Subject: US FDA Advisory Committee Meeting – Docket FDA-2017-N-2732

Date: 26 June 2017 (FINAL)

Deadline: 26 June 2017

Contact Person: Julie Maréchal-Jamil, Director Biosimilars Policy & Science
jmarechal@medicinesforeurope.com

Introduction

- We welcome the opportunity to provide comments at this FDA Oncologic Drugs Advisory Committee meeting based on our considerable experience with 30 approved biosimilar medicines in Europe.
- Medicines for Europe is the trade association representing generic, biosimilar and value added medicines manufacturers across Europe. Our European Biosimilar Medicines Group, a Medicines for Europe sector group, represents the manufacturers of biosimilar medicines in Europe. Our association is a recognized industry stakeholder with the European Medicines Agency, the European Commission, and the World Health Organization. Our association is fully registered under the European Union (EU) Transparency Register as a trade association.
- The European experience with biosimilar medicines can be highly relevant to the US. Our legislative scheme for biosimilar medicines pre-dates the biosimilar approval laws in the U.S. by about a decade. Close to 9 in 10 biosimilar medicines sales (in USD) worldwide were dispensed in Europe in 2016[1]. We also have comparable oversight mechanisms that assure that were there any problems in the safety, efficacy or quality of these medicines we would have caught them.
- Cumulatively, we can offer a wealth of data with 700 million patient days of clinical experience and confirming the safety, efficacy and quality of authorised biosimilar medicines and show their contribution to improvements in access to cost-effective therapy in Europe.

Extensive, Safe and Conclusive Experience

Europe represents 87% of the global biosimilar medicines sales (in USD value) and collectively has over 10 years of safe experience with clinical use of biosimilar medicines. There are 30 medicines approved as biosimilar medicines in Europe encompassing 12 reference products, and spanning a broad number of therapeutic areas and indications[2].

- With the number of EU biosimilar medicines launched to date in up to 80 countries around the world, including the EU, we estimate that collectively our experience comprised some 700 million patient days of treatment with EU biosimilar medicines so far.

[1] IMS Health MIDAS MAT Q4 2016; Europe does not include Russia and Turkey

[2] EMA Biosimilar medicines approvals (Centralised procedure) are available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit , accessed 26 June 2017; biosimilar medicines approvals (Decentralised procedure) are available at: http://mri.cts-mrp.eu/Human/, 26 accessed June 2017

- Authorised biosimilar medicines have behaved as expected by the regulators. We have seen no unusual or unexpected adverse events with biosimilar medicines in Europe (recognizing that the profiles of biosimilar medicines in practice must always be expected to match those of the originator products used for reference).
- Dr. Guido Rasi, Director of the European Medicines Agency (EMA), the scientific body in charge of the biological medicines review process, recently confirmed that for the 29 biosimilar medicines authorised to date, "the EU monitoring system for safety concerns has not identified any relevant difference […] between biosimilars and their reference medicines"[3]. This confirms that we can have full confidence in the EU regulatory system and its ability to safeguard public health for biosimilar medicines, just as we do for all other medicines reviewed and approved in the EU by either the EMA/European Commission (EC) (Centralised procedure) or EU Member States (Decentralised procedure).
- The accumulated experience with the real world clinical use of biosimilar medicines allows the EU regulators to go further, and they recently reaffirmed this in a thoughtful paper in the peer-reviewed scientific literature, stating that "on the basis of current knowledge, it is unlikely and very difficult to substantiate that two products, comparable on a population level, would have different safety of efficacy in individual patients […]"[4].

Growing Importance of the Use of Biologic Medicines as the Standard of Care

In the nearly four decades since the first recombinant biotech medicine was approved[5], biologics have transformed the lives of patients suffering from a broad array of serious and debilitating diseases and conditions. They have allowed some disability and disfiguring diseases to become preventable, allowing patients to pursue normal productive lives. This makes access and cost-effectiveness all the more essential, and biosimilar medicines offer this opportunity for biologics:

