

Table 17: Next Generation Control Strategies: QTPP Definition and Implementation, CQA Definition and Setting Specifications Beyond Clinical Experience

Facilitators –

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Scope:

Robust control strategies are essential in delivering a consistent process and product. With accelerated programs and compressed CMC timelines, there is a need for streamlined next generation control strategies. A quality target product profile (QTPP) can be used to define target levels for attributes that are necessary for the desired analytical target profile. As more understanding is gained for the product and process, definition of critical quality attributes (CQAs) becomes a key component in development of the integrated control strategy. CQAs can be defined using a quality risk management approach as described in ICH Q9. This may include using a combination of prior/platform knowledge, structure-function information, and process and stability data. As knowledge is gained about the product and process, the analytical test panel included on the specifications must also evolve as part of the overall control strategy. Setting of acceptance criteria for specifications traditionally relies on a combination of CMC knowledge, non-clinical experience, and clinical experience. In this roundtable, we will discuss applications of next generation control strategies, their advantages and constraints, and feedback from regulators.

Questions for Discussion:

1. What is the status of QTPPs at your company? What is the content of the QTPP versus the TPP? Is it focused on CQAs and acceptable ranges? Have you provided a QTPP to regulatory agencies?
2. How do your companies develop the control strategy for novel modalities, especially where there is limited prior knowledge? How was the QTPP or CQAs defined (structure-function characterization)? What was the feedback from regulators?
3. How can the control strategy be adapted for next generation (continuous) manufacturing? What technologies and strategies can be implemented to ensure product and process consistency throughout manufacturing?
4. How have you used QTPP and next generation control strategies to set specifications? What was the feedback from regulators?

Discussion Notes:

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

QTPP

- QTPP was used in some form in all companies represented at the roundtable
- Companies had different implementation of QTPP. Some companies start developing QTPP in early stage to guide product development. Others create QTPP to be included in the marketing applications as way to present information for regulators. QTPP can be included in S.2.6 or P.2.6.
- For some companies, the QTPP was 1-2 pages long and was a formal document (either Excel or Word based). For other companies, the QTPP was more abstract and not formally documented.
- The TPP contains clinical targets and is an input to the QTPP, but attendees agreed that it was often difficult to get a TPP from the clinical team especially early in development. The amount of communication between CMC team and the product (i.e. clinical) teams varied between companies, with some companies requiring QTPP presentation to or sign-off from clinical teams and others lacking much communication.
- QTPPs contained different levels of detail. For some companies, acceptable ranges are included to drive development. For others, the targets are very wide and just outline what the CMC team is trying to achieve. Others use QTPP to define the route of administration target which will eventually dictate the container closure, and based on that a list of CQA is derived. QTPP starts to be developed and contains high level quality attributes,. Quality characteristics are added later as product knowledge is gained.
- Mixed experience as to whether CQAs or pCQAs are included in the QTPP.
- There were 2 examples provided where a QTPP was requested by a health authority. As a result, for one company, a high-level QTPP was included in an initial marketing application in the S26 introduction section. The high-level QTPP was primarily directional (i.e. “low levels of process impurities”) and introduced which attributes needed to be controlled.
- QTPP start when the TPP is available and used as communication tool from clinical to CMC. Try to put into, what is the dosage form, dose strength, route of administration, information about the product itself, mode of action and pCQAs, stability and shelf life requirements and container closure. QTPP is updated throughout development to account for changes in cininical dosing/administration and CQAs knowledge and justification of the acceptance criteria.

QTPPs and Control Strategies for Novel Modalities

- QTPPs can be useful for novel modalities since there is less prior knowledge.
- Examples were provided of how smaller companies or those using novel delivery devices may benefit from having a QTPP. There is a need for these groups to define their product and have an aim. It can force companies to think ahead to CMC aspects of their product.

- QTPPs can also be useful for internal communication to illustrate to other teams what attributes are important and how they can be impacted by decisions made (such as a decision to switch from vial to syringe)
- Several companies are using QTPPs across the board for all modalities. Companies find it beneficial and want to be prepared in case of agency questions. Attendees indicated that they thought QTPPs were an expectation from the health authorities and cited the ICH guidelines.
- For non-platform molecules, prior knowledge is lacking, early engagement with research allows to gather as much knowledge as possible prior to transition. This is a resource intensive effort.
- Best approach for new modality is to share with Agency, say which attributes you feel should be controlled and have early engagement.
- Authoring and Approval of QTPPs
- Some companies had informal QTPPs (not documented or signed off). Of those that had formal QTPPs, some only had signatures from the CMC team, others included signatures from non-CMC teams such as Research, Clinical, or Safety.
- Authoring responsibilities varied amongst companies. Some companies had Development groups authoring, others had CMC team lead as the responsible author, and others had the Product Quality Lead as author.

Miscellaneous

- Discussion on acceleration and how CMC is often on critical path when products receive BTB or PRIME designation
- Biosimilars tend to rely heavily on analytical comparability package and a strong QTPP and control strategy are needed
- Potential to provide QTPP or control strategy to regulators upfront to help with acceleration and agreement on CMC strategy
- A strong Quality Management System is necessary to support acceleration
- Control Strategies for Next Generation Manufacturing (NGM)
- Limited experience amongst group on control strategies for NGM. An example was provided of how having glycans as in-process test can reduce the need to include it on the spec.
- Investment in process analytical technologies (PAT) to enhance understanding and for better characterization of products in real time.
- Real-time release testing holds promise for the future but there will always be QC release testing.

Specifications

- Companies generally use a combination of clinical data, non-clinical, and process data to set specifications.

- Discussion around challenges of having very “clean” material in the clinic and, thus, being forced to set tighter specs.
- Companies have had success in using early clinical data (such as Phase 1 or dose escalation) and non-clinical (tox) data to help justify specs that are wider than batch data.
- Multiple companies have had success in justifying wider specs by having clinical teams use older material (i.e. not using the most recently manufactured material). Spiking of impurities in clinical batches for the sake of establishing specs. Is it time for the agencies to start considering such approaches?
- For ADCs, knowing the variability of the input materials (such as the number of lots of drug linker) is important for setting specifications. If there is no variability in input materials, it can allow for justification of wider specs due to changes in materials over time.
- There is the possibility of allowing wider specs initially and using a PACMP to tighten at a later time.
- Companies experience is that regulators mostly requires specs to be based on clinical experience.
- For viral vectors, data obtained from human host cell proteins was not accepted to justify HCP specifications. Request was to tighten specs based on clinical and manufacturing experience.