Session 2 - Table 19: Extractables and Leachables: New ICH Q3E Guidance, Common Practices and Challenges (single use)

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Abstract:

A new ICH Quality guideline (Q3E) on the assessment and control of extractables and leachables (E&L) is being developed. Defined as follows, “extractables” are any chemical entities that will extract from components of a manufacturing or packaging system into a solvent under forced conditions. This provides an effective worst case scenario in terms of what can migrate from a component. Knowledge of these extractables and the conditions under which they form is important in identifying potential “leachables” that can migrate via contact with manufacturing systems, container-closure systems, and drug delivery device components.

The new guideline will be available for public comment in 2025.

Topics and questions to spur discussion at the roundtable

1. For the finished product, which routes of administration and what product types and containers carry the most risk to introduce leachables?

2. During manufacturing, what single use plastics are commonly used and need to be considered for leachables? How to manage change in these consumables?

3. Do you approach E&L with short term (accelerated/stress condition) and/or long term stability studies?

4. When is a theoretical/paper based assessment or “platform” approach acceptable? When would extractable data alone be sufficient to assess manufacturing components?

5. During the product lifecycle, are there health authority questions at the clinical stage? Is the initial marketing application approached differently versus post approval submission?

6. How do you handle a method with a limit of quantitation which leads to a level of leachable above the permitted exposure? How are analytical uncertainty factors (AUFs) incorporated? Other considerations for analytical methods?

Notes:

A CBER principal investigator for analytical, with experience reviewing submissions as an E&L expert, was present at the table and provided some remarks from their perspective both as a reviewer of marketing applications and contributing author to ICH Q3E EWG (expert working group).

Marketing Applications

Insufficient or vague information on E&L was common (~90% of applications) which may arise from the significant gap in what is described in current guidance versus what is expected by FDA in terms of the scientific approach. ICH Q3E, when issued, is expected to address this gap. During the review, some applicants provided relevant information via an RFI (request for information) although for other cases, a PMC (post marketing commitment) was issued as part of the approval letter. For elemental leachables, sometimes no information was provided in the submission, however it is required.

It is recommended to consider including E&L as a topic in the pre BLA meeting with FDA or in scientific advice. In some cases, an E&L expert, representing the applicant, might be requested by the FDA to attend a pre-BLA meeting.

E&L Assessments

The major principles of E&L are described in CFR sections. Current guidances are the respective USP chapters. A risk assessment for E&L that is performed based on individual components, in which low risk components are removed and not assessed further, has a significant deficiency. Biologicals are typically manufactured in multi-step processes using many materials, in which even low risk materials can contribute, cumulatively, to the final leachables profile so it is recommended that the assessment considers the end-to-end manufacturing process including stability/shelf-life and in-use (dose administration). CDER typically expects information from multiple lots; CBER is expected to align to this expectation soon.

According to the CBER representative present, simulation studies with formulation buffer only, i.e., no active ingredient present, can be sufficient when the cumulative approach described above is used and all the relevant product contacting materials are included. The design of studies should focus on accumulation after the last purification step (final material) since the upstream chromatography or diafiltration steps are considered effective in removing leachables. Upstream steps are therefore of less concern however cumulative (additive) contributions to the final product should not be overlooked. For cell therapies in which there are fewer purification steps compared to biologics, the same concept applies in terms of which step in the manufacturing process is the relevant starting point for the assessment.

Maximum hold times, highest temperature, longest stability duration (shelf life) and the maximum allowed in-use duration and temperature should be used as a cumulative worst case simulation of leachables in the actual product.

There are 3 significant concepts to consider in study design and to provide in a marketing application:

- Cumulative assessment that does not, by default, dismiss low risk components
- Focus the assessment from the last purification step onward
- Simulated studies may be acceptable (no active ingredient but including a full list of product contacting materials throughout the process)

For DP leachables, the longest hold time for manufacturing the maximum batch size is not absolutely required by the agency however the approach, assessment and justification, needs to be consistent and scientific.

Many companies want to leverage extractables studies performed only on components, as the extraction conditions are more extreme (solvent, temperature) than product manufacturing and storage conditions. This could be acceptable if a comprehensive assessment including all components in an additive manner is presented with a robust justification for the applicability to the product under review. In general, though, data specific to your process and product is preferred by the regulators. Data from lab-based studies is expected, i.e., a solely theoretical assessment is likely to be insufficient.

Analytical Considerations

If the LOQ for a leachables method is higher than the applicable safety threshold, use of simulated studies with no active ingredient can help to decrease the LOQ.

