Catalyst

Payer intervention has boosted biosimilars uptake by means of incentives such as prescribing quotas; however, obstacles to growth remain.

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EXECUTIVE SUMMARY

Generics market

Germany is Europe’s largest generics market. Sales through the social health insurance system were around €4.3bn ($5.5bn) (ex-manufacturer prices) in 2012, and the market is expected to expand further during 2013 and beyond as more patents expire.

According to 2012 figures from the generics industry association ProGenerika, the market share of generics in Germany is 73% (by defined daily dose), 66% (by units in the whole pharmaceutical market), and 82% (by units in the off-patent market). The market share of generics in Germany is 23% by value (ex-factory price).

Tendering is widely used to keep the cost of off-patent and generic drugs down, with the sickness funds (Krankenkassen) sourcing drugs from the cheapest supplier. Since the Act for Strengthening Competition in Public Health Insurance (Gesetz zur Stärkung des Wettbewerbes in der gesetzlichen Krankenversicherung; GKV-WSG) reform was introduced in 2007, health insurers can agree rebate contracts with pharmaceutical companies, which are under considerable pressure to lower their prices and submit competitive bids.

According to ProGenerika, 66% of the generics market in Germany is subject to tendering (by volume), and additional savings through tendering were €2.4bn ($3.1bn) in 2012 – effectively reducing the value of the generics market by almost 50%.

The largest sickness fund, the AOK, saved €949m ($1.2bn) through rebate contracts in 2012.

Under the reference pricing system, drugs are clustered together into groups of the same or comparable substance, or with a comparable action, and a maximum reimbursement price is set for the group.

Pharmacists can substitute branded drugs with generics. However, they are required to substitute a product that is within the lowest third of the price range unless the prescriber insists on the prescribed drug being dispensed. Since 2007, pharmacists receive 3% of the wholesale price and a fixed dispensing fee to encourage the prescribing of generics over more expensive products.

Critics of tendering believe the generics market in Germany to be extremely challenging, blaming tendering for concentrating the generics market in the hands of a few suppliers. ProGenerika believes tendering is not a sustainable tool for pharmaceutical care, rather a cost-containment measure resulting in a downward spiral of prices. As a result, the trade body believes tendering does not result in fair pricing, which it believes is a fundamental part of a sustainable environment for pharmaceutical care.

Biosimilars market

Germany has led the way in Europe in making biosimilars available, and is the highest volume and value market for biosimilars, but as in other EU countries the market overall remains
quite limited. This is due to a number of factors including the limited number of biosimilars available.

The bulk of the biologics market in Germany consists of originator products still under patent. In 2012, sales of biologic medicines in Germany were €5.14bn ($6.6bn) (sales through the statutory health insurance, including compulsory manufacturer rebates), of which biosimilars accounted for €62.1m ($79.8m), representing only 1.2% of the biologics market.

Moreover, use of biosimilars has varied greatly by region – depending to a great extent on local policies and incentives – and by substance, with strong uptake of epoetin and filgrastim, but weak uptake of somatropin. All of the 12 biosimilar medicines currently authorized for marketing in the EU from five different biosimilar manufacturers are available in Germany.

The key driver of the biosimilars market in Germany has been the biosimilars prescription quotas, and their more widespread use by sickness funds is expected to be the key driver of biosimilars market growth going forward. Inclusion of biosimilars in the reference pricing system is viewed as a negative by the generics industry and has resulted in no price differential between the original and biosimilar products in the case of epoetin, stifling uptake.
GENERICS MARKET DYNAMICS

Germany is Europe’s largest generics market, with sales through the social health insurance system (SHI) (at ex-manufacturer prices) of around €4.3bn ($5.5bn) in 2012. That same year, generics accounted for 66% of the SHI pharmaceutical market by volume and 23% by value (ProGenerika, 2013). In 2012, generics accounted for 81% of the off-patent market by volume. These shares have remained more or less stable since the introduction of the Act for Strengthening Competition in Public Health Insurance (Gesetz zur Stärkung des Wettbewerbes in der gesetzlichen Krankenversicherung; GKV-WSG).

The table below outlines generics uptake and market size in Germany in relation to the US, Japan, France, Italy, Spain, the UK, the BRIC nations (Brazil, Russia, India, and China), Australia, and Canada between 2010 and 2012.
### Table 1: Germany – comparison of generics penetration versus other pharmaceutical markets, 2010–12

<table>
<thead>
<tr>
<th>Country</th>
<th>Volume share (%)</th>
<th>Value share (%)</th>
<th>Market size ($bn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>80</td>
<td>27</td>
<td>53</td>
</tr>
<tr>
<td>China</td>
<td>70</td>
<td>63</td>
<td>26</td>
</tr>
<tr>
<td>Germany</td>
<td>66</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>UK</td>
<td>67</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Brazil</td>
<td>27</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Canada</td>
<td>62</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>France</td>
<td>27</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Japan</td>
<td>23</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Russia</td>
<td>75</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>India</td>
<td>100</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Spain</td>
<td>35</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Australia</td>
<td>23</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Italy</td>
<td>12</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>


*Germany generics volume market share*
Germany generics value market share
Germany generics market size


Figure 2: Germany – comparison of generics value market share versus other pharmaceutical markets (%), 2010–12
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Frost & Sullivan (2011) What Lures the Attention of Global Generic Drug Makers towards China?


GENERICS DRIVERS AND RESISTORS

The German generics industry is feeling the effects of recent efforts to control drug spending by exerting downward pressure on drug prices. While government reforms have sought to increase the use of generics, they have in some cases tended to put even more pressure on the already narrow profit margins of generics players. Consequently, it seems inevitable that some generics players will be forced out of the market.

The figure below shows some of the major factors influencing the generics industry in Germany.

