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The A-B-T of biosimilars

Explaining contemporary life science issues

Edison themes

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Depending on the perspective, biosimilars pose either the greatest threat to innovator drug company profits or have the greatest potential to save on healthcare drug spend. We take a recent perspective through the accidents, the bioequivalence arguments and the tender processes (the A-B-T of biosimilars) that will govern the ultimate role of biosimilar drugs.

What is a biosimilar drug?

Around 10 years ago, the term biogeneric was superseded by biosimilar as it was recognised that the complicated structure of these biologic drugs meant they could not be exactly copied. Regulators, payers and physicians are now realising the place of biosimilars as the patents on the innovator drugs expire. This switch to biosimilar use has not been an easy transition and continues to face hurdles in acceptance by physicians and patients some of which are structural, but some are of the innovator companies' making. We expect biosimilars will eventually replicate their dominance in Europe more widely. One Canadian province expects to save c 5% of its drug budget over three years by switching to biosimilars.

Tenders, switching and interchangeability

The early examples of biosimilar products were directed towards demonstrating that although they might be slightly different molecules, they were effectively bioequivalent (the B in our A-B-T title). In typically small studies, strict bioequivalence might be difficult to prove and the more recent focus has been to show that patients can be switched from the innovator to biosimilar molecule without any detrimental effects. In the US, the FDA has recently formalised this process with its new interchangeable designation. Also important is how biosimilars are reimbursed by payers and the European experience has given us the aggressive biosimilar tender (the T in our A-B-T).

Likely winners

- **Single payer healthcare systems** such as NHS England, where bulk purchasing power for the lowest price biosimilar can result in significant savings to a national healthcare budget.
- **Some innovator pharma and biotech companies** that already have biologic development experience (such as Amgen, Biogen, Eli Lilly and Novartis) and can exploit therapeutic niches or manufacturing challenges.
- **Patients,** who are more likely to receive more cost-effective biosimilar drugs that provide them the same benefit as the innovator or reference molecules.

Likely losers

- **Smaller generic and pure-play biosimilar companies** that have had early missteps in their clinical or regulatory programmes, or face a 'race to the bottom' in tender pricing as innovator companies attempt to retain market share.

Winners and losers: Companies shown above do not translate into buys or sells as other themes (and valuation parameters) may conflict with this one.

Viewpoint

Biosimilar drugs have been suggested to offer healthcare systems some of the biggest savings to their budgets. Among the UK hospital pharmacy directors we surveyed, branded biologic drugs account for their single largest drug spend. However, in the US, biosimilar drugs have been stymied by patent litigation and extensions to the innovator or reference molecules, market structure issues and mistrust by physicians, the latter of which may be counter-detailing by the innovator companies. In contrast, in Europe biosimilars are being embraced because they are frequently hospital-administered drugs and the formulary inclusion decision is largely out of physicians' hands. In many single-payer European markets the variety of tenders for biosimilar drugs almost guarantees aggressive pricing and, while innovator companies can react by cutting prices in early, long-term contracts to retain market share, their sales are suffering.

Edison themes

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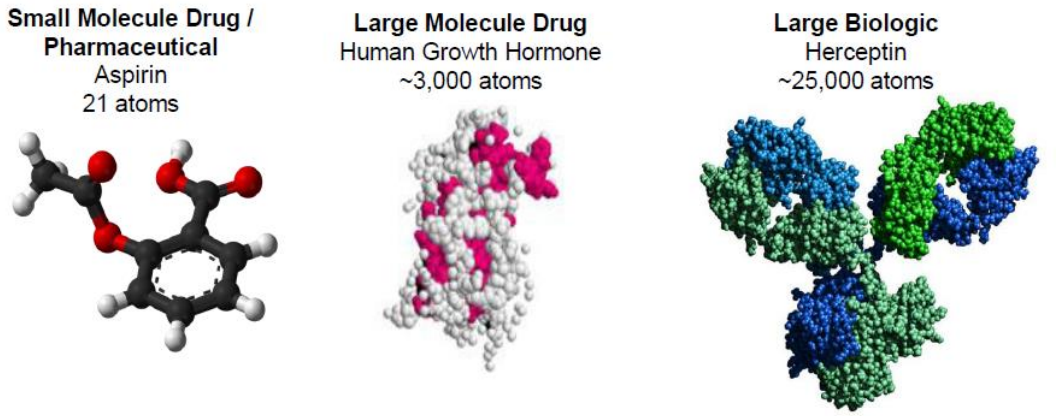
Edison has conducted pricing and market access studies with payers for its clients where a pricing corridor from a Van Westendorp analysis and estimations of market penetration have been determined after presenting and discussing the target product profiles of the drugs. We have used these inputs to better inform out valuation models for our clients' products.