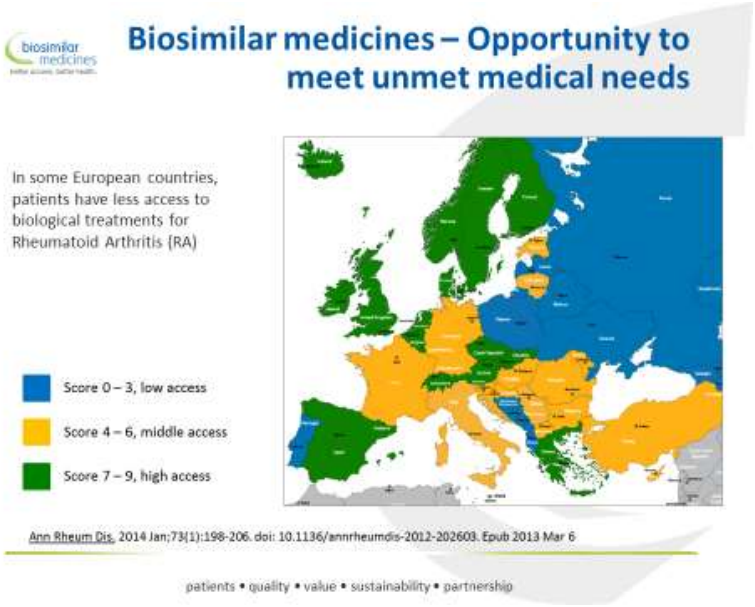
- In the early days, the biologics market accessible for competition was limited to therapy areas representing only around 8% of the total biological market (eg, growth hormone, erythropoietin). However, the emerging biosimilar medicines candidate pipeline will soon encompass around 60% of the total biological market, including important therapy areas such as autoimmune diseases (e.g. infliximab, etanercept), oncology (e.g. rituximab, trastuzumab) and diabetes (e.g. insulin glargine).
- Biosimilar competition can generate significant headroom in pharmaceutical budgets which is generally re-invested into enabling a greater number of patients to have access to essential medicines used as standard of care, new medicines or health services. In Europe, many patients who should receive biological medicines have historically faced restricted access due to their costs. This is the case for

[3] Link to Quote available at: http://www.biopharma-reporter.com/Markets-Regulations/Biosimilars-in-Europe-11-years-28-approvals-0-safety-concerns, accessed June 2017

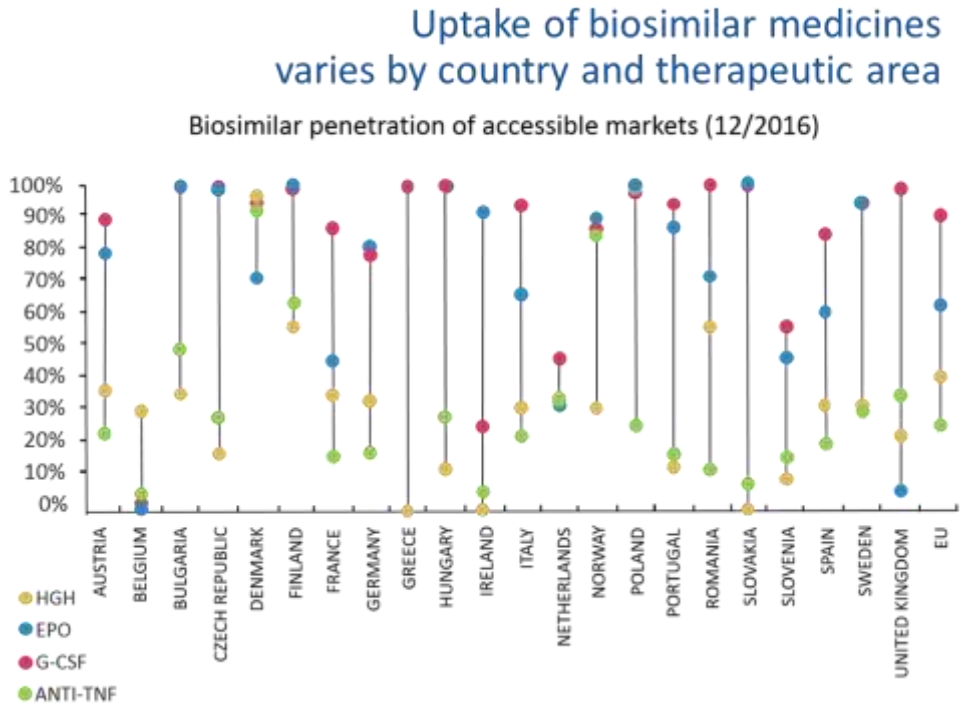
[4] Interchangeability of biosimilars: A European perspective, Kurki et al. 2017 - https://link.springer.com/article/10.1007/s40259-017-0210-0

