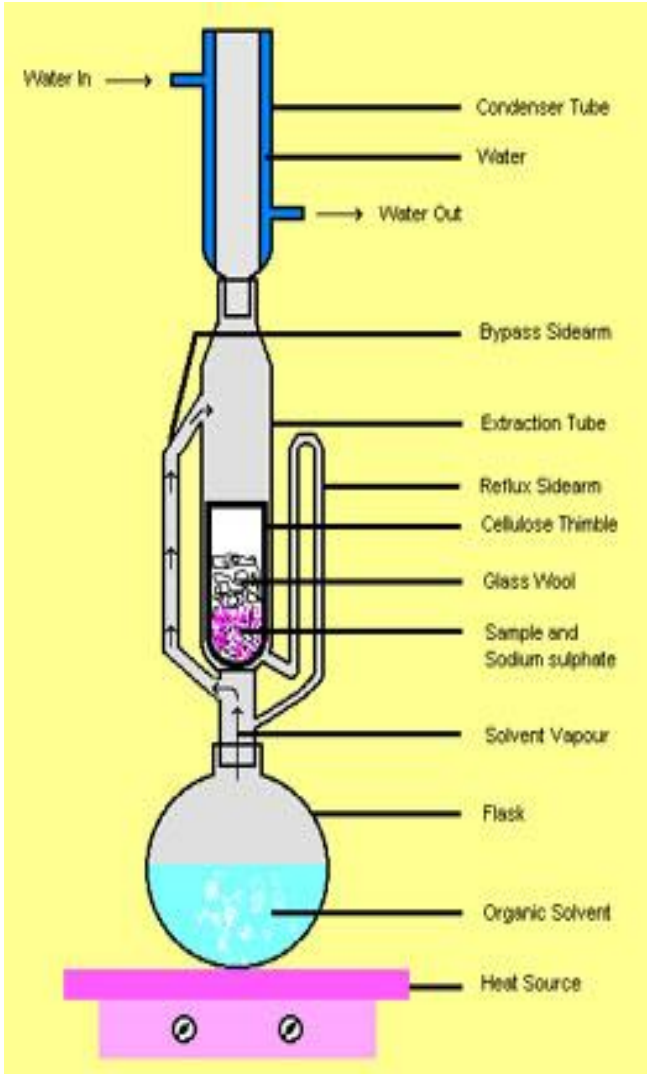
Extractables Studies – Why?

- For qualification of CCS components
- Used to screen for and monitor presence of toxic materials (*e.g.*, nitrosamines etc.)
- Used for quality control for acceptance of CCS components
- Extractables limits ensure limitations on leachables when extractables are correlated to leachables.

Extractables Studies–How?

- Use knowledge of component composition as an initial guide to developing the extraction techniques and analytical methods
- Use solvents of varying polarity, multiple extraction techniques and analytical techniques
- Estimate daily exposure, and safety concern threshold
- Involve toxicologists in assessment

Extractables Studies–How?



- Extraction
- Water
- Polar solvents
- Organic Solvents

Leachables Studies – How?

