Table 29: Analytics for Accelerated Products: Challenges and Opportunities

Facilitators –

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Scope:
With the commitment to deliver future medicines to patients faster and in more cost-effective manners, biopharmaceutical industry and regulatory bodies around the world continue to advance the strategies and approaches for accelerated approvals. From product and process characterization and identification of critical quality attributes, to establishing appropriate methods and control strategies for commercial manufacturing, advanced analytics is of critical importance to accelerated development. What are key considerations in analytics to better support faster and shortened process development? With Breakthrough and Priority Medicines programs in place, what has been our experience supporting accelerated submissions? What are the specific advice from health authorities in the area of analytics from such reviews?

This roundtable discussion will include technical and regulatory considerations in analytics for accelerated clinical development and market authorization applications. Challenges experienced as well as opportunities within the analytics area will be the focus of the sharing and collaborative learning.

Questions for Discussion:

1. Platform or prior knowledge – how far can we go in leveraging what we know from other products?
2. New technologies and their applications – What are opportunities and potential hurdles?
3. Critical Quality Attributes (CQAs) – How do we decide what to test in less time?
4. Control strategy and specifications, reference standard and shelf life – How are these elements satisfied while working with (limited) clinical and process knowledge?
5. Method development, validation and transfer – How do we best navigate the various stages of the method life cycle?

Discussion Notes:

January 26 and 28 –

Platform and Knowledge Management

- Phase 1 focused on both efficacy and safety. Investment is held off until data is collected including stability.

- Accelerating a product by having an in-house platform method by 3-4 months. Doesn't work for every product, but capturing past knowledge allows you to adjust and optimize when needed for new products.

- Big challenge between cell culture and down stream groups and upstream. Good communication is needed.

- R&D focuses on speed, and QC pushes back. QC is slower to adopt newer technologies. It is crucial that R&D knows what instrumentation is available in QC when developing methods.

- Who is the owner of a platform method? This depends on where the method sits. These methods evolve over time and during product development.

- Is there any concern that the platform method may be different once it gets to a release method? Can results differ or the technology is drastically different? See ELISA being straight forward, but SEC and other methods could be more challenging.

- How many platform methods do you have? Have seen that it sometimes requires a base method. This is a good starting point and can be adjusted to minimize time to tweak a method for it to work for a new molecule. Maybe 5-6 weeks for an ideal situation.

- The closer you get to commercial, you see that the platform method must be tested. In some cases this is tweaked to improve method.

- CE-SDS and SEC are primary base methods.

- Platform method for CE work well for mAbs, but still could need tweaked. Other modalities need more method development and tweaking.

- The single biggest gap is knowledge management. Some accounts (i.e. BMS) holds conferences for knowledge sharing across groups.

- Seattle Genetics has a librarian to help with knowing where to find information/knowledge training.

- Some see that methods are tweaked as they are shared across sites and this could lead to methods changing, drifting away from the original method.

- Some companies have groups and meeting to share new methods on a regular basis.

Method Development, Validation, and Transfer

- Risk assess or phase appropriate validation for molecules before phase 3. Products qualified in non-GMP environment while using scientifically sound methods and practices.

- EUA is not required PPQ but method still needs to be validated (from Monday talk, maybe Phil Kraus).

New Technologies and Their Applications

- Blaze system from Intabio allows cIEF (imaging) coupled directly with MS for identification and CQAs.

- Has anyone setup automation for higher throughput? Automating a 96 well plate for glycan methods, for example, to reduce the hands on time. Preparing samples that require derivatization and laborious work can be moved to automation to increase throughput and increase precision.

- cIEF has a lot of sample prep and could use higher throughput.

- Struggling to automate peptide mapping for non-standard molecules. Primary sample preparation.

- MAM MS based methods needed more for more complex modalities.

CQA - How do we decide what to test in less time?

- Standard mAbs have a more established list of CQAs to go through and you can confirm these quickly.

- Deamidization are some of the most challenging CQAs to characterize.

February 1 –

Platform or prior knowledge – how far can we go in leveraging what we know from other products?

The general consensus was that if you have a very well-developed platform that has been used to assess multiple products, you can absolutely leverage that platform approach. If there is good evidence that a certain attribute does not change between your molecules you should be able to skip repeating this analysis. Proper risk analysis is also necessary when evaluating use of the platform methods.

How many products need to be evaluated by a method before said method is considered a “platform method”?

8-10 molecules was the consensus, but people agree it is case-dependent.

Participants also proposed to use the language “platform strategy” instead of just “platform”, as this would reflect the flexibility that a platform method might need from molecule to molecule, in which certain details (like molecule prep pre-analysis, or amount of molecule used) are tweaked, while the general method remains the same.

In compendium methods there is only need for verification, not validation. Can we leverage the power of platform methods to achieve this in non-compendial methods?

Certain methods in the monograph of the pharmacopeia can be driven to this direction. For example, current ongoing revisions of ICH Q2 and ICH Q14 allow for use of prior knowledge and risk assessment to be leveraged for making filing more efficient. Based on this, if the proper and thorough prior knowledge and risk assessment are demonstrated, certain experiments would not need to be repeated (e.g. experiments done during development would not need to be repeated under GMP conditions).

Participants made a note that currently, regulatory authorities are not used to receiving data from prior knowledge and indeed, there is no space in the dossier for previous knowledge.

What are the biggest challenges in terms of analytic methods supporting accelerated products?

- Uncertainty, for example specificity per molecule
- Cannot justify the specifications because clinical specifications only come after the method has been validated (because everything is happening at the same time)
- Late discovery of a CQA that was not covered by the platform
- When you do not have a perfect fit for a product in your platform

Challenges during transfer to QC:

- Lack of trained personnel
- Time constraints

Attendants mention that working with QC as early as possible and doing co-qualification/co-validation if possible, saves time and can greatly accelerate timelines. Attendant that works in QC agrees with this from QC perspective. It is important to keep equipment and other conditions as similar as possible between departments.

If platforms are so powerful, does that imply that we need to be careful implementing new technologies in accelerated products? Are there only hurdles following this route, or also some advantages?

Attendants concluded that there are many advantages to applying new technologies, depending on the benefits that the new technology brings. For example, cutting a lot of time off from a method, or similar benefits.

Extra question: what do people think about post-market commitments for certain methods like HCP?

Probably not easy, would need to be justified with a very thorough control strategy. You could have different findings when you switch the method/reagents. Ultimately, it comes down to the specifics of the product/impurity.