What is a biosimilar drug?

Small, biogeneric and biosimilar molecules

To help define biosimilar drugs, we must first explore the differences between classical small molecule drugs (such as aspirin or penicillin) and biologic drugs (for example, monoclonal antibodies, enzyme replacement therapies and even insulin, which was the first protein approved as a drug). Biologic drugs are mostly proteins but there are complex carbohydrates, peptides and even DNA or siRNA[1] that can be classified as large molecule biologic drugs. Between 2008 and 2017, 22% of drugs approved by the FDA were biologics and there will therefore be a significant market for biosimilar competition to those drugs once the patents expire. Despite over 90% of prescriptions by volume in the US being for (small molecule) generic drugs, 40% of US drug spend by value was on biologics. As shown in Exhibit 1, a typical small molecule drug has a simple molecular structure that contains c 100 atoms or fewer. It is usually made by a short series of chemical reactions (in a synthetic route) and the scale-up from laboratory flask to industrial reactor vessel presents few unmanageable problems. As an aside, small molecule drugs are frequently taken by patients orally as tablets and this solid dose format is usually associated with years of shelf life. Small molecule drugs are mostly prescribed by primary care physicians for either acute or chronic, usually non-life-threatening conditions (such as a throat infection or high blood pressure) and aim to effectively cure the patient (even if chronic administration is required). For a competent chemist, small molecule drugs are easy to copy and in the earlier days of drug development, pharmaceutical companies routinely synthesized competitor drugs (from the information provided in the patent) to test and make better versions. Once the patent protection expires for small molecule drugs, it is routine to make a generic version and indeed the regulatory pathways (in the US and EU) provide for much smaller, and therefore cheaper, studies that in many cases only require the demonstration of bioequivalent blood levels in healthy volunteers compared to the innovator or reference molecule for the generic small molecule drug to be approved.

Exhibit 1: Molecular structures of small molecule and biologic drugs



Source: Mann Bioinvest

Biologic drugs are much larger than small molecule drugs and can be comprised of 10s of thousands of atoms organised into a primary structure (chains of amino acids), a secondary structure (where the long chain folds to form a three-dimensional functional or structural site) and tertiary structures (where sub-units of large molecule join together to form an active drug). In addition, there can be post-translational processing once the basic biologic drug is formed, with methylation or sugar residues added, subtracted or altered. This complicated synthesis is usually

[1] siRNA – small interfering RNA (gene silencing) molecules

too complex and expensive to be done by chemists in a synthetic route and can only be cost effectively done in living cells. However, the cost of goods of a typical monoclonal antibody has declined over the years and is now significantly less than $100 per gram[2]; not at small molecule drug margins, but still very profitable. Initially, this made biologics much more expensive to produce than small-molecule drugs, although for the manufacturers there were other compensations such as orphan drug pricing. Biologics are frequently prescribed by specialist physicians in larger hospitals or clinics, usually administered by injection and used to treat a difficult or terminal condition, such as rheumatoid arthritis or cancer, respectively. The specialist physician channel also implies much smaller patient populations than for typical small molecule drugs in primary care, which brings lower sales and marketing costs and smaller numbers of patients (so lower cost) in clinical trials.

Biologic drugs are produced by a suspension of mammalian, plant or even insect cells that are fed the right nutrients and atmosphere in a bioreactor. The earliest-approved examples of biological drugs were purified extracts of human or animal cells such as insulin or interferon. When produced synthetically, the scale-up from laboratory cell culture to commercial bioreactor can be more problematic than for small molecule drugs. But the biggest difference when comparing a small molecule drug to a biologic drug is that because so many steps and combinations of conditions are needed to make a large molecule in cell culture, the molecules produced are frequently not identical between production batches or when produced by the same company in different manufacturing sites. The term biogeneric fairly quickly fell out of favour (because the drugs were not bioidentical like small molecule generic drugs) and was replaced by the term biosimilar. This recognition of biosimilarity initially helped innovator companies to delay biosimilar competition. For example, branded biologic drugs Lovenox (a complex polysaccharide low-molecular weight heparin anticoagulant drug where the raw material is animal tissue) and Copaxone (a mix of amino acid polymers for the treatment of multiple sclerosis) are marketed by Sanofi and Teva. The manufacturers of these two branded drugs used the defence to regulators that if they did not know the defined molecular make-up of their products, how could a biosimilar manufacturer replicate it?

