The Development Perspective and Recommendations of Biosimilars

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Making biosimilars accessible means reducing their cost of development, which is currently at around USD 100–200 million, keeping small and medium-size companies out of play and leaving most current biosimilars in the hands of big pharma. How this cost breaks down is an interesting subject.

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1. Development Perspective

Making biosimilars accessible means reducing their cost of development, which is currently at around USD 100–200 million, keeping small and medium-size companies out of play and leaving most current biosimilars in the hands of big pharma. How this cost breaks down is an interesting subject; for example, a recent study [1] reported a median (IQR) estimated cost of USD 20.8 (USD 13.8–35.3) million and a median (IQR) treatment duration of 52 (28–68) weeks; when switching and alternating, the cost was USD 27.6 (USD 18.0–36.7) with a median (IQR) treatment duration of 55 (46–78) weeks. The trial duration included the period needed to establish the effectiveness and the extensions during which patients were switched between products. For oncology product trials, which typically continue indefinitely, the trial duration was defined as the period from the date of the reported trial start to the date when the FDA accepted the data. For the two hematopoietic products for which the FDA did not require testing in patients, the cost was for a median (IQR) treatment duration of 15 (14–15) weeks, with a median (IQR) estimated cost of USD 1.9 (USD 1.6–1.9) million. Interestingly, the cost of similar studies for new molecular entities was similar to or even lower than that of the comparative testing since a much larger population of patients is required to establish the statistical significance of findings when the two arms are supposed to be providing an equivalent response. At the same time, the clinical pharmacology studies recruited about 100 participants, with more than 500 patients on average included in the clinical efficacy testing [2].

According to the data reported in ClinicalTrials.gov, 667 clinical studies involving biosimilars were reported [3], 598 were listed as interventional, and 68 were listed as observational. The number of studies conducted was 891 due to the multiple sites involved. The number of studies that reported their testing phase included early phase 1, 4; phase 1, 189; phase 2, 281; phase 3, 163; phase 4, 15; and phase not applicable, 9. There seems to be some discord in defining the study phase; in some, no early phase or phase 2 study is required, and even some listed as phase 3 can more appropriately be called a comparative efficacy study. Assuming the costs of studies as suggested above are not out of the ballpark, these studies must have cost over USD 10 billion, which is not a large number for big pharma. However, to see smaller companies entering the field of biosimilars, reducing the cost of clinical testing (except clinical pharmacology) will be a significant motivation.

The current estimates of the cost of a new biosimilar product coming to market at USD 100–200 million are overestimated since these are based on the cost factors associated with big pharma operations. One of the larger cost elements is the depreciation of the CAPEX, which can quickly run into several hundred million dollars. This number is based on the experience of the author. Additionally, the cost adds up if the submission takes longer and FDA audits and approval are delayed for various reasons, as mentioned above. For example, holding multiple FDA or EU meetings will lead to a longer submission time. Each meeting takes a 4–5 month toll; now that the approval pathway is clear, intelligent regulatory planning could quickly reduce the filing to 18 months. Other delays may come from patent litigation and whether the developer chooses to submit the filing to the originator company.

Choosing the product for development is another dilemma for many since development costs are identical regardless of the potential market. It is no surprise that the market leaders such as adalimumab, with current sales of over USD 18 billion, are the most popular biosimilars. However, the situation with adalimumab will change starting in 2025 when

approved biosimilars that are held back due to litigation will hit the market. The total market of adalimumab is then expected to decrease by 50%. **Table 2** lists the projected sales in the year 2025 and current approvals in EU and US [1].

Table 2. The projected market of biologicals in the year 2025 as impacted by the entry of biosimilars and the development factor.

No	Product (Brand) Company	Global (Billion USD) Market, 2025 [1] [1]	Current Approved US/EU Biosimilars [2] [4][5]	Development Factor [3]
1.	Erythropoietin (Epoetin) Amgen	18	1/3	1 (anemia)
2.	Pembrolizumab (Keytruda), Merck	16	0/0	5 (oncology)
3.	Nivolumab (Opdivo), BMS	14	0/0	5 (oncology)
4.	Adalimumab (Humira) AbbVie	11	7/10	2 (TNF)
5.	Etanercept (Enbrel), Amgen	8	2/3	2 (TNF)
6.	Infliximab (Remicade), Janssen	8	4/4	2 (TNF)
7.	Ustekinumab (Stelara), Janssen	7.5	0/0	2 (TNF)
8.	Bevacizumab (Avastin) Roche	7	3/9	4 (oncology)
9.	Ocrelizumab (Ocrevis)	7	0/0	3 (MS)
10.	Pertuzumab (Perjeta) Roche	7	0/0	5 (oncology)
11.	Secukinumab (Cosentyx)	6	0/0	2 (TNF)
12.	Aflibercept (Eyelea), Regeneron	4	0/0	2 (AMD)
13.	Darbepoetin alfa (Aranesp) Amgen	4	0/0	1 (anemia)
14.	Peg-filgrastim (Neulasta), Amgen	4	4/7	1 (neutropenia)
15.	Ranibizumab(Lucentis) Novartis	4	1/1	2 (AMD)
16.	Trastuzumab (Herceptin), Genentech	4	5/6	4 (oncology)
17.	Rituximab (Rituxan) Biogen	3	3/5	4 (oncology)
18.	Cetuximab (Erbitux): (Lilly/Merck)	1	0/0	5 (oncology)
19.	Eculizumab (Soliris) Alexion	1	0/0	3 (hemoglobinuria)

