DRUG SPENDING AND THE UNSUSTAINABLE HEALTH SYSTEM

The United States has one of the most expensive health care systems in the world. Annual health care cost in 2019 was almost $11,100 per person, representing some 17% of the US national income. The Organisation for Economic Co-operation and Development average cost per patient was around $5500, less than half of that in the United States. Higher health care spending can be beneficial if it results in better health outcomes. However, that is not consistently the case in the United States. Despite significantly higher health care spending, America’s health outcomes are generally not better than those in other developed countries. The United States actually performs worse in some common health metrics, such as life expectancy, infant mortality, and unmanaged diabetes.1,2

US spending on prescription drugs has risen substantially in the past 20 years, climbing from about $88 billion in 1998 to $335 billion in 2018. According to projections of the Centers for Medicare and Medicaid Services, this spending will continue to grow, rising to $560 billion by 2028—an increase of 67%. That rise in drug spending can be attributed to multiple factors, including the number and type of drugs prescribed. Some common reasons include the following:3

- High and rising prices for brand-name drugs: their price index has risen by 60% during a 5-year period between 2014 and 2019
- A lack of competition with generic and biosimilar alternatives due to the US patent system
- The use and cost of specialty drugs
- A lack of transparency in drug prices

A major driver of this growth has been the use of high-priced biological medicines. Spending on biologicals—representing 43% of the total drug bill in 2019—is among the fastest rising drug categories (almost 15% each year during the past 5 years), placing substantial strain on the US health care system.3

BIOSIMILARS IN THE UNITED STATES

With expiring patents and other market exclusivities, there is opportunity for off-patent versions of expensive biological medicines to enter the market, potentially offering better access and savings for health care systems and patients. It is now 15 years ago that the first biosimilar was introduced in Europe (2006), introducing competition in the segment of off-patent biological medicines. In the United States, the first biosimilar was approved almost 10 years later (2015). From the 33 products that have been licensed in the United States between 2015 and 2022 by the US Food and Drug Administration (FDA), only 21 are currently available on the market.3 Almost one-third of FDA-approved biosimilar products are not yet on the market, and the ones that are cluster among 8 reference products.3 In contrast, in Europe, more than 70 biosimilars are available for 17 distinct reference products.6 The Table provides an overview of European Union— and US—approved biosimilars (status: January 2022).

Biosimilar market entry and competition have so far been of muted success in the United States. As such, the benefits of biosimilar competition, lower prices and greater access to important biological medicines, have not yet materialized for American patients. The reasons for this are multifactorial and include among others the strong influence of innovative industry on law-making, physician uncertainty about the safety and efficacy of biosimilars compared with their reference product, complex litigation processes, and large...
numbers of patents enforced by originator manufacturers. \(^{9-12}\)

In this issue, Jensen et al\(^ {13}\) write euphemistically: “unique operational hurdles associated with the adoption of biosimilars pose challenges that have slowed the process in the US market.”

THE EUROPEAN BIOSIMILAR LANDSCAPE

In Europe, a solid regulatory pathway for biosimilars was already established in 2004, and in 2006, the first biosimilar was approved (growth hormone somatropin, Omnitrope).\(^ {7}\) Since then, more than 70 biosimilars, based on 17 reference products, have been approved and made subsequently available on the market (Table).\(^ {6}\)

In a recent IQVIA report, it was calculated that in Europe, biosimilar competition has led to around 5% savings on the overall European drug bill based on official list prices (and estimated some 5% to 10% more when taking into account—confidential—negotiated rebates and discounts).\(^ {14}\) However, these savings are not realized in all European countries. Uptake of and competition from biosimilars in Europe are highly variable and dependent not only on country or region but also on the product (due to differences in dispensing context, product complexity, and therapeutic speciality). Whereas in some countries, biosimilar competition remains poor, in others, it has led to price reductions of 75% up to even more than 90%, for both biosimilars and reference products.\(^ {14}\)

Extensive research from our group has elicited 5 key principles to support successful biosimilar adoption in clinical practice\(^ {15-19}\):

1. Apply a multistakeholder approach. Make sure that all players in the drug chain are involved, are properly educated, and collaborate toward the same goal.
2. Communicate following a 1-voice principle to avoid a nocebo effect when

