Biosimilar vs Biobetter – a two-horse race?

White Paper

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The evolution of a strong biologics market depends on the characteristics of the follow-on agents that comprise each subsequent generation

A **biosimilar** agent has "no clinically meaningful differences … in terms of safety purity and potency" from the reference biologic.

A **biobetter** is aimed at the same target protein as the reference biologic, but is a step-wise improvement on it in terms of efficacy, safety, duration of activity or ROA.

Place your bets! Biosimilar vs Biobetter – a two-horse race?

Since they were first introduced in the early 1980s complex biological agents have changed the approach to the treatment of many long-term immunological and life-threatening diseases, most notably rheumatoid arthritis and cancer. But as the patent protections are coming to an end for many of the first-wave biologicals, will the drug developers back a copycat agent or place a higher bet on a new and improved original to represent them in this competitive therapeutic arena?

The biologics market is relatively new, and its evolution will be determined by the characteristics of the follow-on agents that comprise each subsequent generation. One major decision facing developers of biologic agents is indeed whether to create a close copy (aka a biosimilar) or an improved new entity (aka a biobetter) of an existing biological agent. The differences in the regulatory and development pathways necessary to bring these follow-on agents to market are pivotal in determining whether a biosimilar or a biobetter will be the preferred choice.

The various pathways associated with development of a biosimilar compared with a biobetter will be explored throughout this whitepaper. The lessons learned and difficulties overcome when generics were introduced in the market for small molecule drugs will also be acknowledged and applied to a biologics context.

Small molecules and large biologicals – differences dissected

There are small-molecule chemical drugs and then there are large, complex biological drugs; the respective follow-ons are generic agents and biosimilar agents. These two types of follow-ons are the same in that they have a similar and acceptable efficacy and safety profiles in the same indications as the original (reference) agent; but they differ in many other aspects including development pathways, regulatory requirements, and the patent protection of their predecessors.

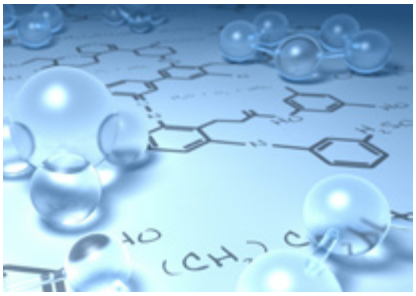
A generic drug contains the same active ingredients as the chemically synthesised, single-molecule original drug it is copying; it is also identical in strength, dosage form, and route of administration (ROA). Apart from the ROA, dosage form and strength, a biosimilar cannot be identical because of the inherent differences in producing a complex protein and nucleic-acid-containing molecule from living tissues and cells.

Although a biosimilar is not identical to the reference (original) biologic agent, it must be highly similar to it in terms of structure, function, clinical efficacy, safety and quality. For approval, the US Food and Drug Administration (FDA) requires that a biosimilar agent has

"no clinically meaningful differences … in terms of safety purity and potency" from the reference biologic.[1] In addition, the European Medicines Agency (EMA) demands similarity with the reference biologic "in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise…"[2]

In the US, the regulatory pathway for biosimilars is abbreviated compared with the originator product (as for generics of small molecules). Much of the evidence required for approval via the abbreviated Biologics License Application (aBLA) is focussed on *in vitro* and *in vivo* analytical studies demonstrating physiochemical and biological similarities between the reference and biosimilar molecules rather than on extensive clinical investigations. Minimal short-term safety and efficacy clinical studies are also required, but proof of concept and demonstration of mechanism of action are not.[3] [4]

This may appear an easier task in terms of development, but the biosimilar must first be created from living cells before it can be compared against the reference agent. Although the biosimilar manufacturer may have access to the marketed reference product, the manufacturing process is proprietary, therefore the biosimilar manufacturer must use reverse engineering, after careful and extensive investigation of the reference compound, to create its likeness in terms of clinical effects.[5]



When is a biosimilar not a biosimilar?