This non-identical property of biologic drugs has some paradoxical effects going back to 1999, when the FDA enforced the orphan drug exclusivity of Biogen's alpha interferon Avonex, thereby preventing Serono's alpha interferon Rebif from being commercialised in the US. Orphan drug exclusivity in the US provides seven years of market exclusivity for the first example of each new molecule approved for a particular orphan indication, in this case multiple sclerosis. This prevents the same molecule from a different manufacturer being commercialised for the same indication. Serono briefly tried to argue that Rebif was a different interferon alpha to Avonex, but at the time the analytical techniques were not sophisticated enough to conclusively prove this, even though alpha interferon is one of the least complex biologic drugs. Serono had to conduct a Phase IV clinical study to demonstrate the superiority of Rebif over Avonex, which it did, and the FDA approved Rebif in 2002 a year ahead of Biogen's scheduled orphan drug exclusivity expiry.

Before biosimilars, there were similar biologics

Before the legal and regulatory frameworks that allowed biosimilar drugs to be approved and marketed, there were biologic drugs that were almost identical to each other. The classical case was that of erythropoietin (EPO) and its derivatives. Human EPO is a 165 amino-acid glycoprotein (with four added sugar molecules) hormone that increases red blood cell production and is used to treat the anaemia associated with chronic kidney disease (CKD), or as a result of cancer chemotherapy. The original recombinant human EPO was approved by the FDA (as a drug, not a biologic) in the late 1980s with all the attendant clinical trial requirements of a new molecular entity. Early and protracted patent litigation between innovator companies manufacturing first-generation

[2] Gronvall, et al, 'Center for Biosecurity Project Team' (2013), p. 60.

EPO derivatives eventually proved academic and gave way to improved and longer-acting EPO-based products such as Amgen's Aranesp in 2001. With a large potential global market for these erythropoiesis-stimulating agents (ESAs) but no mechanism for approving a biosimilar even after the patent had expired, other innovator companies developed competing long-acting ESAs through the usual (and by then available) biological licence application (BLA). These were new biological drug entities that required long and expensive clinical trials and regulatory submissions. Thus Roche's competing ESA Mircera was approved by the FDA and EMA in 2007, although additional US patent litigation delayed US marketing until 2014. In Europe in 2007, while biosimilar was still a nascent term, Roche used Mircera's EU approval to establish competitive (biosimilar) price points in what was until then a branded-only market. This was an inspired move because Europe is comprised largely of single-payer public healthcare systems that are used to purchasing generic drugs in bulk and on a tender basis. This has helped establish Europe as the world's leading biosimilar market, which we explore further below. The non-biosimilar ESA approvals also established early on that the ability to develop biosimilar products was easier if done by a company that already had innovator biological drug development and regulatory experience, such as Roche.

An accidental history

The history of the development of biosimilars has been augmented with a few accidents that initially helped the innovator companies and at least delayed biosimilar competition. In 2009, before any biosimilar product was approved, Genzyme (now a Sanofi company) was prevented by the FDA from supplying its product, an enzyme replacement therapy for Pompe disease, from its 2,000 litre Allston manufacturing facility because there were (glycosylation) differences between the Allston-produced drug and the supposedly same product produced at Genzyme's 160 litre pilot plant facility. The product manufactured at a third 4,000 litre facility in Belgium was eventually approved as the global supply site. Such was the caution by the FDA on the slightly different products manufactured by the same company at different US sites that, while they co-existed, they had separate brand names – Myozyme and Lumizyme.