Figure 4: Germany – key factors influencing the generics industry

<table>
<thead>
<tr>
<th>Drivers of the German generics industry</th>
<th>Resistors to growth of the German generics industry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two year exclusivity deals with minimum volumes for some</td>
<td>Downward pricing spiral under intense competition</td>
</tr>
<tr>
<td>Tends to favor larger generic companies</td>
<td>Drug prices forced downwards</td>
</tr>
<tr>
<td>Greater uptake of generics against brand</td>
<td>Limited price competition for OTC products</td>
</tr>
<tr>
<td>INN substitution automatic</td>
<td>Automatic uptake of cheapest product</td>
</tr>
<tr>
<td>Fixed pharmacist margins</td>
<td>Inability of pharmacists to develop chains</td>
</tr>
<tr>
<td>Existence of a near generic</td>
<td>Pay for delay deals</td>
</tr>
<tr>
<td>Few barriers to market entry</td>
<td></td>
</tr>
</tbody>
</table>

OTC = Over The Counter; INN = International Non-proprietary Name

Source: Datamonitor Healthcare

Tendering is widely used to purchase generics

The 2007 Act for Strengthening Competition in Public Health Insurance (Gesetz zur Stärkung des Wettbewerbes in der gesetzlichen Krankenversicherung; GKV-WSG) introduced the possibility for the social health insurance system to agree rebate contracts with pharmaceutical companies for generic and in-patent drugs. Such contracts are now widely used to purchase generics at heavily discounted prices.
prices. Under the legislation, all public health insurance funds are expected to seek out contracts for bulk supplies of generics at a discounted price, in return for which the generics company’s medicines are made the drug of first choice for pharmacists. Under German law, a generic must be dispensed where one is available unless the doctor specifies otherwise. Although doctors and patients have incentives (in the form of lower patient co-payment, or in some cases zero patient co-payment) to demand medicines that are included in the tender in Germany, doctors still have the right to write “do not substitute” on the prescription form. However, companies that do not get their products onto the list of contracted suppliers stand to lose out significantly in sales terms.

Considering the enormous bargaining power of the health insurance funds, pharmaceutical manufacturers, in particular companies in the generics industry, face immense pressure to decrease their prices in order to win bids in these tenders.

Pricing pressure brought by rebate contracts and competition among suppliers has therefore had the effect of pushing down generics prices, with larger companies able to offer steeper discounts and smaller companies struggling to retain market share. This has radically altered the competitive landscape of the generics market. It is estimated that generic drug prices declined by 30% as a direct result of the GKV-WSG reform (Ghangurde, 2010), with the German generics market having been transformed from a branded market to a commodity market almost overnight.

It was reported that in 2011 the number of rebate contracts rose to a record high of 16,000 (ProGenerika, 2012).

According to Helmut Fabry, who heads generics company Sandoz in Germany, half of the market is not subject to the rules imposed by tenders. “Roughly 70% of volumes in the German generics sector are covered by tenders, but the structure of those deals means only 70% of those packs are dispensed under the rules of the tender,” he noted (Generics Bulletin, 2013a).

Fabry said fears that tenders would drive players out of the market had not yet been realized. Nevertheless, there had been market shortages of oncology drugs such as fluorouracil, while for molecules such as ramipril, one player could capture up to 80% by volume. This, he said, created such economies of scale that it was difficult for other firms to compete. As a result, some funds are starting to raise concerns about security of supply. For example, AOK, Germany’s largest group of statutory funds, has begun awarding supply contracts for each molecule to consortia of three firms (Generics Bulletin, 2013a).

AOK LEADS THE WAY IN TENDERING PRACTICES

The largest of the sickness funds (Krankenkassen), the AOK, leads the way in negotiating generic price rebate contracts. It covered 24 million people across Germany in 2010 and held a 35% share of the German insurance market (AOK, 2011). As a result of its size, many look to the AOK as the leader and promoter of the sickness funds’ interests. AOK operates its tendering on a molecule/drug (rather than portfolio) basis, allowing companies to bid for individual molecules separately or more recently as part of a consortium. In general, the AOK looks for bids that compete based on price, although factors such
as quantity, formulation, pack variations, and supply control are also considered (Kanavos, 2009). According to Ministry of Health figures, AOK rebate contracts saved €949m ($1.2bn) in 2012. The savings across the entire German public health insurance system totaled €2.09bn ($2.69bn) (personal communication, 2013).

The basis of AOK tenders are groups of substitutable drugs including the off-patent original and generic alternatives (Wienands, 2013). The tender usually addresses an active pharmaceutical ingredient (API), including its substitutable groups. Offers on substitutable groups are compared, and the best offer is determined by comparing the economic advantages of the substitutable groups within the API.

The AOK has so far announced 11 rounds of rebate contracts. The contracts are legally effective and the regular term has been set at two years.

While rebates on off-patent drugs will continue to hit the generics market, patented medicines are set to be increasingly targeted by rebate contracts, which will pose a further challenge for companies producing new medicines that end up in the reference pricing system following negative early benefit assessments (IHS, 2011).

The figure below shows companies that have been awarded AOK contracts since the seventh round of contracts (announced in late 2011), and the number awarded to each (including as part of a consortium).
OTHER FUNDS LOOK AT ALTERNATIVE WAYS TO LEVERAGE POWERS

Other notable sickness funds are the Deutsche Angestellten Krankenkasse (DAK) and the Techniker Krankenkasse (TK). These funds operate on a "portfolio contracts" basis, with contracts tendered for portfolios of products rather than a single molecule. Nevertheless, price remains the primary consideration in the tendering process, as well as the ability of manufacturers to meet volume demands. Consequently, as with the AOK, DAK and TK tendering favors larger companies which are able to supply all the products in the portfolio. However, small companies have been able to compete through collaboration in order to jointly bid for contracts.