There are at least two situations when a copy of the original biologic agent is not considered a biosimilar:

- When compounds, called "intended copies" or biomimics, are produced in countries without formal regulatory processes and stringent evaluation pathways, or they were produced at a time before these formal processes were implemented.[6]
- The resulting product after the manufacturing process for an original biologic has undergone a planned change (e.g. scaling, new equipment, process efficiencies). In this case, the regulatory authorities require comparability exercises to be conducted to ensure that the product has a consistent quality, safety, and efficacy using relevant data from the most appropriate process step to detect quality changes in the biologic pre- and post-change.[7] [8] The post-change product may not be identical to the pre-change one; it is a bit like batch variation of the original, but it is not classed as a biosimilar. This is because the overall manufacturing process is very similar to the original, whereas in the case of a biosimilar, the production processes may be very different, resulting from protection related to the manufacturing processes afforded by existing data exclusivity periods.

Biobabel busted... equal, similar, better... what does it all mean?

[1] https://www.fda.gov/downloads/drugs/guidances/ucm444661.pdf
[2] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf
[3] https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf
[4] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf
[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4048039/
[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4839048/
[7] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073476.pdf
[8] http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf

Is there such thing as a bio-equal?

In certain circumstances, and after the biosimilar agent has been approved, the US FDA is unique in its authority to declare a biosimilar agent 'interchangeable' with the original biologic. According to draft guidance issued by the FDA in January 2017[9], in order for a biosimilar to be interchangeable it is "expected to produce the same clinical result as the [original] product in any given patient". In addition, where the drug is expected to be administered more than once to an individual, switching from the original to the biosimilar must not result in a risk related to efficacy or safety that would not otherwise be experienced if the switch had not taken place.

The decision to grant interchangeable status is based on additional data provided by the manufacturer that demonstrates above and beyond biosimilarity to the reference biologic. The FDA recommends that evidence considers a 'totality of factors' in demonstrating interchangeability. This should include pharmacokinetic/pharmacodynamic studies, switching studies, and may necessitate post-marketing surveillance data for both the original and the biosimilar product.[9]

Applying for interchangeable status, therefore, comes with increased R&D costs and time. However, there are rewards:

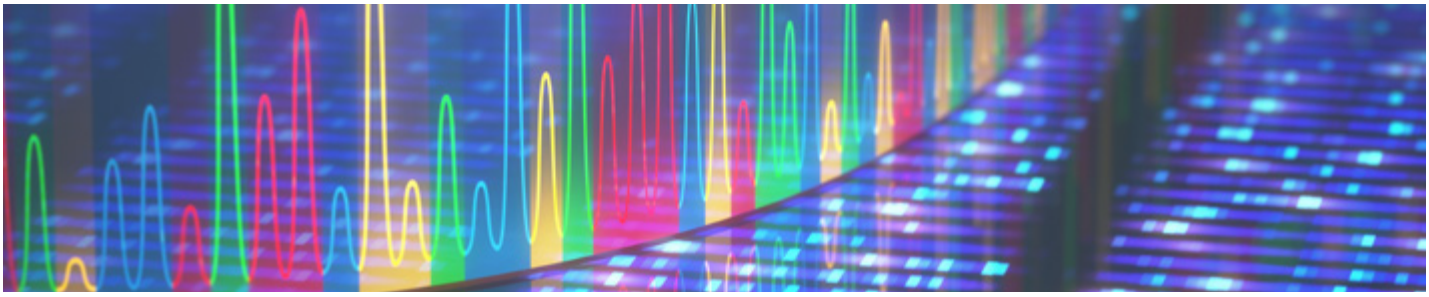
- The major benefit of achieving interchangeable status is that the biosimilar product can be substituted for the original without intervention of the prescribing healthcare provider.[9]
- Additionally, the first interchangeable biosimilar for each reference biologic receives a minimum 1-year market exclusivity period in which the FDA shall not approve interchangeable status for another biosimilar for the same reference drug.[9]

Currently the EU does not have the same approach to judging and granting interchangeable status of biosimilar agents. The decisions relating to interchangeability lie instead with the National Competent authorities and not the EMA/Committee for Medicinal Products for Human Use (CHMP). [10]

What are biobetters – and why are they not biosimilars?

