Table 10: Control Strategy for Extractables and Leachables

SESSION 1:
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SESSION 2:
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SCOPE:
Extractables (E) are compounds that can be extracted from the container closure system (CCS) by selected solvents whereas leachables (L) are compounds that leach into the dosage form from the container closure as a result of direct contact with the formulation. For E/L testing proper detection and screening techniques (such as GC-MS or LC-MS) with acceptable DL and QL are needed. There are several compendial references (USP <661>, <1151>, <601>). As part of the CCS qualification, extractables/leachables studies are performed to screen for and monitor the presence of harmful materials that may be released by CCS components. For market applications, a long-term leachable study of at least one representative batch (per configuration) should be performed. Some situations may allow for a risk-based evaluation (e.g. potential for extraction, knowledge of CCS from other applications…etc.). A correlation between extractables and leachables could be leveraged for quality assessment as well. In case of harmful leachables, acceptable levels should be defined and potential risks should be assessed. This roundtable aims to discuss the control strategy for extractables and leachables.

QUESTIONS FOR DISCUSSION:
1. What should be the control system in case of a harmful leachable? Can specified extractable studies of CCS compounds justify to omit drug product leachable testing? Is it then sufficient to test each lot of CCS compounds once? Is the same strategy applicable to the DS/DP manufacturing process?
2. What are accepted databases for PDE/ADE/EDI levels? Should the interaction between different leachables be assessed? Can PDE levels be regarded independently from each other?
3. How should the cumulative extractable/leachable profile for the DS/DP manufacturing process be covered?
4. How can we provide an E&L assessment for clinical trials in a phase-appropriate effort?
5. How can we address ICH Q3D requirements into our E&L assessments?

DISCUSSION NOTES:
- Single use items sparked the interest for L/E.
- Field is completely different compared to drug substance/bioprocess monitoring.
- Leachable might inhibit cell growth/culture. So, DSP may not always be an issue (in case of problems with the product). However, regulatory agencies will require to monitor process control, therefore it is important to know whether L/E causes a problem.
- There is often little understanding of the materials used; should CQAs be defined?
- Lot testing for consistency of the product seems to be done frequently, although some participants indicate that only with change in vendor .

- Toxicity assessment is done both via central groups and site-specific, with the focus on single L/E. Interactions between them is not often studied.
- L/E testing is done phase appropriate. Prior knowledge often used in early stages. Only at later stages tox studies are involved.
- How to control potentially harmful L/E; a trend seems to be in setting entrance requirements. This way, the vendor is required to show this is met and it takes the testing out of house.