Table 1: Linking CMC and Clinical

Session 1:
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Session 2:
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SCOPE:

Linking clinical outcomes to the CMC process and product quality continues to be a challenge due to the large number of attributes associated with biotechnology products. This is compounded with the reality that clinical trials are often conducted using a small number of lots with limited product variability. Establishing acceptance criteria (e.g., for impurities) based on clinical relevance in conjunction with process capability or manufacturing process control is difficult because of this constraint. Studies evaluating structure-function relationships, such as biological characterization of CQAs, can help inform how product attributes should be controlled. However, these studies are resource intensive, may not be conducted early in development, and typically rely on surrogate biological assays that may not directly correlate with clinical outcomes. The focus of this discussion is sharing approaches to link clinical information and product quality profiles, including the use of prior knowledge in the context of ICH Q11.

QUESTIONS FOR DISCUSSION:

1. What type of approaches are being used to evaluate clinical impact of product attributes? Any experiences leveraging ex vivo systems?
2. Can data from clinical trials across similar products be leveraged? How has prior knowledge been utilized to inform early stage development and control strategies? What is acceptable to leverage and what is not acceptable?
3. Strategies being used to link clinical data and product quality in the context of late-stage or commercial programs.
4. Strategies for exposing patients to a wider range of product attributes (e.g., purposely manufacturing smaller batch sizes, longer exposure to RT/RL during manufacture, etc.)
5. If justified by clinical experience, can specifications for a new manufacturing process or site be broader than current commercial specifications?
6. How to establish biological characterization assays as surrogates linked to clinical outcomes?

DISCUSSION NOTES:

Session 1:

Importance of clinical relevance vs clinical experience.

Patient centric specifications. How can we justify the range? Is there anybody that has intentionally produced a batch with certain level of impurities and used it in the clinic?

Modelling process variability (i.e. manufacturing at the edge of allowable ranges) in order to get slight variations in QA's.

- Allows us to correlate lots to patient outcome
- Could potentially throw off trial results, but leads to understanding of product
- Hard to set specs when variability and clinical outcomes are narrow
- Data package needed to justify broader specs. If you are falling outside your tight range, then you are lacking control. Even if development data shows range can be wider than manufacturing ranges
- Hard to assess the use of conditions outside of normal parameters, safety of patients to be taken in account.

Importance to perform cross-functional risk assessment of CQA.

- Some people do batch by batch analyses. Sometimes it is difficult to reconstruct history of clinical development. Toxicity is easy to analyze. How to bridge the impact of an attribute on immunogenicity is harder. We don't have necessary all the data to do this assessment.

Breakthrough products will have limited data and will require PMCs - How can we bring variability in our process and clinic right from the start of the program?

- Acute vs chronic disease drugs may be looked at differently - human PK studies may be needed for chronic treatments

Concerning comparability studies

- Ideally build as we go the list of batches used in which trial. Educate non-clinical and clinical colleague on the plan. Importance to perform a risk assessment as a cross-functional team (i.e. more than just CMC assessing the changes and the risk). The team write a protocol and review the report. Several quality attributes should be assessed.

Prior knowledge - can data from similar programs be used?

- Experiments from one product can help develop others with less time
- Reponses of body and product can be very different therefore specific data for specific products or indications
- FDA encourages use of prior knowledge, but you need to justify why it is relevant for your product
- Used more and more in CMC (purified mAbs have a lot of prior knowledge) but for clinical studies, every entity behaves differently

Where does prior knowledge belong in BLA? - you have to include the data somewhere.

- Usage of platform database? Could add information from a product that has a wider range in our own molecule justification of specification.
- Like particulate matter, should we build database on other attributes? Should the FDA help with that? We should keep the samples from previous studies to check the consistency of the process and levels of impurities in several batches to defend potential risk to patients.
- Modeling data to get predictive analysis. In-silico studies? Problem of false positive, false negative. What can we use in as part of the bigger assessment? How to find the immunogenic potential of a molecule? How would that be received by the agencies? Pertain to HCP conversation mostly.

Session 2:

- Topic around long time and more challenges now because so few batches to set specs on
- Also such low levels of some impurities
- Immunogenicity… important. Getting strong signals can be difficult

Risk/benefit

- Model systems… in vitro model
- Translating from in vitro to in vivo
- PBMC models
- Relative risks

Use of prior knowledge across products. Have used to some extent. Up to industry to confirm specific parameter across modalities is clinically relevant.

Have to look at use of the product (e.g., oncology, etc). Could use as some justification.

Biotherapeutics area that may be more platformed. Is used often to justify levels of impurities across products. E.g. antibodies, high molecular weight species

Experience to set specifications. Some imperial evidence on some parameters.

Often reg tox material is purposefully prep'd to have higher impurity levels than material for clinic.

Might be able to run studies with unconventionally higher impurities (e.g., animal studies, cell-based assays). Was able to help justify higher initial phase 1 specifications.

Coming to get sci advice is a way to get agency experience across industry. Acceptability of higher impurities would generally be aligned with benefit/risk of given product.

Very early phase work to justify impurities, etc.

MOA's, etc. A lot of literature available to help justify.

Strategy's for exposing patients to wider specifications? How to do? Ethical? Animal model to help buy-down the risk? Clinical group motivated to keep specifications limited during expensive clinical programs.

Dose escalation studies can potentially help back-calculate into justifying higher specification.

Also stability change over time during clinical study could help justify specifications.

Is there potential to have discussion with clinical to help with alignment with CMC?

Clinical generally wants things to run as consistently as possible.

Process changes, suppler changes, etc often cause challenges during clinical development.

Specifications for non-CQA's. Some specs are just to confirm manufacturability over time.

Justification of why a particular attribute truly doesn't matter.

Manufacturing specification vs a release specification. Maybe tighter at CMO than at release.

Clinical bridging?