In June 2008, the DAK suffered a legal setback to its tendering process when the German Federal Cartel Office ruled it had acted unlawfully in the tendering for three drug categories – beta-blockers, fentanyl-based analgesics, and neuroleptics – since the grouping of different active ingredients within one tender favors those companies with larger, more comprehensive portfolios (Kanavos, 2009). On the occasion in question the DAK withdrew the tender request, although it is unclear if similar litigation in the future could force the DAK to adopt an AOK style of tendering.
SICKNESS FUNDS JOIN FORCES TO LEVERAGE GREATER POWER IN TENDERING

Some sickness funds have joined together to form even larger bidding groups in order to force manufacturers to lower their prices even further, an example of which is spectrumK, a group of more than 70 health insurance funds covering over 8 million Germans that work together in order to achieve a higher degree of negotiating ability.

However, after only six rounds of contracts, the combined fund was experiencing a fall-off in interest, with more than a third of the bidding lots attracting only one bidder. For 10 of the 24 lots for which spectrumK had invited offers, it was unable to award any contracts. This suggests companies are not even trying to win deals at low margins. In response, ProGenerika repeated its claims that the German tender system is driving companies out of the market and will lead to supply shortages (Generics Bulletin, 2013b).

Despite the muted response, spectrumK launched a seventh round of tenders in July 2013, inviting bids for 59 lots across 44 molecules, including the antiretrovirals lamivudine and zidovudine. Also, for the first time, epoetin alfa and epoetin zeta were included in a spectrumK tender. The tender is worth €120m ($154m).
Changes to reference pricing system hit producers

Under the reference pricing system, patients are required to pay a prescription charge of between €5 and €10 ($6.4 and $12.8) based on the over-the-counter price of the drug (VOI, 2009). However, co-payments are waived for drugs which are 30% cheaper than the reference price, thus encouraging patients to request these lower-priced generic products. Such drugs are also eligible to have their otherwise mandatory 16% rebates waived. These incentives have, however, led generics companies to set increasingly lower prices in an effort to boost their volume sales.

Table 2: Successful bidders in the sixth round of tenders operated by spectrumK

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Number of bids submitted</th>
<th>Successful bidder(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>1</td>
<td>1A Pharma</td>
</tr>
<tr>
<td>Memantine</td>
<td>8</td>
<td>Betapharm, Heumann, Hexal</td>
</tr>
<tr>
<td>Riluzole</td>
<td>9</td>
<td>Glenmark, Mylan Dura, Sun Pharma</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2</td>
<td>Teva/ratiopharm, Winthrop/SanoFi</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1</td>
<td>Meda Pharma</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>8</td>
<td>Rottapharm/Madaus</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>4</td>
<td>Actavis</td>
</tr>
<tr>
<td>Thiamazole</td>
<td>2</td>
<td>Hexal</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1</td>
<td>1A Pharma</td>
</tr>
<tr>
<td>Levodopa/benserazide</td>
<td>1</td>
<td>Neuraxpharm</td>
</tr>
<tr>
<td>Budesonide (spray)</td>
<td>2</td>
<td>Hexal</td>
</tr>
<tr>
<td>Budesonide (suspension)</td>
<td>3</td>
<td>InfectoPharm</td>
</tr>
<tr>
<td>Budesonide (nebulizer)</td>
<td>2</td>
<td>InfectoPharm</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>1</td>
<td>Dr. Robert Winzer</td>
</tr>
</tbody>
</table>

Source: Generics Bulletin, 2013b
In a move which further pressurized generics manufacturers, standard reference price revisions that came into effect in September 2010 in some cases appeared to be lower than they had previously been, meaning that some generic products that were previously exempt from co-payments became liable for such payments (AOK, 2010b).

The prices of generics and branded drugs have been somewhat evened out as a result of the implementation of the Pharmaceutical Market Reform Law (Arzneimittelmarktneuordnungsgesetz; AMNOG) in January 2011, which resulted in a greater number of innovator drugs entering the reference pricing system through the inclusion of me-too brands and a larger number of therapy areas (Generics Bulletin, 2010c).

The system sees new pharmaceuticals rated against older comparators in tough benefit assessments. The score they achieve is then used to inform the price of the drug, and if there is no additional benefit, the drug is given a similar price to its comparator. The system has proved controversial and several companies have decided against launching their new drugs, or have withdrawn drugs from the market.

The AMNOG could also be damaging to further companies whose me-too products will face competition from generics, with patients being forced to pay additional co-payments to access the originators. Furthermore, the placing of more originator products into the reference pricing system will provide greater opportunities for generic uptake.

**Action taken to increase generic substitution**

Several changes have been made to the rules on generic substitution since 2002, when the Act on Limiting Drug Expenditure (Arzneimittelausgaben-Begrenzungsgesetz; AABG) entered into force. One of the provisions of this act was that doctors were given the ability to specify “no substitution” on the prescription form. In 2007, the GKV-WSG reform enabled the SHI insurers to agree rebate contracts with pharmaceutical companies. It also required pharmacists to substitute the prescribed brand with a generic containing the same active substance covered by a rebate contract where possible (Deutsches Ärzteblatt, 2009).

Following the reforms in 2007, pharmacists receive 3% of wholesale prices and a fixed €8.10 ($10.41) dispensing fee to encourage the prescribing of generics over more expensive products. As a result, pharmacists on average achieved a 36.0% margin on the sales of a single generic medicine in 2010 (Generics Bulletin, 2010b).

In Germany, physicians have allocated drug budgets and can be fined for being over budget. Therefore, they are less inclined to opt out of the automatic generic substitution by de-selecting "aut idem" or prescribing another patented product, unless they feel it is really necessary.

**Germany leads in Europe in terms of pay-for-delay deals**

Reverse payment deals – also known as pay-for-delay – are struck between branded and generics companies to postpone the entry of generic versions of off-patent drugs in exchange for some form of
compensation. For generics companies this can be a cash settlement or simply avoiding the cost of complex and often lengthy litigation. In return, the branded company enjoys a short, albeit highly profitable additional period of market exclusivity.