Tides turn slowly towards biosimilars

Since the early 2000s, a number of biotech companies specialising in biosimilar products have come to the public market. Although these products have eventually gained FDA approval, the lack of monopoly positions seems to be the main reason why significant commercial success remains elusive. Momenta Pharmaceuticals was founded in 2001 and listed on Nasdaq in 2004 on a sophisticated analytical platform that could determine and replicate the precise mix of complex biological products (initially carbohydrates). Today, through the collaborations with partner Sandoz (the generics arm of Novartis), there are two Momenta-derived biosimilar products on the market (generic Lovenox and Copaxone). However, because there have been multiple market entrants for both products, which the FDA has determined are substitutable for the innovator or reference product, pricing has fallen. As a result, Momenta recently had to restructure and remains loss-making.

Building on the rising investor interest in biosimilars, Coherus Biosciences was founded in 2010 and listed on Nasdaq as a pure-play biosimilar company in 2014. Like Momenta, Coherus now has a product on the market, Udenyca, a biosimilar of Amgen's Neulasta,[3] which boosts white blood cell counts in chemotherapy-treated patients. Like Momenta's biosimilar products, Udenyca shares the US market with Amgen's innovator product and Mylan's generic version Fulphila. Also, like Momenta, Coherus remains loss-making although its quarterly losses have halved in the last year as (unlike Momenta) it has started marketing Udenyca alone. Coherus has compared the weighted average cost per syringe of its biosimilar product Udenyca to Amgen's Neulasta noting a 33%

[3] Granulocyte colony stimulating factor (G-CSF) with a PEG half-life extension

discount to the innovator product. This is a typical of the discount to the innovator biologic with limited biosimilar competition in the first few years of launch and in the US there are now three substitutable pegfilgrastim[4] products (including the reference product Neulasta). In biosimilar launches where there is limited competition, discounts to the innovator product of between 30% and 40% are typical. These are much lower than the discounts of c 90% that would be expected with small molecule generics manufactured by many competitors.

The pathway to a pure-play biosimilar company has not been easy and Udenyca had a chequered early history. In 2015 Coherus reported the pharmacodynamic (PD) and pharmacokinetic (PK) profiles of Udenyca (then known as CHS-1701) and Neulasta showing that one of the two Udenyca PK profiles was different to the other and to those of Neulasta. After consultation with the FDA, additional patients were dosed and the data included in a BLA under the FDA's new (at the time) 351(k) biosimilar pathway. After the FDA issued a complete response letter in June 2017 requesting a reanalysis of the immunogenicity data, Udenyca was finally approved in Europe in September 2018 and the US in November 2018.

Take-home point: due to the recent legislation that allows the approval of biosimilar drugs, there has been a second-mover disadvantage while companies become familiar with biosimilar clinical and regulatory requirements. Even so, while the regulatory requirements may now be clearer, investors have had to lower their expectations on the commercial potential of a competitive biosimilar market, relative to the previous monopoly innovator market. This implies incremental profits, rather than those associated with a new biological drug launch. In addition, the requirements for a biosimilar approval fall between those of a small molecule generic drug, and a new biologic entity in terms of cost and time.

B for bioequivalent biosimilars started in Europe

European biosimilar legislation started to be developed in 1998 and came to fruition in 2006 with the first approval of somatotropin. Paradoxically, while biosimilars established themselves in Europe, for nine years there was no legal route to approval in the US without going through a new BLA submission until the FDA's guidance of 2010 and its first approval of a biosimilar to Amgen's Neupogen five years later. As part of the FDA's 351(k) pathway biosimilar legislation, innovator companies were compensated with a 12-year exclusivity period from first approval. This is much longer than the five year market exclusivity granted to small molecules approved in the US and a minimum of eight years exclusivity for biologics approved in the EU. Japan established a registrational biosimilar pathway in 2009.

The first European biosimilar approval was for somatropin (a growth hormone with a simple structure), followed by biosimilar EPO in 2007 and filgrastim (first-generation Neulasta) in 2008. However, European biosimilar adoption and the commercial battles with innovator companies did not really start until the approval of a Remicade (infliximab) biosimilar in 2013. In all (EU, Japan and US) cases, the regulations evolved to address the initially perceived issues surrounding biosimilar drugs and prominent among these were bioequivalence and immunogenicity. The demonstration that an injection of a biosimilar product is bioequivalent to the innovator product may not be as simple as with a small molecule generic drug as Coherus discovered in the example above (due to patient PK/PD variability and inter-patient response rates). Much of the impetus on the regulatory requirement for bioequivalence in biosimilars might have come from the innovator companies to raise the bar for the competition to their reference products. In one respect, once bioequivalence had been established it became a double-edged sword for the innovator companies. For biosimilars approved in the EU, EMA regulations stipulate that once biosimilarity has been demonstrated in one