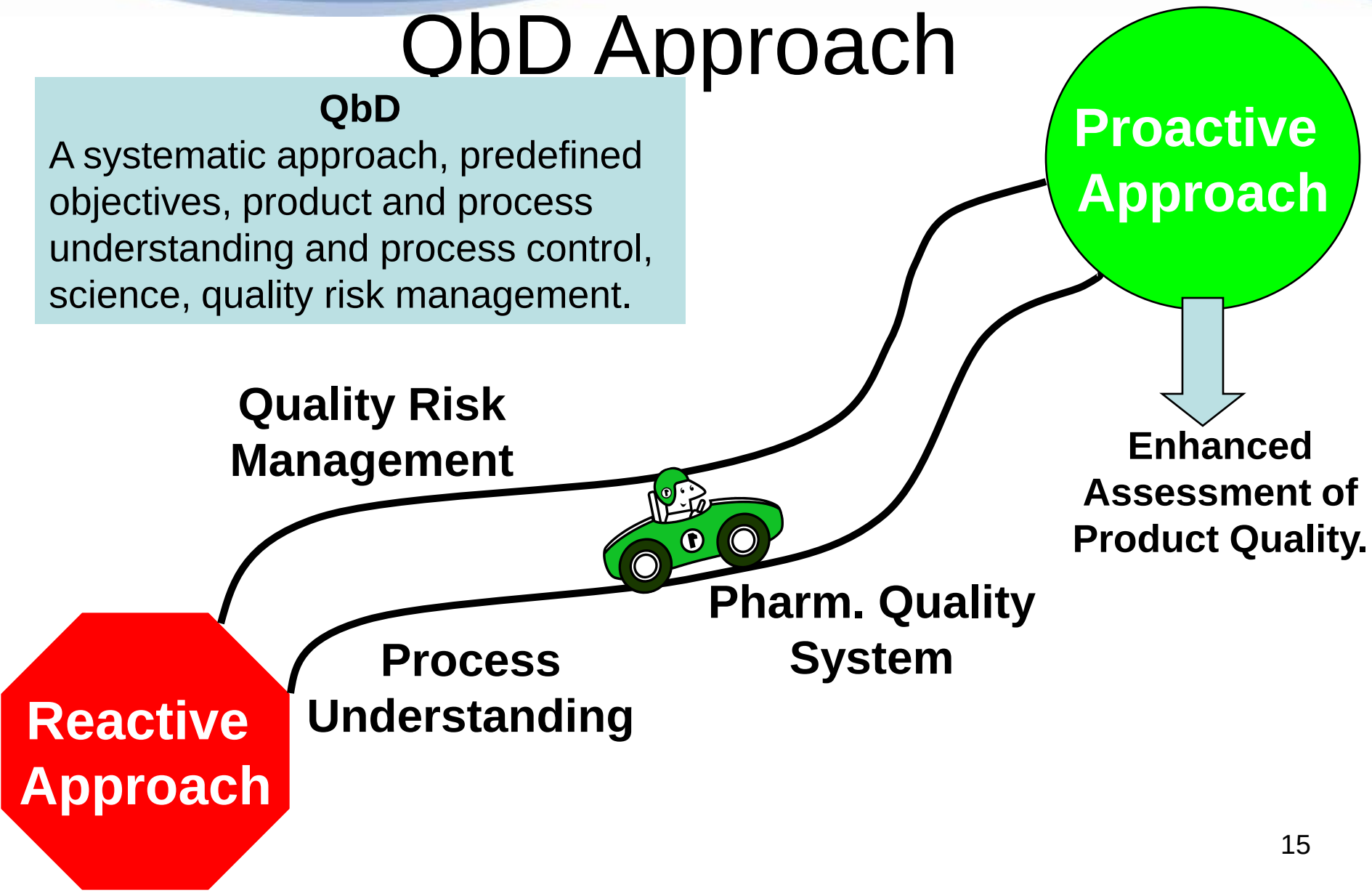
- Conduct leachables studies (during drug product stability testing) based on methods used for controlled extractables studies.

- When possible establish a correlation between extractables & leachables
  - Could be possible to eliminate leachables testing and develop routine extractables testing.