AET calculations often use a default uncertainty factor of 50% and the relevance of this can be questioned since it assumes 100% extraction efficiency which may not be the case and actual recovery can be considerably lower (5-20%). Sponsors should consider using at least a 10-fold safety margin for leachables, similar to the approach routinely used by toxicologists, as this is typically acceptable. For elemental impurities, 30% uncertainty makes sense scientifically.

Product Manufacturing and Configuration Aspects

Many sponsors base calculations on the overall maximum batch size, which leads to a lowest level of leachables in the product. It should therefore be assessed whether a smaller denominator in the calculation is relevant as a worst-case batch (depending on the details of the manufacturing process (bag/hold tank, filter to fill) and product configuration (vial or syringe). Sterile filters may be flushed with water or formulation buffer depending on the process or facility design. It is noted that the leaching power is different since water is less likely to flush away leachables than formulation buffer due to its salts and surfactants. The filter wash should therefore be considered and well as the potential contribution of leachables from excipients.

For the products reviewed at CBER a full leachables study is expected. For CDER, a risk-based approach (in silico combined with extractables info) might be acceptable and if relevant to the process a consideration that the first few vials filled have a higher level of leachables.

For a platform process, is a single E&L assessment appropriate? A simulation study could apply to multiple products as long as the parameters for the products, specifically the manufacturing process, product formulation, container closure and in-use are the same or any differences can be justified or scaled in the calculation.

In-Use Testing

For IV administration in the hospital and clinic setting, a variety of administration plastics (saline bags, catheters and lines etc made with a variety of plastics) are used. The relevant materials contacting the product need to be assessed, and if not provided in the initial marketing application, an assessment might be requested by the regulators. Compatibility of materials is routinely assessed for in-use, but leachables are often not included; a gap that could be addressed via a risk assessment.

E&L studies

Most studies are done in contract labs (CRO) who may state they can reach a particular LOQ. Roundtable participants noted that once a study is conducted with the product, it is not uncommon that the stated LOQ is not achieved so initial statements on LOQ may need to be viewed with caution based on the experience at this roundtable. In some cases, a CRO asks the product developer to provide an AET however this information is not known with a degree of confidence by the product developer. It can also be a challenge to find out the method parameters from the CRO due to proprietary concerns.

Most CROs use a look-up library for the response factor for a given leachable. Each CRO has its own cocktail of components for system suitability on leachables studies. If something else is needed, a separate small study might be designed to determine the relevant response factor.

Often two lab-based studies are carried out, one at the condition relevant for routine manufacturing /long-term storage and another at accelerated conditions (typically higher temperature, shorter duration). The accelerated data set could be the sole study provided in the submitted documents and the results from the long-term study provided post-approval (for example, via the annual update). A data set based only accelerated condition is not used frequently and not recommended.

If a component is changed in the post-approval setting, could a more streamlined approach, risk-assessment only be acceptable? This will depend on the nature and degree of the change.

Additional material: abstract to be presented by FDA at an upcoming conference

Extractables and Leachables Summit 2024

April 18-19, in Philadelphia, PA

Analytical Assessment of Leachables in Biological Drug Products: FDA Approach and Experience in Reviewing Information

Andrey Sarafanov

Biological drug products (biologics, i. e. therapeutic proteins, vaccine-, gene-, and cell therapy-based products) are produced via multi-step processes involving multiple materials contacting intermediates and sourcing numerous leachables into final drug products (DP). Such steps involve (i) purification of intermediates using chromatography, centrifuging, dialysis, filtering, and filling in final container closure system, etc., and (ii) shelf-life storage and in-use hold of DP. The respective leachables-producing contact materials involve chromatography resins, filtering/dialysis membranes, tubing, collecting containers, gaskets, valves, etc. By these, the assessment of leachables risk in biologics is the most challenging compared to other types of DPs. However, current guidances are generally focused on assessment of the leachables only from single manufacturing components, scored to be high-risk for leachables, and by this, underestimate other components scored to have the lower risk. Following these directions, manufacturers typically perform assessments only for the high-risk individual components and underestimate the contribution of other materials to the overall (cumulative) leachables profile in final DP. Other typical issues involve (i) non-validation of analytical methods, resulting in ambiguity in

Analytical Uncertainty Factor (AUF) used for calculation of the Analytical Evaluation Threshold (AET; or reporting limit in an assay), (ii) missing the assessment of elemental (ionic) leachables, or (iii) incorrect leachables study design; altogether also resulting in potential underestimation of the leachables risk. Such issues usually cause multiple back-and-forth communications between the FDA and Sponsor during the application review, typically ending up with post-marketing commitments/requirements (PMC/PMR) that puts an unnecessary burden on both sides. This presentation overviews an FDA experience in reviewing information for analytical assessment of leachables, including examples of the issues, altogether aimed to reduce the efforts of both sides in the submission/review process and facilitate proper evaluation of the leachables risk.