In essence, a biobetter is a biologic compound aimed at the same target protein as the reference biologic, but is a step-wise improvement on it in terms of efficacy, safety, duration of activity or ROA; it is the 'next generation' biologic. The resulting improvement stems from a different formulation, or from changes made to the structure or functionality of the compound. Because of these differences the molecule is considered a new entity, and as such it must follow the complete, not abbreviated regulatory pathway, but is awarded data- and market exclusivity periods.[11]

[9] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf
[10] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000129.jsp&mid=WC0b01ac0580533e0f
[11] https://www.thebalance.com/biobetter-definition-3895896



Biologics - Patent Protection Bolstered by "Exclusivities"

The superior patent claim for small molecules is the 'composition of matter' patent, which protects the chemical name and the structure. However, since biologically produced copies (biosimilars) of an original complex molecule are not identical, this could pose a problem regarding the validity of the protection claimed by such patents alone. In addition, the research and development time for the production of an original biologic can be longer than that of small molecules, and therefore the period of protection remaining after launch on a standard 20-year patent may not allow sufficient time for the manufacturer to recoup its costs.[12]

Protection encourages invention and evolution

In the US, biological drugs are protected by a 12-year period of market exclusivity from the date of first licensure. Generally, this means the date on which the product was first licensed in the US. There are clear guidelines describing what is considered appropriate as a first licensure.[13] These do not include changes such as a new indication, dosing schedule/form/strength, route of administration, or delivery system/device, particularly when filed by the same manufacturer of the referenced product. This should prevent the concept of 'ever-greening' that has been evident with small molecule products, where such subsequent and repeated filings have extended the patent protection period and in essence prevented the market entrance of competitors. [14] [15]

The date of first licensure for the reference product triggers this 12-year market exclusivity period, during the first four years of which, the FDA will not even accept filings for biosimilars of the reference agent, thus providing further data protection.

Additional exclusivity periods (e.g. for paediatric trials and/or orphan status) can be granted, as with small molecule drugs, and will extend the US 12-year market exclusivity in some cases.[16] [17]

There is a clear distinction between biosimilars and biobetters as follow-on biologics; each has its merits and disadvantages regarding development commitments and marketing opportunities (see summary table). The originator company for the first-generation (reference) biologic has the luxury and advantage of knowing both the molecular composition and manufacturing processes, and therefore, has an opportunity to reduce development efforts for its follow-on biologics, whether they chose to invest in biosimilars or biobetters.

[12] https://aiplafda.wordpress.com/2016/03/28/data-exclusivity-for-drugs-in-canada-the-u-s-and-europe/
[13] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407844.pdf
[14] http://www.raps.org/Regulatory-Focus/News/2014/08/04/19945/FDA-Sets-Policy-for-Granting-New-Biologic-Medicines-Extensive-Market-Exclusivity/
[15] https://www.pinsentmasons.com/PDF/pageturner/CompetitionLaw/LevelPEGingCompetitionLawConsideration/#2/z
[16] https://www.fda.gov/drugs/developmentapprovalprocess/ucm079031.htm#howlongexclusivity
[17] https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf

Follow the path or be a trailblazer?

There are many discussions regarding the future of follow-on biologics. Most agree that there is a huge future for biosimilar and/or biobetter agents, some question the validity of assigning biosimilarity in terms of clinical efficacy and safety, especially in patients and indications not specifically tested (i.e. extrapolation), and others ponder the potential for biosimilars to be beaten to, and essentially squashed out of, the market by biobetters.[15] [18] [19] [20] [21] [22]

Collectively, these opinions and forecasts may influence decisions made by biologics manufacturers and ultimately impact the global future of biopharmacology and, importantly, disease management.

Why find a path to follow, when you can walk were there is none and leave a trail?

Extrapolation can extend indication approval

Extrapolation is the practice of allowing evidence and proof of similarity to the reference drug in one indication to be extended to all other indications that the reference drug is approved for. There are some concerns relating to the fact that the biosimilar agent is:

a) not identical to the reference, and
b) it has not been specifically investigated for therapeutic efficacy in the extrapolated indications.

