

Table 29: Extractables and Leachables- What's Being Requested and What's Everyone Doing?

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SCOPE:

To ensure patient safety and product quality with the increased manufacturing use of plastic and disposable components, regulatory agencies have been requesting more comprehensive extractable and leachable programs for biologics. Many companies use holistic approaches employing both risk-based evaluation and testing strategies to systematically assess potential risks associated with all process stream contact materials and container closure systems (CCS). This roundtable discussion will focus on understanding the evolving extractable and leachable (E&L) regulatory landscape and the successful approaches and strategies used by companies to ensure safety, quality, and compliance.

QUESTIONS FOR DISCUSSION:

1. How much E&L content and data are going into regulatory filings at various stages of development (e.g., Phase I through phase III to commercial)? Is E&L phase specific regulatory filing content being driven by agency expectations and queries?
2. Are companies executing leachable testing for both drug substance (DS) and drug product (DP) final containers over their respective shelf lives? How many lots for DS and DP? Life cycle management programs?
3. For new modalities like gene therapy with very limited quantity of product available, what special E&L considerations or strategies have been used successfully or are being considered (e.g., Simulation studies vs. leachable studies)?
4. Is it plausible to successfully leverage platform CCS historical leachable studies from similar products, formulations, and storage conditions to scientifically justify a low risk that can replace product specific leachable studies or significantly limit leachable testing?

DISCUSSION NOTES:

- Extractables and leachables (E&L) data is not being included in initial IND. One company reported that DS and DP studies were requested at Phase III. Most companies reported conducting E&L studies for both DS and DP with the process validation lots through shelf life.
- Asian countries are starting to ask for DS and DP extractables/leachable data (e.g., multiple lots, frozen, lyo etc.)
- DS data is being requested even when the DS is frozen. Companies are reviewing supplier extractable information to determine if sufficient (ex. Worse-case scenario, BPOG protocol, USP <1665> and <665> draft, not expected to be finalized until~ 2525) and whether further studies are required such as extractables studies with excipients (e.g., simulation study) or leachable studies.
- PQRI safety thresholds being challenged by EFPIA May 2019 Brussels conference (EFPIA, European Federation of Pharmaceutical Industries and Associations). 1 mg/day or PDE for non-mutagens (safety demonstrated Harvey et al; in line with Q3a) as compare to 5 ug/day PQRI SCT. It was mentioned that this seems unlikely to succeed based on recent regulatory interactions. Q3a 1 mg/mL used for process related impurities, why leachables are different

(comment leachables perceived as contaminants as opposed to process related impurities is the differentiator).

- With the use of single use technology, there is more focus on volatiles
- E&L studies are supporting material to the dossiers and only changed if triggered by a post approval change which may require further E&L
- Possible to use platform data, must be justified
- DS intermediates, only requested when they have long hold times
- ICH Q3E – updated E&L guidance, addresses single use technology
- 50:50 of getting approval with minimal E&L, but it can be a post-approval commitment
- E&L regulatory queries commonly received by all participants