Roundtable Session 1 – Table 15: Recent Experiences with Regulation of Biosimilars at the FDA

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Abstract:

Biosimilars have been available in the USA for over a decade, and in Europe for almost two decades. The development of biosimilars is grounded in the comparison of a proposed biosimilar product to an FDA-licensed biological product, referred to as the reference product. The comparative data for biosimilarity are generated from detailed analytical (structural and functional) characterization, animal studies, and/or comparative clinical studies. Under BsUFA III (FY 2023-2027), FDA is committed to ensuring effective scientific coordination and review consistency, as well as efficient governance and operations across the biosimilar biological product review program. Additionally, as a part of BsUFA III commitment, FDA launched a regulatory science research pilot program to further enhance regulatory decision-making and facilitate science-based recommendations in areas foundational to biosimilar development.

Discussion Questions:

- Experiences with development and regulation of biosimilars after over more than one year of BsUFA III.
- Opportunities and challenges in KASA (Knowledge-Aided Assessment and Structured Application) and PQ/CMC (Pharmaceutical Quality/Chemistry, Manufacturing and Control) projects for biosimilars.
- Opportunities and challenges with EC (Established conditions) and PACMP (Post-Approval Change Management Protocols) implementation and submission for biosimilars.
- What is the value of comparative efficacy studies, along with clinical pharmacokinetic studies that compare US and EU reference products during biosimilars development?
- How will the post-approval pharmacovigilance data for marketed biosimilars help to develop alternatives to and/or reduce the size of studies involving human subjects?

Notes:

- In general it is seen that biosimilars are a working concept. Companies are getting better with respect to authoring their submissions. In addition, the agencies also gained experience which overall leads to less IRs being sent out. Overall, the expectations of the agency did not change. Suitable assays are needed and analytics need to be kept up to speed. While the standard remains unchanged more experience is common now.

- A limited need for clinical studies and comparative efficacy studies would be seen as helpful. While this is actively discussed within the agency it is still a slow process. Some other agencies seem to be more advance at this point (e.g. MHRA doesn't require comparative clinical studies anymore). A guidance document to which clinical studies are need would be seen as beneficial. For PK studies the requirements are clear because of the existing guidance.

- Regarding analytics biosimilars are more complicated than generics. However, as CQAs, product specific items, and MOA are known it becomes clear which assays are needed. The question if bridging could be done with analytics only without additional PK study remains open.

- It is mentioned that the use of an US reference product is very expensive. Additionally, three-way PK studies pose a high risk of failure. Two-way studies would be preferred by the biosimilar companies. In general, a high patient to patient variability is seen and this might be even higher than the lot to lot variability. Overall many different impacts on PK are known and also published. It is recommended to harmonize study subjects recruiting criteria for the PK study.

- SC formulations: Hyaluronidase is an active pharmaceutical ingredient. What is need per the agency? Would matching PK be enough? The agency also requires a similarity exercise. Generally it is possible to make a proposal and reach out to the agency for discussion.

- Will all biosimilars be interchangeable in the future? It may get there, but interchangeability must be specifically asked for. FDA published a paper in 2022 where the switch from biosimilar to reference product and back was studied. No negative impact was seen in this study (Herndon TM, Ausin C, Brahme NN, Schrieber SJ, Luo M, Andrada FC, et al. (2023) Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLoS ONE 18(10): e0292231. https://doi.org/10.1371/journal. pone.0292231). Therefore interchangeability without specific switching study might be possible in future if a sound justification is provided. This would be a case by case decision. In addition it is mentioned that it might be unethical to perform additional studies (switching studies) without need.

- EMA has a more accepting approach compared to FDA. This might be due to the fact that EMA started earlier with biosimilars and has more experience. FDA and EMA are exchanging thought about this topic. Future harmonization would be wished for. Overall knowledge of the companies and reviewers is growing.

- Is it possible to have additional indications for biosimilars? If the new indication is not approved for the reference product it is a new product and not a biosimilar. Toxicology studies cannot be used because they belong to the reference product. There is no shortcut, it would be a new submission with repeated studies. It cannot just be added to the label.

- Can existing data of clinical studies be leveraged to prevent the repetition of the toxicology study? Dosing would be needed for a new indication. However, the CMC package (full package for biosimilar) could be leveraged
- Can a biosimilar be combined with another biosimilar to become a new combination product? This would be a new product because no reference product exists.
- Are there trends regarding new companies in third world countries? Those companies exist but are not as advanced as the known biosimilar companies.
- Comparative clinical studies are the most expensive piece for the biosimilar. Therefore it might not be attractive for smaller products which leads to a lack of competition for many products. Additionally, biosimilars cannot get to the markets although approved because of IP issues.
- In which cases are Advisory Committee Meetings held? This was done in the initial phase to get some general education on the topic. Also the buy-in for regulators, patient communities and public acceptance was needed. The discussions are closed now and the meetings are therefore not needed anymore. It would only be done if it is seen to be value adding but it is unlikely to happen anymore.
- As the agency has access to all applications they could judge if the still huge studies are required. This is an ongoing discussion.