[5] In 1982, the first synthetic insulin was approved in the EU - https://ec.europa.eu/health/sites/health/files/human-use/50years/docs/50years_pharma_timeline_v3.pdf, accessed June 2017

instance in rheumatology where sub-optimal access to standard of care has been documented.



- We have also experienced the challenges of expanding familiarity with biosimilar medicines amongst stakeholders, especially physicians and patients. Many had not initially realised that all biologics, including biosimilar medicines, approved by the same regulatory authority are safe and effective and made to the same quality standards. Educational efforts continue as the use of biosimilar medicines further evolves.
- Meanwhile, each of the 28 EU Member states is using biosimilar medicines to some extent. The clinical use of biosimilar medicines remains highly variable[Error! Bookmark not defined.] depending on the product, the therapeutic area or the country. This underlines that beyond awareness and education, the proactive design and enforcement of national policies is paramount. Among those, key features are certainly procurement practices and the availability of benefit sharing schemes involving all actors of the healthcare system. Over time the use of biosimilar medicines has increased as familiarity with them has increased and more have become available – including multiple version of biosimilar medicines to the same reference product by different manufacturers (see EMA's list of centrally authorised biosimilar medicines[2]).



- Despite these disparities, a common denominator is that when introduced, biosimilar medicines continue to positively impact patients' access to medicines, particularly in those countries experiencing challenging economic and budget constraints.

Benefits of Biosimilar Medicines Appear Soon After the End of Monopoly for Biologic Therapies

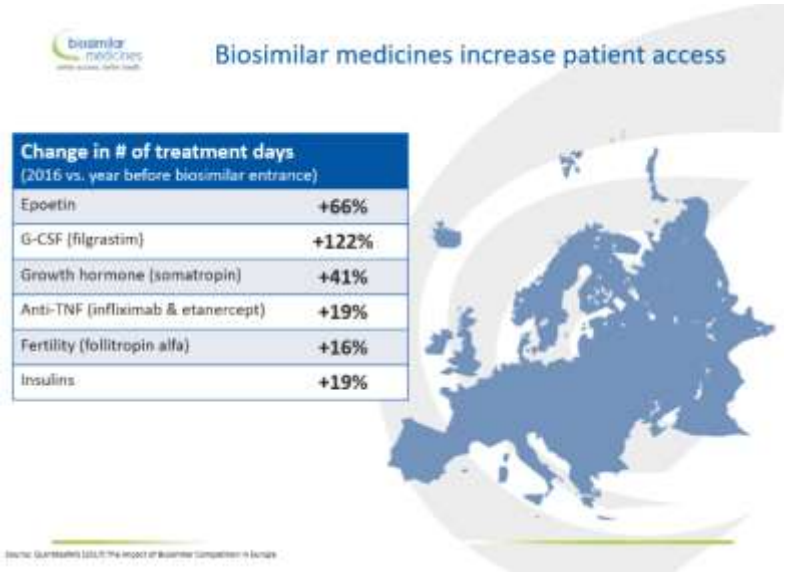
In Europe we have 10 years of marketing exclusivity for all medicines, and a patent system that is comparable to the US. The EMA reviews and approves biosimilar medicines to standards that are largely shared with the US and other highly regulated markets[6], although there are some important distinctions in the governing statutes. The EC approved the first biosimilar medicine in Europe in 2006 and so we have had

[6] Notably ICH and WHO guidelines

the opportunity to gain greater experience than the US whose first biosimilar was approved in 2015. The results are encouraging.