Many companies with branded drugs in Germany have chosen to implement pay-for-delay strategies. However, their legality has been challenged, notably by the European Commission, which carried out a high-profile inquiry into pay-for-delay practices in Europe. Germany was found to have the highest number of pay-for-delay cases, totaling some 20 agreements between 2006 and 2008, in contrast to the average of 14 across EU member countries (European Commission, 2009).

In 2010 the commission began an investigation into decade-old agreements between Lundbeck and several generics companies that delayed market entry of generic versions of Lundbeck’s antidepressant citalopram. The commission said that by paying out tens of millions of euros to delay market entry, Lundbeck had violated antitrust laws. It announced a fine of €93.8m ($120.6m) in June 2013 (Malone, 2013).

Lundbeck is appealing against the commission’s "erroneous" decision and hopes the appeal will shed light on the commission’s "legal and factual errors" and mark an important legal precedent for other firms navigating Europe’s complex patent system (Malone, 2013).

Branded and generics companies enter into settlement agreements for differing reasons, although the decision for both will be the result of a cost-benefit analysis of sorts. For branded companies, the relative strength of the associated patent litigation case and brand market size is paramount, while for generics companies – for which assessing the strength of a case is difficult – the perceived cost of litigation often lies behind the decision to reach a settlement agreement (European Commission, 2009). While such deals are beneficial to generics players, they delay generic entry and therefore potential cost savings for payers.

**German elections of 2013 not expected to have an impact on the generics market**

A federal election was held on 22 September 2013 to elect the members of the 18th Bundestag of Germany. The Christian Democratic Union/Christian Social Union (CDU/CSU) of Chancellor Angela Merkel achieved its best result since 1990, with nearly 42% of the vote and nearly 50% of the seats. However, its coalition partner the Free Democrats (FDP) failed to get over 5% of the vote, thus denying them seats in the Bundestag for the first time in their history. As a result, Merkel will have to look to the opposition Social Democrats (SPD) for a grand coalition, or to the Green Party to form a majority government, although the latter option is seen as less likely by both parties. While a theoretical Red-Red-Green coalition of SPD, The Left, and the Greens would possess a majority, resistance against the Left Party remains widespread among the SPD and some Green politicians.

However, whatever the makeup of the new German government, fundamental changes to pharmaceutical regulation or the off-patent market are not expected, according to ProGenerika (ProGenerika, 2013).
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Generics Bulletin (2013a) Tenders are not only option, Issue: 28 June 2013.


KEY GENERICS PLAYERS

The table below summarizes key M&A activity involving generics producers in Germany since 2006.

<table>
<thead>
<tr>
<th>Acquirer</th>
<th>Target</th>
<th>M&amp;A deal type</th>
<th>Date</th>
<th>Deal value ($m)</th>
<th>Deal status</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teva</td>
<td>ratiopharm</td>
<td>Majority acquisition</td>
<td>August 2010</td>
<td>4,990</td>
<td>Completed</td>
<td>Biomanufacturing</td>
</tr>
<tr>
<td>Pharmaceutics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupin</td>
<td>Hormosan Pharma</td>
<td>Majority acquisition</td>
<td>July 2008</td>
<td>n/r</td>
<td>Completed</td>
<td>Biomanufacturing</td>
</tr>
<tr>
<td>Dr. Reddy's</td>
<td>Betapharm Arzneimittel</td>
<td>100% acquisition</td>
<td>March 2006</td>
<td>577.3</td>
<td>Completed</td>
<td>Active pharmaceutical ingredient manufacturing</td>
</tr>
<tr>
<td>Krka</td>
<td>TAD Pharma</td>
<td>100% acquisition</td>
<td>November 2007</td>
<td>141.7</td>
<td>Completed</td>
<td>Biomanufacturing</td>
</tr>
</tbody>
</table>

n/r = not reported

Source: Medtrack, October 2013, Copyright Informa UK

Teva extends dominance in German marketplace through its acquisition of ratiopharm

Teva announced in August 2010 the completion of its $5.0bn acquisition of the German generics company ratiopharm. This acquisition allowed Teva to strengthen its tendering position with the AOK, gaining some 37 molecule exclusivity contracts with Germany’s largest insurance fund (Generics Bulletin, 2010).

Indian producers use acquisitions to strengthen position in German market

Indian generics producers Lupin and Dr. Reddy's have tapped into the German generics market through the acquisition of domestic generics producers. In March 2006, Dr. Reddy's acquired Betapharm Arzneimittel for $577m and in July 2008 Lupin acquired Hormosan Pharma for an undisclosed sum, positioning Dr. Reddy's strongly in the German generics market.

Meanwhile, Sun Pharmaceutical Industries may be moving away from its conservative approach to mergers and acquisitions, if a recent fund-raising plan is anything to go by. In 2012, the Indian firm raised more than $1.5bn to fund potential new buys, putting the spotlight on Stada Arzneimittel, the German firm that Sun had been speculated to be eying (Ghangurde, 2012). However, as of October 2013, no acquisition had taken place.
Bibliography


BIOSIMILARS MARKET DYNAMICS

Germany is considered to be the leading biosimilars market in Europe, for a number of reasons:

- It was the first market in which formally authorized biosimilars were launched.
- Payer intervention has boosted uptake by means of incentives such as quotas for biosimilars.
- Doctors undergo education sessions to strengthen the biosimilar concept.
- Branded drug prices are high relative to other EU countries.
- Generic consumption levels are high, suggesting that biosimilars will also be relatively well accepted.

Drivers of biosimilar uptake in the German market

The figure below shows some of the major factors influencing the biosimilars industry in Germany.

![Figure 6: Germany – key factors influencing the biosimilars industry, 2013](source: Datamonitor Healthcare)

THE BIOSIMILARS MARKET IN GERMANY

Germany has led the way in Europe in making biosimilars available, and is the highest volume and value market for biosimilars, but as in other EU countries the market overall remains quite limited.
This is due to a number of factors: for example, only three substances have been approved as biosimilars in the EU (somatropin, epoetin, and filgrastim), and the bulk of the biologics market in Germany consists of originator products still under patent.