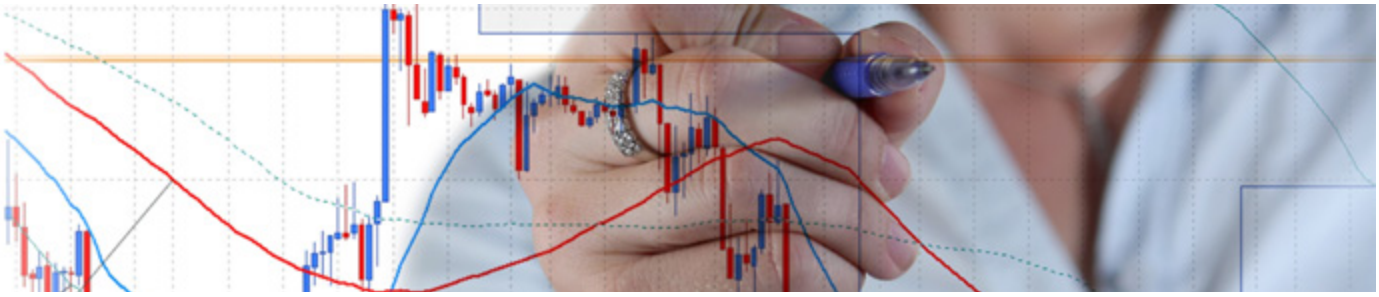
However, given the very nature of the production of biologics (reference or otherwise) there is potential for inherent differences, even between batches of the reference drug, and this is presumably why a totality of evidence approach is adopted by regulatory authorities as proof of the follow-on being "highly similar" to the reference.

This is demonstrated by the fact that several biosimilars licenced in the EU have been granted extrapolated approval for all reference product indications.[23] In each case, there has been valid scientific reasoning to support the decisions to do so. The evidence has been gathered based on guidelines provided by the EMA that consider the totality of associated similarity.[24]

Importantly, the structure, function and physiochemical nature of the biosimilar and reference molecules must be demonstrated. Clinically, the exposure, and pharmacodynamic and pharmacological effects must also be shown, but the patient populations do not have to represent all indications that the reference drug has been approved for.

A recent publication regarding CT-P10 (Truxima™), the first biosimilar referencing Rituximab, succinctly describes the biosimilarity data types that were used to approve CT-P10 in the same indications as Rituximab, but without the same clinical investigations required by the reference agent. This clearly indicates the truncated information required as totality of evidence.[24]

[18] http://gabi-journal.net/biosimilars-versus-biobetters-a-regulators-perspective.html
[19] https://fas.org/sgp/crs/misc/R41483.pdf
[20] https://www.financierworldwide.com/competitive-strategies-in-life-sciences-biobetters-versus-biosimilars/#.WQgIPLfr3cs
[21] https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-biosimilars-whitepaper-final.pdf
[22] http://www.biopharma-reporter.com/Bio-Developments/Generation-of-biobetters-could-push-out-biosimilar-development-says-expert
[23] https://www.ncbi.nlm.nih.gov/pubmed/25298038
[24] https://link.springer.com/article/10.1007/s40259-017-0226-5
[25] https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm167991.htm



As highlighted by Weise et al [23], the concept of totality of evidence regarding the acceptance of similarity was demonstrated by the CHMP when it allowed extrapolated use of a filgrastim biosimilar in healthy recipients for stem cell mobilisation. This decision was based on comparable pharmacodynamic, safety and immunogenicity profiles in human volunteers and patients, and was made despite the concerns that specific studies for the efficacy and safety in this population had not been conducted.

Choosing the most appropriate investigative population is key, as demonstrated by the decision to compare immunogenicity of biosimilar epoetins in patients with renal anaemia (a licenced indication), where the risk of developing pure red cell aplasia (PRCA) is higher than in those with chemotherapy-induced anaemia (another licensed indication). In this case extrapolation of safety data from a high-risk population to a low-risk population was accepted by the EMA.[23]

Indeed in each case, post-market monitoring has confirmed the efficacy and safety of the biosimilar agents in the extrapolated indications.

Post-marketing Monitoring is Key

As with any marketed agent, gathering real world evidence for efficacy and safety is paramount to monitoring the continued benefit-risk performance.

With biologics, it would seem that while the regulatory pathways are encouraging for the production of follow-on agents, there are some perceived uncertainties about the continuity of the efficacy and safety profiles; this relates to reference agents and their follow-ons in both proven and extrapolated indications. These uncertainties rise from the fact that unlike small molecule generics, biological follow-ons cannot be manufactured according to the same single recipe, following the same strict process methodology as the original reference agent, and from fears that potential changes may be detrimental.

