Table 7: Extractable and Leachable Studies: Best Practices, Case Studies, and Regulatory Update

Facilitators –

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Scope:

Extractable and leachable (E&L) studies are required for successful registration of parenteral biologics and they are of high concern from regulatory agencies. The E&L profile is monitored not only from a safety perspective, but also impacts biological product stability, quality, and efficacy. Over the last two decades, industry consortiums (ISO, PQRI, ELSIE, BPOG) and regulators (USP multiple chapters) issued best practices and guidance to address E&L; however, important technical and regulatory gaps still exist. New challenges face the biopharma industry development of biologics and vaccines, due to the introduction of innovative materials used for single-use manufacturing or primary packaging systems, and novel modalities like cell and gene therapies. Low (microgram) dose products have their own challenges. Gaps exist regarding agreed standards for overall risk management and application of QbD principles. Hence, ICH Q3E is in-progress for assessment and control of E&L. The roundtable will discuss best practices, case studies, and ongoing regulatory initiatives.

Questions for Discussion:

1. How much E&L data is typically included in Phase 1/2 vs Phase 3 vs BLA filings?
2. Are there region-specific E&L expectations and what questions from regulatory agencies are commonly seen?
3. At what stage of development are E&L studies performed? What guidance is most useful regarding thresholds for identification, qualification, and quantification? Or for iv versus sc administered products?
4. How many DS and DP lots are typically subjected to E&L studies?
5. How are combination therapy / drug delivery devices addressed?
6. For new modalities like cell & gene therapy, with limited numbers of products approved, what special E&L considerations are required and what strategies have been successful?
7. Can prior knowledge be used in lieu of actual E&L studies – when utilizing platform manufacturing or common formulations?
8. What does our industry expect from the outcome of ICH Q3E?

Discussion Notes:

January 25 and 27, February 2 and 4, *combined* –

- Lack of clear E&L guidance is a problem. Larger companies develop their own E&L process and expertise, but can make an initial mistake of too aggressive testing conditions and characterizing extractables that have no clinical or practical relevance.
    - Heavy reliance on evaluating E&Ls from a new chemical entity approach and then turning to the toxicologist for help to evaluate against an assessment of permitted daily exposure. This approach may be overly conservative and certainly inconsistent.
- Good to start thinking about E&L studies early and with a risk-based approach (for example if using unfamiliar or outside of platform single use systems). General agreement not to put E&L data into early phase regulatory filings – wait until the process is locked (late Phase 3 and certainly BLA).
    - All the companies start the E&L work in late P2 or prior to pivotal study start when the process, formulation, container closures are being finalized
    - No data submitted during P1/2
    - Data included in BLA only (unless there was a specific question – in that case the response was provided)
- Some Health Authorities are asking for leachable study results on three stability lots (DS or DP), but general consensus that one representative lot is sufficient.
    - Extractable data is supportive
- Optimistic that the ICH Q3E guidance in-preparation will provide common sense and clear approaches to performing E&L studies. For example,
    - What solvents are recommended? Why not just use water?
    - How to address clinical in-use studies (now we have a plethora of dose administration sets) with respect to E&L impact?
    - Use of platform knowledge to do product specific E&L. This could be analogous to modular viral clearance approach
    - How to approach risk analysis
- Most Biopharm companies are using guidance that has been issued by PQRI (Product Quality Research Initiative) for their parenteral product.

- BPOG has a standard extractable solvent/condition and analytical methods that several single use bags, vials and packaging companies are using. Hopefully ICH Q3E will reference some of the current standards.