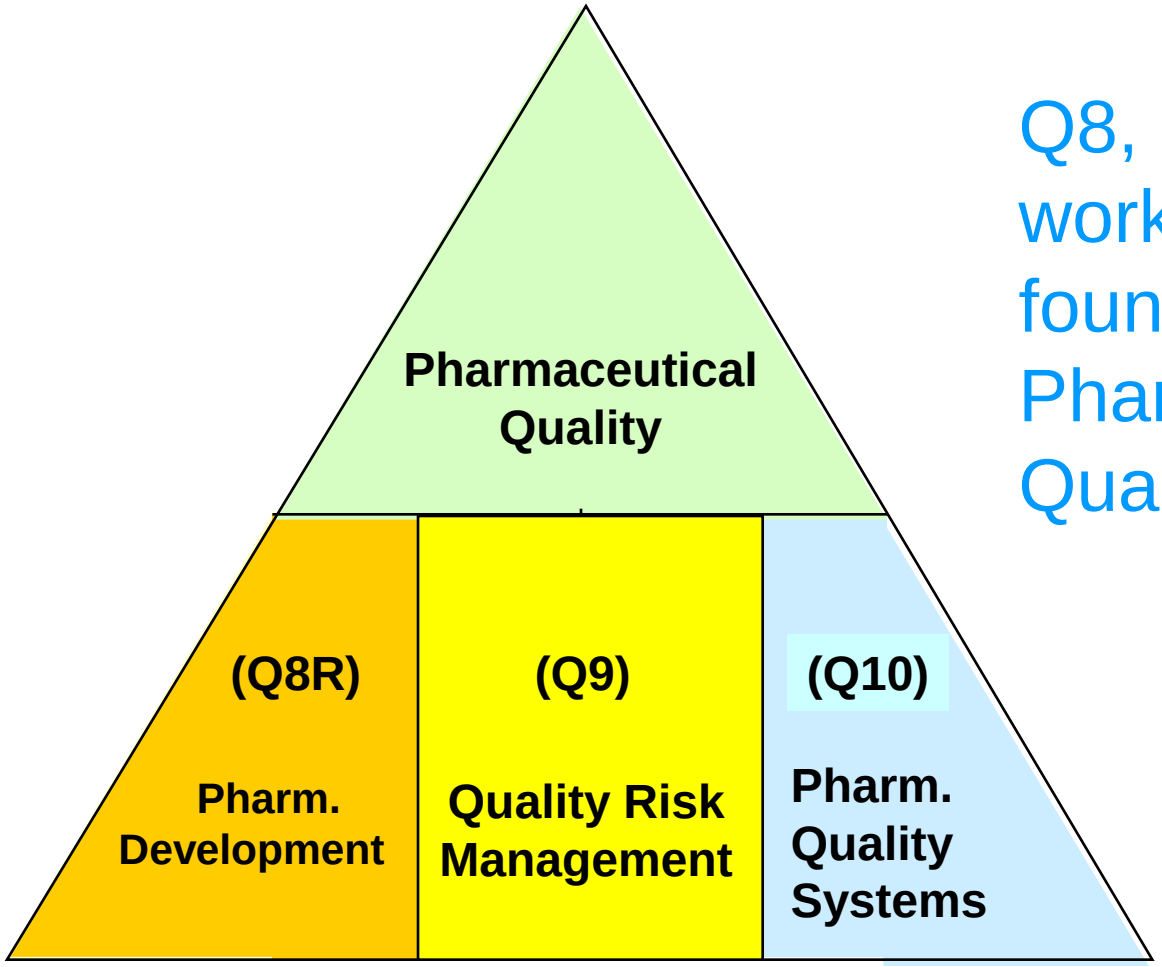
QbD Approach

QbD

A systematic approach, predefined objectives, product and process understanding and process control, science, quality risk management.



ICH Quality Roadmap



Q8, Q9, and Q10 work together as a foundation for Pharmaceutical Quality

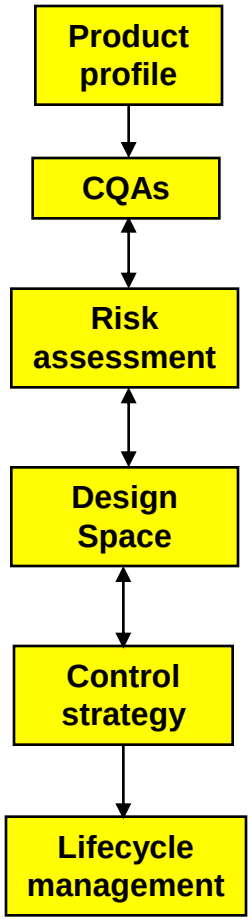
ICH Q8(R2) Concepts

- Quality should be built in by design
- Enhanced product knowledge and process understanding
  - Facilitates establishment of design space
  - Provides opportunities for flexible regulatory approaches
    - Risk-based regulatory decisions (review & inspection)