Learn from Experience

The biologics market is relatively new compared with that of small molecules. The introduction and continued use of generic agents in this expanding space is not without its own complications, but having a real-world awareness of the performance of generics has enabled the market to thrive and importantly offer affordable healthcare for many patients globally.

Small molecule generics need only demonstrate bioequivalence to a reference product within an accepted 80%-125% margin of difference. Generic agents do not have to demonstrate bioequivalence with each other, and it is feasible that two generic agents can legitimately have a 45% difference in their bioavailabilities, although the FDA has stated that analysis of bioequivalent data spanning 12 years revealed an average 3.5% difference in drug absorption between branded and generic agents.[25]

Despite this, there have been several reported cases of generic agents not matching the efficacy and safety of the branded agent.[26] In most cases, post-marketing surveillance has been instrumental in discovering these defective agents. Recently, the FDA expressed concerns relating to generic versions of extended-release methyphenidate hydrochloride; it acknowledged the information gathered via the FDA Adverse Events Reporting System (FAERS) database, very shortly after the launch of two particular generic agents, as the key to raising concerns. The FDA explained that even though the number of cases was not huge in comparison with the number of patients using the drugs, it was the relatively high number of cases reported for the generics in comparison to the branded agent that caught its attention and consequently led to the FDA intervention.[27]

The experiences gained in the generics market demonstrate that efficacy and safety issues of these marketed copies can be monitored and managed effectively based on the guidelines and practices of regulatory authorities; it is encouraging to see a similar overarching approach to the safe and effective use of follow-on biologics.

Similar or Better – post-marketing vigilance applies to all

The clinical investigation required prior to authorisation for biosimilars is generally insufficient to reveal rare or latent adverse events. In fact the same can be said for most drugs and biologicals entering the market. It is, therefore, mandatory for manufacturers to create, present, and adhere to post-authorisation plans for pharmacovigilance and risk management. These should include regular monitoring of the scientific literature to identify any safety-related issues with use of the individual agents.[28] [29] [30] [31]

Unlike generics of small molecule agents, the production processes for biologics (reference or otherwise) mean there will be an inherent difference in batch production, and over time. There have been concerns raised regarding the "evolution" of biologics and the impact this may have on efficacy and overall safety issues as the compound undergoes changes caused, ironically, by improving manufacturing processes.[32] Even though comparative studies are required to show that the compound has not changed on a physiochemical level before and after a process change, these studies may not be long enough to reveal any potential negative impact on safety. This will only be discovered as the evolved biologic is distributed to a wider patient population, as may occur with the market entry of a biosimilar. Logically, the older the biologic, the greater the chance for deviation from the original with an increasing number of available biosimilar agents, and the fact that the manufacturing processes for each are more likely to have been altered over time.

It is, therefore, important in the post-marketing phase that manufacturers of biologic agents keep track of any safety issues being reported. Currently, all biosimilars carry the same name as the original biologic agent. Therefore, keeping track of specific individual biosimilars may become difficult with the introduction of several biosimilar agents for the same reference biologic.

[26] https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm153270.htm
[27] https://www.fda.gov/Drugs/DrugSafety/ucm422569.htm
[28] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000258.jsp&mid=WC0b01ac0580b18c76
[29] https://link.springer.com/article/10.1007/s40264-013-0121-z#Sec10
[30] https://www.tga.gov.au/book-page/pharmacovigilance-biosimilars
[31] https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf
[32] http://www.bmj.com/content/357/bmj.j1707

The difficulties with tracking post-marketing safety performance of drugs with indistinguishable names have been clearly demonstrated with generics of small molecule agents. Analysis of a subset of FAERS data collected on a handful of antipsychotic agents revealed that in almost 84% of the 2,500 reports reviewed, the type of suspect product (i.e. original or generic) could not be determined. This, despite the fact that generic agents accounted for more than 90% of the prescriptions dispensed.[33][34] The analysts suggested that "more detailed reporting practices" are necessary. This presumably would include citing information to clearly identify the manufacturer of the individual products.