Moreover, use of biosimilars has varied greatly by region – depending to a great extent on local policies and incentives – and by substance, with strong uptake of epoetin and filgrastim, but weak uptake of somatropin. In 2012, sales of biologic medicines in Germany were worth €5.14bn ($6.6bn) (sales through the statutory health insurance, including compulsory manufacturer rebates), of which biosimilars accounted for €62.1m ($79.8m), representing only 1.2% of the biologics market. All of the 12 biosimilar medicines from five different biosimilar manufacturers currently authorized for marketing in the EU are available in Germany according to the German generics industry body ProGenerika (ProGenerika, 2012).

The main reason for the limited size of the German biosimilars market is that most originator biologics are still under patent there. Patented drugs accounted for 96.2% of the biologics market by value in 2011, at €4.94bn ($6.35bn), while the biosimilar-accessible market represented the remaining 3.8%, which was broken down into biosimilars (1.2%) and off-patent originators (2.6%) (ProGenerika, 2012).

By volume, patented originators represented 98.7% of the market, at 931.5 million defined daily doses (DDDs), with products open to biosimilar competition showing volume sales of just 12.7 million DDDs (1.3% of the biologics market). Of this 1.3%, off-patent originator medicines accounted for just over half (6.8 million DDDs), and biosimilars for the remainder (5.8 million DDDs). However, the market is expected to begin showing stronger growth from 2013 as more biological products come off patent, particularly in 2014 and 2015 (ProGenerika, 2012). At the same time, numerous biosimilar products are already in the drug development pipeline, with monoclonal antibodies (MAbs) expected to represent the next major wave of biosimilar development.

Indeed, in September 2013 the European Medicines Agency approved the first biosimilar MAbs: Celltrion's Remsima and Hospira's Inflectra, which both contain the same substance, infliximab, and are versions of Johnson & Johnson/Merck's Remicade. The products will be marketed under a partnership deal between Celltrion and Hospira.

BIOSIMILAR PRICING ISSUES

The use of biosimilars is encouraged by their inclusion in the German reference pricing system, which for many years has governed generic medicines uptake. Under this system, a maximum reimbursement threshold is set for each defined group of products (excluding drugs deemed to be innovative). This can be a mixed blessing for generics firms; however, the industry has said that biosimilars should not become part of the fixed reference pricing system before they have gained a robust market share (Müller, 2013). Indeed, the reference pricing system has meant that there are currently no differences between biosimilar epoetin prices among different manufacturers.

Biosimilars are not subject to the new early benefit assessment procedure that is now applied to innovative drugs in Germany, as they are not considered to be new active substances. As in other EU
countries, automatic pharmacy substitution of biosimilars for originator drugs is not allowed and the choice of product is made by the physician.

So far, biosimilars have tended to enter the German market at about a 30% discount to the originator prices. In some cases originator companies have reduced their prices in order to compete more effectively against biosimilars, and this in turn has led biosimilar manufacturers to lower their own prices even further (see below).

As can be observed in the table below, biosimilar price discounts compared with branded biologics range from 18% to 31%, with some discounts likely to be a result of the brand having to reduce its price due to inclusion in the reference pricing system.

The table also illustrates drug formulary prices of biosimilars against reference biologic products in 2010.
<table>
<thead>
<tr>
<th>Molecule</th>
<th>Product name</th>
<th>Manufacturer</th>
<th>Pack size*</th>
<th>2013 price ($)</th>
<th>Price of biosimilar as a proportion of the branded price (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>filgrastim</td>
<td>Neupogen</td>
<td>Amgen</td>
<td>30m/0.5ml</td>
<td>229</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48m/0.5ml</td>
<td>361</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Filgrastim-Hexal</td>
<td>Novartis (Sandoz)</td>
<td>30m/0.5ml</td>
<td>158</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48m/0.5ml</td>
<td>248</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Nivestim</td>
<td>Hospira</td>
<td>30m/0.5ml</td>
<td>158</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48m/0.5ml</td>
<td>248</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Ratiograstim</td>
<td>Teva [ratiopharm]</td>
<td>30m/0.5ml</td>
<td>158</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48m/0.5ml</td>
<td>248</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Biograstim</td>
<td>CT Arzneimittel</td>
<td>30m/0.5ml</td>
<td>175</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48m/0.5ml</td>
<td>248</td>
<td>69</td>
</tr>
<tr>
<td>epoetin alfa</td>
<td>Erypo</td>
<td>Johnson &amp; Johnson</td>
<td>30,000IU</td>
<td>315</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Binocrit</td>
<td>Novartis (Sandoz)</td>
<td>30,000IU</td>
<td>316</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Abseamed</td>
<td>Medice Arzneimittel Putter</td>
<td>30,000IU</td>
<td>315</td>
<td>100</td>
</tr>
<tr>
<td>epoetin theta</td>
<td>Eporatio</td>
<td>Teva [ratiopharm]</td>
<td>30,000IU</td>
<td>317</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Biopoin</td>
<td>CT Arzneimittel</td>
<td>30,000IU</td>
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<td>epoetin zeta</td>
<td>Silapo</td>
<td>Cell Pharm</td>
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<td>Hospira</td>
<td>30,000IU</td>
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<td>Pfizer</td>
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<td></td>
<td></td>
<td>12mg</td>
<td>942</td>
<td>n/a</td>
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<td></td>
<td>Omnitrope</td>
<td>Novartis (Sandoz)</td>
<td>5mg</td>
<td>321</td>
<td>82</td>
</tr>
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</table>
BIOSIMILAR TENDERING IN THE RETAIL SETTING WOULD RESTRICT PROFIT GROWTH

So far there has been one unsuccessful attempt by the sickness funds (Krankenkassen) to tender for biosimilars. In August 2013, AOK tendered for filgrastim but the tender failed as no manufacturer put in a bid (Bruce, 2013). With contracts guaranteeing a minimum volume over a two-year contract term, biosimilar producers may be more able to offer discounts without denting profits than brand manufacturers. However, there is a risk that some biosimilar producers may be frozen out of the market for two-year periods, potentially delaying the entry of "second wave biosimilars" (ie ones following the launch of an initial biosimilar). Also, as seen within the generics sector, the tendering process would likely lead to intense price competition, which would restrict profit growth of biosimilar manufacturers.

