Extractables and Leachables: Trends in FDA Process Questions

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Trends in E&L Process Questions

01 Categorizing E&L Questions

02 Definitions for Secondary Characterization

03 Number/Types of Questions per Category

04 Example Questions

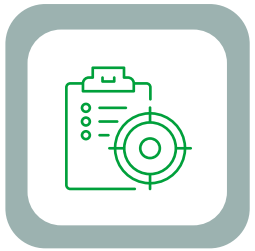
05 Summary

Categorizing FDA Questions 2018 to 2023

Why categorize?

Identify trends in Health Authority Information Requests

Share learnings and experiences globally



Identify key points to increase the likelihood of a successful submission

Primary Category

- Product Extractable
- Product Leachable
- Process

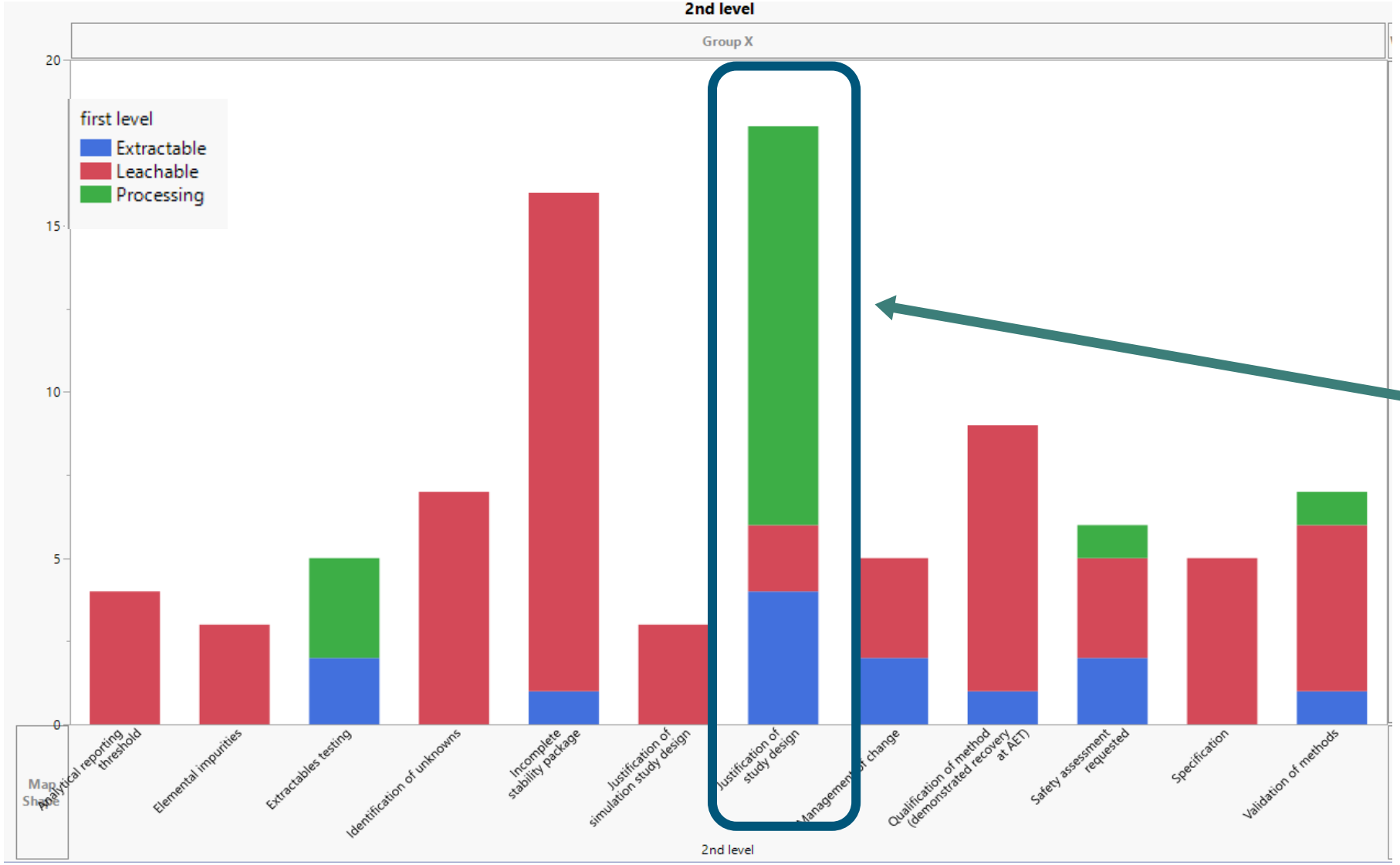
Secondary Category (multiple could be applied)

- Management of component change
- Justification of study design
- Qualification of method
- Safety assessment requested
- Specification
- Validation of methods
- Analytical reporting threshold
- Elemental impurities
- Extractables testing
- Identification of unknowns
- Incomplete stability package
- Justification of simulation study design

Secondary Categorization - Definitions

Category	Definition
Management of component changes	Justification leachables testing on ‘old’ CCS representative of ‘new’ CCS
Justification of study design	Explanation/Justification of study design
Qualification of method	Demonstration of recovery at AET i.e. leachables method can detect leachables at AET
Safety assessment requested	Provide safety assessment for leachables
Specification	Justify or tighten specification
Validation of methods	Provide method validation documentation
Analytical reporting threshold	Update to AET requested by reviewer
Elemental impurities	Perform assessment and/or safety assessment
Extractables testing	Request for extractable data
Identification of unknowns	Provide structure and/or CAS numbers or identification
Incomplete stability package	Request for leachables/multiple time point studies
Justification of simulation study	Explanation/Justification of the simulation study design

Question Types per Category – 2018 to 2023



Note: Many questions could have been re-categorised or placed in >1 category

Justification of study design most common for processing

Note: Analysis did not distinguish product types

Process Example Questions

Contact time

- Contact time for tubing is specified as 12 hours, extractables testing was performed for 5 hours. Justify.

Material differences

- Filters used in exhibit batches are different to those proposed for commercial manufacture. Justify.

Extraction solvents

- Study performed without buffer agents. Please repeat the study with the formulation buffering agents.

Adequate method validation

- Justify how the method is suitable with regards to sensitivity, detection limit and coverage of all leachables – provide a method validation report.

Applying AET

- Compounds were observed over the AET in extractables data. Provide leachables studies to demonstrate that the observed extractables are not present above the safety concern in bulk solution or final product. Alternatively, propose mitigation strategies, e.g. flushing, to reduce the extractables below the AET and provide data.

2024 Trends

Examples of more recent questions:

Extractable - Justification of study design

Justify why maximum filling time is longer than some polymeric contact materials compatible time or align your proposed maximum filling time with shortest polymeric contact materials maximum contact time.

Leachable - Safety assessment requested

For polymeric contacting components of manufacturing equipment one leachable is above AET or SCT. Please explain how you control/qualify this leachable above the limits so its risk can be mitigated.

In Summary

- Manufacturing Process should be considered carefully in E&L studies (in a similar manner to the CCS)
- Ensure your study design and data are representative of your process!
  - Use representative equipment and formulation
  - Consider your processing equipment hold times in comparison to the extractables performed and your commercial manufacturing process
- Use suitable, qualified methods such as USP <665>
- If extractables are over the AET how will you mitigate the risk?
  - Safety assessment?
  - Flushing equipment?
  - Demonstrate that leachables methods can detect processing leachables?
  - Perform leachables with the manufacturing equipment?

Appreciation Slide!

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