The Role of PD Biomarkers in Biosimilar Development – To Get the Right Answer One Must First Ask the Right Question

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The potential for pharmacodynamic (PD) biomarkers to improve the efficiency of biosimilar product development and regulatory approval formed the premise for the virtual workshop *Pharmacodynamic Biomarkers for Biosimilar Development and Approval* hosted by the US Food and Drug Administration (FDA) and Duke Margolis, September 2021. Although the possibility of PD biomarkers replacing the to-date routine comparative phase III confirmatory study currently expected by the FDA was discussed, the motivation and feasibility for biosimilar sponsors developing such markers and the regulatory risks entailed largely were not. Even more fundamental is the already established greater comparative value of the pharmacokinetic (PK) study as the most sensitive clinical assay for detecting subtle differences between two products. Consequently, the comparative analytical assessment and the head-to-head PKs will have already answered the core questions as to the biosimilarity of the candidate product to its reference. No further actionable information is obtained with either a PD study or a comparative clinical phase III study even as they may provide some reassurance of what is already known. When a suitable PD biomarker is available for the originator reference product they have already been used for biosimilar development. We must carefully consider the core requirements and timelines inherent in biosimilar development and how they occur in parallel rather than in the series we see for originator products. In order to improve the efficiency of biosimilar development, we need to ask the right questions based on a full understanding of how biosimilars have been developed to date and can be in the future.

The US Food and Drug Administration (FDA) and Duke Margolis hosted a virtual workshop, *Pharmacodynamic Biomarkers for Biosimilar Development and Approval* September 20, 2021,[1] as a forum for regulators, biopharmaceutical developers, academic researchers, and other stakeholders to discuss the current and future role of pharmacodynamic (PD) biomarkers in improving the efficiency of biosimilar product development and regulatory approval. The context for this question is important to consider up front as it contains significant assumptions that may warrant recognizing. This includes what biosimilars are and are not, and how the regulatory process may or may not be able to be expedited while maintaining the safety, quality, and efficacy of the products finally approved by the FDA. Nonetheless, the overall goal for biosimilars is the same as for all medicines, namely better and more timely access by patients to enable individual and collective clinical benefits.

A biosimilar is made to match its reference product in the manner of generic to a small molecule drug, and, in both cases, under current US law,[2,3] the subsequent version is limited to the indications and presentations of its reference product. This means that, in the United States, biosimilars cannot offer more indications or presentations (including, for example, route of administration) than their reference products and as such are limited in how they can be differentiated from their reference or indeed from each other. Notably, in Europe, additional indications and presentations for biosimilars are allowed in some cases.[4] This illustrates how a biosimilar in different markets can be an identical product, but be labeled differently and used for different purposes based on legal constraints, not scientific or clinical ones. This can impact how they are developed and how the collective data set to support their approval may differ at its point of evaluation by different regulatory authorities. This is especially important for biosimilars, because unlike originator products, the United States may not be the first market pursued by a biosimilar sponsor.[5–8]

The assumptions made by the FDA, and others, for how biosimilars are developed and what efficiencies matter most to their sponsors need careful consideration and must be defined and fully articulated. As is always the case in science, having a carefully thought through and well-designed hypothesis is also key. Finally, where economics is also involved, and the ethics of timely and affordable patient access to critical medicines make this inevitable for biosimilars, incentives and motivations need to be acknowledged too. Whether these extend to actual conflicts of interest is also worthy of some thought but will not be addressed in any detail in this commentary.[9]

The FDA Duke Margolis workshop assumed that biosimilars are important for patient access and care, and that more efficient development with no compromise in quality may be possible. A role for PD biomarkers was suggested, including where such biomarkers do not exist for the reference products to which the biosimilars refer. More specifically, PD biomarkers were proposed as a potential alternative to the comparative clinical efficacy study that

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have been largely routine in the United States to date.[10] Some biosimilars have already been approved based on PD studies,[11] however, this was only where they already existed for the originator. No wholly new PD biomarkers have been developed by biosimilar sponsors. Further, acknowledgment of the extent to which the expectations of the comparative clinical efficacy study have already changed also needs to be considered.[12–14]

This commentary is based on a reaction by the authors to these premises, stated and unstated, and to the discussions at the workshop itself (available online along with the presentations given[1]).