- Biosimilar medicines have shown that they can contribute to a competitive multisource biologics market that in turn significantly increases access to biological medicines in Europe.
- Data analysis of 7 EU Member States[7] (France, Germany, Italy, Spain, UK, Poland and Norway) shows that biosimilar medicines have generated considerable savings over the past years and have therefore alleviated budget constraints.
    - Biosimilar medicines price across markets for epoetin, filgrastim and infliximab indicates the level of price erosion: biosimilar medicines are either priced significantly lower, lower or at the same level as the originator medicine.
    - More importantly, the price change of biosimilar and originator medicines since the launch of the biosimilar medicine for epoetin, filgrastim and infliximab illustrates the impact of competition through the whole product class. The observed significant price erosions on list price level leave a noteworthy gap between the biosimilar and originator prices (note: officially available list prices, not including confidential discounts). For epoetin products, the biosimilar medicine price change was ranging between -24% and -57% while for the originator medicine's price changed in the range -6% to -59%.

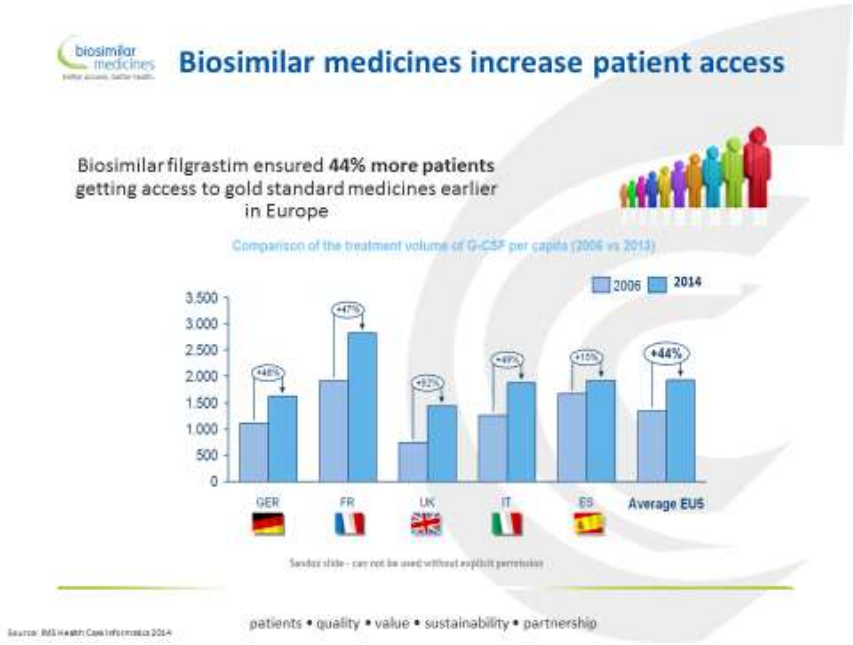
- By enabling savings on those biologics to which biosimilar medicines are available, they free up resources for new originator medicines (biologic or chemical in nature), and so also foster innovation and the "virtuous cycle" in health care. This benefit is most pronounced for the biosimilar medicines which have been on the European market the longest (epoetin, filgrastim, somatropin) but it is also becoming clear for the more recently launched biosimilar medicines (infliximab, etanercept, follitropin alfa, insulin glargine) data[8].



[7] Payers' price & market access policies supporting a sustainable biosimilar medicines market, Simon Kucher & Partner, 2016 - http://www.medicinesforeurope.com/wp-content/uploads/2016/09/Simon-Kucher-2016-Policy-requirements-for-a-sustainable-biosimilar-market-FINAL-report_for-publication.pdf, accessed June 2017

[8] The impact of Biosimilars Competition, QuintilesIMS May 2017 - http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf

- The availability of biosimilar filgrastim has triggered an average of 44% increase in the EU5 in the number of patients treated. This is enabled because of the increase in the cost-effectiveness for this treatment.