Role of Quality Risk Management

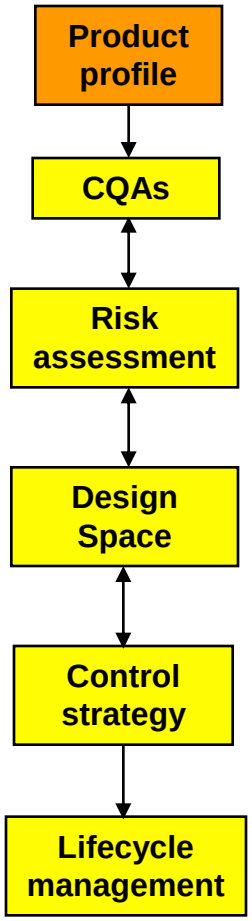
- Role of risk assessment
  - Early identification of risk
  - Risk analysis and evaluation
  - Risk reduction as needed
- Risk communication for continuity between
  - Development and manufacturing
  - Industry and regulators
  - Multiple manufacturing sites
- Review of risk can be incorporated
  - On periodic basis
  - As part of investigations of deviations
  - As part of change control and continuous improvement

QbD Approach to Extractables and Leachables



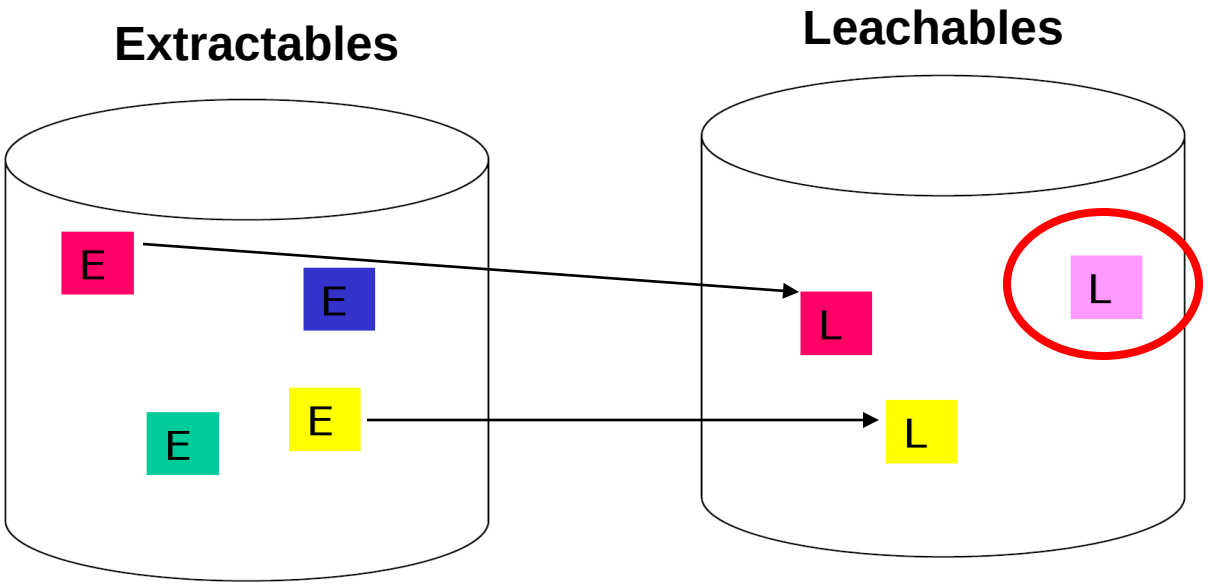
- Desired product profile
- Critical quality attribute (CQA)
  - Minimum level or absence of leachables Formulation and CCS selection and design to consistently meet CQA
- Risk assessment to identify source of variability (material, process) on CQAs
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

