Biosimilars: No Rationale for Clinical Efficacy Testing

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The US FDA got its charter to approve biosimilar biologics in 2009 [1] once the patents expire on new biological drugs; the goal of this charter for the FDA is to expedite the entry of biosimilars to increase accessibility: availability and affordability. The FDA has issued ten regulatory guidance documents [2] and it redrafted [3] one pivotal guidance on analytical testing after the author pointed out inconsistencies in the original guideline [4].

As of July 2020, the FDA has approved 27 biosimilar products, comprising 19 monoclonal antibodies, seven cytokines, and one fusion protein since the first biosimilar was approved in 2005. Data for one cytokine has not been reported by the FDA yet. The regulatory submissions that lead to these approvals provide a keen insight into how the developers are approaching the development and how the FDA is assessing the submitted data. There are four key studies pivotal to the approval of biosimilars comprising analytical assessment, nonclinical pharmacology, clinical pharmacology, and clinical efficacy. The 26 approved products submitted over 1100 analytical similarity, 96 animal pharmacology, 42 \textit{in vitro/ex vitro} pharmacology, 52 clinical pharmacology, and 32 clinical efficacy studies. There was no consistency in the number of studies submitted for the same molecule; five adalimumab biosimilars submitted 31 - 105 studies; five trastuzumab biosimilars submitted 48 - 111 studies, and four infliximab biosimilars presented 48 - 80 studies. Dozens of animal toxicology studies were rejected by the FDA as being irrelevant. However, none of the accepted animal toxicology studies failed. All PK/PD studies also passed, a few requiring repeat testing due to the choice of wrong population acceptance criterion.

A few clinical pharmacology studies had to be repeated to meet acceptance criteria due to inappropriate choice of the study designs. Finally, no clinical efficacy study failed, and two products were approved without clinical efficacy testing.

Biosimilarity is a judgment made by the regulatory agencies for a product that has a “clinically meaningful difference” with its reference product. There are several fundamental arguments against the use of clinical efficacy testing to establish biosimilarity. The FDA requires stepwise testing wherein the development reaches the clinical efficacy testing only after confirming analytical similarity, animal toxicology and clinical pharmacology assessment. And even then, the FDA must identify a “residual uncertainty,” before extensive clinical efficacy testing is suggested. Since all except two products conducted clinical efficacy testing, it was not made clear by the FDA what was the “residual uncertainty?” Were these studies conducted voluntarily by the developers to support their marketing program, or they were required by the FDA remains uncertain. However, if we can establish that these studies are not necessary, then conducting these studies will be considered unethical for a variety of reasons.

One strong argument against conducting clinical efficacy testing comes from the experimental design that is mostly a noninferiority testing requiring that the developer establish a range of differences between the biosimilar and the reference product as clinically acceptable. While the proponents of clinical efficacy argue that this acceptance criterion can be established on clinical judgment, the choice, nevertheless, remains arbitrary. The proof of this arbitrariness comes from the analysis of studies conducted on the same molecule with a highly variably acceptance criterion. The mode of action of biological drugs often leads to a broad dose-response relationship confound-
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ing any real difference. The assessment of clinical efficacy is straightforward in the case of a new drug, where a placebo control quickly establishes efficacy vis-à-vis the observed side effects.

Further compounding the lack of utility of clinical efficacy comes from the current practice of testing a product in just one of several indications, leaving doubt, if the efficacy can be extrapolated among the indications. However, the FDA allows extrapolation of all indications, even if the testing is conducted in just one indication. Does this allowance leave much to doubt about the safety and efficacy of a biosimilar? However, requiring testing in all indications will defeat the purpose of the pathway to approve biosimilars leading to cost that may even be higher than developing a new drug.

The validity of clinical efficacy testing can be challenged on a logical ground as well. So far, none of the efficacy testings failed provided the biosimilar product met all other stepwise similarity testings. Was it because all products were biosimilar, or the efficacy testing was not sensitive enough to identify differences? A more pressing concern arises if the FDA accepts the results of efficacy testing to overcome the lack of similarity in analytical, nonclinical, and clinical pharmacology assessment. Given that there will never be data available to judge relative safety and efficacy, the risk of approving products that are not biosimilar gets higher. One factor that adds significant variability to clinical data is the selection criterion of the study population. In the case of oncology antibody testing, it is almost impossible to find naïve subjects or patients with similar prior treatment; additionally, the clinical markers cannot be established given the peculiarity of the disease for each patient. All of these observations establish a premise that it is not possible to create a testing plan that can be reasonably rational.

