# Breakout Session IV

## Topic: Finished Dosage Form Considerations

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### Discussion Points

- Finished dosage Form Testing Protocols – What is the Industry Doing?
- Oral, Parenteral, and Inhalation Issues
- How to Deal with Other Routes of Administration with Less Defined Dosing/Exposure (Topicals, etc.)
- Definition of Short-term, Chronic use

### Top Takeaways

1. Some companies are performing elemental impurity testing / screening on finished dosage forms along with assessing final dosage form elemental impurity risk based on known concentrations from individual ingredients.
2. Routine testing will not be performed unless a risk assessment indicates it is necessary.
3. There is a need for flexibility in methodology and scientific justification of that methodology. Some companies didn't want to be limited to compendial methods.
4. Companies have to develop strategies and scientific rational on how the data is gathered or generated. Strategies may differ from company to company based on their specific types of products and processes.
5. Some drug manufacturers believe that excipient suppliers will be supplying more information than will occur, since ICH Q3D does not obligate excipient suppliers to generate data.
6. Some manufacturers, regulators and academia have completed testing on a range of excipients and finished drug product forms (OTC, parenteral, oral, inhalation, topical, etc.) and no reported issues have been brought to light at this time.
7. Drug manufacturers should ensure their suppliers understand the implications and impact an excipient change would have on the number and level of risk assessments they would need to perform. Certain excipient changes could be critical and have a high impact in many risk evaluations. It is crucial that excipient suppliers notify their customers of any changes that may impact the excipient's elemental impurity levels.

## Questions:

1. **Is testing the finished dosage form part of your control strategy? If so, what is its purpose?**
    a. Some type of testing / screening on finished dosage forms to justify control strategies. It is part of the Risk assessment, but testing is not on quality control release basis.
    b. Some companies are testing finished product and using results as an investigation tool to identify risk.
    c. Drug companies are coming from many different directions for control strategy. Companies need to have flexibility but document scientific rational for the directions they are taking.
    d. Drug companies need to have a general understanding of the elemental impurity levels and potential level variations for both their APIs and excipients, not just for their finished dosage form.

2. **Do you envision testing the final product routinely or as a qualification exercise?**
    - **If a sample of final product were to fail to meet limits for one or more of the elements, do you have a plan for Out of Specification (OOS) investigation?**
    - **What would be the impact of a deviation?**
    a. Not for routine testing but part of the product qualification.
    b. If levels are below 30% of ICH Q3D PDE, then routine testing might not be needed on finished dosage forms; however, this information alone may not be sufficient to assess risks that could result from changes in an excipient's or API's sourcing / manufacturing process.
    c. Companies believe an OOS investigation for elemental impurities would be the same as any other OSS.

3. **Have you performed analysis, gathered data?**
    a. Yes most companies have some type of data. The data at this time is limited.
    b. Companies have to develop strategies and scientific rational on how the data is gathered.
    c. The method and the limit of detection should be justified based on the type of information needed (i.e. based on dosage).

4. **Do you plan to perform ongoing testing for excipients that are deemed as Plant based or Mined? Materials where Elemental Impurity levels could fluctuate.**
    a. No desire to perform blanket testing on an on-going basis. Will use risk assessment but it is not predictable regarding excursions. Sometimes we have no clue about the ranges, seasons, natural sources, etc. Although as more knowledge is gained and shared greater understanding is expected
    b. Depends on what information is initially available. If there is no historical data, then some type of testing is needed for appropriate risk assessment.
    c. It depends on what percentage of the material is in the drug product? If it is sufficiently small, there may not be an issue.

5. **What is your expectation as a drug manufacturer for the information you may receive from your Excipient and API supplier? - Do you plan on screening excipients to understand potential concentrations?**
   - **If yes, a one-time event or ongoing?**
     a. Some are using the IPEC Information Exchange Form to gather standardized information from excipient and API suppliers. Also, some are using the IPEC PDE calculator for risk assessment purposes.
     b. Drug Manufacturers should communicate to suppliers the implications and impact of changes to the excipients in the number and level of risk assessments that they would need to repeat/perform. Certain changes may be critical and have high impact for many risk evaluations.
     c. Some drug manufacturers believe that excipient suppliers will be supplying more information than will occur.

6. **Have you ever considered / proposed modified limits based on either:**
   - **Route of administration – please specify other routes considered and basis for definition of limits.**
   - **Treatment duration – how was this factored in? e.g. Haber's law or other modified forms of this.**
   - **Therapeutic area e.g. anti-cancer treatment**
   - **If submitted what was the regulatory authority response?**
     a. Companies have not begun to assess the modified limits yet but see that this will be important in the future.
     b. There were not many companies in attendance that had products that fell into these categories.
     c. Topicals may need different limits. Companies are still working this out. Companies are searching toxicological studies and data is being gathered.
     d. Post Workshop Publication on Dermal Absorption may be useful when assessing risks for different routes (*Establishing Limits for Dermal Absorption of Elemental Impurities, Sep 02, 2015, Andrew Teasdale, Katherine Ulman, Jean Domoradzki, Phyllis Walsh, Pharmaceutical Technology, Volume 39, Issue 9, pg 44–51*)

7. **Have you ever factored in bio-availability in either calculating permitted limits or analysis (e.g. digestion media)?**
     a. The rooms that discussed this question missed the point of the question.
     b. The question should have been on Bioaccessability = percentage available for absorption; form of element in the material (e.g. clay, mined material)

8. **What is the definition of Short-term, Chronic use**
     a. FDA guidance's define these terms already. Short term = less than 14 days, infrequent episodes

## Outstanding Issues / Concerns

1. Large volume parenteral (LVP) manufacturers cautiously welcomed the revised arsenic limit in the ICH Q3D Step 4 guideline; however, there is a concern about how regulators may interpret this.
2. Companies need to understand, as per ICH Q3D that every component does not need to meet the specific limits for each element listed; however, the finished product ultimately needs to meet the PDE limits for each element.
3. There are concerns that the major pharmacopeias may not totally align in a timely fashion. This may cause major implications in the industry.
4. USP uses different language in General Chapter <232> than exists in ICH Q3D. The language in USP General Chapter <232> makes it difficult to justify why one would not test for certain elements, in particular USP General Chapter <232> could be interpreted as advocating the routine screening of class 1 elements
5. Recent FDA guidance on validation emphasizes the need to specifically evaluate method robustness differing currently from the requirements defined in USP General Chapter <1225>. What should the industry follow when utilizing USP General Chapter <233> for Elemental Impurity procedures?
6. Biologics are special cases due to the biological variability and related safety issues; therefore, the risk assessment must take into consideration and address this variability. A similar approach is needed for fermentation products due to contamination (e.g. gaskets).
7. Regulatory agencies need to state their implementation plans and define their expectations for how industry should report compliance for an ICH Q3D risk assessment.