



The Ripples Around Development of Biosimilars

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ABSTRACT

Developing a biosimilar or follow-on-biologic to an innovator product is far more complex with significant investments throughout the value chain than developing a generic pharmaceutical product. The regulated markets have rather stringent requirements for establishing bio-similarity with respect to the molecule as well as its clinical safety and efficacy with respect to the innovator. Demonstrating similarity for clinical safety and efficacy with respect to the innovator product may be one of the key factors limiting the biosimilar approvals in the European Union. There are multiple players in this risky biosimilar development game but there are many factors to watch out for-both before and after they gain an approval which could make or break their programs.

Keywords: Biosimilars, Similar Biologics, Bio-Pharma Regulatory Affairs.

INTRODUCTION

A biosimilar or the “follow-on biologic” represents the biologic, which is being “re-produced” to the innovator biologic and is the equivalent of a generic to an innovator pharmaceutical product. With the initial blockbuster biologics approaching the end of their patent expiry or having expired, there has been a continuous influx of multiple players trying to develop and commercialize biosimilars targeting niche but global markets. The complexity of biosimilars being biologic products; is seen throughout the developmental lifecycle and the paths for biosimilars and generics are rather divergent in most markets of the world with varying degrees of regulatory control, in both the pre and post commercialization stages.

Regulatory Concerns and Ground Realities of Development of a Biosimilar Molecule

Development of biosimilar program requires strong financial support throughout its complex lifecycle unlike that seen in generic development. Establishing comparability to the reference molecule is one of the first steps in developing a biosimilar. For generics, comparison with just the structure of the reference product is often sufficient to establish bio-equivalence without furnishing extensive proof of concept and comparable safety and efficacy in clinical trials. However, for a biosimilar gaining approval in regulated and some semi-regulated nations, establishing comparability is neither accomplished with a few tests, nor is there a substantial reduction in the requirements at any stage from CMC (Chemistry, Manufacturing and Control) to pre-clinical studies or the clinical trials and finally the post authorization studies. This often results in the development being expensive, time-consuming and sometimes more elaborate compared to a new biological entity gaining approval.

In the CMC stage, “Process-is-the-product” is one of the most commonly associated adages with biologics; for a

new developer starting with a different clone, the process will be different but it need not mean that the resulting product will not be a “biosimilar”. More often than not, the biosimilar developer has to go about a round-about method for matching the reference product. The clone and the upstream process often lend to variability with respect to the structure, conformation and activity and may affect the glycosylation, charge variants and the impurity profile with a possible effect on immunogenicity. With the advance in analytical techniques, even primary structure of large molecules like mAbs can be confirmed, and extensive, expensive testing is often employed to reflect the molecule’s putative behavior in humans. The analytics employed add significantly to the cost of development.

The pre-clinical requirements differ in the major markets of the world and conducting these in the “relevant species” is not always feasible. For the biosimilar programs which have demonstrated suitable “biosimilarity” at the CMC and pre-clinical study stage, a feat in itself requiring time, abundant resources, expertise and patience; clinical trials are pivotal. As per the EMEA guidelines¹, clinical trials must be designed to not only demonstrate “clinical safety and efficacy *per se*” as the innovator has previously established it but a comparison of “clinical safety and efficacy” of the biosimilar with the innovator is required. Clinical requirements for extrapolation of indications may not be uniform for all programs of the same molecule under the same regulator. This makes the clinical trials far more complex and expensive due to comparative trials and the cost of sourcing the rather highly priced innovator reference products for the trial while increasing the time to market. Even established players with biosimilar approvals in Europe, have had to take a break to re-design some of the other programs for complex molecules like monoclonal antibodies. Also in these regulated markets- the policies of the governments with respect to uptake of biosimilars



and switching/interchangeability of biosimilars maybe game-changers post- approval.

In markets with stringent adherence to their regulatory framework, the extent to which biosimilarity must be established for firstly the CMC of the molecule and demonstrating significantly similar clinical efficacy and safety, has yet no standard template despite regulatory guidance being available or under active discussion. "Totality-of-the-evidence" as mentioned by the US FDA comes across as a holistic term and all eyes will be set on the first biosimilar which will meet these lofty standards! To get the US FDA nod, the developers are endeavoring to replicate the safety, efficacy/potency and purity of the innovator so as to have a "true-biosimilar" in all aspects and not a "bio-better" or a "bio-inferior"! Interchangeability & substitution of biosimilars is going to be a key factor in the uptake of biosimilars post approval. In USA, the State of Virginia has passed its first Biosimilar Substitution Law which regulates biosimilar substitution with measures for "substituting" only those biosimilars deemed "interchangeable" by the FDA followed by notifying both the prescriber & patients along with maintenance of records. This is viewed as rather prohibitive for the widespread uptake of biosimilars. With three more states with similar bills passed (Utah, Oregon & North Dakota; the latter has no sunset clause for the bill to expire in a set timeframe), ten states and lately, the California Governor have rejected such a law for their states.