[4] The INN or non-proprietary name for Amgen's Neulasta is pegfilgrastim. Each approved biosimilar product bears the reference INN name with the addition of a four-letter suffix, for example pegfilgrastim-cbqv in Udenyca's case, in the FDA's Purple Book to indicate that it is a biosimilar. For simplicity, we have not used suffixes in this note.

indication, it can be extrapolated to all the other indications for which the originator product has been approved. This extension across all indications only had to be justified by sufficient scientific arguments, rather than expensive clinical trials, making the clinical programme to achieve approval for all the indications for a biosimilar drug – in biosimilar EPO's case, for all the cancer and non-cancer indications – much cheaper and easier than it was for the reference molecule.

Thus from 2016 in the EU, biosimilars to the branded anti-inflammatory Remicade (infliximab) were able to be prescribed for patients suffering from Remicade's eight approved indications in gastroenterology, rheumatology and dermatology. By 2017, biosimilars to Amgen's anti-tumour necrosis factor anti-inflammatory drug Enbrel (etanercept) and Roche's oncology drug Rituxan (rituximab) had been approved by the EMA in multiple indications and by a number of different companies. The attraction of cheaper biologics for single-payer healthcare systems became embedded in the commercial realities of biopharmaceuticals in Europe.

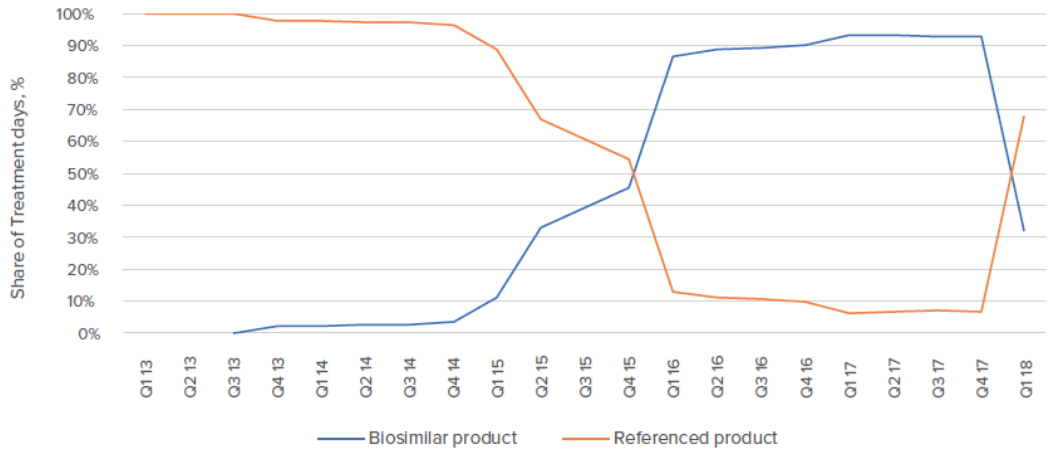
Biosimilar frictions and tenders

The innovator companies' message to prescribers remained that because biosimilar molecules were non-identical to the reference molecule, patients' responses could be different to the reference product, or worse, patients' immune systems could recognise the biosimilar as foreign and raise anti-idiotypic antibodies against it. This mistrust amongst physicians is one of the reasons why biosimilars remain at an earlier stage in the US than Europe, where nine years of experience has largely assuaged them. The FDA's recently finalised interchangeability guidelines may perhaps address this concern in the US. The issue of interchangeability has largely been removed in Europe by a number of switching studies, where patients are switched back and forth between reference and biosimilar products. The largest of these studies was the NOR-SWITCH study funded by the Norwegian government where nearly 500 patients receiving Remicade either remained on the reference drug or were switched to an infliximab biosimilar for 52 weeks. Switched patients had non-inferior clinical outcomes to those on the reference product.