Tendering already occurs in the hospital setting, with hospitals stocking several epoetin drugs, for example. This is for reasons both clinical (providing the option of an alternative in the event that a patient reacts badly to one) and financial (enabling the hospital to play manufacturers off against each other in order to obtain the best price).

PRESCRIBING QUOTAS ARE KEY FOR BIOSIMILARS UPTAKE

Patient access to biosimilars in Germany varies widely by region, depending on factors such as physician prescribing practices and the level of incentives from regional sickness funds, including prescribing quotas. For epoetin, for example, where quotas are widely used, biosimilars accounted for 69% of the market by volume in the northern Bremen area, but for just 16% in Saarland in the southwest of the country (Müller, 2013).

However, the development of the biosimilars market in the short term has become less certain after negotiations between health insurers and doctors failed to reach agreement on prescribing quotas at
the end of 2012. While they acknowledged that biosimilars offered significant savings potential, neither the payers nor the prescribers were willing to raise the obligatory prescribing quotas for 2013 (Europharmatoday, 2013). However, it has been reported that new biosimilars rules, designed to boost their uptake, will be introduced in Germany soon, and both tenders and prescribing quotas are expected to be used (Bruce, 2013).

The R&D-based industry body, the Verband Forschender Arzneimittelhersteller (VFA), is understandably opposed to the use of quotas, saying that the decision to prescribe a drug must always remain with the doctor and must be primarily based on medical considerations. Quota requirements ignore the differences between original products and biosimilars and deprive physicians of part of their medical decision-making freedom, "and shift the decision-making focus from medical to putative economic aspects" (VFA, 2012).

**Biosimilars approved in the EU**

As of October 2013, 14 biosimilar products, containing a total of three active ingredients – somatropin, granulocyte colony-stimulating factor (G-CSF), and epoetin – had active marketing authorizations in the EU. In all, 16 authorizations have been issued, but two of these – Teva's filgrastim ratiopharm and BioPartners' Valtropin (somatropin) – were subsequently withdrawn. In addition, another was rejected.

The table below summarizes biosimilars that have been approved, rejected, or withdrawn in the EU up to October 2013.
### Table 5: Biosimilars approved, withdrawn, and rejected in the EU, up to October 2013

<table>
<thead>
<tr>
<th>Reference product</th>
<th>Molecule</th>
<th>Biosimilar</th>
<th>Manufacturer</th>
<th>Marketing approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approvals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neupogen</td>
<td>filgrastim</td>
<td>Nivestim</td>
<td>Hospira</td>
<td>June 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zarzio</td>
<td>Sandoz</td>
<td>February 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Filgrastim-Hexal</td>
<td>Sandoz</td>
<td>February 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ratiogranstim</td>
<td>Teva (ratiopharm)</td>
<td>July 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Filgrastim-ratiopharm</td>
<td>Teva (ratiopharm)</td>
<td>July 2008*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tevagranstim</td>
<td>Teva</td>
<td>July 2008</td>
</tr>
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<td></td>
<td></td>
<td>Biogranstim</td>
<td>CT Arzneimittel</td>
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</tr>
<tr>
<td>Eprex</td>
<td>epoetin zeta</td>
<td>Silapo</td>
<td>Stada</td>
<td>December 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retacrit</td>
<td>Hospira</td>
<td>December 2007</td>
</tr>
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<td></td>
<td>epoetin alfa</td>
<td>Binocrit</td>
<td>Sandoz</td>
<td>August 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epoetin alfa-Hexal</td>
<td>Hexal</td>
<td>August 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abseamed</td>
<td>Medice Arzneimittel Pütter</td>
<td>August 2007</td>
</tr>
<tr>
<td>Humatrope</td>
<td>somatropin</td>
<td>Valtropin*</td>
<td>BioPartners</td>
<td>August 2006</td>
</tr>
<tr>
<td>Genotropin</td>
<td>somatropin</td>
<td>Omnitrope</td>
<td>Sandoz</td>
<td>April 2006</td>
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<td><strong>Refusals/withdrawal of MA application</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Avonex</td>
<td>interferon beta 1a</td>
<td>Biferonex**</td>
<td>BioPartners</td>
<td>n/a</td>
</tr>
<tr>
<td>Humulin</td>
<td>insulin</td>
<td>Insulin**</td>
<td>Marvel</td>
<td>n/a</td>
</tr>
<tr>
<td>Roferon A</td>
<td>interferon alfa 2a</td>
<td>Alpheon***</td>
<td>BioPartners</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Standalone approvals (non-biosimilar)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eprex</td>
<td>epoetin theta</td>
<td>Eporatio</td>
<td>Teva (ratiopharm)</td>
<td>October 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopoin</td>
<td>Teva (ratiopharm/CT Arzneimittel)</td>
<td>October 2009</td>
</tr>
</tbody>
</table>

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As shown in the table above, in 2009 the European Medicines Agency (EMA) granted marketing authorizations for a novel CHO cell-derived rhEPO, epoetin theta, which was developed by Merckle Biotec (Ulm, Germany) using epoetin beta as a comparator. However, epoetin theta is not a biosimilar but has been developed as a standalone product (NCBI, 2011). Ratiopharm received marketing authorization for Eporatio and Biopoin, but subsequently informed the EMA that it was withdrawing its application for a third product, Ratioepo, for administrative reasons (EMA, 2010a).