BACKGROUND – EXPECTATIONS FOR BIOSIMILARS

In the United States, a biosimilar can only be approved by the FDA 12 or more years after the originator biologic to which it refers was first licensed.[3] As such considerable experience, both with its manufacture and its clinical use, will likely have been obtained for those biologics that have been sufficiently commercially successful for biosimilars to be pursued. Often, the originator reference product has been commercially available for considerably longer than 12 years due to patent limitations and other ongoing life cycle management with the originator product, such as adding further indications based on additional clinical studies.[6] This will add to the collective regulatory and clinical experience by all stakeholders, including physicians and patients. However, this may not include a full understanding of the mechanism of action (MOA) and the US statute enabling biosimilars[3] makes it clear that the MOA of a biosimilar need only be shown to be the same to the extent that it is understood for its reference product. This is important. Additional studies to understand the MOA are not required of a biosimilar sponsor, and to date have not been expected by the FDA. However, to the extent that understanding the MOA(s) can facilitate more efficient development of the biosimilar, for example, through enabling *in vitro* functional assays, it (they) may become more relevant.[11]

The general premise of biosimilar development, akin to that of generics, is that a medicine matching that of a branded originator product can be made by a different sponsor at a reduced cost because the sponsor knows what they are making, and that further market entrants will enable a competitive marketplace to ensue. Two elements contribute to such potential competition and these ultimately govern commercial viability for the subsequent market entrant(s):

1. The cost of getting to market from initial development through licensure for the biosimilar; and
2. the cost of making the biosimilar on an ongoing basis and supplying the marketplace reliably with a quality product.

The cost of development is a sunk cost, a one-off for which the return on investment may be amortized for some period of commercialization of the biosimilar depending on the number of market entrants and shared period of sustainable pricing. It has been estimated that the cost of development of a biosimilar can be up to 100 times that of the average generic. Namely $100–500 million vs. $1–5 million. Exact numbers will vary, often driven by the cost of the reference product needed to do the comparative clinical studies. Timelines for biosimilar development are 5–10 years for a biosimilar[15] vs. 10–15 years for an originator product.[16] As such, the companies that are able to invest and that also have the expertise are limited.

Meanwhile, the originator biologic may have evolved over its lifetime, using comparability[17] to support manufacturing upgrades and other changes, but as long as it remains regulatorily "the same," namely a single 351(a) Biologics License Application (BLA), it will be referring back to the clinical trials[18] that supported its initial licensure.[19] The goal posts of the originator create the design space for the biosimilar.[20] The biosimilar, licensed as a BLA under 351(k), will likewise be referring back to those original pivotal clinical studies of the reference as its regulatory basis for approval, but by doing so through the demonstration of a highly similar analytical match.[21] As such, elements of comparability applied to the originator over its lifetime are pertinent to the biosimilar, but the basic premise is that a molecular match will result in the same clinical consequences for patients when either current version of the product is used, originator reference, or biosimilar. The extrapolation is between the active moieties in the reference and the biosimilar,[22] and consequently the biosimilar can have indications of its reference for which it, itself, has not been studied clinically. Such extrapolation is the principal attraction of the biosimilars' pathway for sponsors as it may allow a reduced cost of development and more timely market access. This can be attractive commercially. It also means that the assumption of the same MOA for the biosimilar and its reference is based on the analytical match, irrespective of whether that MOA is fully understood for the reference product. This does allow for the theoretical possibility that a biosimilar sponsor develop a PD biomarker based on the MOA for the reference to which it plans to make the biosimilar, but it does not make such a prospect more feasible than a comparative clinical study. The latter itself already being open to questions of scientific and therefore ethical validity.[23] Hence, the title of this commentary.