The healthcare systems in most European countries have provided a largely single-payer-driven preference for promoting the use of biosimilar products. Regional purchasers in European countries now often purchase biosimilar drugs in bulk tenders in the same way as for baskets of generic small molecule drugs. Tenders can be open, closed or mixed depending on whether the innovator company is included or possibly excluded. In each case, tenders (which can have durations of years) resulted in average biosimilar discounts in 2016 of c 40% in open tenders, c 60% in closed tenders and c 30% in mixed tender markets. In addition, biosimilars have been favoured more in some markets than others, with Norway and Denmark having close to 100% biosimilar infliximab uptake for example, compared to just under 25% in France in 2016. This is because in Nordic Europe, biosimilar tendering tends to be exclusive (which can exclude the innovator), more aggressive and pragmatic. Exhibit 2 demonstrates the effect of biosimilar tenders for infliximab in Finland.

In the US, the longer period of market exclusivity for innovator products and counter-detailing by innovator companies continues to limit the uptake of biosimilars where they have been approved, as does the extended periods of patent exclusivity. The European patent for the world's best-selling drug Humira (adalimumab, with c $20bn in 2018 sales) from AbbVie expired in October 2018 and there are now five approved biosimilars in Europe. Humira remains patent protected in the US until 2023, despite being first approved there in 2002. Eight Humira biosimilars have been approved by the FDA and are waiting to launch. In Q119 AbbVie Humira sales ex-US fell by 23% quarter on quarter, five months after the first biosimilar launch largely due to the aggressive European tender processes.

Exhibit 2: The share between biosimilar and reference product treatment days (%) of infliximab in Finland



Source: IQVIA

Biosimilar investment perspectives

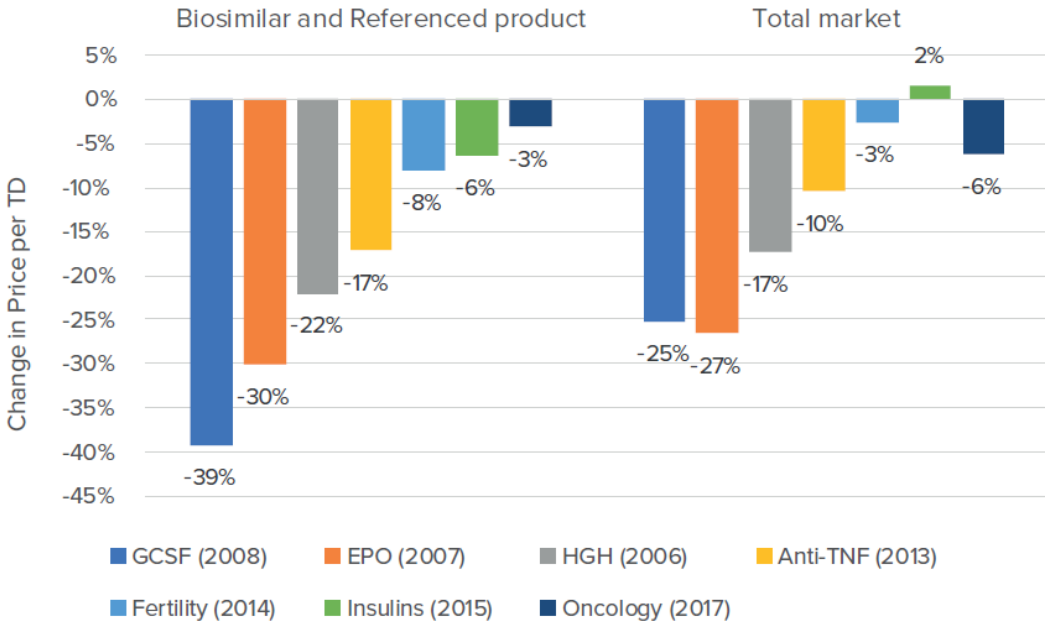
Biosimilar drugs represent significant savings to global healthcare systems and offer patients in lower- to middle-income economies access to innovative biologic drugs for the first time. From an investment perspective, things may not be as positive. Just as in small molecule drugs, multiple biosimilar companies competing in tenders can aggressively drive prices down and, while the attractiveness of the generic small molecule drug sector has declined significantly over recent years as a smaller number of consolidated competitors compete for tender contracts, the biosimilar market may have similar (if not as aggressive) dynamics. Exhibit 3 shows the change in price per treatment day since biosimilars have been introduced in Europe. It is important to note in the right-hand panel of Exhibit 3 that although the total market may have declined by up to 27%, this is caused by many factors and is the combination of exclusion of the innovator companies in some tenders, discounting by new entrants and higher volumes of prescriptions. So, although the price for each biosimilar product may be up to 39% lower than the previous monopoly price, much higher volumes and few selling or marketing costs result in biosimilar manufacture being profitable.