In 2012, the WHO proposed that biosimilars should have a different naming convention to generics; this has since been debated as to the need, or indeed the accuracy, of naming a biosimilar different to the reference agent, despite the general acceptance that there are inherent differences between biosimilars and their reference products. Arguments include the deviation from current practices with non-biologics and generics, the confusion that might be caused at the prescribing and dispensing level, and the increased burden envisaged for doctors and pharmacists having to know the names of the different products.[35][36]

Proposed naming convention will facilitate more accurate pharmacovigilance

Despite these arguments, in 2016[37], and later in 2017[38], the WHO and the FDA, respectively each published naming guidelines that followed the same basic convention of using the core name plus a four-letter suffix; there is additional guidance around the permitted composition of the suffix.

This break with traditional drug/generic naming and the proposal to somewhat individualise biosimilars via a naming convention will essentially allow rapid and accurate identification and tracking of adverse events associated with an individual manufacturer's biologic agent, in order that any safety problems can be appropriately addressed. This naming convention along with the strict guidelines published by the major regulatory authorities globally will go some way to ensure the safe and effective use of these treatment options; it is comforting to see that patient welfare is at the heart of the decisions made and that individual manufacturers are being encouraged to take responsibility for the products they market. These are good things.

[33] https://www.ncbi.nlm.nih.gov/pubmed/25670505?dopt=Abstract
[34] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/12/WC500218557.pdf
[35] http://www.gphaonline.org/gpha-media/gpha-resources/1naming-biosimilars#
[36] http://www.gabionline.net/Biosimilars/General/WHO-naming-of-biosimilars
[37] http://www.who.int/medicines/services/inn/inn_bio_bq/en/
[38] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

Positive Financial Impact of Generics for Health-Care Systems

The FDA's Office of Generic Drugs (OGD) recently voiced its pleasure at the financial impact that the introduction of generic agents has had on the U.S healthcare system over the last 10 years, with an estimated US$1.68 trillion savings. Indeed, this positive influence is hoped to continue considering the record-high approval (full or tentative) of more than 800 generic agents in 2016.[39]

Similarly, it has been estimated that the overall 2014 pharmaceutical spend in Europe was reduced by €100 billion resulting from an approximate 60% price reduction caused by the entrance of generic agents onto the European market.[40]

Even if there appears to be no overall/direct decrease in the expenditure for pharmaceuticals, generic agents at the very least allow increased patient access for the same or similar spend, and this translates into overall cost savings, particularly for common and chronic disease as demanded by the increasing prevalence reflecting an aging population.

Biologic agents have proven successful in treating certain chronic inflammatory- and life-threatening diseases. However, the daily treatment costs for biologic agents have been estimated at up to 20 times more than that for small molecule agents.[41]

Will the financial impact of biosimilars be as positive as that of generic small molecules?

It is hoped that the introduction of biosimilar agents will mimic the positive financial impact of the introduction of generic agents regarding the cost of treatments, but it is not expected to be as significant, since biosimilars are anticipated to cost 15% to 30% less than biologics compared with a saving of 50% to 90% with generics of small molecule drugs. The lower cost reduction for biosimilars may be the reflection of the relative costs for developing these agents: the predicted costs of developing a generic drug is commonly between $1 million and $4 million compared with $100 million to $250 million for a biosimilar.[42]

Since 2005, when the original guidelines for approval of biosimilars were introduced in Europe, 28 such agents have been approved; the latter 6 within the first quarter of 2017.[43]

The US was a little later in joining the biosimilar approval scene and its first was not introduced until March 2015; by April two years later, four more had been approved.[44]

We appear to be in the middle of a biologics patent cliff that started essentially in 2013 and will extend into 2020 when, according to one source, 2020 will provide a huge opportunity for biosimilar competition when patents for 12 biologics, with global sales exceeding US$67 billion, will have expired.[45]

[39] https://blogs.fda.gov/fdavoice/index.php/tag/generic-drugs/
[40] https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/IIHI_Generics_Healthcare_Brief.pdf
[41] http://www.gabionline.net/Biosimilars/Research/Opportunities-for-biosimilar-development
[42] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/#R6
[43] http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars
[44] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM549201.pdf
[45] http://www.gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020

The race is on…

One would expect the biologic follow-on market to be dominated by biosimilars. This may be the case in the short term as the predicted 2020 patent cliff looms, but what then? The group of biologics associated with this current patent cliff will be replaced by what is being called second-wave biosimilars; and already the race has begun to be the first in the third-wave biosimilars aimed at replacing originals coming off patent beyond 2020.[46] Will the wave of follow-on biologics beyond 2020 be dominated by biosimilars, or will other factors influence decisions to be "better" rather than "similar"?[20]

What factors will influence the outcome?

