Roundtable Session 2 – Table 6: Regulatory considerations and experiences for control strategies in different regions (e.g. considerations for host cell proteins and how to justify attributes not on the C of A)

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Abstract:

As biologic manufacturing processes evolve, collaboration between regulatory agencies and the biopharmaceutical industry is crucial for maintaining the highest standards of product quality and patient care. However, approaches to aligned global regulatory practices are challenging as regulatory expectations may vary from region to region, creating region specific regulatory approaches. Additional factors, such as streamlined control strategies for well characterized attributes and/or demonstration of robust manufacturing processes, adds further complexity to aligned approaches due to differences in opinions on the justifications needed for these approaches. In this roundtable, we will discuss regulatory experiences and feedback from different regions with a special focus on host cell proteins and justification of attributes during manufacturing development to commercialization

Discussion Questions:

1. What are the control system strategies and considerations taken during manufacturing development used to monitor or control attributes such as host cell proteins?

2. How do you prepare justifications of attributes or align on regulatory strategies when there are process changes and/or limited batch history? What are the considerations needed for justifications of attributes not on the CoA?

3. Was there regulatory feedback that influenced or changed your overall strategy? Have you received feedback from different regulatory agencies that can provide guidance on agreements or disagreements on the justification of your control strategies?

Notes:

Introduction while people come to the table,

Mass spec. for HCP releasing, just curious about if anyone is doing it.

They don't discuss it for release but for characterization. Use for identity only, typical use ELISA for release.

Protein Metrics, MS CRO, uses standard peptides, for quantification.

A profile or picture of what is in the product is typical.

How does the Mass spec. fit in submissions?

Only using only ELISA

Using commercial for BLA, good coverage test, in depth characterization with MS to see if HCPs identified can have an impact CQAs

Question: What coverage is good enough? No one gets a concreate number >80% coverage.

Commercial kit for BLA by cygnus but characterize of the kit is important.

Table participants believe that they have a good cygnus kit

Bigger companies have their own platform HCP kits. Challenges lie on big process changes. And needing more characterization to prove the clearance and what's in the product.

Can you look at past process changes to look at clearance? Some have.

Still need to show that the kit is work.

Questions came back to using HCP analysis by LC-Mass Spec.

Companies focus on using MRM on ~10 HCPs peptides, companies use general XIC for quantification (top 3 peptides). There is some comp to ELISA report both results.

Working with GSK, MRM while Johnson uses XIC for general profile.

Has anyone tried to release with LC-MS? No Standard Method

How do you validate LC-MS HCP analysis is a sticking point, Making sure during development you are picking up and how does that correlate to the traditional ELISA.

Importance to do risk assessment on the HCP

Example, over 100 ppm so did LC-MS to characterize and showed no high concerning HCP and didn't get questions from the FDA on it.

Lenti virus vector HCPs are hard to characterize but there is a lot of clearance on the CAR-T process. Several dilutions during group up of cells.

Question to high HCP example above, Did you have to do more characterization with higher HCPs?

Required a process change which took care of the Hitch hiker.

IF can show the process clears and demonstrate that you don't have the HCP, does it have to be on release?

They group says they always try to have the not to have HCP testing for release spec, by showing that the process is consistent, but have not had luck in all countries. Good enough in some but not others. Leads to a different region CoA. Smaller regions more conservative. Easier to just include in CoA.

At Licensure, what purity assays can we validate out of the process.

Pro A, process related impurities, leachable can be validated out

HCP is not there yet.

If you understand the process, you can validate out some.

Does anyone have an experience where you had higher and had to do something?

> Example talking about Cell therapies, HCPs form lenti, use a surrogate to demonstrate clearance in the CAR-T product. There is a large amount of media changes that reduces the Lenti virus proteins.
>
> Cell line development, showing that each step shows the total amount of HCP to show clearance.

ELISA and LC-MS data together. Use the MS data as leverage. Unfortunately, MS analysis can be scientist specific one peptide or 3 peptides gives a different results.

> Might need to think about harmonization, is there is a standardization (going with 3 peptide is more acceptable) the software can provide. Debated between group and companies. This makes it difficult to ever have in QC.

Example: MS for one PTM, have to give all parameters in the method to be consistent, to be quantification, Questions on transferring tech can get very complicated. Concern there.

There was a question on assays being done in every regions that you have got feedback from,

> There was a waver for a radioactive assay to only do that test in the main lab (different region) and not at the region the product is being sold.

Discussion went back to Protein metrics on how people do quantification of peptides.

> highest Peak (charge state) is used most of the time.

Question on commercial kits, how has people handled them.

> The change in the kit has given a difference, process showed in process different.
>
> LLQ has shown to be different too. Some get coverage analysis for 60-70% is good for early studies >80% was good for others.
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> In-house kits have a large amount of reagents, will not have to resupply.
>
> Commercial ELISA kits have dilutional linearity issues so had to do such higher LOQ.

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