Roundtable Session 1 – Table 5 – Transitioning Analytical Methods to Commercial Control Strategies and Specification Settings

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Abstract:
Discuss how sponsors can evolve development-stage analytical methods into robust commercial control strategies for CGT products developed under accelerated timelines, particularly for rare diseases. Explore how early development specifications can be set when product and process knowledge are limited, including the use of risk-based justification, platform knowledge, prior clinical experience, method capability, critical quality attributes, and manufacturing experience. Consider when and how specifications should be refined as knowledge increases, and how analytical method readiness supports comparability, process validation, and regulatory expectations at commercialization.

Discussion Questions:

1. How early is too early to lock specifications?
2. What should carry the most weight when product-specific data are limited? - Platform knowledge, link to reference, prior knowledge
3. Are we over or under specifying CGT therapies for rare diseases? - empty-full- cell markers - are the examples of characteristics that could be safely removed?
4. What triggers specification tightening or widening? - consider the limited number of batches with rare disease therapies
5. Would you rather have a highly capable but poorly understood analytical method, or a less sophisticated method with a clear and proven link to clinical outcomes?

Notes:

Q1. When is earliest you can lock specifications.
It depends. Hard in this space because of process changes a lot. Some are easy to set. Can use some platform knowledge to get things started. Can set them wide – shouldn't go too early, but after the process is locked.
Could go though list – safety is easy (compendial methods). Residual plasmids. Plasmid amount in process will vary.
Can lean on guidances for safety.
Wouldn't have to lock specs before phase 3? Ideally yes.
Question – how wide can then be ? Set them in discussion with the regulators. What if regulator challenges you? Need to be science based – any justification that the regulator doesn't know about? Regulators are supportive. Spec could be combination of product and process – maybe the regulator has seen things before we don't about.
Probably helps to know why the regulator wants to set a particular specification.
Regulators are receptive to conversation.
But there are new products that regulators don't about. e.g. LVV and AAVs.
Example of replication competent lentivirus – requirement to test despite lack of evidence of risk. Example of 70% viability – lack of evidence. More about process control. But the regulatory concern is understandable. Difficult to systematic study to get data in a clinical setting. In Novartis viability specification example, they corrected the spec.

Q2. What should carry the most weight when product-specific data are limited? - Platform knowledge, link to reference, prior knowledge

For AAV, there is a lot of knowledge – can leverage this to accelerate to clinic. e.g. Impurities . Not sure if there is a framework for implementing platform knowledge. Could break down question by product type. For residuals and identification, could have platform. Prior knowledge is most useful. For example:
LODs for different technologies are different – makes it difficult to compare data. Report result for phase one, may not be worth trouble. Use collect report result data.
Difficult when have to accelerate – but could
Is AAV3 relevant to AAV9. Different serotypes can behave very differently. Product-specific (different transgene) can change properties. Won't know until you do large scale manufacturing.

Does everyone use report results or set up a high spec? If no data, shouldn't set a spec. Before then, report result. Can separate report results into characterisation section.

Link to reference? Know your process is really helpful. Don't rely on a platform – use prior knowledge.
Reference was very useful. Not always an obvious reference. Depends on the product.

Q3. **Are we over or under specifying CGT therapies for rare diseases? - empty-full-cell markers - are the examples of characteristics that could be safely removed?**
Are requirements too tight. E.g. Empty capsid/full, viability, replication competent virus. Depends on tissue culture infectious titre 50. Infectioous titre could be removed if have good potency assay. A lot of variability because it is not predictive. No-one removes it – has anyone seen it removed? Yes. Can run it as a characterisation method. Use it for batch trending.
Dose by PCR. No connection because of cell line dependence. LV assay was a lot less variable.
Love to get rid of replication competent AAV.
If there is a surrogate method – can replace.
rcAAV – people characterise as a safety test, but now really more of a residual assay. This change of category can be acceptable to regulators.
Impurity tests – raw material used that is washed out, but often requirement at start to monitor. Could use prior knowledge to help justify removal sooner.

Q4. What triggers specification tightening or widening? - consider the limited number of batches with rare disease therapies
Any experience in spec widening? Example of spec change as a result of method change - capilliary electrophoresis. It was successful – they improved sensitivity. Both methods used for stability. But was a large endeavour – characterisation impurities.
mAb broadened specification for carbohydrate – had to demonstrate with clinical data. Needed to do clinical bridging.
Empty capsid – unclear how to set spec. May be a requirement to tighten. If change method, with different sensitivities (or accuracy), Will eventually reach limit set by process.
Partial genomes, are they functional, correlated with potency?
Example of discovering partial capsids with method change. Then changed process to remove partials. This impacted potency specification because producing more full capsids and impact on dose. What methods are best for this problem - CDMS is used, but not necessary applicable in QC.
Is this issue faced with LV? No. Discussion around AAV structure.

Q5. Would you rather have a highly capable but poorly understood analytical method, or a less sophisticated method with a clear and proven link to clinical outcomes?
Need both types because you don't know what data will be useful in the future. The more characterisation you can do, the better. But comes with financial cost.