[1]: Market data from open source; [2]: Biosimilar approved in US and EU based on data as of April 2022 posted by the FDA and EMA; [3]: “Development Factor” is a term coined to project the time and cost to market, 1 = lowest; 5 = highest, assessed by the author.

Here is also presenting a parameter, “development factor”, to indicate the cost and time factor to take a biosimilar to the market. The primary consideration is the phase 3 study; in some cases, such as the TNF products, an efficacy study can be a smaller psoriasis study, but the oncology drugs will remain at a high development cost, at least for now. The lower development factor also comes for products with PD or clinical markers that are easier to monitor.

Since the cost to take a product to market depends on building a sound regulatory plan, one comes across difficulties in complying with the different global authorities, which seem to have divergent requirements; this prevents many companies from going global with their biosimilars.

Monoclonal antibodies comprise the majority of biological products. It is now well established that the manufacturing cost of these antibodies is USD 95–200 per gram, regardless of the type of antibody involved [6]. For oncology antibodies, the dosing is generally 150–800 mg [7]. As an example, Rituxan (rituximab) DS is priced at USD 10,000 per gram [8]. This should encourage developers, as they will have a substantial margin even at a 70–80% price reduction.

2. Recommendations

Biosimilars have come of age; now is the developer's turn to make them accessible. A few recommendations taken from the experience of the last 17 years of the life of biosimilars and a longer engagement by the author in their development teach people that:

(a)Since 60% of all new drugs are biologics, there will be a long list of eligible biosimilars for the future.

(b)More than 100 biological products have expired patents and expired exclusivity waiting for biosimilar candidacy.

(c)Veterinary biological products are additional choices for biosimilars that have been neglected.

(d)It will take a price drop of 70% or more across all biological products to make biosimilars accessible to all. However, many countries have already reached this stage.

(e)The COGs of all antibodies are between USD 95 and 200 per gram, and they are priced at 100×; despite the price drop, there will still be high profit margins.

(f) The adoption of biosimilars will require taking stakeholders into confidence, particularly prescribers and patients.

(g)Countries where forced switching and alternating are doing just as well despite restrictions.

(h)Global markets will require approval from the EU and US. Both agencies offer fee-free advice. Design studies are acceptable in both the EU and US. US protocols will likely be acceptable to the EMA, but not the other way round.

(i) Regulatory guidelines are neither binding on the agencies nor the developers. Therefore, people need to question them, challenge them, and create a rational development plan that does not originate from the agencies.

(j) Biosimilars and interchangeable product guidelines will undergo substantial revision, reducing the burden of testing and replacing it with advance testing tools.

(k)An analytical assessment is most pivotal to approval; people need to adopt newer technologies and plans, not redundant testing. People can reduce testing by limiting product-related attributes. People can outsource analytical assessments to avoid delays in regulatory approval.

(l) Do not offer to conduct any animal testing; it is not the role of regulatory agencies to tell companies what not to do.

(m)Design creative clinical pharmacology protocols to reduce the size of studies and secure all data from one study.

(n)Do not offer to conduct clinical efficacy testing and challenge the suggestion made by the regulatory agencies to identify the "residual uncertainty".

(o)If a clinical efficacy test must be conducted, choose an indication where markers are better defined to reduce the study size, such as using psoriasis to test adalimumab.

The best evidence to support above perspective that changes are coming in the regulatory guidelines came in March 2022, when the FDA announced a grant of USD 5 million for a variety of project types, including analytical methodology (including bioassay) development, in silico tools, real-world evidence, pharmacology studies, and ancillary studies in parallel to planned or ongoing clinical trials and combinations of these project types. In some cases, funding of a novel pharmacokinetic/pharmacodynamic study may be considered. The FDA is particularly interested in projects that efficiently and convincingly achieve intended objectives. Therefore, novel, efficient, and convincing strategies to validate such tools and standards are welcome. A novel method or tool without validation or a feasible approach to validation will not be acceptable [9].

Now that biosimilars have come of age, it is time for developers to grow up [10].

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