Market Access

# Factors Supporting a Sustainable European Biosimilar Medicines Market

## Final Project Report

A study undertaken by GfK Market Access on behalf of the European Biosimilars Group (EBG), a sector group of the EGA, about the future sustainability of the biosimilar medicines market

Prepared for the European Biosimilars Group, a sector group of the European Generic medicines Association (EGA)

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# 1 Executive Summary

Biosimilar medicines provide a major opportunity for cost savings throughout Europe by making a significant contribution to the sustainability of National Healthcare Systems (NHS) whilst improving patient access to innovative medicines in both the short and long term. However, in order to deliver these benefits it is imperative that the biosimilar medicines market remains sustainable.

A sustainable biosimilar medicines market is one which is attractive and delivers continuing benefits to four key stakeholder groups (Physicians, Payers, Patients, and Industry) in both the short and long term. The concepts of "attractiveness" and "benefit" differ amongst stakeholders, but potentially include: opportunities to treat more patients with appropriate therapies (Physicians), cost savings and financial sustainability of healthcare systems (Payers), improved access to medicines (Patients), and a reasonable return on investment with the continued attractiveness of R&D investment in new medicines development (Industry).

Policy development to establish and maintain a sustainable biosimilar medicines market requires holistic understanding of the dynamics of the market from all stakeholder perspectives, common shared understanding amongst all stakeholders of the comprehensive benefits that biosimilar medicines offer, and rational decision-making aligned with this shared understanding.

Policies and approaches in isolation (relating to Pricing, Switching, Substitution, Indication Extrapolation, Evidence Development, Clinical Guidelines, and Biosimilar Assessment & Access Decisions) are important building blocks for a sustainable market. However, it is the effect of policies in combination ("policy collision") that will deliver, or possibly fail to deliver, a sustainable market.

Four elements, considered holistically, provide a "**Sustainability Policy Framework**" for the biosimilar medicines market:

1. Education and Understanding
2. Experience and Use
3. Sustainable Pricing
4. Rational Decision-making


All four elements are required for sustainability. They are synergistic and are not independent of one another. Sustainable pricing policies in the absence of education, understanding, and experience, and rational decision-making in the absence of a differentiated value proposition, will lead to an unsustainable biosimilar medicines market.

## 1.1 Objectives and Scope of Study

- To identify the key policy areas that will drive the establishment of a sustainable biosimilar medicines market
- To develop a clear high-level understanding of the interactions and dynamics within and between policy areas
- To identify a set of policy measures that should be implemented by policy makers (national and European level) and other stakeholders to help drive the growth of the biosimilar medicines market
- To outline the benefits that these will bring, with particular focus on the benefits for European National Health systems (increased savings to the National Health systems whilst treating more patients) and the economy (growth impact and job creation)

The study was undertaken across 7 countries: France, Germany, Hungary, Italy, Poland, Spain, and the UK. Conclusions are based on in-depth contributions from 71 experts and policy influencers at the National and Regional levels (some who influence pan-European policies), and from multiple stakeholder groups - Physicians, Payers, Pharmacists (hospital and retail), Patients, and Industry. As a consequence, the resultant insights reflect the perspectives of multiple stakeholders.

Quantitative modelling was based on 3 representative but significantly different, biologic products (Herceptin®, Avastin® and Humira®) in the EU5, and dynamics were based on a Delphi panel of expert opinions. The five forces of supplier power, buyer power, impact of new entrants, impact of substitute products, and competitive rivalry were addressed. A ranking of the attractiveness of various policy combinations from a sustainability and benefit perspective was made based on a biosimilar medicines market **"Sustainability Index"** (*see chapter 10*) and the calculation of the magnitude of the benefits (cost savings, additional patients treated) that the policy combination was likely to produce.

## 1.2 Sustainability Policy Framework

A European biosimilar medicines industry based on policy alignment within the four elements of the "Sustainability Policy Framework" will be sustainable and deliver significant benefits to all stakeholders. Within each of the elements there are key concepts that must be considered.

**Education and Understanding**

- There is a need for **clear** information from **unbiased** sources, that is non-promotional, targeting doctors, other healthcare professionals, payers and patients
- Stakeholders require an appreciation that **biosimilar medicines are not generic medicines**. The development and manufacturing processes of biosimilar medicines are more complex and much more expensive than of chemical small molecule medicines
- Education is required on the **scientific concept of biosimilar medicines**, their approval process, and their safety and efficacy
- The concept of "Indication Extrapolation", an essential aspect of the biosimilar medicines regulatory pathway, should be clearly **communicated and explained to all stakeholders in a context and language that provides complete understanding and support.**

**Experience and Use**

- Accelerated **experience and uptake of biosimilar medicines** will be important for short term benefit (to payers, physicians, patients, and biosimilar companies) and the long term sustainability of the market and healthcare systems
- Physician (and other stakeholder) **confidence and trust should be established** via encouraging and incentivising appropriate early use, and encouraging the collection and publication of Real World Evidence (RWE) (*see appendix*)
- In the long term, provided that patient benefit is core to the decision, and once confidence and trust have been established, the following approaches would also be supportive of the biosimilar medicines industry sustainability:
    - **The Physician should always be involved in both procurement and utilisation decisions**
    - **Procurement and utilisation policies should be evidence-based and risk-minimised, and evolve to include multi-stakeholder input and agreement:**
        - **Early Use:** predominantly a physician driven decision
        - **Intermediate Use:** physician/pharmacist/payer driven decision (multi-stakeholder approach)
        - **Well Established Use:** predominant pharmacist/payer driven decision
    - **Procurement and utilisation policies should be transparent and multifaceted, not driven by consideration of cost alone**

**Sustainable Pricing**

- Policies that maintain and **encourage competition** favour sustainability
    - It is important to ensure regulation does not create an uneven playing field between biosimilar medicines and the originator product, or between biosimilar medicines themselves, as fair competition requires a level playing field.
- Avoid pricing and procurement policies that drive prices to levels that **threaten the financial viability** of the biosimilar medicines industry and **undermine continued investment** by the pharmaceutical industry in future innovation (R&D). Situations where, in the longer term, all stakeholders eventually lose include:
    - Limited **return on investment** (ROI). Dramatic price reduction will reduce the attractiveness of investment in future biosimilar medicines and consequently threaten the continuity of cost savings and patient access benefits.
    - Negative impact on **innovation.** A lower reference price will reduce the attractiveness for manufacturers to invest in future innovation

**Rational Decision Making**

- Pricing, procurement, positioning, and utilisation decision-making processes of National Healthcare Systems should be **transparent** and should **not delay time to pricing, reimbursement or market access of biosimilar medicines.**
- Pricing approval and market access (including access to National and Regional tenders/procurement processes) should be as close as possible to the date of biosimilar marketing authorisation
- Biosimilar medicines should not require a Health Technology Assessment (HTA) in situations where assessment of the biosimilar medicine is futile and does not add value
    - In situations where an originator (reference) product has not been recommended for reimbursement, or restricted to a conditional recommendation, or patient access has been denied on economic grounds by the HTA body, the policy should not exclude an HTA assessment of the biosimilar medicine if there is reasonable chance that it will be able to demonstrate cost-effectiveness
- Pricing, procurement, positioning and utilisation decision-making should **encourage**:
    - Recognition of the value of differentiated "Product Offerings" (e.g. Drug delivery, Value-Added Services, Point of Care, Dose Strengths)
    - Recognition of the value of outcomes data to Payers (economic), Physicians (clinical), and Patients (disease management)
    - Encourage diferent stakeholders to work together (e.g. Payers co-funding the generation of relevant outcomes data)
    - Look at cost in the context of additional factors (e.g. outcomes and service provision) and apply weights in procurement decisions to reflect factors other than price.
- Procurement decision-making should **avoid**:
    - Systems that distort the market or lead to an arguably unfair position of dominance (e.g. exclusive tendering policies, originator long term contracts/tenders prior to biosimilar approval)
    - Measures that lead to conflict between stakeholders (e.g. Physician / Pharmacist, Payer / Physician, Payer / Industry)

## 1.3 Impact of Policy on the Sustainability of the Biosimilar Medicines Market

The policies that make the **strongest contribution** to the sustainability of the biosimilar medicines market are those that:

- Increase prescriber confidence and trust (information, education, evidence)
- Encourage early use and experience
- Promote competition
- Encourage transparent, multi-criteria decision-making in the procurement process that drive cost savings and improved market access

Policies that **weaken and undermine** the sustainability of the biosimilar medicines market are those that:

- Lead to conflict between stakeholders (e.g. Physician/Pharmacist, Payer/Physician, Industry/Payer)

- Drive prices to levels that threaten the financial viability of the biosimilar medicines industry and make continued investment unattractive to both the originator pharmaceutical industry (future innovation) and the biosimilar medicines industry (new biosimilar medicines)
- Require significant incremental investments in the development of a biosimilar medicine above and beyond regulatory requirements
- Distort the market or lead to an arguably unfair position of dominance (e.g. exclusive tendering policies, originator product long term contracts/tenders prior to biosimilar product approval)
- Establish procurement/tender/contracting systems that are not transparent and in which the decision criteria are unclear to the participants
- Create an uneven playing field (e.g. mandatory price discounts that increase with order to market entry- the later a manufacturer is to market, the higher the discount it must provide)

### 1.4 Quantitative Impact of Policy

Quantitative analysis indicated that the optimal policy combination consistent with a sustainable biosimilar medicines market was the same for all three products studied (Herceptin®, Humira® and Avastin®). This comprised of:

- Intensive programs to develop ”education and understanding” of biosimilar medicines (amongst all stakeholders)
- Policies that encourage early use and growth of biosimilar medicines experience
- Policies that encourage capturing and communicating Real World Evidence (RWE) in order to build confidence and trust (but not as a requirement for market access)
- A sustainable competitive pricing environment with price levels consistent with financial viability and a fair return on investment
- An environment where extrapolation to other indication(s) is well understood and accepted by all stakeholders as a proven regulatory concept, endorsed and applied to all medicinal products by regulatory agencies following an in-depth scientific review process. Indication specific data in all of the reference indications is not a requirement at launch for access or utilisation (underpinned by education/understanding and RWE programs)
- Procurement and utilisation policies which evolve over time[1] involving multiple stakeholders, including physicians, in the choice of therapies available for patients, and how those therapies should be used within prescribing guidelines

The combination of these policies delivers greatest benefits across all stakeholder groups.

[1] Early Use: Predominantly a physician driven decision; Intermediate situation: (multi-stakeholder approach) where the decision is physician / pharmacist / payer driven; and Well established use: Predominantly a pharmacist/payer driven decision.