As of July 2013, when the EMA issued its approval recommendation for biosimilar infliximab, three other biosimilars were under review by the EMA; one containing filgrastim, and two containing follitropin alfa.

**UPTAKE OF BIOSIMILARS IN GERMANY**

**BIOSIMILAR EPOETIN**

Epoetin is used to treat severe anemia associated with kidney failure or chemotherapy, with Eprex/Erypo (epoetin alfa; Johnson & Johnson), Aranesp (darbepoetin alfa; Amgen), and NeoRecormon (epoetin beta; Roche) dominating the German market. The patent on epoetin expired in 2004 in Europe and has led to a number of biosimilar approvals there, including biosimilar versions of epoetin alfa and epoetin zeta. However, immunogenicity concerns – specifically the association with pure red cell aplasia (PRCA) – will be a concern with biosimilar epoetin products and will need to be addressed, most likely in the post-marketing phase because of the rarity of the side effect (EMA, 2010b).

There is some evidence that the use of biosimilar epoetin is able to bring down the costs of prescribing. A 2012 study of the use of biosimilar epoetin in managing chemotherapy-induced anemia in cancer patients, covering five countries (France, Germany, Italy, Spain, and the UK), found substantial savings with the biosimilars compared with the originator products. The study evaluated the comparative cost-efficiency of epoetin alfa (originator product Eprex and the biosimilar Binocrit),
epoetin beta (NeoRecormon), and darbepoetin alfa (Aranesp). Under weight-based dosing, the average cost of biosimilar epoetin alfa treatment across the five countries was €4,726 ($6,074), compared with €5,484 ($7,048) for originator epoetin alfa, €5,652 ($7,264) for epoetin beta, and €8,465 ($10,886) for darbepoetin alfa (NCBI, 2012). The following epoetin biosimilars have entered the German market:

- Epoetin alfa biosimilars – Epoetin Alfa Hexal, Abseamed (Medice Arzneimittel Putter), and Binocrit (Sandoz), all of which were launched in Q4 2007.

- Epoetin zeta biosimilars – Silapo (Stada) and Retacrit (Hospira), which entered the market in Q1 2008.

Uptake of biosimilar epoetin has been strong in Germany, spurred principally by the use of regional prescribing quotas, which have been a critical driver of biosimilar usage. Biosimilar prescribing has also been encouraged by the health insurance funds, which engage with physicians by way of seminars and "Dear Doctor" letters to help build their confidence in the biosimilar concept, in combination with drug utilization studies. One regional health insurance fund wrote to doctors outlining a biosimilar quota of 60%+ for biosimilar epoetin prescribing, for example (Walsh, 2013).

In the third quarter of 2009, biosimilars accounted for about 37% of the German epoetin market by value (including products marketed by Sandoz, Hexal, Hospira, Medici, Teva/ratiopharm, and CT Arzneimittel). By the third quarter of 2012, this share had risen to 57%, with the value shares of the originator products from Roche and Johnson & Johnson standing at just over 20% each (Walsh, 2013). Meanwhile, ProGenerika reported that biosimilar epoetin held a 77.5% share of the epoetin market by DDDS in 2012, with a corresponding 75.6% value share (using prices after mandatory rebate and pharmacist discounts) (ProGenerika, 2012).

However, the launch of biosimilar epoetin led to something of a price war. Following the creation of a fixed reference price group in 2007, three biosimilar products entered the market later that year at 30% below the originator price. The originator then reduced its price, followed by further price cuts by the biosimilar manufacturers, and then again by one of the originators (OHE, 2010).

BIOSIMILAR FILGRASTIM

Granulocyte colony-stimulating factor (G-CSF) is used to treat neutropenia (white blood cell deficiency) in patients undergoing chemotherapy. Both lenograstim and filgrastim are short-acting GCSFs which must be taken daily (either by subcutaneous injection or intravenous infusion) for up to two weeks after each chemotherapy cycle. This compares with the longer-acting Neulasta (pegfilgrastim; Amgen), which is required just once per cycle. Filgrastim, however, represents the "best case scenario" biosimilar, being a small (175 amino acids), simple biologic which lacks complex post-translational modification, while it also has a good safety profile.

Penetration rates for biosimilar G-CSF in Germany have been below the EU average, reaching just 59% of the daily G-CSF market by volume (standard units) as of February 2013, compared with the EU average of 71% (Walsh, 2013). ProGenerika on the other hand reported a 64.5% uptake in terms of
DDDs in 2012, as well as 60.4% value uptake (using prices after mandatory rebate and pharmacist discounts) (ProGenerika, 2012). Here again there are significant differences in biosimilar volume penetration in the German regions, varying from 68.9% in Thuringia to 29.4% in Saarland (Müller, 2013).

BIOSIMILAR SOMATROPIN

Somatropin is used to correct growth hormone deficiency in children and adults. A number of branded versions of the drug are available in Germany, although the market is dominated by Genotropin (Pfizer). Dosing is weight-dependent, and must therefore be adjusted throughout the average six years of treatment. Somatropin is one of the simplest biologic drugs and has an established safety profile, rendering the biosimilars of this class considerably less risky to produce than more complex biologics. Biosimilar development and characterization is therefore straightforward.

However, the human growth hormone market is a small and saturated one with a largely pediatric patient population, and ease of administration and physician trust rather than cost are particularly important.

Two biosimilar growth hormones, Sandoz’s Omnitrope and BioPartners’ Valtropin, have received marketing authorization in Europe, although one of them, Valtropin, was later withdrawn for commercial reasons, having been only briefly on the German market in the first half of 2009 (EMA, 2012). There is much to suggest that Omnitrope was something of a “proof-of-principle” for Sandoz, designed to demonstrate the company’s biosimilar credentials rather than as a serious commercial enterprise, and served the additional purpose of driving forward the approval pathway.

