Roundtable Session 1 – Table 18: Bioconjugates - Effective Regulatory CMC Strategies for Manufacturing and Development

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Abstract:

Bioconjugates, such as Antibody-Drug Conjugates (ADCs), represent a rapidly evolving modality in biopharmaceuticals, offering targeted therapies in multiple therapeutic areas including oncology. However, their complex nature poses unique technical and regulatory challenges from manufacturing of these highly complex molecules for first-in-human clinical studies to process optimizations during development, validations of the different component nodes, and finally, post-approval CMC life-cycle management of these products. Collectively, these require both practical and innovative regulatory strategies to achieve successful global clinical trial and marketing applications.

The purpose of this CASSS round table session is to facilitate an in-depth discussion on effective CMC filing strategies for the manufacturing and development of bioconjugates. Industry experts and representatives from the FDA and other regulatory authorities will come together to share their experiences and insights on regulatory challenges and strategies from early development to commercialization of these complex molecules. The aim of this collaborative dialogue is to foster a deeper understanding of the current global regulatory landscape and the future direction for bioconjugate filing strategies.

Discussion Question 1:

Regulatory expectations for DS and DP are clear but not so much for the intermediates, e.g., drug-linker and mAb. Can we apply a scientific, risk-based approach for the intermediates vs. a more robust control strategy for DS and DP utilizing prior knowledge, product and process understanding and controls?

Notes for question 1:

Status quo is separate control systems of “critical intermediates” in addition to the conjugate drug substance and drug product. In the case of ADCs, the critical intermediates are typically the linker-drug used in the conjugation process, and the antibody intermediate, although a myriad of approaches can be taken for defining intermediates for the overall control strategy.

What are some of the graded risk based approach we can take? For example, critical quality attributes that affect the final DP can or may need to be controlled at earlier intermediate stages.

Alternatively, certain attributes that are on both the antibody intermediate and drug substance may only need control on the drug substance, for example, for lower risk critical quality attributes

Roundtable agreed that scientifically based strategies such as the above mentioned should allow for reduced testing at intermediate points, however, the regulatory hurdles of written guidance of FDA statements at conferences remains, i.e. you need DS level control for

intermediates. Several white papers that are coming out contain approaches to reduce the level of control that needs to be demonstrated at the intermediate state. Additionally, primary agencies such as FDA and EMA may be more willing to accept new approach for reduced testing, however other smaller agencies may not be willing to take risks for several reasons – but in this case, if global filings are expected, full DS-like control strategies for intermediates may just be the simpler approach. Luck has been had going to the primary health authorities and having those conversations ahead of time. Many of the countries ask the same questions repeatedly because there is a little bit of learning that needs to happen and as a result they are asking for more information then they probably need.

To some extent, treating the LD and the mAb intermediate with separate DS-like control systems allows for storage and shelf-life claims on those steps. Otherwise, continuous manufacturing from antibody intermediate production through conjugation may be an option to avoid separate control systems, but this option seems very unfeasible, given that there are often different sites for LD, AI, DS manufacturing, and single target mAbs may be paired with multiple LDs. Additionally, there is an inherent business risk of not having end-to-end control at key steps, but these are not to be confused with the true end-to-end quality control expectations of regulators. The round table acknowledged this is a difficult ask, but to continue making scientific based arguments that push removal of CQA testing at the antibody intermediate stage if possible in the hopes that the expectations for the level of control of intermediates may be reduced.

Discussion Question 2:

Can validations of the different components/nodes be done independently, e.g., use of clinical batches of the drug-linker and mAb to validate DS? Can the same strategy apply to DP validation? How can we streamline analytical tests/validation requirements?

Notes for question 2:

As it relates to process validation, the struggle is the science vs the regulatory requirement, especially with China and Japan, as they want all of it and its very challenging to try to reason that.

Bolt therapeutics and Genentech have both had successes using clinical intermediates to validate a downstream process, i.e. use clinical antibody intermediate in process performance qualification drug substance conjugations. A point was made that even if the run is at scale and is identical to the GMP process, but it is termed “engineering run”, the acceptance of using that in a process validation study is not acceptable, so a note to be careful with the terms used for runs. It seems that perhaps the further upstream you implement clinical process, the more success there will be in this. For example, there are cases where non-validated feedstock can be used for PPQs, which there was a negotiated agreement with the agency. However, using a non-validated clinical drug substance for a PPQ drug product campaign may not be acceptable and is usually always a review issue. There was also a question of pre-licensure inspections, and whether the end-to-end process needs to be performed all at once. This does not seem feasible, given that multiple sites can be involved in the manufacturing of LD, AI, DS and DP, so each of those sites would need to schedule their own PLIs – unlikely to be able to perform at the same time. There was a case where the agency was willing to inspect based on a process similar to that of the actual product, this was pre-negotiated. The agency can then decide later to come and inspect during the actual manufacture. In the small molecule realm, examples of

validating at a smaller scale and scaling up without further validation was an option, as well as completing qualification/validation runs after the filing. The roundtable highlighted challenges on scale and having to revalidate for new scales, as it is often difficult to plan for the true commercial supply needs by the time process validation activities should start.