### Cost Savings

System dynamics[2] modelling, which took into account how policies impact one another, indicates that significant cumulative cost savings are likely over the 10-year period from the entry of an originator product's first biosimilar medicine. The table below shows the potential cumulative savings for the three products under the **optimal policy combination** that GfK has identified.

| Molecule | Cumulative 10 year Savings[3] (EU5) |
|---|---|
| adalimumab (Humira®) | 26% |
| bevacizumab (Avastin®) | 24% |
| trastuzumab (Herceptin®) | 25% |

The cumulative savings were calculated by considering the cumulative budget impact of the 'originator' if biosimilar medicines did not enter the market minus the cumulative budget impact of 'originator plus biosimilars' (over the 10 years post-entry of the 1st biosimilar). The 10-year time horizon ensures the evolution of biosimilar volume share and net pricing are appropriately reflected in the cost savings calculation.

Higher cost savings would be possible, but would result in a less sustainable biosimilars market with a consequent decrease in the magnitude of benefits to all stakeholders, particularly the decline of continued attractiveness for R&D investment in new medicines development and reduced competition in the market.

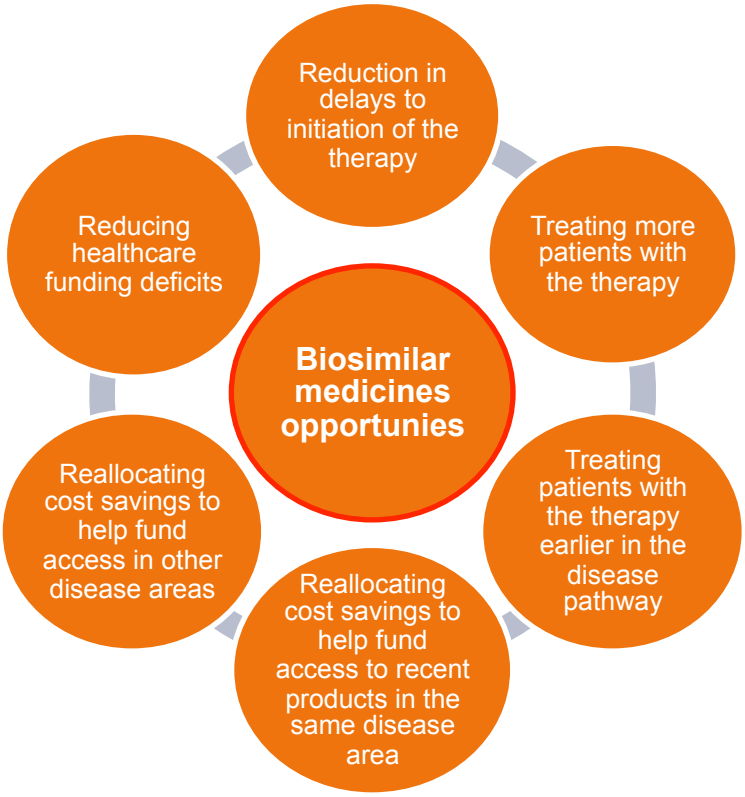
### Improved Patient Access

The interview program and subsequent analysis indicated that the cost savings generated by the introduction of biosimilar medicines with the optimal combination of policies might be utilised in various ways to increase patient access to biological medicines dependent on country, product, and current clinical practice. These included:

[2] System dynamics is an aspect of systems theory as a method for understanding the dynamic behaviour of complex systems. The basis of the method is the recognition that the structure of any system — the many circular, interlocking, sometimes time-delayed relationships among its components — is often just as important in determining its behaviour as the individual components themselves. Because there are often properties-of-the-whole which cannot be found among the properties-of-the-elements, in some cases the behaviour of the whole cannot be explained in terms of the behaviour of the parts.

[3] EU5 is composed of France, Germany, Italy, Spain, and the UK




# 2 Project Goal & Objectives

## 2.1 Project Goal

The goal of the project was to provide a high level, independent, expert opinion-based assessment of the factors that together will create a healthy and sustainable European biosimilar medicines market.

## 2.2 Project Objectives

The objectives of the project were:

- To identify the key policy areas that will drive the establishment of a sustainable biosimilar market
- To develop a clear, high level understanding of the interactions and dynamics within and between policy areas
- To identify a set of policy measures that should be implemented by policy makers (national and European level) and other stakeholders to help drive the growth of the biosimilar market
- To outline the benefits that these policies will bring, with particular focus on the benefits for European National Health systems (increased savings to the National Health systems whilst treating more patients), patients (improved access to medicines) and the economy (growth impact and job creation)

# 3 Background

This study was commissioned by the European Biosimilars Group (EBG), which is a sector group of the European Generic medicines Association (EGA). The vision of the generic and biosimilar medicines industries is to provide sustainable access to high quality medicines for all European patients. The EGA is determined to continue to work with Europe's policy makers, legislators and regulators to create the right environment to support and strengthen the economic sustainability of the industry, ensuring continued contribution to European patients and society while fully complying with all applicable competition laws.

EGA Member Companies will contribute directly to the EU2020 objective of increasing "the average healthy lifespan in the EU by two years."[4] Access to biosimilar medicines will be critical to achieving this objective and EGA Member Companies are striving to increase patient access to biosimilar medicines by 50% across Europe by 2020[5] in partnership with all stakeholders.

# 4 Methodology

The study was conducted in four stages:

- Systematic secondary research
- Primary research (stakeholder interviews)
- Quantitative modelling
- Final report and recommendations

**Systematic secondary research**:

GfK undertook a thorough review of existing papers, presentations, policies, and positions around biosimilar medicines, biosimilar medicines market dynamics, and market sustainability utilising both public and proprietary data sources with particular focus on 7 countries - France, Germany, Hungary, Italy, Poland, Spain, and the UK.

The insights from this exercise were used to inform the development of an issue and policy focussed interview guide that was used during the primary research stage of the project.

**Primary research (stakeholder interviews)**

Five key stakeholder groups were identified from the secondary research and targeted for in-depth interviews:

- **Payers**- This was a broad category that included both National and Regional level payers (both budget holding and influencing), as well as health economists, and HTA agencies

[4] Europe 2020 – for a healthier EU, available at: http://ec.europa.eu/health/europe_2020_en.htm
[5] EGA Vision

- **Key Opinion Leaders (KOLs)**- Leading clinician KOLs specialising in inflammation and oncology, and who have influence on Guideline development, as these are two of the disease areas that will be most impacted by new biosimilar medicines coming to market in the period 2014 - 2020
- **Pharmacists**- High level hospital pharmacists who have significant input into drug formularies
- **Pan-EU Influencers**- This group consisted of high ranking individuals who not only influenced policy in their own countries, but also at the European level through organisations such as the EMA, European Commission, and WHO
- **Patients**- Representatives of patient advocacy groups

A total of 71 stakeholders across 7 countries - France, Germany, Hungary, Italy, Poland, Spain, and the UK - participated in individually tailored, one-hour interviews. The interviews were undertaken between January and May 2014, and were carried out under “Chatham House” rules, in which interviewees’ comments are confidential and not attributable back to them.

For each stakeholder group, GfK was interested in establishing insight around 3 key areas:

- **Sustainability**- views on the relative importance of factors defining sustainability
- **Changes & Differences**- views on how current biosimilar medicines policies might change in the short term with the arrival of biosimilar medicines in inflammatory disease and oncology, and change in the long term influenced by experience. Differences between inflammatory diseases and oncology; and between the early biosimilar medicines (2007-2013) and later biosimilar medicines (2014-2020).
- **Policy**- views on the relative attractiveness, feasibility of implementation, strengths and weaknesses of various possible future Policy Options that will have an impact on the sustainability of the biosimilar medicines industry.

The research attempted to identify areas of policy where stakeholders closely align, areas of policy where significant differences of opinion exist, and areas where policy change would establish a sustainable biosimilar medicines industry that delivers benefits to all stakeholders.

Interviews focused on 7 major discussion areas:

- Pricing and procurement policies
- Utilisation policies
- Indication extrapolation
- Evidence generation
- Clinical guidelines
- Assessment of biosimilar medicines
- Incentive policies to encourage development of experience and use

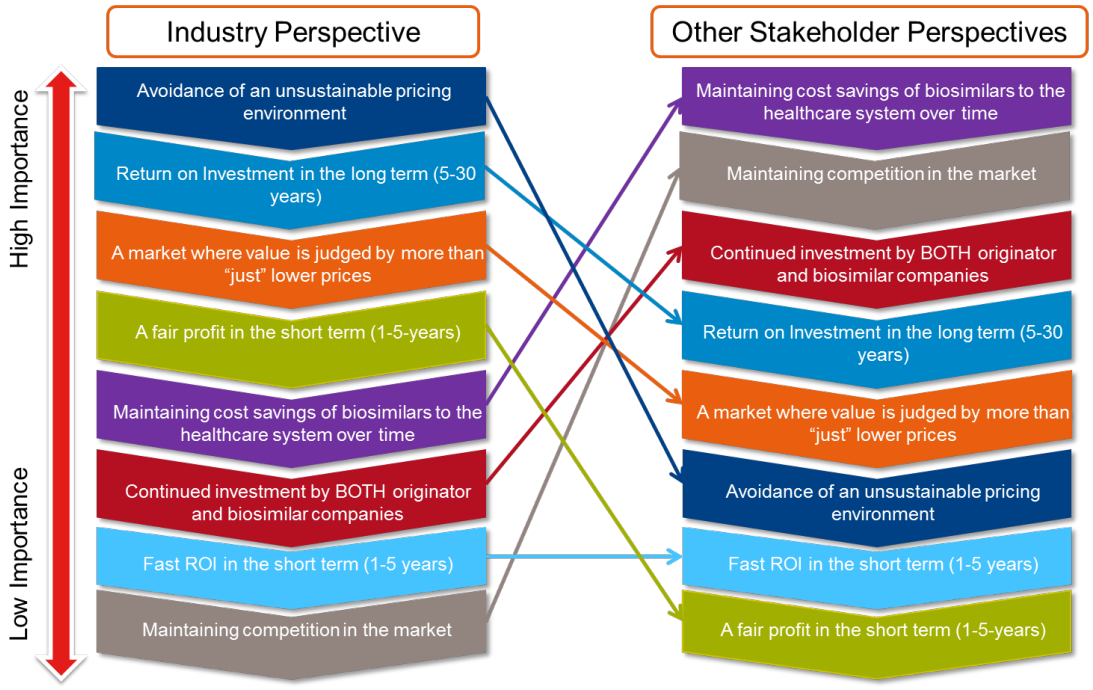
# 5 Insights from Primary Research

The **initial** unprompted comments of interviewees regarding the factors that define and drive sustainability indicated that there is considerable variation in knowledge and opinion both between and within stakeholder groups. Stakeholders were **initially** not aligned on the factors that drive sustainability, nor did they agree on the relative importance of these factors. Initially they tended to measure sustainability relative to the metrics that are important to them, whilst not considering factors that might be relevant to other stakeholders.