Sandoz launched Omnitrope in Q2 2006 in Germany, but the product has since struggled to capture market share from the reference product, Pfizer’s Genotropin, and the uptake of biosimilar growth hormone has been marginal (Müller, 2013). As in other EU countries, the low uptake is largely due to physician reluctance to use it in view of the time growth hormone takes to exert its effects, and factors such as the delivery device and convenience.

BRANDED MONOCLONAL ANTIBODY THERAPIES FACE IMMINENT BIOSIMILAR COMPETITION

The next big event on the biosimilars front is the prospect of biosimilar monoclonal antibodies (MAbs). Unlike first-generation biologic drugs, whose market shares are either stagnant or declining, MAb therapies represent a high-value proposition for biosimilars manufacturers, with the branded versions commanding high prices and large market shares.

The costs of treating cancer and immune-related diseases will grow in line with epidemiological trends, providing payers with a strong incentive to drive uptake of biosimilar MABs as aggressively as they dare. However, while the biosimilars currently on the market are gradually gaining acceptance among the physician community, barring the occurrence of any significant safety issues, MAbs represent a harder sell. The large size and complex nature of MAbs relative to older biologics means that demonstrating similarity becomes more difficult, with antibody structural complexity, functional uncertainty, and limitations in analytical technology all contributing to the numerous obstacles to
development, approval, and commercialization.

While the primary amino-acid sequence must necessarily be identical between the biosimilar MAb and its reference product, the degree of similarity in protein conformation and post-translational modification has yet to be established. Moreover, the multiple active sites of MAbs mean that the potential to extrapolate safety and efficacy data from one indication to another becomes clouded, especially so in cases where the mechanism of action is incompletely understood (Schofield, 2009).

Nevertheless, despite the difficulties associated with commercializing biosimilar MAbs, there is evidence to suggest that most of the current biosimilars players are intending to enter the arena, as are numerous originator companies.

The first worldwide approval – under official guidelines – of a biosimilar MAb occurred in 2012, when South Korea authorized Celltrion’s Remsima, a version of Johnson & Johnson/Merck & Co’s Remicade (infliximab) (Haydock, 2012).

Now, in Germany and the rest of the EU, the marketing of biosimilar infliximab is in prospect following the marketing authorization of Celltrion’s Remsima and Hospira’s Inflectra by the EMA in September 2013. However, the launch of Remsima/Inflectra is likely to be delayed in the EU after Remicade obtained a six-month extension to its supplementary protection certificate, stretching its effective patent protection to spring 2014 (Schofield, 2013).

Crucially, the EMA decided to extrapolate the use of Remsima/Inflectra from rheumatoid arthritis to the other indications held by Remicade. This suggests that extrapolation of indications is regarded by the EU authorities as acceptable, even for complex molecules such as MAbs. It represents a significant positive move for biosimilars, and a negative signal for innovators, as it sets a precedent for many other originator MAbs that have been approved for multiple indications such as Roche’s Avastin (bevacizumab) and Herceptin (trastuzumab); AbbVie’s anti-tumor necrosis factor (TNF) competitor to Remicade, Humira (adalimumab); Roche/Biogen Idec’s cancer and rheumatoid arthritis product Rituxan (rituximab); and Merck Serono/Bristol-Myers Squibb’s anticancer Erbitux (cetuximab) (Malone, 2013).

It is unlikely that German reference pricing for infliximab will be triggered before the biosimilar has reached a market share of 20%, and for now Remicade is probably the only branded anti-TNF product at risk of being referenced to the biosimilar price. AbbVie’s Humira, which addresses the same market, will not be brought into the reference pricing system until its own biosimilars reach the market, possibly in 2018/19 (Malone, 2013).

Generally speaking, the higher costs associated with MAb development will probably translate into a more moderate discount to the brand price than the 30–40% that is typical for biosimilars currently on the market. Nonetheless, the potential savings derived from biosimilar MAb use will be substantial owing to the high cost of the originator products, ultimately driving uptake in the face of opposition from certain brand firms.
EMA BIOSIMILAR MAB GUIDELINES FINALIZED

The development of biosimilar MAbs in the EU is covered in the final guidelines issued by the EMA in June 2012 (EMA, 2012). The main points of the guidelines are:

- Pharmacokinetic properties will form a significant part of the application proposal with a comparison of the properties of the biosimilar to the reference product.

- Randomized, parallel-group comparative trials should be used to demonstrate similar clinical efficacy. In addition, a homogeneous population group should be used in order that clinical efficacy can be demonstrated. Patients from non-EU countries may be included, though evidence of efficacy and safety of the reference product in that region should be demonstrated in order to define an equivalence margin.

- The same safety parameters as were used by the reference product in its development should be applied to the biosimilar MAb. Special attention should be paid to comparing the type, severity, and frequency of adverse reactions between the biosimilar and the reference MAb.

- Extrapolation of safety and efficacy data to other indications of the reference drug may be possible based on overall evidence of comparability, with adequate justification. One set of studies may be required, whereas for two very different indications, more than one set of studies will be required. In addition, immunogenicity studies should be conducted for each indication. An accompanying guideline explores immunogenicity in more detail.

- An extensive pharmacovigilance and risk management plan should be put in place in line with current EU legislation, with risk-minimization measures where appropriate. These plans will probably exceed routine pharmacovigilance requirements and may need to involve more proactive activities such as registries or population databases.

While the new guideline will show the way to prospective developers of biosimilar MAbs, the products are complex to develop and the cost of doing so is likely to be high, limiting the number of entrants to the biosimilar MAb market. However, a bonus for biosimilar MAb producers is that non-EU patients may be included in clinical trials (Schofield, 2010). This means that in principle data from clinical trials in the US and India, for example, could be used as part of the approval package in the EU, which would significantly reduce the costs of development.

The figure below outlines the major drivers and resistors to biosimilar MAb entry in Germany.
Bibliography