In the case of monoclonal antibodies, the mechanism of action is generally known, allowing the use of in vitro/ex-vitro methods to compare efficacy; these tests can be more robust and reliable than the study of clinical responses in patients, particularly in the case of anticancer drugs, where it is almost impossible to secure a naïve patient population or even a sufficiently large number of population and the high variability of response; do these studies bring added confidence to the safety and efficacy of the biosimilar product?

Responsible regulatory guidance should require minimal testing needed to assess the safety and efficacy of a product, and if clinical efficacy testing is not useful, these studies should be discouraged and not just added as supplementary proof. The same holds true for animal toxicology testing that is ruthlessly conducted by developers even when it makes little sense, like testing a monoclonal antibody in a rodent species that does not have receptors and cannot show a toxic response—it is required when a new molecule is developed, but it must be discouraged in the testing of biosimilars. Even when developers use animal toxicology to justify any difference in the analytical assessment, there can never be an assurance of the safety testing in animals because these studies never fail because they are conducted at the higher end of the efficacy-toxicity curve to induce a toxic response. As evidenced by the data submitted by the developers, none of the studies failed. It is almost comical that the antibodies approved in India are tested in rodents only because testing in monkeys (who have the receptors) is against the religious practice.

Better use of animal testing comes in comparing PK profile (PD may be added if relevant but not likely) to establish structural similarity, as recommended by the FDA and these studies can be conducted in a small number of animals, not establish any statistical equivalence but an overall profile comparison.

The FDA continues to discourage irrelevant and unnecessary studies, as demonstrated by a recent guideline on the testing of insulin products where immunogenicity testing was removed as a requirement if all other similarity criteria were met. The FDA responded to my petition and made the change that will go a long way in supporting faster approval of insulin products [5]. The justification for this waiver comes from the understanding that differences in immunogenicity do not affect the PK/PD profile.

The basis of removing clinical efficacy testing comes from a robust analytical assessment first. However, this reliance must be strengthened by focusing on testing that is more discriminatory rather than filing hundreds of tests that may not be relevant. A good example is

the statistical acceptance criteria of the critical quality attributes that were recently revised by the FDA in response to my petition [6]. This scientific thesis should limit analytical similarity testing to primary, secondary, and tertiary structure testing and other safety-related attributes and remove the testing of critical quality attributes included in the release specification that determines what is safe and effective for a patient.

Further support for obviating clinical efficacy testing comes from the robustness of PK/PD studies and as a matter of record, no product was approved by the FDA that did not show high similarity at the PK/PD stage; however, there is a need to analyze data more relevant adding more PK parameters like the distribution volume and rate of its change as an indicator of receptor binding, to make these studies more discriminatory.

We have come a long way over the past 15 years of evaluating the safety of biosimilars in Europe and US; we have better confidence in declaring that a biosimilar product has “no clinically meaningful difference” with the reference product, and now we have to make the approval guidance rational without compromising the safety of the product.

My proposal for rationalizing the testing of efficacy came in 2019 [7] and the majority of the biosimilar industry agreed with me [8] in a publication a few months after my analysis, while failing to point out the scientific rationale. In this article, I am bridging the gap but describing in clear words how we can make biosimilars more accessible by reducing or eliminating all studies that are not relevant, whether these are analytical similarity, animal pharmacology and toxicology, clinical pharmacology and more particularly the clinical efficacy testing.

The FDA has always promoted science as it was made evident in the Biosimilars Action Plan that was revealed by the FDA after I filed a petition against the FDA to make the guidelines rational [9]. The FDA and EMA are open to suggestions from the developers but unfortunately, the developers, who have all been the big pharma, have failed to understand that biosimilars are not new biologics and since most of them have been involved in the development of new drugs, their mindset remains fixed to more studies than necessary. I have said it repeatedly that it takes more science to develop a safe biosimilar than it takes to develop a new biological drug. It should also take less investment if we are to see the biosimilars deliver the promise they were supposed to-more available drugs.

Bibliography

1. https://www.fda.gov/media/78946/download

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