Developers engage in discussions with the regulators throughout but it is difficult for others to glean any inference to fast-track their own process. The EMA guidelines have inspired the biosimilar guidelines for many countries across the world and going by the spate of approvals, they are far more coherent than the US FDA guidelines². The EMA has had 14 biosimilar approvals previously and in the last few months, it has approved or recommended the approval of quite a few biosimilars. The uptake of these biosimilars has not been the same for all innovator products & even for the same biosimilars, the uptake is quite heterogeneous across the EU member nations. In recent months, the first biosimilar mAb has been approved by the EMA³; for the innovator product, Remicade called "Remsima" developed by Celltrion, also called "Inflectra" by Hospira have been approved for all indications of the innovator product. Apotex has recently received recommendation for approval of its filgrastim biosimilar, "Grastofil". Another biologic by Teva, "Lonquex" has received an EU approval^{4,5} and may prove to be a direct challenge to the innovator and biosimilar products for Filgrastim and Peg-Filgrastim line-up. The next recommendation was for Biopartner's "Somatotropin Biopartner" biosimilar, which is the first prolonged release biosimilar for Eli Lilly's human growth hormone "Humatrope". Also the first biosimilar for follitropinalfa has received a recommendation, "Ovaleap" by Teva Pharmaceuticals for the reference product of Merck's "Gonal-F". The second generation biologics or

"biobetters" are going to be under intense scrutiny to see how significantly they can affect the uptake of biosimilars in primarily the developed markets. Innovator biologic developers have taken this quite seriously and some of their second/ next-generation products are either in the market or in late stage clinical programs!

The EMA is doing its best to dispel the cloud around "safety and efficacy" of approved biosimilars in EU. The perception of the safety and efficacy of biosimilars is going to be another factor which may come into prominence in some/primarily regulated nations but in times of austerity and pressures on healthcare costs, these concerns may be seen receding into the background.

On approval, the extent of post-authorization safety study (PASS) required for regulated markets is much higher than that of local markets. With time, research shows Anti-drug Antibodies against even fully humanized mAbs. With increasing access of biologics (as biosimilars), time may transform immunogenicity into another significant factor in the biosimilar uptake equation, where it may not be fair to associate immunogenicity with the biosimilar *per se*. In the regulated markets, long term scrutiny may throw up unexpected results which may not be very promising for the widespread acceptability of biosimilars.

Global Scenario of Biosimilar Product Development:

The Asian sub-continent has been stealing the limelight for becoming the new hub of developing and manufacturing biosimilars for the globe in an effort to reduce the cost of goods (COGS). South Korea, Malaysia, China, and India prominently are working on their infrastructure and regulatory front to promote biosimilar investment and tie-ups. India and China have many biosimilars approved in their domestic markets; they are trying to replicate similar successes in the regulated markets.

For this rather risky proposition of developing biosimilars (with very promising returns if successful), dynamic alliances between unlikely players are being forged (and un-done) to make the most of the biosimilar opportunity. We see a mix of innovators from Amgen, Novartis to generic giants such as Teva to the new financiers, Samsung, Fujifilms investing heavily into this abyss of development.

The premise of biosimilars is providing "safe and efficacious" biologics affordably; but the lingering question is with such huge investments throughout the life-cycle- would biosimilars still be affordable when they are finally approved? All the stake-holders must on their end ensure the quality, safety and efficacy aspects of biosimilars while the regulators help them achieve "reasonable" investment biosimilar programs with an eye on the time-to-market to address the un-met need of the masses. Perhaps we would have to wait and watch with the next generation of biosimilar approvals for complex molecules like mAbs in the regulated markets to

understand how they price their molecules and recover their investments while the innovators discount so as to nullify the price advantage over biosimilars or introduce bio-betters.

CONCLUSION

In the near future, there may be a day when there will be finally an influx of “highly similar” biosimilars (by both characterization and clinical evidence), with slight differences (insignificant clinically?) from the innovator. These differences maybe more substantial than the lot-to-lot intra variation of the innovator to itself and may reveal their effects on post-marketing surveillance of the biosimilar and different ethnicities may cough up different results. In regulated markets, the monopoly of any one product (primarily the innovator) will be avoided, but the competition may trickle down to only a few which would actually end up braving the pitfalls of the “biosimilarity- proof of concept and efficacy through clinical trials- efficacy in real world (effectiveness) after Phase IV Post Marketing Surveillance”. And there is always a possibility, of a “bio-better” also emerging from these few, perhaps with respect to the risk/benefit ratio rather than just the potency and efficacy. Meanwhile, those failing to establish themselves suitably in the regulated markets with rather stringent standards may

find themselves scrambling to establish safety and efficacy in the semi-regulated markets where “clinical safety and efficacy *per se*” of the biosimilar is often sufficient for approval.

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