QbD Approach to Extractables and Leachables



- QTPP-Acceptable levels of leachables
- Considerations
  - Dosage form and route of administration
  - Patient population
  - Chronic vs. short-term use
  - Patients daily exposure
  - Formulation that is stable and not reactive
  - Delivers consistent product performance
  - Container closure systems with low and safe levels of leachables

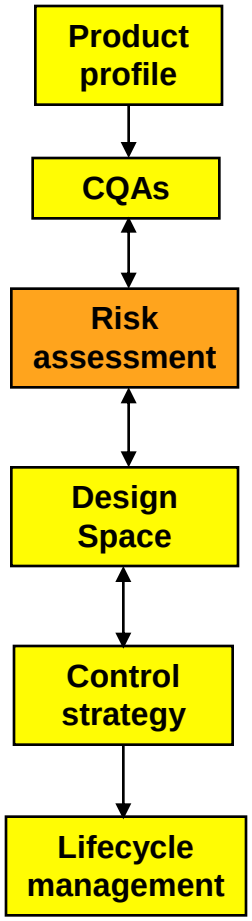
"CCS Understanding"



- Not all extractables are leachables
- Not all leachables are extractable
- When possible, develop a correlation between extractables and leachables
- Control and/or characterize the leachables that are not-correlated.

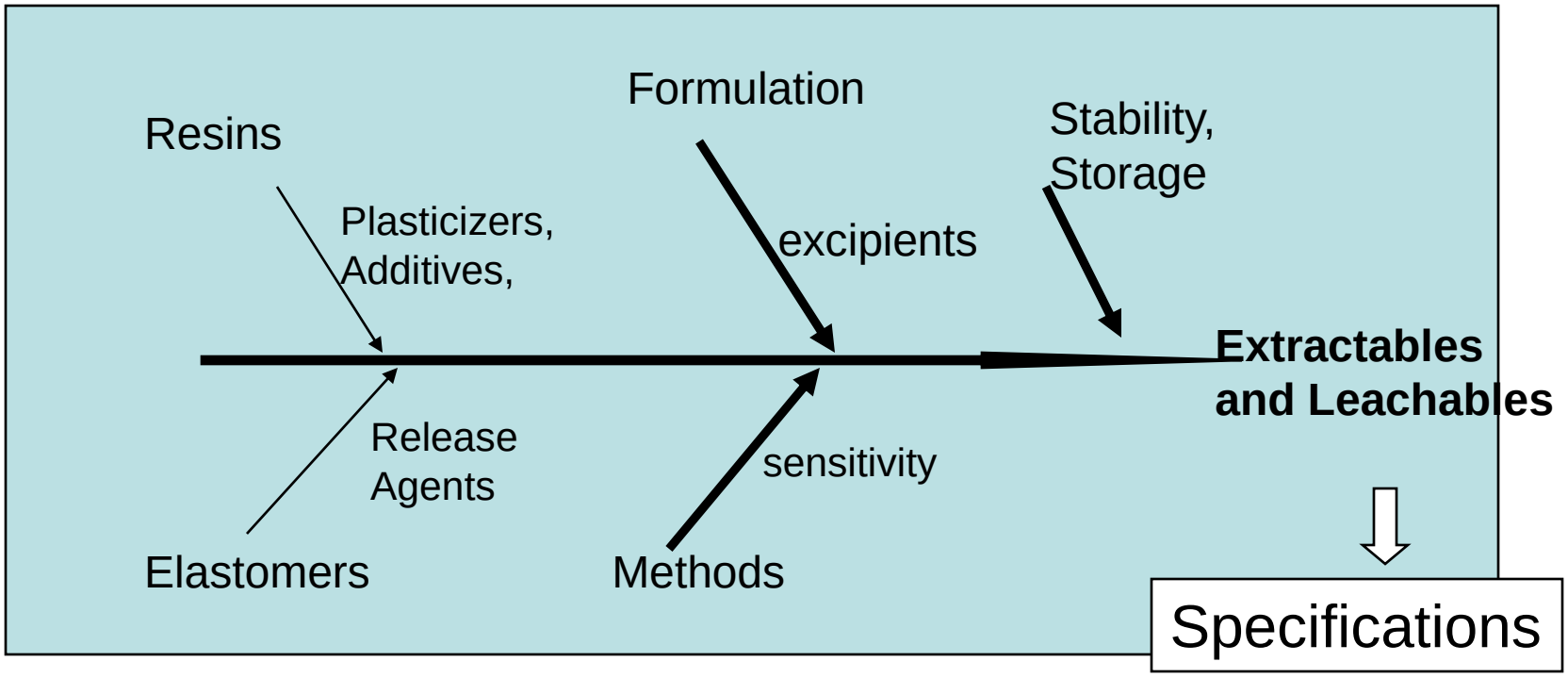
Anthony Grilli, Leachables and Extractables Testing, A Primer on Regulations and Methods