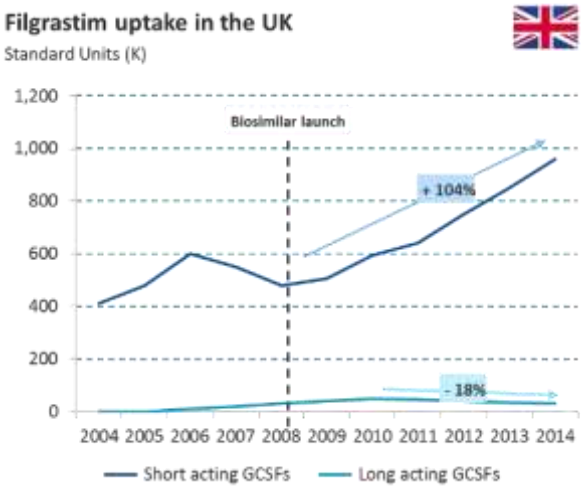
Benefit of Earlier Access to Treatment is Better Care

Often a delay in treatment results in poor outcomes for the patient. Hence, the ability to start treatment earlier can be very important to the value of that treatment to the patient, but also to the health care system as a whole as an economic matter. Below are a set of examples illustrating how the improvement of the cost-effectiveness of treatment was improved through the introduction of biosimilar medicines and how individual countries have changed their practices and re-invested the savings into better care.

- After the launch of biosimilar filgrastim (also referred to as G-CSF[9]) in the United Kingdom (UK) in 2008, the National Institute for Health and Care Excellence (NICE) guidelines were updated to reflect the improved cost-effectiveness of biosimilar filgrastim vs. alternative treatments[10]. As a result, filgrastim restrictions were relaxed and use recommended for primary prophylaxis of neutropenia. Previously, common practice was to limit use to secondary prophylaxis only. As a consequence, overall consumption of filgrastim short-acting increased by 104% between 2009 and 2014. The launch of biosimilar filgastim therefore also led to improved patient outcomes, by enabling greater numbers of patients to access these treatments at an earlier stage of the therapy cycle.

[9] G-CSF: granulocyte-colony stimulating factor. "Recombinant G-CSF (rhG-CSF) produced in E. coli (filgrastim, not glycosylated) and CHO cells (lenograstim, glycosylated) are in clinical use. So far, only biosimilar filgrastim products have been applied for and licensed." – EMA Concept paper on the revision of the guideline on non- clinical and clinical development of similar biological medicinal products containing recombinant granulocyte- colony stimulating factor - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/07/WC500190635.pdf, accessed June 2017

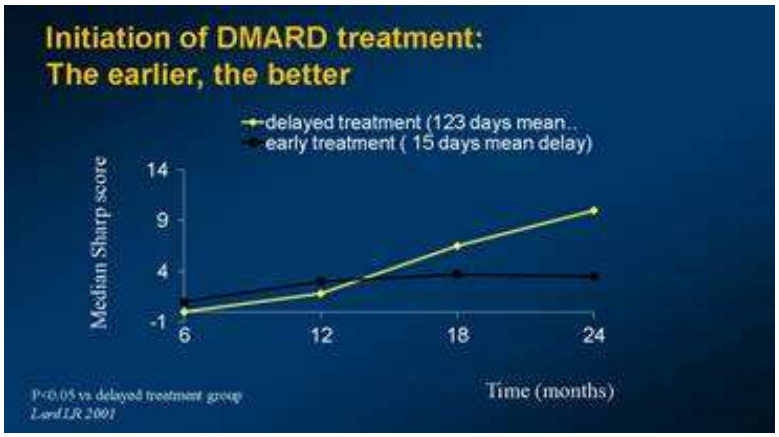
[10] NICE guidelines, www.NICE.org.uk



- A similar example was reported in Sweden where the requirement to have the opinion / formal approval of three physicians before the initiation of the treatment with filgrastim was waived after the introduction of the filgrastim biosimilars based on revised cost-effectiveness of the treatment. This led to a 5-fold increase in the clinical use of G-CSF in the Southern Healthcare Region.
- For both infliximab and epoetin, revisions to the UK NICE guidance was introduced after the biosimilar medicines were launched. For infliximab, a use in a new indication was introduced: the 2015 guidance recommends the use of infliximab biosimilar medicines in adults with non-radiographic axial spondyloarthitis whereas it was previously not used at all. For epoetin, the increased cost-effectiveness led to the authorisation for use in cancer treatment-induced anaemia. The effectiveness was previously recognised however the treatment was not considered cost-effective with solely the originator medicine available.
- In therapeutic areas like rheumatology[11] and cancer, beyond the lack of access, delayed access is well known to negatively the prognosis for patients. While the biologics can be very effective in preventing disease progression, later treatment cannot reverse damage already done. These have long term