THE ROLE OF CLINICAL STUDIES IN BIOSIMILAR DEVELOPMENT

The definition of a biosimilar is *that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product*.[24]

To date, there has been an expectation by the FDA for head-to-head comparative clinical studies between the biosimilar candidate and its reference product in each 351(k) BLA submission. This has, according to the FDA, not been an *a priori* re-establishment of safety, purity, and potency of the biosimilar, but a confirmation of the expected similarity of clinical outcomes, including immunogenicity in the most sensitive indication. As such, the FDA has *de facto* routinely waived the statutory requirements of the Biologics Price Competition and Innovation Act (BPCIA) sufficient to demonstrate safety, purity, and potency in an indication of the reference[25]:

> (cc) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient

> to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product

In a few cases, the comparative efficacy studies with conventional clinical end points have been waived based upon the availability of PD biomarkers, for example, absolute neutrophil count for filgrastim and pegfilgrastim biosimilars.[9] Thus, the feasibility for pharmacokinetic (PK)/PD studies as the sole clinical studies adequate for biosimilar licensure is already established, but notably none were with PD biomarkers not already available for the originator product.[9] The premise of the recent meeting was that such PD biomarkers may be attractive to biosimilars sponsors for future biosimilar development given that conducting such PD biomarker studies are presumed to be a reduced resource investment compared to comparative phase III studies.

Two arguments can be made against this premise:

1. The value of a new PD biomarker by a future biosimilars sponsor presupposes its acceptance by the FDA, and that it can be developed in an economically feasible and timely manner even when it has not already been established by or for the originator product used as reference for the biosimilar.
2. The bigger and more daunting assumption apparently being made is that a PD biomarker is a useful alternative to a comparative clinical phase III type study. This is because it entails acceptance that the latter is useful in and of itself and offers new information over and above a comparative PK study.[26] Here, we are particularly sensitive to clinical studies being experiments on human subjects and the ethical sensitivities that any such studies must always address by being the only way to get necessary information.[27]

This commentary will not discuss the feasibility of development of new PD biomarkers by biosimilars' sponsors other than to observe that they are not a trivial undertaking and add to regulatory uncertainty of biosimilar development (both through resources invoked and interference with timelines). Further, the BPCIA is clear that a biosimilar application need only include information demonstrating that *the biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but* ***only to the extent the mechanism or mechanisms of action are known for the reference product*** [emphasis added].[28] As such, a PD biomarker has no intrinsic value for regulatory purposes for a biosimilar, if it is not already established for the reference product.

Consequently, the assumption that an adequate PD biomarker is even possible, let alone sufficient (especially for those products that may have multiple MOAs attributable to different aspects of the active moieties they contain) is an open question for many biologics that could become reference products for biosimilars. Even if a PD biomarker could be identified, it is difficult to clinically verify the biomarker as sufficient and/or new evidence may arise questioning its validity at any time.[29] This compounds the regulatory risks for biosimilar sponsors not least for those biologics where a single MOA may not be involved, or may differ across indications.

But the more fundamental question and vastly more important question is whether a PD biomarker study *in lieu* of a comparative clinical phase III type study is the right question to be collectively asking as we look to improve the efficiency of development of safe, effective quality biosimilars.[12,13,23] We would suggest that it is not.[25,30]

PK IS THE MOST SENSITIVE COMPARATIVE CLINICAL ASSAY FOR DETECTING DIFFERENCES

Whereas an analytical match between a biosimilar and its reference is essential, and the analytics upon which that match is established continue to improve,[31] the sensitivity of clinical studies remain limited,[32] and what is meaningful can be a matter of judgment. Hence, primary and secondary end points for originator product development and the pivotal clinical studies in each indication for which it is licensed is important. The biosimilar does not need to provide clinical data on all indications of the reference as they can extrapolate between the biosimilar and everything already established clinically for the reference.[22]

