Table 5: Trace Metals – Challenges And Controls in Raw Materials and Fermentation Media

Facilitators –

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Scope:

Raw materials used in bioprocessing must be free from any elements that may potentially affect the quality and safety of biopharmaceuticals. The nature of upstream processing presents an environment that increase potential for these elements to interact with target cells during bioprocessing. Numerous studies have demonstrated that certain trace metals are tied to certain critical quality attributes (e.g. copper and manganese in relation to glycosylation) so control of levels during upstream operations can greatly affect the production process. Given that suitable ranges for different trace metals vary tremendously, participants in this roundtable will share and brainstorm on best practices for raw materials containing trace metals for cell culture production and downstream processing steps along with the analytical techniques that can be most easily applied for reliable answers.

Questions for Discussion:

1. What standards must be met when sourcing raw materials for bioprocessing?
2. Do you confirm the quantity of each trace metal of interest in your cell culture media?
3. What practices/strategies are used to ensure that one has a stable supply of quality raw materials for bioprocessing?
4. How many trace metal levels do you control? Which ones are most critical?
5. What is the ideal control strategy for trace metal control in the manufacturing process?
6. Are you able to use one detection method across all metals of interest? If so, what is your method of choice?
7. Do you need to do sample extraction prior to detection? If so, what types of controls do you use and what is your biggest source of matrix interference?
8. Have your implemented additional mitigations steps with the media manufacturers to control contamination coming through the supply chain of high-risk raw materials
9. Have you encountered regulatory hurdles to filing raw material control strategies based on regional requirements?

Discussion Notes:

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

The discussion focused first on fermentation media. Fermentation media are complex materials and when a risk assessment is performed to highlight which raw materials are critical, they are universally recognized as raw materials of potential impact on product and process quality.

The typical outcome from the risk assessment is that at least three batches of fermentation media are used as part of process validation to ensure that the process is robust to natural variability of the media.

However, this does not prevent the emergence of unexpected events during cell culture, about 70-80% of which are generally attributed to raw materials. In the majority of cases, events have happened because of the levels of trace metals that they may contain. Elements like copper, manganese, iron or magnesium influence the fermentation process – yield, titer, waste etc.

To help the investigations that follow these unexpected events, organizations have in-house matrixes in place, detailing which raw material typically contributes to which amount of trace metal, thereby helping to identify the most likely culprit.

The team's recommendation for better controls is three folds:

- Use chemically defined fermentation media above media of natural origin; this allows for a clear composition in terms of components being present and their quantities. There is no obvious situation that chemically defined fermentation media cannot be used.
- Build and continuously refine these in-house matrixes to capture trace elements contributors
- Tracking of which medium goes into which batch is also essential

In addition, making sure that the media used during development is the same as that intended for commercial manufacture – not a different supplier or grade, will increase number of input batches and understanding of what the commercial product will be. Accelerated stability studies may also be useful to determine whether the product is likely to behave the same further down the line of the process or on stability. Molecules like EDTA may be able to neutralize surplus ions but this is not a strategy that is typically used.

The team went on define what an ideal state would be for the industry:

- Understand what levels of trace metals are acceptable for robustness of the process – a lower and higher limits are most likely, as the trace metals are also critical to some of the fermentation process
- Ensure controls of those trace elements that are critical through analytical testing. If the same elements are critical for most processes, working with the suppliers to ensure appropriate control (on the Certificate of Analysis). For different elements, ensure testing as part of acceptance of the product for commercial manufacture.

- This may allow more flexibility of sourcing alternative materials in a case of emergency like the pandemic – if their critical attributes are known, then it is easier to select an appropriate replacement for assessment. This will be of benefit to the whole supply chain.

The observations, challenges and recommendations can be applied to other materials, such as polysorbates (PS) used in most monoclonal antibodies' formulations. Oxidation of PS is a problem that will more likely arise at some point, especially for PS 80 and knowing now much oxidation is permissible would allow to better define what is an acceptable input batch or what is not.

The regulatory environment around raw materials is not harmonized, some countries are more stringent than other with regards to information on controls of raw materials that need to be provided. China for example, through its DMF platform for raw materials, require development and manufacturing control and description for raw materials used for parenteral formulations.

The team's recommendation for the ideal state is aligned with the principles outlined in ICH Q8 and Q12:

ICH Q8 extract:

> A comprehensive pharmaceutical development approach will generate process and product understanding and identify sources of variability. Sources of variability that can impact product quality should be identified, appropriately understood, and subsequently controlled. Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an opportunity to shift controls upstream and minimise the need for end product testing. Product and process understanding, in combination with quality risk management (see ICH Q9), will support the control of the process such that the variability (e.g., of raw materials) can be compensated for in an adaptable manner to deliver consistent product quality.
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> This process understanding can enable an alternative manufacturing paradigm where the variability of input materials could be less tightly constrained. Instead it can be possible to design an adaptive process step (a step that is responsive to the input materials) with appropriate process control to ensure consistent product quality.

And ICH Q12 extract for where Established Conditions are documented in the Common Technical Document (CTD) for registration:

		reference is made to Chapter 3, section 3.2.3.1 – *Identification of ECs for the Manufacturing Processes*
3.2.S.2.3	Control of Materials	Starting material specifications (test, elements of analytical procedure and acceptance criteria) Raw material/reagent/solvent critical controls