Risk Assessment



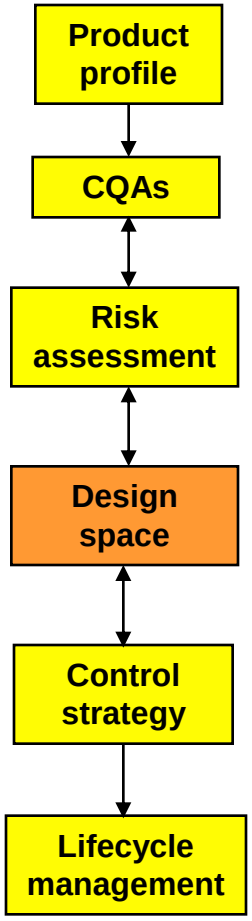
- Understand risks of E/L
  - Dosage form risk
    - Inhalation, parenteral > ophthalmic > transdermal > oral > topical
  - Patient population
    - For example, highly sensitive or immune compromised patients
  - Use prior knowledge for selecting and studying CCS
    - For example, high pH formulations and glass

Risk Assessment – E/L's



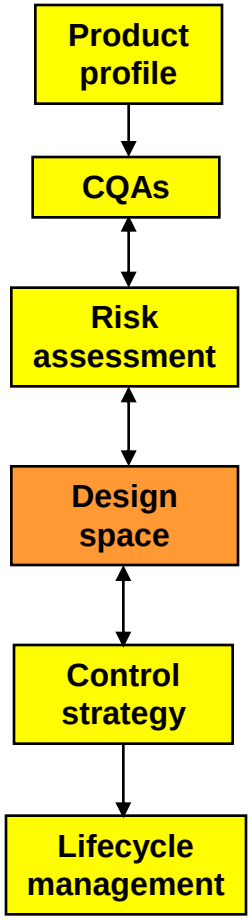
- Understand potential contributing factors toward E/Ls

Designing the Product



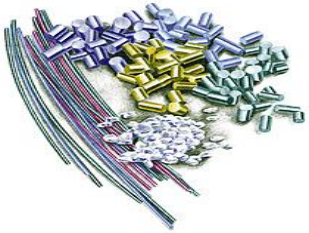
- Material selection for CCS components is driven by
  - Safety assessment of extractables/leachables
  - Desired performance parameter outcomes
  - Formulation compatibility considerations
- Primary vs. secondary packaging components
  - Elevated risks for packaging components in contact with drug or patient
- Work with supplier
  - Understand CCS manufacturing process and composition, as much as possible, especially for higher risk components
- Make safety assessment of materials to guide the choice of materials and to decrease risk later in development