Discussion Question 3:

Currently, the regulatory dossier contains 4 - 6 sections with 3 - 5 sections just for the DS and one for DP. Is this the most efficient? Is there a need for a flexible, fit-for-purpose approach or is this optimal?

Notes for question 3:

Roundtable generally agreed that separate sections (e.g. process, analytical, stability) sections for LD (if not located in DMF), AI, DS, and DP all made sense when it came to regulatory updates. Compartmentalization of the sections allowed for easier targeted updates to the dossier. This type of filing strategy is aligned with the FDA guidance that was provided over a decade ago. There may be opportunities to bundle the various process steps together, depending on the section, and the revision of ICH M4(R2) may support some of these efforts, but in general, the roundtable agreed that compartmentalization of the intermediates, DS, and DP continues to be the acceptable and recommended approach.

Discussion Question 4:

DMFs present a beneficial opportunity but are currently limited by regional differences. Can there be convergence?

Notes for question 4:

If there is a DMF for an active small molecule drug, and the drug is being used for an ADC, then it's feasible to use the DMF in the ADC filing. Seek to get the open portion of the DMF and put it in your submission. There has been experience with having the vendor of the LD provide the DMF to the submitted country HA; however, the sponsor may be completely blind to what is being submitted. Additionally, the vendor may have reservations of providing this type of IP to the HAs, as well as not want to be required to provide manufacturing updates etc., every time they change the process. Overall, having the vendor submit the DMF is generally a difficult path. Optimal path is for the sponsor to acquire the DMF and submit it with the dossier. One idea to ensure the sponsor can get the DMF is to write this into the agreement with the CDMO prior to signing the contract. Both CDER and CBER welcomes DMFs as part of the filings. In general, whatever the sponsor can do to obtain the DMF is advised, as it is acceptable to submit the DMF as the LD portion of the filing. A question was asked if you could cross-reference INDs. You can do it if it is in the same review division (same office), if it goes to a different office then they may give you a hard time.

Discussion Question 5:

Analytical testing - can tests be validated out? Is there a need for a separate spec. for unconjugated antibody/free-drug? Need for determination of DAR and DAR distribution?

Notes for question 5:

The example of removal of binding ELISAs on the DS/DP control system, provided a validated MOA reflective cell-based assay is in place, was discussed. There have been successes with having both ELISA and cell-based assays in parallel throughout development, with a data package presentation supporting that the binding is not needed, e.g. both ELISA and cell-based assays are showing similar behavior. One caveat is that if we take the approach to reducing intermediate control testing, i.e. removing binding ELISAs from the antibody intermediate, the drug substance may still require binding and cell based assays. Due to limited GMP runs for a data package, roundtable suggested that non-GMP characterization studies supporting the removal of DS ELISA binding testing should be acceptable.

There has been success in removing DAR distribution, in particular, DAR 0, for commercial control systems. This took the approach of good process understanding that the distributions were well controlled, and the specification for average DAR would ensure control of the distribution to a confident range.

The question of charge-based assay removal was brought up – no successes in removing the assay. However, as per the workshop, if an ICIEF assay is not specific for the CQAs it is meant to control, perhaps alternatives like multiple-attribute monitoring can be considered as a suitable replacement for what is, otherwise, an unsuitable ICIEF control strategy method.

The question of end-to-end linkage of product quality was discussed, i.e. a “linkage study” holding antibody intermediate/LD to the edge of the shelf-life, and then performing conjugation, and holding that material to the end of the shelf-life. Try to leverage modeling because you have the stability data. While end-to-end control is expected, there are ways to mitigate the risk of unknown PQ changes that may only be discovered by performing this extensive “linkage study”. One example was to shorten the individual shelf-life of the intermediates and DS/DP as a means to mitigate this unknown risk. For example, if you have data to support 5 years of shelf-life individually on your AI or DS, perhaps you shorten to 4 years for both as a mitigation in order to not have the full end-to-end experience from said “linkage study”.