Table 18: NDA to BLA/Biosimilar – Are You Ready for the New Grey Zone?

Facilitator: John Kim, *Teva Pharmaceuticals*

Scribe: Lesley Redfern, *AbbVie Inc.*

SCOPE:

Transition products (eg, insulin, hyaluronidase, human growth hormone or somatropin, desirudin, pancrelipase, pegvisomant and thyrotropin alfa products) are expected to shift from an NDA filing pathway to BLA/biosimilar pathways in March 2020. The goal of this round table is to discuss the challenges facing manufacturers and regulators in navigating the landscape starting in March 2020.

QUESTIONS FOR DISCUSSON:

1. What are the challenges in shifting from a small molecule mindset (NDA) to a large molecule mindset (BLA/biosimilar)?
2. Where is the guidance clear versus where is the "grey zone"?
3. What are the characterization expectations for transition products (eg, related to higher order structure, or mechanism of action)?
4. What are the challenges in control strategy, especially when material is sourced from a traditional API supplier?
5. How can we apply lessons learned from the early days of biosimilars when regulatory strategies/pathways were evolving and unclear?

DISCUSSION NOTES:

1. What are the challenges in shifting from a small molecule mindset (NDA) to a large molecule mindset?
    - Very challenging for those wanting to file a biosimilar of a transition project after March 2020 transition.
    - Submission of CMC changes as part of lifecycle management once a BLA. This may require more effort as a BLA, particularly if the NDA was not kept to current standards and modernized with new concepts and technology or if the change would impact information that was not required for an NDA but is required for a BLA which includes, for example:
        i. Facility diagrams
        ii. Level of detail for reference standards
    - New set of reviewers that will require help to become familiar with their new products and to ensure consistency of reviews. The principles are similar in that the reviewer will ensure that quality products can be manufactured consistently and that there is enough information to perform their review. However, there is a different mindset and skill set to ensure the products meet the legal requirements. Reviewers have been preparing for several years and meeting with sponsors, NDA reviewers and communicating to understand the products history.

- Some do not see as a big challenge, as in the rest of the world, the transition products are already considered as biologics.

2. Where is the guidance clear versus where is the grey zone?
   - Two guidance documents have been issued for transition products, please see link to guidance and products impacted:
   - https://www.fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act
   - Pharmacopeia monographs will still be applicable for analytical procedures and as for NDAs, the sponsor will be required to verify the analytical procedure is suitable for use for the specific product. The use of pharmacopeial monographs for reference standard may be more challenging.

3. What are the characterization expectations for transition products (e.g related to higher order structure, or mechanism action?
   - Each product needs to be characterized as much as can with techniques available, this is especially true for complex products

4. What are the challenges in control strategy, especially when material is sourced from a traditional API supplier?
   - Proposed ruling that if the sponsor referred to a DMF as an NDA, then the sponsor can still reference a DMF. However, for new products submitted after 23 March 2020, it will not be possible to refer to a DMF.

5. How can we apply lessons learned from the early days of biosimilars?
   - Biosimilar versus biobetters. Biobetters will not be possible for some products as greater potency could be problematic. FDA language for biosimilars includes clinically meaningful in USA. EU does not contain this language therefore has a different bar. Biobetters would fail biosimilar pathway, therefore there are other more suitable pathways for these products.
   - For a biosimilar a new clinical study would be required. Biosimilars always have clinical and toxicology components and it is not possible to fully demonstrate biosimilarity with analytical characterization alone. The innovator toxicology and clinical data can be leveraged to reduce the data generated for a biosimilar.
   - Biosimilar products do not need to be manufactured by the same process as the innovator. Comparability of the innovator and biosimilar products molecule need to be highly similar and any differences need to be justified that they do not impact safety or efficacy.