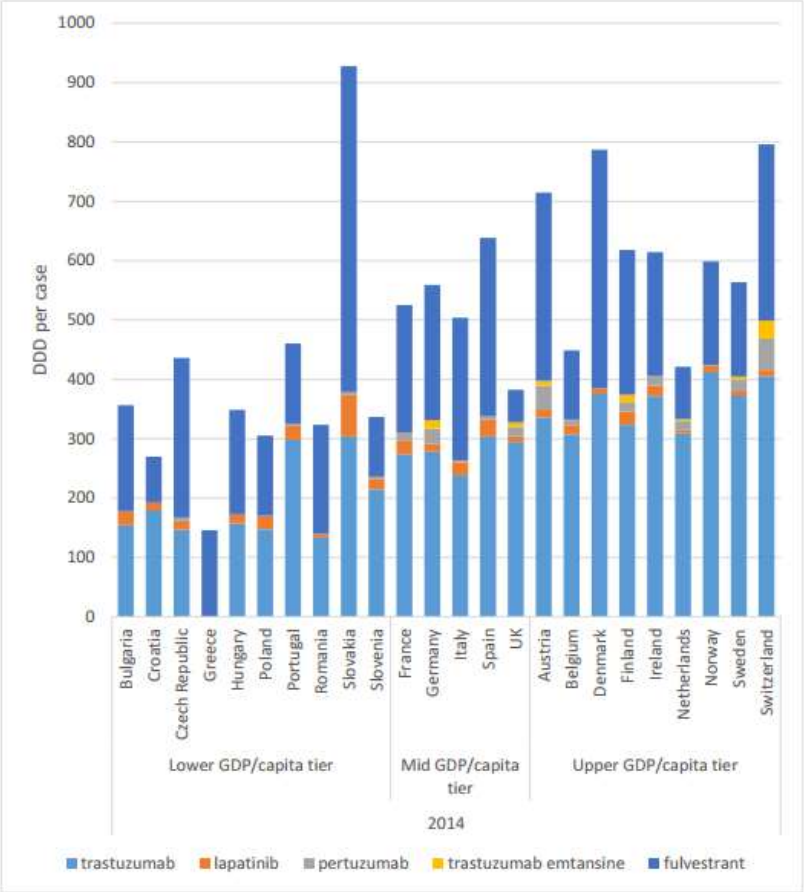
[11] Early versus Delayed Treatment in Patients with Recent-onset Rheumatoid Arthritis: Comparison of Two Cohorts Who Received Different Treatment Strategies, Leroy R. Lard, MD, Henk Visser, MD, Irene Speyer, MD, Irene E. vander Horst-Bruinsma, MD, Aeilko H. Zwinderman, PhD, Ferdinand C. Breedveld, MD, Johanna M.W. Hazes, MD, PhD

consequences. The early use of Disease-modifying anti-rheumatic drugs (DMARDs) have been demonstrated as improving patient outcomes[11] - see below.



- As far as cancer medicines are concerned, including breast cancer medicines, access to the standard of care varies considerably between countries depending on their economic status[12].

- Data shows (see figure) that for breast cancer medicines (targeting HER2+ breast cancer), lower income countries (Growth Domestic Product -GDP/capita) largely correlates with lower (biologic) medicines usage in Defined Daily Dose (DDD – unit defined to standardise the comparison of drug usage between different drugs or by different healthcare environments).



[12] Comparator Report on Patient Access to Cancer Medicines in Europe revisited, 2016, http://lup.lub.lu.se/search/ws/files/11713673/IHE_Report_2016_4_.pdf

- In 2014, patients in Japan, Spain and South Korea had access to fewer than half of the new cancer drugs launched globally in the prior five years[13]. This indicates the important of biosimilar medicines and the opportunities for improvements in care that they offer for more cost-effective treatment options.