However, once prompted to also consider the possible perspectives of other stakeholders, the list of relevant factors expanded and there was notable alignment on the key factors, with some inter-stakeholder differences regarding the relative importance of these. All stakeholders agreed that for the market to be sustainable there was a need to have a common shared understanding of the requirements for, and benefits of, a sustainable biosimilar medicines market, as well as to achieve a "balance" between the different stakeholder needs and objectives.

This led to a consensus that a sustainable biosimilar medicines market is one that is attractive and delivers continuing benefits to four key stakeholder groups (Physicians, Payers, Patients, and Industry) in both the short and long term. The concepts of "attractiveness" and "benefit" differ amongst stakeholders, but include: opportunities to treat more patients with appropriate therapies (Physicians), cost savings and financial sustainability of healthcare systems (Payers), improved access to medicines (Patients), and a reasonable return on investment with the continued attractiveness of R&D investment in new medicines development (Industry). Figure 1 shows how the perspective of Industry differs from that of all other stakeholders among eight factors of sustainability.

**Figure 1: Prioritisation of Sustainability Factors by Industry and Other Stakeholders (e.g. Payer)**



The depth of understanding of biosimilar medicines, the scientific rationale underlying their regulatory approval, and the key differences to generic medicines, varied significantly between stakeholders. Some scepticism was expressed (mainly by physicians) as to the actual level of similarity between originator products and biosimilar medicines.

A key insight was that the development of awareness and understanding – based on education, experience and its dissemination - will create confidence and trust in biosimilar medicines, and lead to closer alignment around the benefits of a sustainable biosimilar medicines market and the factors that drive it.

Cluster analysis[6] of all the insights from the interview program indicated that there are four key areas of focus where closer policy alignment could lead to a sustainable biosimilar market and significant benefit for all stakeholders:

1. Education and Understanding
2. Experience and Use
3. Sustainable Pricing
4. Rational decision-making

These four elements, considered holistically, provide a "**Sustainability Policy Framework**" for the biosimilar medicines market:

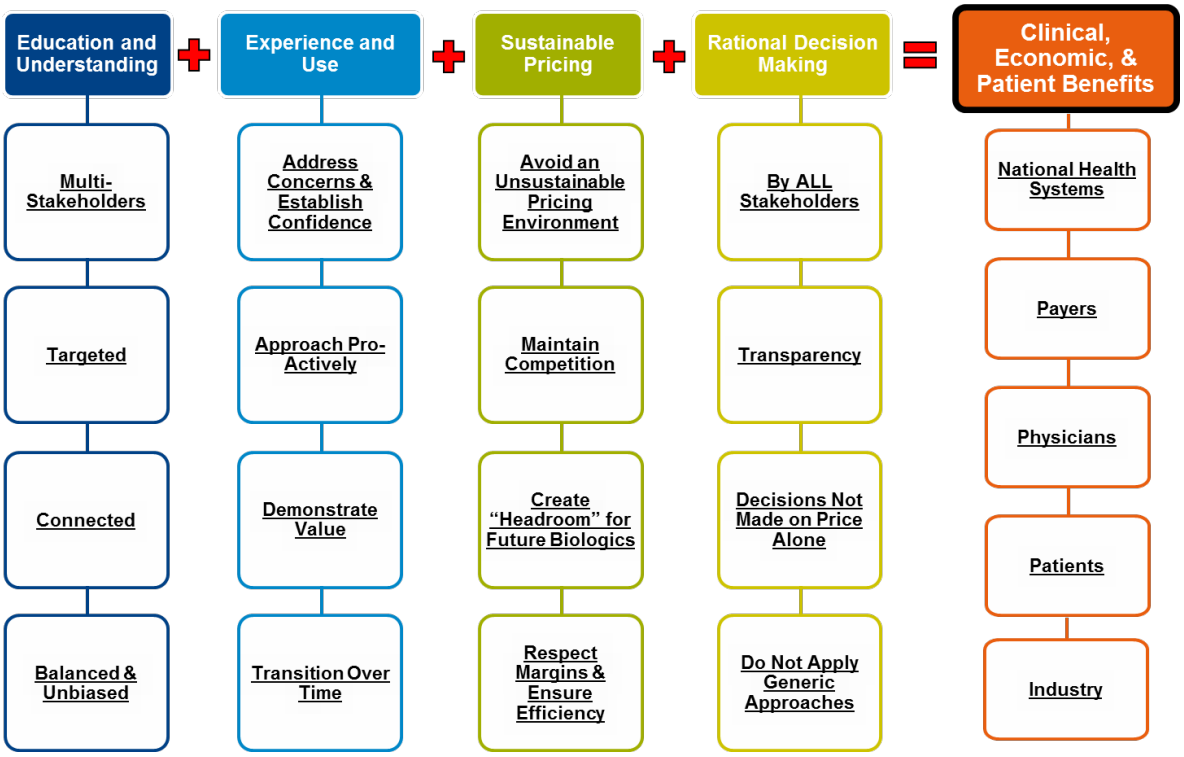

The primary research program indicated that **all** elements are required for sustainability. They are synergistic and are not independent of one another. Sustainable pricing policies in the absence of education, understanding, and experience, and rational decision-making in the absence of a differentiated value proposition, will lead to an unsustainable biosimilar medicines market.

Our hypothesis, which was subsequently tested and validated in the quantitative modelling phase of the project, was that: "A European biosimilar medicines industry based on stakeholder and policy alignment in these four areas will be sustainable and deliver significant benefits to all stakeholders."

For each element of the Sustainability Policy Framework, the research identified a series of insights that need to be addressed in policy development:

[6] Cluster analysis is the task of grouping a set of objects in such a way that objects in the same group (called a cluster) are more similar (in some sense or another) to each other than to those in other groups (clusters)




These insights and GfK's recommendations are described in more detail in sections 6- 9 of this report.

# 6 Education and Understanding

Although all stakeholders interviewed in the study were familiar with biosimilar medicines and most agreed that they must be treated differently than generic medicines, some admitted that their colleagues are not as familiar with the intrinsic differences between biosimilar and generic medicines and why the policies governing them must be different. Unequivocal multi-stakeholder understanding and acceptance of biosimilar medicines is critical for supporting long term sustainability.

A concern among some physicians is that patients' lack of understanding may be a hurdle to uptake, as the perception of taking a less expensive medicine may make some patients apprehensive. Although the price competition following the volume uptake of biosimilar medicines is a significant value proposition to payers, this may not resonate as strongly with patients. They will need convincing value messages that relate more directly to them, such as equivalent safety and efficacy between the biosimilar and originator medicines, and the improved access to medicines that the availability of biosimilar medicines allows.

It is also expected that biosimilar medicines companies provide information to stakeholders and contribute to the better understanding of the scientific concepts for biosimilar medicines, their approval process, and their quality, safety and efficacy. Special care must be given to ensure physicians not only receive, but also fully absorb the information.

All healthcare professionals need to understand that, "the current concept of development of biosimilars follows the principle that an extensive state of the art physicochemical, analytical and functional comparison of the molecule is complemented by comparative non-clinical and clinical data that establish equivalent efficacy and safety in a clinical "model" indication of the molecule that is the most sensitive to detect any minor differences (if these exist) between biosimilar and its reference monoclonal antibody also at the clinical level."[7] "This "model" indication has to be scientifically duly justified by the applicant, and any extrapolation to other indications not specifically studied is based on an in-depth scientific review process. As such, a biosimilar development is therefore not so much "abridged" but rather "tailored" towards a distinct scientific objective – that is, to establish biosimilarity, not to re-establish benefit for the patient"[8],which has already been established with the reference product.

For physicians, it appeared important that biosimilar medicine information must also come from independent and unbiased sources in order to be convincing and effective. Some examples of influential entities are European and national regulatory agencies (e.g. EMA), as well as the European Commission. Additionally, physicians require materials to effectively communicate information to patients. This is especially important as physicians are typically the main information source for patients. A hurdle that physicians described is the significant time constraints they face in acquiring new information, as most of their time is spent directly treating patients. They would prefer the information be proactively provided to them, instead of having to seek out the information on their own.

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[7] Schneider CK, Borg JJ, Ehmann F. et al: A response from the scientific and regulatory perspective in support of the EU biosimilars framework. Nat. Biotechnol 2012; 30:745-8

[8] Christian K Schneider: Biosimilars in rheumatology: the wind of change – Ann Rheum Dis 2013; 72:315-318 doi:10.1136/annrheumdis -2012-202941

The interviews clearly revealed that unbiased and already available information is not sufficiently accessed or known. Examples of unbiased information are the EMA Q&A on biosimilar medicines for the general public, the EMA European Public Assessment Reports (EPARs) on every approved biosimilar product, and the European Commission consensus information document, *What you need to know about biosimilar medicinal products.*[9]

### "Indication Extrapolation"

The possibility to extrapolate efficacy and safety data to other indications of the reference product, for which no formal clinical studies have been performed with the biosimilar medicine, is called "extrapolation of indication(s)". This appears to constitute a paradigm shift for physicians and other stakeholders. However, extrapolation to other indication (s) is a proven regulatory concept, endorsed and applied to all medicinal products by regulatory agencies following an in-depth scientific review process. "The reliability of this regulatory approach is supported by the extensive European experience, which to date has allowed patient access to safe and efficacious biosimilars with the same therapeutic indications as innovators."[10]

Furthermore it has to be understood that one or more indications of the reference product are not granted automatically to the biosimilar product. Any extrapolation of data requires sound scientific justification in each and every indication and is based on the totality-of-evidence from a thorough comparability exercise with the reference product.

The scientific concept of extrapolation, applied to biosimilar medicines, is explained in detail in the Weise et al publication. – Biosimilars: what clinicians should know [11]

In very general terms, extrapolation of data will require meeting the following criteria:

1. Demonstration, through advanced product characterization, that the biosimilar is highly similar to the originator product in terms of analytical and biological attributes.

2. Further demonstration that the biosimilar is similar with respect to safety (including immunogenicity), pharmacokinetic/pharmacodynamic properties and clinical efficacy in a sensitive indication.