<table>
<thead>
<tr>
<th>Drug (international nonproprietary name)</th>
<th>Brand name originator</th>
<th>EMA-approved and launched biosimilars</th>
<th>FDA-approved biosimilars</th>
<th>US marketed biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td>11</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Avastin</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Clexane</td>
<td>1(^ {b})</td>
<td>0(^ {b})</td>
<td>0</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Eprex</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Follitropin alfa</td>
<td>Gonal-f</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>NovoRapid</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Humalog</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Neulasta</td>
<td>9</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Ranibizumab</td>
<td>Lucentis</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rituximab IV</td>
<td>MabThera/ Rituxan</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Somatropin</td>
<td>Genotropin</td>
<td>1</td>
<td>0(^ {b})</td>
<td>0</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Forsteo</td>
<td>4</td>
<td>0(^ {b})</td>
<td>0</td>
</tr>
<tr>
<td>Trastuzumab IV</td>
<td>Herceptin</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>73</strong></td>
<td><strong>33</strong></td>
<td><strong>21</strong></td>
</tr>
</tbody>
</table>

\(^ {a}\)EMA, European Medicines Agency; FDA, Food and Drug Administration.

\(^ {b}\)In the United States and European Union, more products are licensed through other pathways.\(^ {7,8}\)
switching patients from reference product to biosimilar.

3. Inform the patient properly: the treatment is initiated or continued with an equally effective and safe alternative.

4. Compensate health care professionals for their time and effort associated with switching patients.

5. Report transparently about the savings generated from introducing biosimilars and the allocation of savings within the health system.

ARE THESE BIOSIMILAR IMPLEMENTATION PRINCIPLES UNIVERSAL? THE MAYO CLINIC EXPERIENCE

In this issue of Mayo Clinic Proceedings, a multidisciplinary team from Mayo Clinic report on how they organized the implementation of biosimilars throughout their organization. Jensen et al\textsuperscript{13} started their biosimilar implementation strategy by aligning health care professionals through multidisciplinary team formation and selecting formulary-preferred biosimilars. Next, a therapeutic interchange protocol was developed, allowing a smooth product exchange by the pharmacist. By doing so, they strengthened formulary compliance and reduced prescriber burden. This was further reinforced by making the formulary-preferred biosimilars also the default option in the electronic prescribing system. The team disentangled the complicated relationship between different, mainly profit-driven stakeholders in the market and used behavioral economics principles (like facilitating prescribing formulary-preferred biologicals in hospital software) to bend the curve. From that perspective, the paper by the pharmacists from the Mayo Clinic is exemplar on how a determined multidisciplinary team together with a well-organized plan can drive successful biosimilar implementation in practice.

To determine whether this biosimilar implementation strategy increased the use of formulary-preferred contracted biosimilars, the authors made a comparison in units and expenditure before and after this formulary change. Six months after introduction of the intervention, uptake of the preferred choices was strong at around 60% to 80%, and a considerable cost reduction of approximately 25% (totaling $23 million in savings) 12 months after implementation was reported to have been achieved.

 Whereas substantial savings were attained, patient access did at large not increase (see their Table 3). The authors explain that this may be due to overall decreased clinical activity because of the COVID-19 pandemic. The negative impact that COVID-19 had on biological prescribing was also observed in Europe and reported in the IQVIA 2021 biosimilar competition report.\textsuperscript{20} With clinical activities returning to normal, it may be expected that a double win may become visible: more patients treated for less money.

It may also be expected that by strengthening the buying power, larger discounts can be negotiated, thereby further benefitting patients. Besides the competitiveness of the product’s price, other criteria may also be valuable to take into account, such as supply conditions or product administration device, when selecting 1 or multiple preferred products for the formulary.\textsuperscript{21} The FDA has deployed large educational efforts to promote the use of biosimilars. It may well be that this kind of multidisciplinary action from within the health system may be key to making biosimilars also a success for patients in the United States.

CONCLUSION

The article by Jensen et al in this issue of the Journal is a valuable exemplary paper that indicates how hospital systems with a multistakeholder approach can make important headway in the biosimilar deadlock in the United States, making biological treatments more affordable and accessible to patients. Their approach deserves support and following by similar teams in other health systems in the United States and beyond.
REFERENCES


2. Peter G. Peterson Foundation. Spending on prescription drugs has been growing exponentially over the past few decades. Accessed April 8, 2022. https://www.pgpf.org/infographic/spending-on-prescription-drugs-has-been-growing-exponentially-over-the-last-few-decades


20. IQVIA. The Impact of Biosimilar Competition in Europe 2021


POTENTIAL COMPETING INTERESTS

A.G.V. is one of the founders of the KU Leuven Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL Fund). He is involved in consulting, advisory work and speaking engagements for a number of companies, i.e., AbbVie, Accord, Amgen, Biogen, Medicines for Europe, Pfizer/Hospira, Mundipharma, Roche, Novartis, Sandoz, Boehringer Ingelheim. L.B. and A.G.V. declare that the commentary was conducted in the absence of any commercial or financial relationship that could be perceived as a potential conflict of interest.

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