Table 1: Linking CQAs, Clinical Outcomes, and Attribute-based Specs for Fast to Approval Therapies

Facilitators –

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Scope:

There are many challenges for setting specifications for fast to approval therapies. Teams are often working with few batches, a single manufacturing and/or testing site, and limited stability data. Specifications based on batch data and statistical analysis alone may be too narrow for commercialization, but health authorities expect that clinical relevance will be justified for wider levels.

A key to justifying clinically relevant specifications is to determine the appropriate correlations between quality attributes and clinical performance.

The focus of this roundtable is to discuss various approaches to incorporating clinical outcome data for specification development and justification.

Questions for Discussion:

1. How is clinical information provided/discussed in your company?
2. Is there any analysis performed to correlate CQAs to clinical outcomes?
3. Have you incorporated the evaluation of CQAs for clinical relevance in Phase III trials?
4. Are there challenges with structure-function relationship studies and characterization studies, and how were they overcome?
5. What other data have you used successfully (e.g. in-vitro, similar products...)
6. What is the strategy for setting specifications for attributes that are determined to be non-critical, but are generally expected to be monitored for process consistency? (for example, charge variants..)

Discussion Notes:

January 25 and 27 –

How is clinical information provided or discussed in your company?

Clinical information implies any observation in your trial, adverse events reported or any desirable clinical outcome.

In a project team your share the clinical data with the team. Work with developing program and the relationship coming between CQA and clinical is not easy because everyone is not in the same framework. In developing world, this is a difficult place. Proteins which are well characterized are lot easier and the concept of well defined CQAs is extremely complex.

Even with the companies with biologics in early development space we try to identify the different quality attributes but in project teams it becomes difficult to tie the clinical efficacy and safety with the quality attributes.

For gene therapies there are not too many batches and so it becomes difficult to make it parallel and link it with the clinical data. And as you come to later phase you make the CQAs tighter and tighter and it becomes more apparent.

For biosimilars, lot of CQAs are based on literature and not specific. The clinical relevant information, lot more information is available than it was available from the originator. Mainly public information are leveraged. CQAs are narrowed not based on clinical information but based on other sources of information. For eg, glycosylation of antibodies may not tight at the beginning with the originator but it was tightened later. Another eg is deamidation level can't be laxed from the beginning due to safety issues. It has to be tight from early even without complete information. Once you have enough clinical data back, you then go back to CQAs from early phase and evaluate those values. Very often the agencies would come back to tighten CQAs from the process capability perspectives. For protein - based products, we need to have tight limits from the beginning due to aggregation issue. Relationship between cell-based assay and vector level also becomes important.

Specs for HMW for example-

In writing justifications of specs- even in the BLA, clinical team can support

Tim- When planning clinical trials- even PTP can be modified - topdown approach vs bottom up.

Most companies take the most conservative approach. Specially in a CMO setting.

QTPP- is a project plan

Without a QTPP there is no road map

In Phase 2 and 3, you have to have a plan

CQA and clinical Performance:

There have been recent publications and conference publications.

One experience-

After all phase III data were collected analysis was performed by a CMC specialist

Deamidation linking to bioavailability -further linking to potency- to set the specification for potency

Another example, collaboration:

Test patient serum sample if it correlated with the secondary endpoints.

Question: If half antibody level impact clinical outcome

Elevated level of a CQA has an impact.

Question: How sensitive do these analysis need to be?

Another example with vaccines:

For a vaccine that is unstable- a 6 month old sample for example

Correlated the potency at the time of administration

There was no dose response.

Negative experiences:

Culturally we are stuck in 3 sigma world.

ICHQ6B- has been identified as a priority for revision.

Cannot set specifications based on 1-2 lots.

Agency feedback during WCBP meeting-We don't use our dose-ranging studies

Low doses give us information in setting specs.

Regulatory agencies are advocating for dose ranging studies.

Challenges with CMC data coming from multiple sites:

For demand purposes, 3-4 CMOs may be involved.

Even under the EUA, initial data may come from one site.

Multiple lots:

We are talking about multiple lots.

A patient may get more than one lot.

On the other hand, cannot correlate DS lots to patients.

From a manufacturing point of view, unless a mfg change is made, generally a process is considered stable, then you are in a good place.

On the other hand, you are in a bad place considering future, the long term product life cycle.

Example- ADCC, we know which glycans modulate ADCC,

Mode of action is the tricky part-you don't know which bioassay reflects the MOA.

Example Humira- dfifferences in manufacturing had impact on patients. How much do we understand about the activity. Even for monoclonals, downstream cascades can be complicated.

In the oncology space, for some molecules, the MOA is not clear. Therefore which specifications are important is not clear.

In the CMO space, over 90% of projects, the bioassay is not available until PPQ stage.

How does one decide which activity (ADC, is a CQA?

What attributes are determined to be not critical, but monitored for process variance:

-not a clinically relevant spec.

-charge variant,

Multiple facilities-

A different way to measure process consistency

What is our experience as regulators to establish the link?

To design studies supporting the link is very difficult. As you progress you learn it. With process changes, the link becomes more important.

For fast to approvals, is there another platform for late stage projects?

For CMC teams with lot of clinical data some studies were done to establish the relationship. This is a great opportunity especially for shelved projects where pressure is not that much. For Phase 1

limited data may be available for safety (immunogenicity) and so may be Phase 3 which is far stretched out. You are ready to submit at that time.

For toxicologic studies we are not putting dirty lots for data but some do it and again it's a compromise.

For vaccines you have to have multiple manufacturing sites due to limited materials, the CQAs changes necessitating evaluation. During comparability studies you can learn something valuable. Change in cell culture conditions or even cell line can be the real challenge.

Changes or opportunities coming out for other antibodies, for eg COVID 19 situation – for eg bringing in more knowledge

For structure function correlation people do accelerated studies that may not be real conditions.

When we develop potency assays we always try to check if it is stability indicating and kind of correlates with structure. Accelerated stability studies have a place in that we can compare different materials, but make predictions based on accelerated conditions for for normal conditions may not apply. For development stage, yes accelerated studies give an idea on the degradation pathway. For many countries, cold chain supply may be difficult to obtain and you end up with deviations. For accelerated studies, it is very important to do the study below the melting temperature of the protein. For vaccines. Aluminum may accelerate aggregation of protein in the vaccines. In the delivery of COVID19 vaccines, the -70°C chamber was a challenge.

For vaccines, you must have some stability data at 25C and limited at 40C. We have already seen challenges on that front.

For non-CQAs what the strategy is to set up specifications.

Eg charge variants. Mostly it is conservative approach, two sided. We have seen challenges from EMA to enforce two sided limits. But some limit is expected, based on the process capabilities. You may not want to set up specifications for non-CQAs, for eg BPG.

With the new vaccines, the paradigm has shifted specially for regulatory approvals.