3. Relevant mechanism of action and/or the receptor(s) involved in the extrapolated indications are the same. If the mechanism of action is different or unknown, additional convincing data are necessary

The majority of stakeholders interviewed do not challenge the European Medicines Agency's scientific assessment and the European Commission approval of biosimilar medicines and consequently accept the scientific concept of biosimilarity, including the regulatory concept of extrapolation of indication(s). Physicians, who do not feel sufficiently reassured by the EC approval to use the product in indications for which no separate safety and efficacy study was performed,

[9] http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf
[10] Kurki P, Bielsky M-C, ECCO position challenged by European drug regulators, J Crohns Colitis (2014), htpp://dx.doi.org/10.1016(j.crohns.2014.01.022
[11] Weise et al: Biosimilars what clinicians should know – blood (ISSN 1528-0020)

request additional data generation in some or all indications. Some stakeholders noted their surprise that the EMA had approved indication extrapolation for biosimilar infliximab, although felt that national authorities should abide by the EMA's scientific decision.

There is however a general understanding that it is unreasonable to expect a biosimilar medicines manufacturer to generate clinical data in every indication approved for the reference biological medicine, as is required for a new innovative biological medicine. Requiring these clinical data, in addition to demonstrating biosimilarity, would not add to patient safety, seriously challenge the EU-specific regulatory approval pathway for biosimilar medicines, dramatically increase their development costs, and consequently reduce possible cost savings, and delay patient access to biological treatments – thereby leading to overall market unsustainability. In addition, as stated in the Weise et al paper "a repetition of the entire development programme of the reference product is scientifically not necessary and could even be considered unethical".[12]

A minority had concerns about long term safety and, in the case of anti-TNFs, with the scientific basis supporting extrapolation to gastrointestinal indications. In order to allay the concerns of the minority and generate greater physician confidence in all disease areas, additional education programmes could additionally be supported by Real World Evidence (RWE), which will allow physicians to assess how biosimilar medicines perform in real world clinical practice and enable overall comparison of outcomes with reference products.

[12] Weise et al: Biosimilars what clinicians should know – blood (ISSN 1528-0020)

# 7 Experience and Use

## Accelerating Experience and Use

The sustainability of the biosimilar medicines market would be strengthened by early delivery of benefits to all stakeholders. However, the interview programme clearly indicated that a major barrier to early biosimilar medicines use (and consequent benefit delivery) is lack of confidence that biosimilar medicines outcomes in real world clinical practice will indeed be similar to those observed with the reference products.

Early delivery of benefits can be achieved by ensuring market access as soon as possible after licensure, and encouraging the development of experience with biosimilar medicines. The quantitative analysis indicated that accelerated experience and uptake of biosimilar medicines will be important for short term benefit (to payers, physicians, patients, and biosimilar medicines companies) and the long term sustainability of the market and healthcare systems.

Physician (and other stakeholders) confidence and trust should be strengthened by the introduction of programs to grow biosimilar experience by promoting appropriate early use and encouraging the collection and publication of Real World Evidence (RWE). Such RWE studies should, where possible, capture outcomes data but should NOT be a requirement for market access. RWE studies will serve as "facilitators" for developing early experience, confidence and trust.

## Programs to develop experience with biosimilar medicines and encourage appropriate early use

Policies that incentivise[13] the early uptake of biosimilar medicines should be considered. In many European markets, physicians are encouraged to use biosimilar medicines, rather than more expensive originator products. This can take many different forms but the ultimate goal is to encourage uptake of similar medicines that would result in overall cost savings.

Examples of incentivisation policies:

Payers play a critical role in biosimilar medicines uptake, as is evidenced by the success of Germany's quota system, which drives physicians to prescribe a certain percentage of biosimilar drugs. A quota system is an effective way to develop experience and increase the utilisation of biosimilar medicines, but the setting of quotas must be thoughtfully implemented so as to not undermine a physician's prescribing choice. Interviewed physicians were adamant about maintaining ultimate prescribing control, especially in these early days of biosimilar medicine use.

A complementary or alternative incentive system that should be considered is that of "gainsharing." In this system, a proportion of the savings that a hospital realises from prescribing biosimilar medicines can be partially returned to the hospital for reinvestment. For example, if a hospital saves €500,000 from prescribing biosimilar medicines, €250,000 of the savings might be realised by the

[13] The term "incentivise," as used in this paper, describes a concept in which stakeholders are stimulated through policies to consider use of biosimilar medicines.

overall national healthcare budget, whilst the other €250,000 can be given back to the hospital in the form of a higher budget for the following year.

Irrespective of the incentivisation policies (or programmes) in place, a physician's prescribing decision should ultimately be led by drug efficacy, drug safety, his or her own level of knowledge of the drug, and its appropriateness for the specific patient.

## Guidelines

Treatment guidelines are viewed as a valuable tool across all areas of medicine. In oncology and rheumatology in particular, physicians note a high dependence on guidelines from international bodies such as the European League Against Rheumatism (EULAR), the European Society of Medical Oncology (ESMO), and the European CanCer Organisation (ECCO), to similar bodies at the national level, to those developed at a local level by hospital formulary committees. Regulatory approval alone is usually not sufficient for incorporation into clinical guidelines and hospital treatment protocols. Incorporation of new treatment paradigms in clinical guidelines is driven by a combination of evidence and experience. There are currently very few clinical guidelines available that specifically address the use of biosimilar medicines, although there is an expectation that such documents will be developed / published in the near future. Furthermore, as guidelines are generally developed using the body of clinical data available, the inclusion of guidance on biosimilar use in extrapolated indications may prove to be problematic. It is yet to be seen how this can be overcome and it may require a different approach to guideline development to encompass and include biosimilar medicines.

National or international guidelines developed by organisations, such as EULAR, ESMO, ECCO or national medical societies, are more influential to stakeholders than regional or local guidelines and the European Public Assessment Reports (EPARs) issued by the EMA at the time of biosimilar medicines approvals. The general stakeholder opinion was that these organisations should class biosimilar medicines in molecular groups, rather than recommending one individual drug over another. Any locally developed clinical guidelines must be wary of favouring one product over another.

Several interviewees (particularly in Italy and Spain) identified the need, driven by economic austerity, to integrate economic criteria in the clinical guidelines. However economic aspects need to be developed in the context of clinical guidelines and not be driven by price alone.

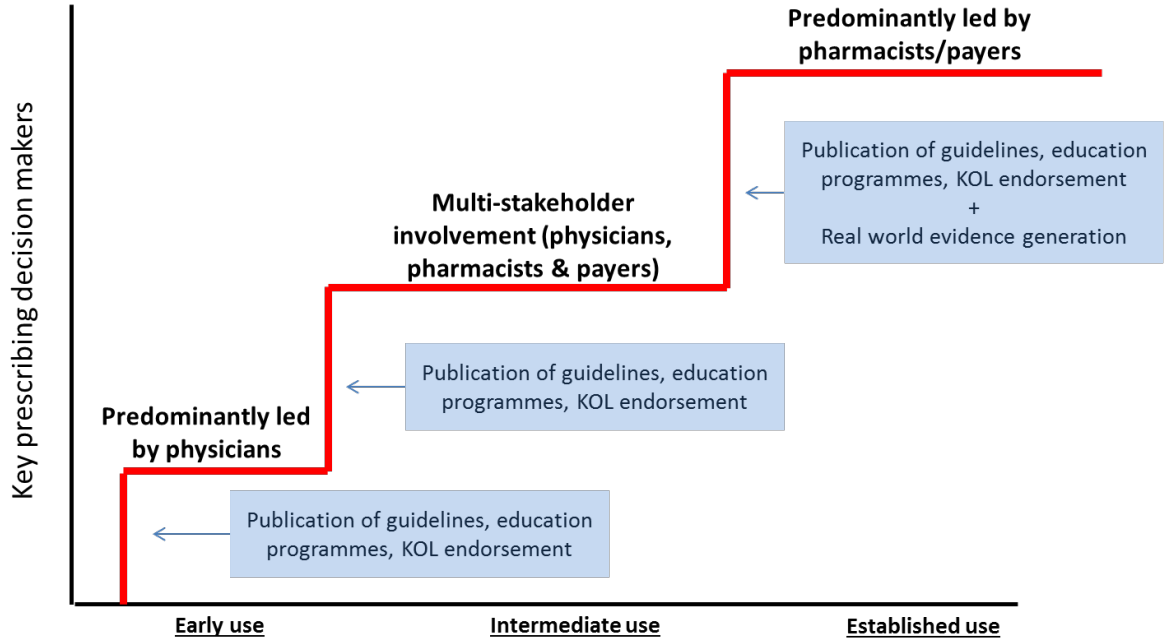
In order to increase appropriate utilisation of biosimilar medicines, it will be essential to have endorsement by recognised international bodies, such as EULAR and ECCO, as well as by national disease-specific medical societies. Such guidelines are likely to be highly influential on the recommendations made by regional and local decision makers.

## Other drivers of Utilisation

The key to increasing confidence in biosimilar medicines, and hence, increasing the possibility that non-clinical stakeholders may eventually become involved in the procurement and utilization decisions, is dependent on unbiased stakeholder education, clinical data, and real world experience. Figure 2 represents how GfK anticipates stakeholder perception towards drivers of utilisation will evolve over time and the key factors that will play a role in this.

**Figure 2: Drivers of utilisation**




Utilisation policies should evolve to include multi-stakeholder input and agreement. Such policies should be evidence-based and risk-minimised:

- **Early Use:** predominantly a physician driven decision
- **Intermediate Use:** physician/pharmacist/payer driven decision (multi-stakeholder approach)
- **Well Established Use:** predominantly pharmacist/payer driven decision

It will take time for physicians to gain sufficient experience with biosimilar medicines to such a degree that they willingly share control with pharmacists or with other HCPs. Pharmacists themselves were aligned with this way of thinking and many admitted that they would not have the experience to harbour the responsibility of choosing one biological medicine over another.

Figure 2 also highlights that clinical guidelines, un-biased education programmes, and KOL endorsement will encourage the transition between early, intermediate and well established use. However, in order to move to the "well established use" phase (predominantly led by payers and pharmacists) it will need to be supported by experience based on Real-World Evidence (RWE) generated during the first two phases. In any case, physicians should always remain involved in both procurement and utilisation decisions involving multi-stakeholders.

# 8 Sustainable Pricing

A major pillar of value that biosimilar medicines offer are cost savings relative to the originator and therefore better access to treatments. However, payers should not anticipate paying 'generic medicines like' prices for biosimilar medicines. The investment that biosimilar medicine companies must make in biosimilar medicines development is significant. Biologic medicines are extremely complex to develop and manufacture. It is estimated that developing a biosimilar medicine takes 8 to 10 years and costs between USD$100 million to USD$200 million[14]. Additional post-marketing requirements are very costly and not comparable to small molecule generic medicines.