The extensive use of comparability in support of manufacturing changes on the originator biologics over their lifetimes has established regulatory confidence in the use of analytics and quality attributes as the basis for anticipating clinical outcomes.[33] The good news is that this will necessarily be the experience that is relevant for each biosimilar to those reference products, not least as the most popular and widely used biologics will become the reference products to which biosimilars are and will be made in the future. Although each sponsor must develop their own analytical methods and specifications for any biologic (originator or biosimilar), this regulatory science is now established[34] and its plausibility is widely accepted.[17] In addition, when PKs are used in a comparative manner (pre- and post-manufacturing change or between a biosimilar and its reference) the power to detect differences is considerable.[35] It is not the PK profile *per se* that is most important, but the ability to detect tiny differences between two test products in a complex physiological setting that matters.

Likewise, the sensitivity of a PK study for showing a match in physiological response to a biologic is accepted, even if the clinical meaning of that response derives solely from the experience of the originator product (or the pre-manufacturing change product).[23] Where available, a PD biomarker can further augment the PK match, but it does not add greater sensitivity.[36,37]

The clinical PHASE III type study by definition gives a clinical outcome but is the least sensitive response and remains important to wholly new molecular entities where no head-to-head comparator is available, and where safety and efficacy are being established for the first time.

CONSISTENCY IN APPLICATION OF REGULATORY SCIENCE IS IMPERATIVE IRRESPECTIVE OF BUSINESS MODEL

The better the analytical match between a biosimilar and its reference, the less likely a clinical study will be to show any differences

in a head-to-head study with clinical outcomes as the read out (this being the rationale for the original FDA proposal for a Biosimilar Biological Product Development (BPD) Type 3 meeting[38] ahead of clinical trials being conducted). For this same reason, such studies are not routinely conducted after manufacturing changes using comparability principles.[17] Additional clinical studies will be required only in some cases.[39] In the United States, the use of comparability is not public information, but in Europe its use is extensive and public.[33] The products largely continue to match analytically between the United States and the European Union such that the use of comparability is reasonable to assume as having occurred in the United States too.[40]

Only rarely have there been reported failures in the application of comparability, and whereas important to learn from these have not led to significant opposition to its continued use (and indeed comparability is the interchangeability standard for biologics with patient transitions of care the norm, albeit not easily documentable as they are not reported). In addition, for instance, neither additional clinical studies nor the creation of PD biomarkers have been proposed to enhance the predictability of the analytics when comparability is used. Where comparability has failed, in all instances, it was the absence of an analytical match of a critical parameter that was ultimately shown to be the omission, be it, for example, aggregation[41,42] or a change in glycosylation.[40,42–44]

CONCLUSION

Besides analytical comparison, a comparative PK study between the biosimilar and its reference originator product is the most sensitive assay for detecting differences between the two.

We appreciate that the intent of the FDA and Duke Margolis workshop, *Pharmacodynamic Biomarkers for Biosimilar Development and Approval* was to re-examine how best sponsors may improve the efficiency of their biosimilar development program. We wholly concur with the importance of such efforts given that the time and cost of biosimilar development will necessarily impact the level of competition and its sustainability in the US market. It will therefore also impact the cost to patients and hence their ability to access these life-changing medications whether as a biosimilar or as an originator product.

We also agree that there can be no compromise in the safety, purity, and potency of the biosimilars licensed by the FDA – in addition to being hazardous to patients this would also risk a loss of confidence in the products approved by the Agency and quite possibly in the Agency itself. However, we suggest that PD biomarker development is not an avenue that it will make sense for biosimilar sponsors to pursue when the better and already established highly sensitive option of comparative PK studies are already available. This along with an opportunity for a global comparator product,[18] based on already public information from the regulators themselves as well as the originator sponsors, could vastly improve regulatory reliance and the efficiency of biosimilar development globally were it to be prioritized by all stakeholders. In addition, it would entail absolutely no compromise in the quality of biologics, including biosimilars, approved by the FDA and made available to patients in the United States today. Indeed, other regulators and institutions would appear to be initiating these approaches based on the current state of regulatory science in the highly regulated markets.[12,13,23]

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CONFLICT OF INTEREST

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