Understanding the Process



- Understand sources of variability for each material, component, and processing used in the CCS
- Evaluate the impact of this variability on CCS performance and safety as it pertains to drug product
  - Rational experiments
  - Determine who (NDA applicant or supplier) will do experiments
- Work with supplier(s) to ensure appropriate raw material quality, in-process/release controls for CCS components to maximize chances for successful development

Design Space
Materials - Process - Product



Materials

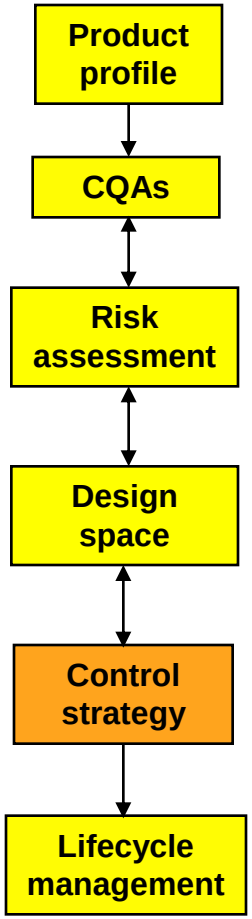
Process

Product

Design Space

While it is possible to have a Design space for CCS, it is not necessary as part of a QbD approach.

Control Strategy

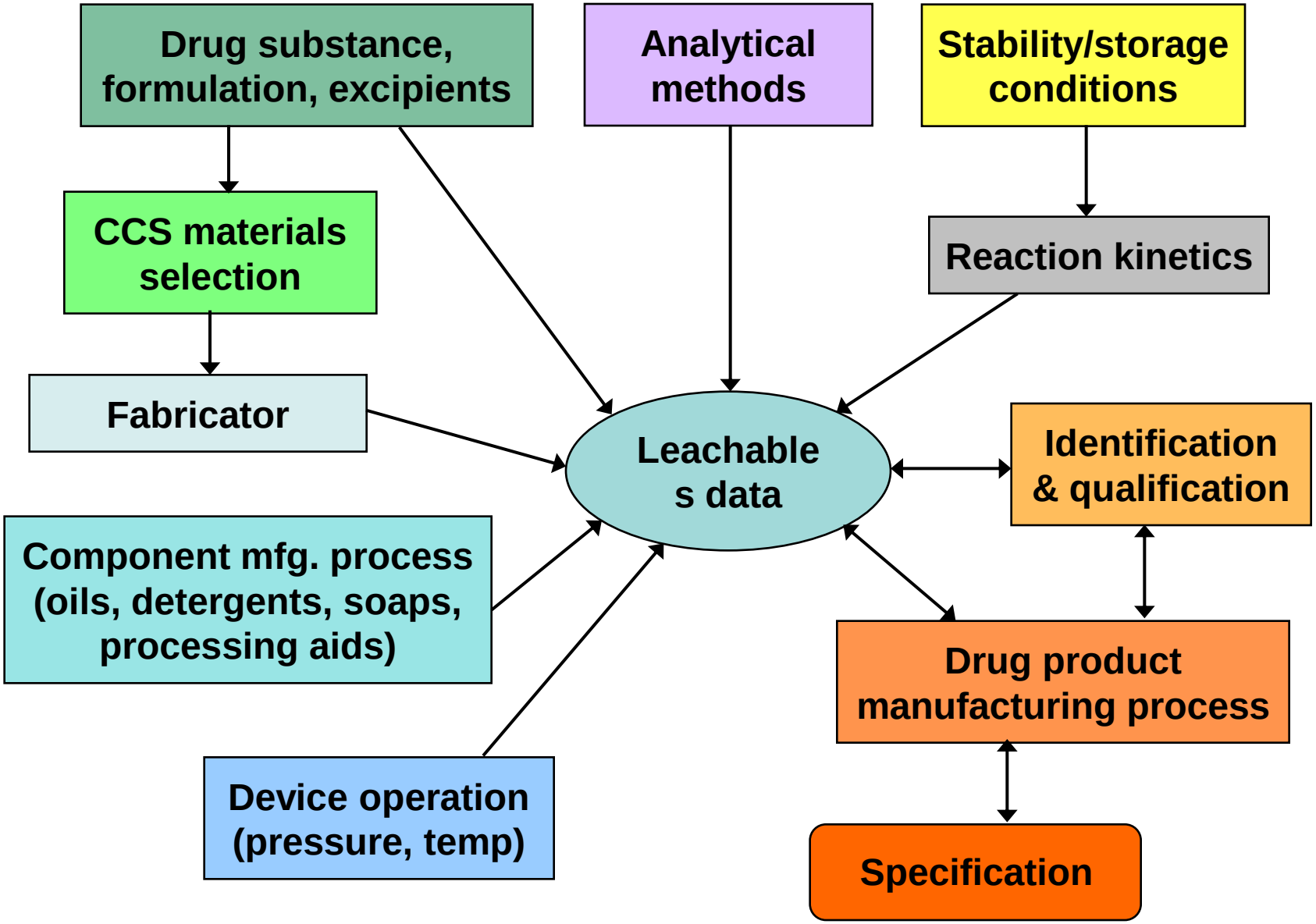


- Prior knowledge useful as a starting point.
- The planned set of controls, derived from current product and process understanding that assures process performance and product quality
- Control strategies can include
  - parameters and attributes related to materials and components,
  - facility and equipment operating conditions
  - In process controls
  - finished product specifications
  - associated methods and frequency of monitoring/control
  - move the control upstream (extractables) to where the source of variability is likely.
  - Leachables testing when necessary

Extractables

Leachables

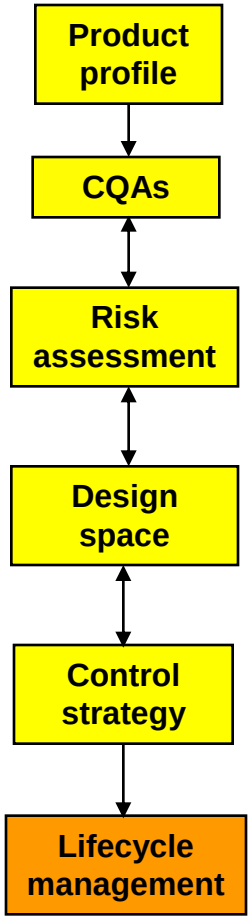
Setting Leachables Specification



Control Strategy – Specifications

- Setting leachables specification is a circular, labor-intensive process if a proactive approach is not adopted
- Specifications are usually based on data; however, amount of research and development plays a significant role