Conversely, it is also important to understand the situation that governments face with perpetually increasing healthcare costs. Patients expect to receive the best possible care, but providing a high quality of care with a limited budget, in the face of growing drug prices and expanding country populations, is an extremely difficult feat. In response, governments continue to implement cost containment measures across their healthcare systems. The introduction of biosimilar medicines are viewed as a welcome measure that can alleviate some budgetary pressure, without compromising the quality or comprehensiveness of care.

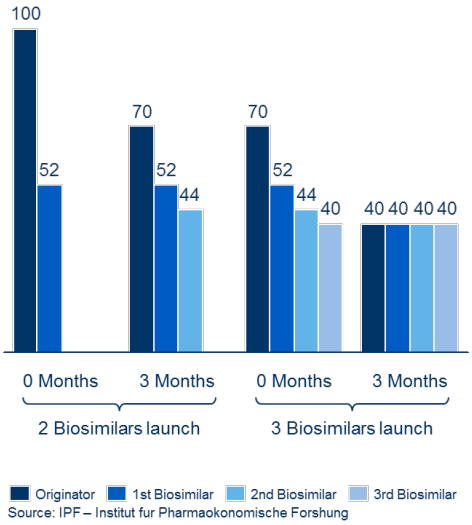
Stakeholders felt pricing policies that artificially hinder competition and force dramatic, downward pricing pressure on manufacturers should be avoided. Decision-makers involved in price setting and reimbursement should ensure a level playing field and not induce a situation in which biosimilar pricing must meet different requirements to originator pricing. Maintaining and encouraging competition is the best way to ensure that all stakeholders, especially healthcare systems, receive the most value.

Stakeholders extensively discussed the overall pricing structure a country should implement: mandated discounting, completely unregulated pricing, or some combination of both. One of the most draconian pricing policies in Europe is the mandated discounting policy found in Austria. It's important to note here, that Austria does not have a specific biosimilar pricing mechanisms, but simply applies the country's generic pricing policy. Here, the biosimilar discount against the originator is predetermined and significant. According to the *Institut für Pharmaökonomische Forschung*, an independent Austrian research institute, the first biosimilar medicine launched must be priced at 52% of the originator. If a second biosimilar is launched in the market (in the same indication), it is priced at 44% the originator price, whilst the originator product must drop its price to 70% of its previous price at this point. Once a third biosimilar medicine would be released, all three, as well as the originator, would be forced to 40% of the originator product price. This is reflected in Figure 3 and was used as a basis of discussion with interviewees to review the strengths and weaknesses of an example of a mandated discounting policy. In reality and as a consequence of authorities wanting to apply a purely generic-type pricing policy, companies have opted not to launch in Austria and no 3rd biosimilar has come to market in Austria yet.

[14] Federal Trade Commission. Emerging health care issues: follow-on biologic drug competition. June 2009 Report. Available at: http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf. Accessed May 26, 2014

**Figure 3: Generic and biosimilar medicines pricing policy- Austria**




Not a single respondent mentioned this pricing model in a positive light, and only two stakeholders were in favour of a mandated discounting policy at all, albeit a much less severe one than the example given. Input from French pharmacist representatives was that although it appears to be an effective way to force prices lower, this type of pricing policy is not sustainable for the biosimilar medicines industry in the long run. A former Head of UK Drug Pricing took an even stronger stance against it, stating that, "The Austrian model is self-defeating, not sustainable, and makes the market less attractive to both biosimilar and originator medicines industries."

Stakeholders showed some support for a completely unregulated pricing market, but the largest convergence of opinion was on a semi-regulated market. With this method, a country would set a modest upfront discount that all biosimilar medicines must meet, but then allow manufacturers to compete freely on price thereafter. In GfK's opinion, the only upside to a semi-regulated market is that governments can guarantee a reduced drug price, but this will likely be attained anyway through manufacturer competition in an unregulated pricing market.

The lowered price ceiling of a semi-regulated market is arbitrary at best, as was evidenced by the extreme anticipated upfront discount range of 20-50% that was mentioned by stakeholders. Moreover, it can have the unintended consequence of pushing biosimilar medicine companies out of the market. An **unregulated pricing market is the best way to foster competition, which will likely lead to significant cost savings, compellingly differentiated product packages, or a combination of both. In all cases, the healthcare system and patients will benefit.**

Ultimately, **thoughtful biosimilar medicine pricing will incentivise manufacturers to continue investing in new biosimilar medicines, thereby giving healthcare systems sustained savings and allowing more patient access to the best possible therapy options**. The savings gained can be used towards facilitating access to more recent (and usually more expensive) products. This context produces an interesting dynamic for originator and biosimilar medicine companies, because instead of competing against one another, it could be argued that developers of new innovative medicines actually *need* biosimilar medicines**. Fostering a healthy and sustainable biosimilar medicines market will only come from avoiding prescriptive pricing policies that hinder competition and artificially force/mandate prices downward.**

# 9 Rational Decision Making

### Procurement

Tendering is one of the methods used for medicines procurement throughout Europe, especially in the hospital setting where many of the current and future biosimilars are used. It can take many forms, from large National tenders where a single product is selected for use over an extended period of time down to small single hospital tenders where one or more similar products are selected. For the different stakeholders interviewed, each type of tender has positive and negative elements in relation to the sustainability of biosimilar medicines and there is no preferred ideal solution. However there are some clear aspects of tendering that can seriously impact the sustainability of biosimilars that should be addressed by those with responsibility for the tendering processes at national, regional and local levels. Sustainability of the market will depend on strong and continuing competition and any procurement system including tendering, should encourage this.

Centralised tendering in which companies present a bid to a National payer for a unified price country-wide was supported by only a small minority of the stakeholders interviewed. As companies only have to work with a single entity, it can be seen as less laborious than administering multiple smaller systems and in the short term can potentially lead to lower prices for high volume commitment. However, because centralised tendering generally limits the number of buyers in the market to a single winner, it can make the market much less attractive to those who do not win the tender, potentially leading to fewer competitors in the future. Additionally, relying on a single supplier for a medicine can be detrimental to the health system, as any disruption in supply can lead to severe drug shortages for patients. Health systems can mitigate supply risk by having multiple drug suppliers.

In regionalised and local tendering systems, tenders are initiated by smaller entities, such as single hospitals or groupings of regionally based hospitals. This type of system allows for greater intra-country competition due to the increased number of purchasers and the generally staggered timing of the individual tender processes. It can also be a difficult process for manufacturers to manage, as tendering criteria and transparency can vary greatly by region and buyer.

An additional variable that is introduced through the tendering process is the timing for submission into a tender and the period over which the tender runs. Some tenders have a rigid schedule for applicant submission and can also run over extended periods, up to 3 years in certain cases. This can have a major impact on the ability of a new market entrant, including biosimilars, to access the tender system and can significantly delay uptake of biosimilar medicines. This challenge, as highlighted in the interview process, can have a significant impact on the sustainability of biosimilars and consideration should be given to developing a more flexible tender process. Allowing for tenders to be re-opened at the point of a new market entrant and limiting the tender period to a maximum of 1 year are policy options that could potentially be employed to address this.

Irrespective of the tendering system used, most stakeholders agreed that more transparent tendering processes are needed. A common theme brought up by stakeholders, especially those from Spain, was the significant tendering process variation within a country, or even within a region. A standardised tendering process would provide a level playing field for biosimilar medicine companies to compete. Taking this a step further, payers must also become more transparent about their tendering decision criteria and the process used to determine the winning bid. Strong competition requires fairness, and fairness can only be achieved if the is a level playing field where

all parties understand the rules and the process for selection is transparent. The European Union has overarching procurement laws that define standardised tender processes, but these are often loosely adhered. If enacted appropriately, increased governance of the tendering process would alleviate many of the procurement issues that could limit the sustainability of the biosimilar medicines market (such as lack of transparency) that were raised by stakeholders interviewed.

Furthermore, there was a strong consensus that the tender process must include input from the clinical community and provide clinicians with prescribing choice. Driving the tender decision from the payer level and expecting the pharmacist to implement the final decision was not seen to be conducive to a sustainable situation for biosimilars. Without general support from the clinical community any tender decision may be difficult or impossible to uphold. Clinical leaders in the interview programme were vocal that, in the early stages of biosimilar medicines use, they must maintain prescribing autonomy. In order to attain long term sustainability for biosimilars, stakeholder confidence and trust must be strengthened; unilaterally forcing prescribers to accept biosimilar medicines may irreparably damage the confidence and trust that is required for a sustainable biosimilar medicines industry. The term 'multi-stakeholder approach' has been used, in this context of procurement decision making, to indicate the benefit of having consensus between the payer, pharmacist and physician in determining the right approach to tenders in a sustainable biosimilar medicines market.

Some respondents also expressed the view that tenders may not be appropriate in the early stages of biosimilar medicines use and that other mechanisms that deliver cost savings whilst developing and delivering confidence and experience may be more beneficial for all stakeholders in the short term.

Most stakeholders agreed that major factor for the decision to procure a biosimilar medicine will be price but other factors which allow manufacturers to deliver value in other areas through product and service differentiation should be encouraged. This may include elements such as support for education programmes or improved drug packaging or delivery. In determining value, payers should consider multi-criteria tenders.

Based on the insights from the interview programme, our conclusion is that hospital tendering may have a positive effect on biosimilar medicines market sustainability, provided:

- The tendering system encourages, not restricts, competition
- The decision-making criteria are transparent to all parties
- The tendering system is sensitive to the differences between biosimilar medicines and generic medicines. The development and manufacturing processes of biological medicines are more complex and much more expensive than of chemical small molecule medicines
- The tendering process does not drive prices to levels that threaten the financial viability of the biosimilar medicines industry and make continued investment unattractive to both the originator pharmaceutical industry (future innovation) and the biosimilar medicines industry (new biosimilar medicines)
- The tendering system does not distort the market or lead to an arguably unfair position of dominance (e.g. originator long term contracts/tenders prior to biosimilar approval). The timing and type of tenders must be aligned with the opportunity to deliver benefits to all stakeholders

- The tenders must include input from the clinical community and particularly in the early phases should provide clinicians with a prescribing choice

### Health Technology Assessment (HTA)

The policy on HTAs for biosimilar medicines is in a period of evolution and differs by market[15]. For example, in the UK, NICE has only reviewed one biosimilar medicine to date (human growth hormone- somatropin), and has indicated that it will not be reviewing individual biosimilar medicines under the STA programme in the future. Conversely, the Scottish Medicines Consortium (SMC) has reviewed all biosimilar medicines that have entered the Scottish healthcare system.