Typically, because biologic drugs are produced in cells and small molecules by chemical synthesis, the cost of goods sold used to be much higher for biologics than for small molecules. This differential may no longer be as great because the processes for producing and purifying biologic drugs have improved over the last 20 years and the first-mover disadvantages are now at innovator companies who are tied into their initially approved processes.

Investors are often attracted to generic drug investments when company management cite the value of the branded market, rather than the resulting market after multiple aggressive competitors compete together. While some companies will make some money out of biosimilar Humira, for example, it will not be a zero-sum game with $20bn in 2018 revenues probably representing the final peak in value of the global adalimumab market value as price increases in the US are more than absorbed by biosimilar competition ex-US.

Although biosimilar competition will mean many more patients will receive Humira or a biosimilar than can currently afford it, Exhibit 3 suggests the total value of the market is likely to end up being less even when higher volumes are split between many players at a lower price. This is not to say that no companies will benefit. Larger innovator companies such as Novartis with a history of both biologic manufacture and generic distribution will benefit the most, as will any other company that can exploit a niche where a biosimilar is very difficult to manufacture.

Exhibit 3: The change in price per treatment day and the total market for each product since the introduction of biosimilars in Europe



Source: IQVIA

The US market lags the rest of the world in biosimilar penetration. Partly, this is due to the effectiveness of the patent attorneys and the marketing groups at innovator companies. But once exclusivity is lost in the US, we expect the US biosimilar market to continue to lag behind Europe because of the fragmented payer system. Tenders and strategic contracting have a smaller effect if confined to individual health insurers and, paradoxically, US hospitals and clinics (even treating patients covered by Medicare, for example) are likely to be reimbursed at a higher rate, if they use higher-priced (branded) products. In addition, in advance of biosimilar competition, innovators have contracted with payers for multi-year contracts that cover some years after the loss of exclusivity at prices between branded and biosimilar to retain market share. This is not a static situation as Coherus have found recently where UnitedHealthcare, one of the largest US health insurers will be favouring Amgen's reference product (Neulasta) over Coherus's (Udenyca) biosimilar because Amgen offered higher rebates (to UnitedHealthcare). Payers may also prefer Amgen's reference product as it is available as an 'at home' version whereas Coherus's biosimilar can only be administered at (and with the added cost of) a physician's office visit.

Another reason why the US biosimilar market is likely to lag the rest of the world is that for biosimilar uptake to advance significantly in the fragmented US healthcare system, someone needs to make a profit, rather than just save costs. Cost saving is the principal biosimilar selling point in ex-US single-payer markets but its impact is significantly reduced in highly fragmented healthcare systems. For example, in dialysis clinics in Europe (initially), and more recently in the US, patients are treated on a capitated basis (a fixed cost per patient per dialysis session). If a dialysis clinic can obtain biosimilar ESAs (which often form part of CKD patient treatment) at a significant discount to the branded version, until the capitated cost is recalculated, the biosimilar price offers them a significant profit increase. Biosimilar ESAs have been enthusiastically embraced by for-profit and public dialysis providers like Fresenius Medical Care. There may be potential for this type of profit enhancement by US hospitals where procedures are reimbursed according to fixed-cost disease related groups, but for the moment this role for biosimilar drugs in the US appears to be latent.

Biosimilar conclusions

Biosimilar drugs are helping transform the access for patients and healthcare systems to the latest and most effective drugs. The market share and value losses by the innovator companies will be balanced to some extent by new biosimilar companies and other innovator companies that have turned their hands to biosimilar production and regulatory approval. Even 13 years after the first EU biosimilar approval, it is still early in the biosimilar story with new biosimilar entrants like Formycon, Rovi and Xbrane ensuring further fragmentation. The percentage of biosimilar to their total product revenues of Amgen (two products) and Biogen (three products) in Q119 was only 1% and 6.5%, respectively.

In the same way as the patent cliff (many branded small molecule drugs lost exclusivity at about the same time towards the end of the 2000s) gave way to the biologic drug era and increased profitability for biotech and pharma companies, the rise of biosimilars also highlights the need for continued innovation and new medicines. Some of these are likely to come from companies developing gene and cellular therapies.

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