  - Formulation
  - CCS material
  - Analytical methods
- If extractable studies are performed ahead of time, the burden of setting leachables specifications becomes easier as
  - an extractables-leachables correlation can be accomplished in a single stability study

Lifecycle Management



- Lifecycle monitoring and improvement in CCS material and process
- Work with suppler related to changes in CCS process
  - Business decisions
  - Alternate sites for better access
  - Better knowledge of materials
- Development of libraries for alternate CCS materials to be interchanged ahead of time since the component marketplace is constantly changing

Summary

- Extractables and leachables (E/L's) pose a safety and quality concern to certain types of products
- The QbD approach can provide a framework for a more scientific, risk-based approach to E/L's
- Risk understanding and management is key
- Specification is only part of quality control strategy
- Higher level of understanding can facilitate continual improvement during product lifecycle

Available References

- ICH Q8(R2) *Pharmaceutical Development* (Aug 2009).
- ICH Q9 *Quality Risk Management* (Nov 2005).
- FDA Guidance to Industry, *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999).
- FDA Guidance to Industry (draft), *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products* (November 1998).
- FDA Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products (July 2002).
- PQRI Recommendation (draft), *Safety Thresholds and Best Practices for E/L in Orally Inhaled and Nasal Drug Products* (September 2006).

Acknowledgements

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