The vast majority of stakeholders felt that biosimilar medicines should not have to go through full HTAs because:

- The concept of a "biosimilar medicine" is based on the premise that the cost utility and subsequent clinical benefit and quality of life for the patient will be the same and hence evaluation should be based on budget impact or cost-minimisation basis
- The time and cost of preparing for a full HTA evaluation for a biosimilar will put extra pressure on the manufacturers and may ultimately increase prices and / or delay patient access
- Review of all biosimilar medicines will not be an effective use of time/resource for HTA agencies

Existing HTA systems need to be adapted to reflect the above.

In most cases, a traditional HTA would be futile and would not add value to the decision making process, as the assessment will be focussed purely on cost-minimisation.

However, in the following circumstances, GfK believes that an HTA of a biosimilar should be considered:

- When the originator product has not been recommended for reimbursement based on cost
- When the originator product has been subject to a conditional recommendation based on cost

In these circumstances, the biosimilar medicine may be able to demonstrate cost-effectiveness (due to its lower price) where the originator was unable to. However, it may be the case that a group HTA (or Multiple Technology Assessment- MTA) is undertaken on all the technologies (originator and biosimilar medicines) within a particular class, rather than undertaking separate HTAs for each individual biosimilar medicine.

[15] http://news.ohe.org/2014/04/09/biosimilars-hta-roundtable/

### Other areas of decision-making:

Many of the respondents who had involvement with pricing, procurement and utilisation decision-making believed that decision-making processes should incorporate and encourage**:**

- Recognition of the value of differentiated “Product Offerings” (e.g. Drug delivery, Value-Added Services, Point of Care, Dose Strengths)
- Recognition of the value of outcomes data from Payers (economic), Physicians (clinical), and Patients (disease management)
- Stakeholder collaboration (e.g. Payers co-funding the generation of relevant outcomes data)
- Looking at cost in the context of additional factors (e.g. outcomes and service provision) and applying weights in procurement decisions to reflect factors other than price.

# 10 Quantitative Analysis

## 10.1 Approach to quantitative modelling

Several forecasts exist in the literature[16] of the sales evolution (volume, price, value) of biosimilar medicines and the potential cost savings they will deliver to National Healthcare Systems (NHSs) and others payers. As can be expected, given the high levels of uncertainty, and the differences in assumptions on which the forecasts are based, a wide range of outcomes are possible.

What these forecasts do not show however is how they will change when alternative policies, as identified in our study, are applied. Specifically, they do not show:

- The effects (magnitude of impact) of individual policies in isolation
- Which policies in combination make the strongest contribution to the sustainability of the biosimilar market and deliver the greatest benefits (to all stakeholders)
- Which policies combine to weaken/undermine the sustainability of the market resulting in fewer benefits

Our approach was to develop a simple base case forecast for three products in the EU5 (Herceptin®, Avastin®, Humira®) based on existing forecasts from IMS, Data Monitor and GfK's internal knowledge.

We then used a systems dynamics approach, using an internal Delphi Panel[17] informed by the insights from the interview program, to understand how the base case forecasts would change if different combinations of policies from the policy areas identified in the study were applied.

Given the limitations of the data and time horizons involved, the approach was simply to look at percent changes in benefits to stakeholders (cost savings to NHSs, additional patients treated, etc.) with the objective of:

- Ranking policies in terms of their attractiveness to the various stakeholders
- Quantifying the relative magnitudes of the benefits they deliver to the various stakeholders (this being a proxy for their level of contribution to the sustainability of the biosimilar medicines market)

[16] *IMS, Datamonitor*

[17] *A forecasting method based on the results of questionnaires sent to a panel of experts. Several rounds of questionnaires are sent out, and the anonymous responses are aggregated and shared with the group after each round. The experts are allowed to adjust their answers in subsequent rounds. Because multiple rounds of questions are asked and because each member of the panel is told what the group thinks as a whole, the Delphi Method seeks to reach the "correct" response through consensus*

**Herceptin® (Trastuzumab), Avastin® (Bevacizumab), and Humira® (Adalimumab)**

There are significant differences between the three products modelled as outlined in the following table. These differences are fully incorporated in the base case forecasts and in the systems dynamic modelling.

| | Trastuzumab (Herceptin®) | Adalimumab (Humira®) | Bevacizumab (Avastin®) |
|---|---|---|---|
| **Timing of First Biosimilar Entry**[18] | Early Entry<br>(2015-2016) | Mid-term Entry<br>(2018-2020) | Late Entry<br>(2020-2022) |
| **Indications**<br>**(assumes full extrapolation of Originator indications)** | Metastatic breast cancer; Early breast cancer; Metastatic gastric cancer | Rheumatoid arthritis, Polyarticular juvenile idiopathic arthritis, Axial spondyloarthritis, Ankylosing spondylitis (AS), Psoriatic arthritis, Psoriasis; Crohn's disease, Paediatric Crohn's Disease, Ulcerative colitis | Metastatic colorectal cancer, Metastatic breast cancer, Non-small cell lung cancer (NSCLC) - unresectable advanced, metastatic, Renal Cell Cancer, Epithelial ovarian, fallopian tube, or primary peritoneal cancers |
| **Sector** | Mainly Hospital | Split between Hospital and Retail | Mainly hospital |
| **Future Dynamics** | Competition between Herceptin Subcutaneous, biosimilars, and new products (e.g. Kadcyla®, Perjecta®) | As a late biosimilar anti-TNF to enter the market, experience with earlier biosimilar anti-TNFs will impact uptake. Arrival of new oral therapies | Many new indications in development (eg. glioblastoma, melanoma, multiple myeloma, Diffuse large B cell lymphoma) |

[18] Consensus: GaBI Online. Datamonitor, R&D Insight

The systems dynamics assessment was driven by 5 key dynamics:

| | |
|---|---|
| 1. The elasticity of volume share to price | **This dynamic addresses how the patient volume share of the product will be split between the originator and the biosimilar medicine, and how this will evolve over time assuming the only differentiator is net price relativity** |
| **2. The elasticity of patient access to price** | This dynamic looks at the extent to which affordability is currently a barrier to patient access to the product and the percentage uplift in patients having access to the product (either originator or biosimilar) at the new lower price levels |
| **3. Evidence strength** | This dynamic looks at the extent to which the patient volume shares of the biosimilar medicine will be influenced by the amount of supporting data / evidence available |
| **4. Commercial strength** | This dynamic looks at the "Strength of the Suppliers" (capability, experience, portfolio) and the extent to which the patient volume shares of the biosimilar medicines will be influenced by this |
| **5. Buyer Strength** | This dynamic looks at the "Strength of the Buyer" and is used to adjust the patient volume shares of the biosimilar medicines for factors such as product differentiation, availability/cost of new entrants, and the threat of introduction of substitution. The "Power of the Buyer" is modelled by assuming the more competitors in the market (i.e. number of biosimilar medicines available), the lower the net prices)[19] |

**Pricing dynamics** were addressed using an index approach:

| |
|---|
| • The net price of the originator prior to the arrival of biosimilar medicines |
| • The net price of the originator after the arrival of biosimilar medicines |
| • The net price of the biosimilar medicines relative to the net price of the originator (post arrival of biosimilar medicines) |

[19] The analysis assumed both cross-product competition and originator-biosimilar competition

Two alternative **competitive strategies,** which the interview program indicated were the most likely, were modelled:

| | |
|---|---|
| **"Hold the Gap"** | Strategy is to establish/maintain a price differential between originator and biosimilar medicine<br><br>A "pricing gap" (between the new net price of the originator and the biosimilar medicine) of 15% is assumed |
| **"Narrow the Gap"** | Strategy is to minimise the price difference between originator and biosimilar medicine<br><br>A "pricing gap" of 5% is assumed |

## 10.2 The evaluation of policies in isolation

Several policies, selected from the **Sustainability Policy Framework,** were analysed in isolation:

1. **Intensive programs to develop "Education and Understanding"**
2. **Policies to encourage capturing Real World Evidence (RWE)**
3. **Programmes to develop biosimilar experience and encourage use**
   (e.g. A proportion of cost savings being made available to the hospital where savings are made for re-investment in healthcare delivery within that hospital)
4. **Sustainable Pricing Policies and Price Levels:**

| Base Case | High Price | Medium Price | Low Price | Very Low Price |
|---|---|---|---|---|
| Hold the Gap strategy<br><br>Originator at 95% of original price;<br><br>Biosimilar medicine at 85% of 95% (ie 85% of new net originator price)<br><br>Biosimilar medicines price index = 0.80 | Narrow the Gap strategy<br><br>Originator at 95% of original price<br><br>Biosimilar medicine at 95% of 95% (i.e. 95% of new net originator price)<br><br>Biosimilar medicine price index = 0.90<br><br>Interview program assessment: Low probability | Hold the Gap strategy<br><br>Originator at 85% of original price<br><br>Biosimilar medicine at 85% of 85% (i.e. 85% of new net originator price)<br><br>Biosimilar medicine price index = 0.72<br><br>Interview program assessment: High probability | Hold the Gap strategy<br><br>Originator at 75% of original price<br><br>Biosimilar medicines at 85% of 75% (i.e. 85% of new net originator price)<br><br>Biosimilar medicines price index = 0.64<br><br>Interview program assessment: Medium probability | Hold the Gap strategy<br><br>Originator at 55% of original price<br><br>Biosimilar medicine at 55% of 55% (i.e. 55% of new net originator price)<br><br>Biosimilar medicine price index = 0.30<br><br>Interview program assessment: Very low probability |

**5. Level of stakeholder acceptance of "Indication Extrapolation":**

| Scenario 1 | Scenario 2 | Scenario 3 |
|---|---|---|
| European Commission (EC) approval fully accepted by all stakeholders | Physicians and Payers do not feel sufficiently reassured by the EC approval (i.e. the scientific principles underlying the biosimilar approvals) | Physicians do not feel sufficiently reassured by the EC approval to use the biosimilar product in indications for which no separate safety/efficacy study was performed and request additional data generation in some or all indications |

**6. Utilisation Scenarios:**

| Scenario 1 | Scenario 2 | Scenario 3 |
|---|---|---|
| Early Use:<br><br>Predominantly a physician driven decision. | Intermediate situation:<br><br>A multi-stakeholder approach (physician / pharmacist / payer driven decision). | Well established use:<br><br>Predominantly a pharmacist/payer driven decision. |