It has been suggested that the respective development timelines for the reference biologic, biobetter and biosimilar agents are 15, 10 and 8 years, with corresponding development costs of US$million 1,200, 500 and 250.[47]

With this in mind, perhaps the production of biobetters rather than biosimilars would seem a more attractive option. There are several other influential reasons for this, including:

- the opportunity to get to market sooner than a biosimilar (no waiting period for loss of exclusivities)
- the benefits afforded by patent/exclusivity protection
- the opportunity to charge a premium rather than a discounted price
- the connotations of being a "better" drug.

The R&D pathways for both biosimilars and biobetters will be reduced in comparison with the reference biologic product. In each case the target is known and has been validated; for biosimilars there is no need for a full clinical evaluation, and additionally there is the potential for extrapolated approval of reference indications. One down-side, at least in the US, is that the FDA requires the reference product to be previously licenced in the US.[3] Currently, five of the US licensed biologicals have been referenced for biosimilars. But as this pool of reference candidates is mimicked, manufacturers may turn more to development of biobetters where this restriction does not apply.

With regards to biobetters, knowing the target and the real-world performance of the reference product may reduce the comparative R&D investments. This is because the necessary clinical trials can be designed related to known safety concerns of the original, and biomarkers may be used to help expedite evidence collection of superior safe and effective performance, the major criteria for claiming to be a biobetter.

Understanding the pros and cons of developing follow-on biological agents raises a question: will development of biosimilars be leapfrogged by that of biobetters given the potential for market exclusivity at a premium price?

To be better or similar ... that is the question

[46] http://www.formycon.com/en/press-release/formycon-announces-details-of-further-pipeline-product-fyb202-is-a-biosimilar-candidate-for-stelara-ustekinumab/
[47] https://www.slideshare.net/LizNerad/ibm-biobetter-presentation

As Winston Churchill once said,
"To improve is to change; to be perfect is to change often."

The last word…

Of course producing an effective biological agent, whether it is similar or better, is not the measure of success – the acceptance and market uptake is.

- For biosimilars the major resistance to market uptake might be one of trust: just how similar is this agent with regard to efficacy and safety especially in an extrapolated indication.
- For biobetters the major resistance may be the incremental cost to consumers in relation to the incremental effectiveness and safety experienced.

Resistance is a common reaction to change, but it is not insurmountable and it should not be allowed to paralyse innovation and evolution. As consumers' influence on healthcare decisions increases, especially with the demand for value for money, an expansion in the choice of treatments will be beneficial. This is because the increase in the number of licensed biosimilars is likely to be reflected by a reduction in treatment costs in the long term. In addition, the incremental improvements achieved by each subsequent follow-on biobetter agent could translate into a more targeted approach to biological medicine, particularly in areas of oncology and long-term immunological diseases. For each of these to happen, there must be change and evolution.

Summary table

Consideration	Biosimilar	Biobetter
Pathway	Abbreviated BLA	BLA
Impact of Reference exclusivity protection	Obliged to wait for loss of reference exclusivities (~12 months)	Not impeded by reference exclusivities
Exclusivity protection	None – unless first interchangeable	Concurrent 4-yr data exclusivity & 12-yr market exclusivity (+/- 6mo Paediatric exclusivity)
R&D time	Reduced vs Reference product in terms of: – Demonstrating similarity (in totality) – Opportunity for indication extrapolation	Reduced vs Reference (but not as short as for a biosimilar) because: – Validated target known – Reference Safety issues known – Biomarkers known
Costs of R&D	Reduced vs Reference and related to: – cost of clinical trials	Reduced vs Reference and related to: – more efficient production processes – costs of better targeted/designed clinical trails
Extrapolation	Extrapolation and licensing for reference indications possible without specific clinical trials	Extrapolation not permitted
Market acceptance	Some reservation likely: – Not identical to reference – Discount not as great as with small molecule generics	Some reservation likely: – More expensive than biosimilars – Incremental clinical benefit compared with incremental cost to consumer
Other	Launch of a biobetter for the same indications possible before launch of biosimilar; this will impact market entrance	Opportunity to charge a premium price with market exclusivity as a branded drug

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