Stakeholder engagement, dialogue and Education at the heart of successful biosimilar medicines use

At the heart of the acceptance of biosimilar medicines in Europe is the buy-in by all those most impacted by their availability. It has taken time for this familiarity to increase, but the following are activities that have contributed. These are lesson learned that the US can learn from. Multi-stakeholder engagement and dialogue has been the foundation and success factor of EU policy making on biosimilar medicines at EU level but also at national level. This has been led by a variety of individuals and organisations, public and private at all sizes and levels.

- The European Commission and the European Medicines Agency have undertaken huge stakeholder outreach initiatives which have proven particularly beneficial[14]. These European initiatives have been supported by further similar actions at Member State level.
    - In Germany, the region of Westfallen-Lippen has pro-actively engaged in informing and educating the concerned stakeholders on biosimilar medicines, resulting in increased use of biosimilar medicines compared to the other regions where such educational and outreach programmes did not exist.
- Initiatives, specific to the European and National member states legal and regulatory framework, have contributed to raise awareness and the overall level of understanding of biologics, including biosimilar medicines. It is explained how all medicines are authorised in the EU by those responsible for safeguarding public health using the same standards for all medicines and thereby assuring safe, efficacious and high quality medicines irrespective of the regulatory pathway used.
- Three important European consensus documents have been generated and form a significant resource that is publicly available to help all stakeholders understand what biosimilar medicines are, what opportunity they offer and how they can improve access to care and ensure the sustainability of health systems for the longer term.
    - What you need to know about biosimilars (2013)[15],
    - EC Q&A for patients (2016)[16]
    - Biosimilars in the EU – Guide for Healthcare professionals (2017)[17]

---

[13] IMS Health Finds Global Cancer Drug Spending Crossed $100 Billion Threshold in 2014 (May 2015) http://www.imshealth.com/de_DE/about-us/News-and-Events/ims-health-finds-global-cancer-drug-spending--crossed-$100-billion-threshold-in-2014

[14] EC Directorate General on Internal Market, Industry, Entrepreneurship and SME - Corporate responsibility in the pharmaceutical industry - Platform on Access to Medicines in Europe - Market access for biosimilars - http://ec.europa.eu/growth/sectors/healthcare/competitiveness/corporate-responsibility/

[15] What you need to know about biosimilars (2013) - HTTP://EC.EUROPA.EU/DOCSROOM/DOCUMENTS/20961

[16] EC Q&A for patients (2016)HTTP://EC.EUROPA.EU/DOCSROOM/DOCUMENTS/8242

[17] Biosimilars in the EU – Guide for Healthcare professionals (2017) HTTP://WWW.EMA.EUROPA.EU/DOCS/EN_GB/DOCUMENT_LIBRARY/LEAFLET/2017/05/WC500226648.PDF

- Several Medical Societies and healthcare professional groups[18] have issued positions on biosimilar medicines which increasingly show convergence as understanding and experience increase. This in turn is reinforcing the confidence in the EU system for oversight of medicines as a whole.

Conclusions

The European experience with biosimilar medicines is one of the success stories of better health care access and cost-effectiveness. However it has taken time and a lot of effort by many elements in the healthcare systems of the 28 Member States, as well as centrally. In Europe, we are seeing a growing acknowledgment of the essential role biosimilar medicines have played to date and yet also an awareness of what can be achieved in terms of opportunities to be seized going forward. New biosimilar medicines will continue to offer the opportunity to significantly improve treatment access for millions of patients, helping both longevity and quality of life. Adding to the experience in gastroenterology, rheumatology, dermatology, key biotherapeutic treatments for cancer have become the standard of care over the years. Single source originator products have contributed tremendously to better outcomes. However, the intellectual property (patents and exclusivity) on these products are expiring opening the door to competition. This will also enable reinvestment in the next generation of originator products in the most needed clinical areas as well in needed health services for the patients of today and tomorrow.

It is important to see biosimilar medicines as a natural evolution of the biopharmaceutical landscape for which there already exists a substantially large body of evidence and knowledge at the time of initial approval. The good news is that biosimilar medicines deliver on their promise, offer greater cost-effectiveness and are already well known in health care, and are well understood by our regulatory authorities and stakeholders of the healthcare system.

[18] http://www.medicinesforeurope.com/wp-content/uploads/2017/03/M-Biosimilars-Overview-of-positions-on-physician-led-switching.pdf