**7. Rational Decision Making:**

| Pricing | Procurement | Product | Other |
|---|---|---|---|
| Transparency<br><br>Pricing approval as close as possible to the date of biosimilar marketing authorisation | Transparency<br><br>Access to National and Regional tenders as close as possible to the date of biosimilar marketing authorisation<br><br>Avoidance of systems that distort the market or lead to an unfair position of dominance (e.g. exclusive tendering policies, originator long term contracts/tenders prior to biosimilar approval)<br><br>Apply weights in procurement decisions to reflect factors other than price | Recognition of the value of differentiated "Product Offerings" (e.g. Drug delivery, Value-Added Services, Point of Care, Dose Strengths) | Look at cost in the context of additional factors (e.g. outcomes and service provision)<br><br>Biosimilar medicines should not require HTA in situations where assessment is futile and does not add value<br><br>If originator access has been denied on economic grounds by HTA body, policy should not exclude an HTA assessment of the biosimilar if there is reasonable chance that it will demonstrate cost-effectiveness |

**Multi- stakeholder evaluation of policy attractiveness**

For each policy in isolation (and for policies in combination) the attractiveness of the policy (combination of policies) was "scored" from the perspectives of each of the key stakeholders (Physician, Payer, Patient, Originator company, Biosimilar company) using a red, amber, green "traffic light" system where:

- **RED** implies the policy is unattractive
- **AMBER** implies the policy is neither attractive nor unattractive
- **GREEN** implies the policy is attractive

The scoring criteria and red/amber/green thresholds were informed by the Delphi expert panel:

**Scoring criteria**:

The scoring criteria were multifactorial and the same for all products, but differed by stakeholder group:

<table>
<tr><th>Physician</th><th>Payer</th><th>Patient</th><th>Originator</th><th>Biosimilar</th></tr>
<tr><td>Increase in number of patients treated (as % of number treated in a world without biosimilar medicines) (Objective measure)</td><td rowspan="2">Cost savings (as % of costs in a world without biosimilar medicines)</td><td>Average of Physician & Payer scores (to reflect greater access opportunity to the drug and increased funding of / access to other therapeutic options)</td><td>% revenue loss (versus base case)</td><td>% revenue gain or loss versus base case</td></tr>
<tr><td>Level of Improvement in health outcomes in the disease area (subjective measure)</td><td>(Proxi for improved access to medicines overall)</td><td>Price level in the market</td><td>Price level in the market</td></tr>
</table>

### 10.3 The evaluation of policies in combination

The sustainability of the biosimilar medicines market is defined by the effect of policies in combination and their attractiveness overall to the key stakeholders.

The following policies were selected from the "**Sustainability Policy Framework**"

| Policy Option | Policy Description |
|---|---|
| 1. | Intensive programs to develop "Education and Understanding" |
| 2 | Policies to develop biosimilar experience and encourage use |
| 3 | Policies to encourage the capturing of real world evidence (RWE) |
| Pricing | |
| 4.1 | Pricing: Base case |
| 4.2 | High price scenario |
| 4.3 | Medium price scenario |
| 4.4 | Low price scenario |
| 4.5 | Very low price scenario |
| Indication Extrapolation (IE) | |
| 5..1 | IE Scenario 1: European Commission (EC) approval fully accepted by all stakeholders i.e. the scientific principles underlying the biosimilar approvals ; |
| 5.2 | IE Scenario 2: Physicians and Payers are reluctant to accept the EC approvals |
| 5.3 | IE Scenario 3 Physicians do not accept the EC approval and request additional data generation in some or all indications. |
| Utilisation Policy (UP) | |
| 6.1 | UP scenario 1- Early Use - Predominantly a physician driven decision. |
| 6.2 | UP scenario 2- Intermediate situation (multi-stakeholder approach) where the decision is physician / pharmacist / payer driven. |
| 6.3 | UP scenario 3- Well established use:<br>Predominantly a pharmacist/payer driven decision. |

All individual polices were combined into many different scenarios. Each scenario comprised of a set of policies selected from the 6 broad categories above.

**Multi- stakeholder evaluation of scenario attractiveness**

The attractiveness of each scenario was evaluated from the perspectives of each of the stakeholder groups using the "traffic light" scoring criteria described previously.

The "scores" for each stakeholder are combined, and for each scenario a simple indicative "**Sustainability Index**" (SI) is calculated.

The Sustainability Index is calculated by allocating the following scores to each stakeholder group:

- **Red = 0**; **Amber = 1**; **Green = 2**

The perfect policy combination would be one that scores green with all stakeholders – Giving a sustainability score of 10 (= 5*2).

The sustainability score is calculated for all scenarios. This is then expressed as a fraction of 10. This number (between 0 and 1) is the **"Sustainability Index."** The higher the sustainability index, the more sustainable the biosimilar market (and the higher the overall benefits delivered across all stakeholders). The "Sustainability Index" is a simplification of the "**Efficiency Frontier**" approach that is often used in Economic Theory.

***Example of policies in combination and biosimilar medicines market sustainability***

*Although the products (trastuzumab, bevacizumab, and adalimumab) are significantly different, the attractiveness of each scenario was found to be broadly similar for each of the products; but there were significant differences in attractiveness and sustainability between scenarios*

| Scenario | Patient | Physician | Payer | Originator | Biosimilar | **Biosimilars market Sustainability index** |
|---|---|---|---|---|---|---|
| Base case | | | | | | |
| **Scenario 1** | | | | | | **0.9** |
| Scenario 2 | | | | | | 0.6 |
| Scenario 3 | | | | | | 0.6 |
| Scenario 4 | | | | | | 0.8 |

A scenario that is not sustainable (i.e. red) for one or more stakeholder will have a negative impact on all other stakeholders in the medium term. For example, in Scenario 2 above the biosimilar and originator companies both have a poor sustainability score. In this scenario, the market will provide fewer incentives for biosimilar entrants, leading to reduced competition and potentially higher prices for Payers, thereby decreasing access to biosimilar medicines for Patients and Physicians. Originator companies will also have fewer incentives to develop new therapies, thereby not providing Physicians and Patients new treatment options that are possible under other scenarios.

## 10.4 Conclusions of Quantitative Analysis

For all 3 products, the most sustainable scenario and the one which delivers greatest benefits across all stakeholder groups was a scenario that comprised the following **combination of policies**:

| |
|---|
| • Intensive programs to develop "Education and Understanding" (all stakeholders) |
| • Policies that encourage early use and growth of biosimilar medicines experience |
| • Policies that encourage the capturing and communication of real world evidence (RWE) in order to build confidence and trust (but not as a requirement for access) |
| • A sustainable competitive pricing environment with price level consistent with financial viability and a fair return on investment (medium price scenario). Pricing and procurement policies transparent |
| • Extrapolation to other indication (s) is well understood and accepted by all stakeholders. Indication specific data in all of the reference indications is not a requirement at launch for access or utilisation (underpinned by education/understanding and RWE programs) |
| • Utilisation policy which is evolutionary in nature. Early Use: Predominantly a physician driven decision; Intermediate situation: (multi-stakeholder approach) where the decision is physician / pharmacist / payer driven; and Well established use: Predominantly a pharmacist/payer driven decision. |

### Cost Savings

System dynamics modelling indicates that significant cumulative cost savings over the 10 year period from the entry of a product's first biosimilar medicine are likely under the above optimal policy combination.

| Molecule | Cumulative 10 year Savings[20] (EU5) |
|---|---|
| adalimumab (Humira®) | 26% |
| bevacizumab (Avastin®) | 24% |
| trastuzumab (Herceptin®) | 25% |

[20] *EU5 is composed of France, Germany, Italy, Spain, and the UK*
*Cumulative savings = "Cumulative budget impact of 'originator' IF the biosimilars did not enter the market - Cumulative budget impact of 'originator plus biosimilars' (over the 10 years post-entry of the 1st biosimilar)*
*10 year time horizon ensures the evolution of biosimilar volume share and net pricing appropriately reflected in cost savings calculation*

The cumulative savings were calculated by considering the cumulative budget impact of the 'originator' if biosimilar medicines did not enter the market minus the cumulative budget impact of 'originator plus biosimilars' (over the 10 years post-entry of the 1st biosimilar). The 10-year time horizon ensures the evolution of biosimilar volume share and net pricing are appropriately reflected in the cost savings calculation.

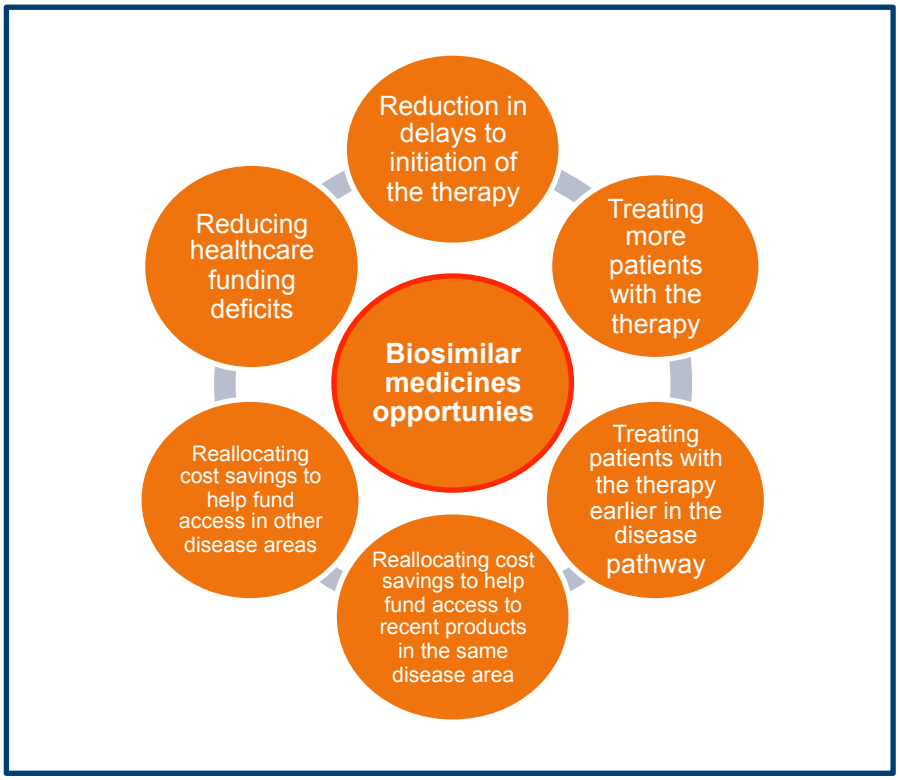
Higher cost savings would be possible but would result in a less sustainable biosimilars market with a consequent decrease in the magnitude of benefits to all stakeholders, particularly the decline of continued attractiveness for R&D investment in new medicines development and reduced competition in the market.

**Improved Patient Access**

The interview program and subsequent analysis indicated that the cost savings generated by the introduction of biosimilar medicines with the combination of policies detailed above might be utilized in various ways to increase patient access to biological medicines. These included:

- **Treating more patients with the therapy** - in situations where cost, cost-effectiveness, and affordability is currently a barrier to access
- **Reduction in delays to initiation of therapy**
- **Treating patients with the therapy earlier in the disease pathway** - where clinically appropriate
- **Reallocating cost savings in the same disease area** to help fund access to recent innovative products without which access to these therapies would be limited due to budgetary considerations
- **Reallocating cost savings to help fund access in other disease areas**
- **Reducing healthcare funding deficits**




**Humira® (adalimumab)**

- The treatment of inflammatory diseases (such as Rheumatoid Arthritis – RA) with anti-TNFs is well established in the EU5, but some barriers to access do exist and these vary across Europe. Many of the patients who would benefit from anti-TNF treatment, but are currently denied treatment, or whose treatment is delayed on economic grounds, will benefit from anti-TNF biosimilar medicines due to the cost savings that their introduction will bring.[21]
- Adalimumab is likely to be the 3rd of the major anti-TNFs (after infliximab and etanercept) in terms of timing of biosimilar market entry in Europe. Quantitative modelling indicates that many of the benefits of biosimilar anti-TNFs will be delivered progressively from the launch of infliximab biosimilars until after Humira® (adalimumab) patent expiry. The lower infliximab prices that will be experienced following the entry of infliximab biosimilar medicines in 2014 are expected to have an immediate positive effect on patient access to Enbrel® (etanercept) and Humira® (adalimumab) due to likely net price reductions across all anti-TNFs , generating cost savings across all anti-TNF products that could potentially be utilised to fund treatment of more patients with anti-TNF therapies in countries/regions where there is currently limited access and to help fund access to the expected future oral RA therapies which early evidence suggests may offer better outcomes in some patients.

[21] *Within the interview program, physicians and payers in the southern European markets (Italy and Spain) reported significant economic barriers resulting in reduced access to, or delay in, the initiation of anti-TNF therapy, minor barriers (mainly delays) to access under current clinical guidelines / HTA Guidance were reported in France / UK, whilst there appeared to be no significant access barriers in Germany.*

- Under the above optimal policy scenario, with cost savings of up to 26%, the potential to treat more patients with Humira® or adalimumab biosimilar medicines will vary across Europe. As for Herceptin, the opportunity to treat more patients with Humira® is higher in Italy and Spain where austerity and current economic guidelines limit access with the opportunity to treat more patients likely to be significantly higher in Poland and Hungary.
- Based on extrapolation of results from the system dynamics model, GfK estimate that cost savings of 25%-30% may be possible across the whole of anti-TNF use in EU5, with the opportunity to treat more patients under current treatment guidelines. The extent to which earlier use (facilitated by the economic advantages offered by biosimilar medicines entry) might lead to improved clinical outcomes and long term reduction in healthcare resource utilisation should be a subject for future research.

**Avastin® (bevacizumab)**

- Three factors lead GfK to believe that there will be significantly more patients who will benefit from treatment with bevacizumab on the market entry of biosimilars
    - Cost and affordability is a barrier to access in some of the approved indications of use
    - Avastin® has a limited conditional or no HTA recommendation in some markets (England; Scotland; most of the regions in Spain and Italy). Entry of bevacizumab biosimilar medicines is likely to lead to greater HTA recommendation for access and reimbursement.
    - The biosimilars market will relatively mature by the time that bevacizumab biosimilar medicines are launched. Greater experience and improved confidence will likely result in more rapid uptake of biosimilar bevacizumab and faster delivery of the benefits to patients and payers by comparison to the earlier biosimilar monoclonal antibodies.
- Other potential areas of increased patient access identified in the interview program, outside of the scope of our quantitative analysis and which we recommend should be explored further in an appropriate research context, included:
    - Increased treatment with bevacizumab in combination with other novel targeted agents (it was reported that it is often the total cost of combination that results in patients being denied access), and
    - Treatment through progression in patients where this would be clinically appropriate. Several of the KOL's interviewed expressed an opinion that Avastin® may be licensed though progression in several tumour types (CRC, NSCLC) by the time of patent expiry, but expected real world utilisation would be significantly constrained by cost.

**Herceptin® (trastuzumab)**

- The treatment of HER2[22] positive breast cancer in EU5 with Herceptin® currently has low barriers to access, with patients who would benefit from this product receiving it in most cases. The primary research shows that the opportunity to treat more patients with Herceptin® is higher in Italy and Spain where current austerity measures and economic guidelines limit access to Herceptin®. This is probably also the case in Poland and Hungary (both outside the scope of our quantitative analysis)

- There remains, however, the need for innovative treatments in HER2 positive breast cancer. A challenge for these new products will be affordability and access. Our analysis indicates that the cost savings generated by the entry of trastuzumab biosimilar medicines (under the above optimal policy combination, up to 25% savings) could be used to help fund access to the emerging new therapies in this area

- The arrival of trastuzumab biosimilar medicines, together with the arrival of new innovative products, will provide the opportunity to deliver a broad range of benefits for all stakeholders. In particular:
    - Produce significant cost savings (25% - 10 year cumulative)
    - Provide opportunity for more cost-effective management of the HER2 positive breast cancer population
    - Result in better overall health outcomes in the HER2 breast cancer population

And will at the same time maintain an environment that is attractive for Industry by delivering opportunities and returns for developers of biosimilar and new innovative medicines.

[22] *Human epidermal growth factor receptor 2*

# 11 Conclusions and Recommendations

- The overall stakeholder sentiment towards biosimilar medicines is positive
- For all stakeholder groups, awareness and understanding of accurate unbiased information about biosimilar medicines needs to be improved; as does awareness and understanding of the requirements for a sustainable biosimilar medicines market. Unless addressed this will be a barrier to uptake and the delivery of continuing benefits to all stakeholders in both the short and long term.
- Confidence and trust should be established by encouraging appropriate early use and encouraging the collection and publication of real world evidence (RWE). However RWE should not be a requirement for access
- Biosimilar medicines are intrinsically different from generic small molecule medicines. The policies governing pricing, procurement, and utilisation of generic medicines cannot be directly transferred over to biosimilar medicines.
- Clinical guidelines developed by pan-European and national organisations (medical societies) are the most impactful, and should be further developed to appropriately incorporate biosimilar medicines based on scientific rationale and evidence
- Biosimilar medicine utilisation drivers should evolve over time as stakeholders develop more confidence and trust
- Payers must avoid arbitrary, prescriptive pricing policies that place artificial downward pricing pressure on manufacturers. Payers should allow companies to compete freely on price. Forcing biosimilar companies into a mandatory discount is detrimental to market sustainability
- Procurement decision-making should be transparent. Payers must not use exclusive tendering, as it hinders competition, and should welcome multi-faceted tenders in which companies can compete on additional aspects of value other than just price alone

# 12 Appendices

## 12.1 Definitions used in the Report

**Extrapolation of indications**:

- The decision whether to extend the efficacy and safety data from an indication (a medical condition, disorder or disease) for which the biosimilar has been clinically tested to other conditions for which the branded product is approved, is known as “extrapolation”.

**Industry**

- “Industry” is a broad term used in the study for pharmaceutical industry including all biological (both originator and biosimilar medicines) manufacturers

**Interchangeability:**

- The medical practise of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.

**Payer**

- “Payer” is a broad term used in the study to cover budget holding; budget influencing; pricing, procurement, and formulary decision-making individuals / authorities at the European, National, Regional, or Local levels.

**RWE – Real World Evidence**

- RWE are large data sets gathered from community “real world” use of a medicine outside of the controlled environment of clinical trials with restricted inclusion criteria. RWE allows investigators see how medicines perform in ‘real-life’ and how patients use them when they are not screened for age, weight, education levels and willingness to comply with instructions.
- In addition to the standard safety monitoring requirements of licensure (PSUR) - Post Marketing studies, Observation of Use studies, Retrospective Chart Reviews, Prospective Registries, Drug Utilisation Audits (DUAs). Such studies should, where possible, capture outcomes data. Such studies should NOT be a requirement for market access, but should be considered “facilitators” for developing early experience, confidence and trust.

**Substitution:**

- Practise of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.

**Sustainability Index**

- The “Sustainability Index” is a simplification of the “Efficiency Frontier” approach, well documented in Economic Theory. Scores are allocated for each stakeholder group: Red = 0, Amber = 1, Green = 2, where the colour represents the attractiveness of a policy or policy combination from the perspectives of the stakeholder group. The perfect policy combination would be one that scores green with all stakeholders (Physicians, Payers, Patients, Originator Product and Biosimilar manufacturers) giving a sustainability score of 10 (= 5*2). The sustainability score is calculated for all scenarios. This is then expressed as a fraction

of 10. This number (between 0 and 1) is the "Sustainability Index". The higher the sustainability index, the more sustainable the biosimilar medicines market. It is used to identify the most attractive policy combination(s) that would deliver continuing benefits to the key stakeholder groups in BOTH the short and long term.

**Switching:**

- Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

## 12.2 Overview of stakeholder composition by country and type

| | |
|---|---|
| **France** | **12** |
| KOL- Oncology | 2 |
| KOL- Rheumatology | 2 |
| Pan-EU Influencer | 2 |
| Payer | 2 |
| Pharmacist | 4 |
| **Germany** | **10** |
| KOL- Oncology | 2 |
| KOL- Rheumatology | 2 |
| Payer | 3 |
| Pharmacist | 3 |
| **Hungary** | **5** |
| KOL- Oncology | 1 |
| KOL- Rheumatology | 1 |
| Payer | 2 |
| Pharmacist | 1 |
| **Italy** | **13** |
| KOL- Oncology | 2 |
| KOL- Rheumatology | 2 |
| Pan-EU Influencer | 2 |
| Payer | 5 |
| Pharmacist | 2 |
| **N/A** | **3** |
| Pan-EU Influencer | 1 |
| Patient | 2 |
| **Poland** | **5** |
| KOL- Oncology | 1 |
| KOL- Rheumatology | 1 |
| Payer | 3 |
| **Spain** | **12** |
| KOL- Oncology | 2 |
| KOL- Rheumatology | 2 |
| Pan-EU Influencer | 3 |
| Payer | 3 |
| Pharmacist | 2 |
| **UK** | **11** |
| KOL- Oncology | 2 |
| KOL- Rheumatology | 2 |
| Pan-EU Influencer | 1 |
| Payer | 2 |
| Pharmacist | 4 |
| **Grand Total** | **71** |

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