

IGBA REFLECTION PAPER – CHALLENGES AND OPPORTUNITIES FOR ACCESS TO BIOSIMILAR INSULINS AND ANALOGS

KEY TAKEAWAYS

- Today, **only half of the 69 million patients** requiring insulin therapies are able to access these medicines regularly: the **global potential for biosimilar insulins and analogs'** use as a significant lever for greater access equity for patients living with diabetes **remains largely untapped**.
- **Key barriers to equitable global access** include:
 - o Lengthy, costly and at times inefficient **regulatory approval pathways** which limit the number of companies able to bring biosimilar insulins and analogs to market in countries around the world.
 - o Lack of market predictability and general challenges in **purchasing and procurement practices** can especially hamper supply for biologic medicines that are complex and costly to manufacture.
 - o **Lack of acceptance and trust in biosimilar medicines** among providers and patients can limit utilization, and continued preference by healthcare stakeholders, including payers, for original brand biologic medicines can challenge the viability of biosimilar competition.
- Collectively, the biosimilar medicines industry can advocate for policies that pave the way for **sustainable competition and reliable access**, addressing the key known barriers to global access, however it fundamentally relies on policymakers, regulatory authorities, and payers to make these policy decisions.
- There are tremendous opportunities for collaborative action by stakeholders to unlock patient access through use of biosimilar insulins and analogs; stakeholders must join in recognizing the **power of global alignment and good practice sharing in overcoming our common access challenges**.

HIGH-LEVEL RECOMMENDATIONS FOR COLLABORATIVE ACTION BY STAKEHOLDERS

Enhancing Regulatory Efficiency for Greater Access

- **International regulatory convergence** on evidence requirements for the review and approval of biosimilar insulins and analogs, as well as **international regulatory reliance**, can help speed up biosimilar medicine development, approval and the broadening of biosimilar availability, overcoming unnecessary regulatory complexity, as well as relieving regulatory capability and capacity constraints.

Improving Market Predictability & Resilience for Timely and Stable Access

- Experience and good practice sharing for market policy and pro-competitive measures in the biosimilar insulins and analog market to foster a sustainable multi-player environment, remove barriers and align incentives across all stakeholders to use biosimilars as an access lever.

Advancing Understanding and Trust In Biosimilars for Sustained Access

- Sustained educational efforts by trusted authorities across stakeholder groups, including leading the dissemination of educational materials, to advance shared knowledge of key concepts related to biologic medicines and experiences, as well as actively tackling misleading information by focusing on concepts that may be challenging for patients and health care providers to accept.

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BACKGROUND

This year, 2021, marks the 100th anniversary of a tremendous medical achievement: the discovery of insulin, a peptide hormone responsible for regulating blood glucose levels and an essential, life-saving treatment for diabetes. However, this centenary is also cause for reflection. Despite the existence of insulin, complications from diabetes continue to be one of the leading causes of death and disability globally. In fact, diabetes newly entered the WHO's top ten causes of death in 2020 after seeing a 70% increase in the last two decades.¹

Diabetes is a chronic disease in which the pancreas either produces little or no insulin (Type 1 diabetes) or when the body becomes resistant to or doesn't produce enough insulin (Type 2 diabetes). People with Type 1 diabetes need to take insulin to survive, and many people with Type 2 diabetes will progress to needing insulin after trying oral medicines and disease-modifying behaviors, like healthy diet, physical activity and tobacco cessation.²

According to the WHO, there are more than 420 million people living with diabetes worldwide; this number is anticipated to grow to over 570 million by the year 2030.² Approximately 69 million people living with diabetes currently require insulin and analogs to manage their condition, but estimates suggest that **only half of those in need have regular access to insulin**, and even **fewer are able to afford insulin** and related health technologies.³

Insulin is a biologic medicine, which means it is developed from living cells instead of chemicals. Biologic medicines are generally more complex to develop and manufacture than chemically synthesized 'small-molecule' drugs, and due to their origin from living cells are all inherently variable. Although this does not impact the quality, safety or effectiveness of biologic products approved by mature regulatory authorities, it means that generic drug pathways for follow-on competition are not applicable because a biologic product cannot be copied exactly, even between batches of the same brand product.

Instead, original brand biologic medicines face competition from biosimilar medicines, which are biologic medicines proven to be highly similar to the original reference product, with the same clinical outcome for patients. In other words, a biosimilar medicine is as similar to the reference biologic as batches of the reference biologic are to each other. This means that patients can confidently use approved biosimilar medicines instead of the original brand biologic medicine. Indeed, biosimilars have been used for over 15 years, with more than 2 billion patient days of accumulated clinical experience in the EU alone.⁴

¹ "WHO reveals leading causes of death and disability worldwide: 2000-2019" WHO News Release, 9 December 2020, available at: <https://www.who.int/news/item/09-12-2020-who-reveals-leading-causes-of-death-and-disability-worldwide-2000-2019>

² "Insulin and associated devices: access for everybody" WHO Stakeholder Workshop Report, 16 November 2020, available for download at: <https://www.who.int/publications/i/item/insulin-and-associated-devices-access-for-everybody-who-stakeholder-workshop-21-and-23-25-september-2020>

³ WHA Resolution on Reducing the burden of noncommunicable diseases through strengthening prevention and control of diabetes (A74/A/CONF./5) May 2021
https://apps.who.int/gb/ebwha/pdf_files/WHA74/A74_ACONF5Add1-en.pdf

⁴ European Biosimilar Medicines Group (Medicines for Europe), based on : MIDAS MAT Q2 2020 data; rituximab and trastuzumab DDDs calculated via IQVIA Real World Data, Oncology Dynamics physician surveys on average cycles; pre-2009 analysis includes extrapolated treatment days for biosimilars launched between 2005 – 2008; country

Biosimilar insulins and analogs have been approved by several mature regulatory authorities and have contributed to expanding patient access to more affordable insulin therapies in many countries. For many reasons, however, biosimilar insulins and analogs have not reached their full potential in expanding patient access to these life-saving treatments around the world.

Further opportunities exist for collaborative action by stakeholders – international and local, public and private – to overcome barriers to equitable access to insulin, including biosimilar insulins and analogs.

ENHANCING REGULATORY EFFICIENCY FOR GREATER ACCESS

Robust regulatory evaluation is critical to ensure the quality, safety and efficacy of medicines made available to patients. Equally important, however, is recognizing the impact of discrepant regulatory requirements on the ability of patients to access these medicines.

Many medicines, particularly complex medicines like biologics (including insulin and analogs), are developed by pharmaceutical manufacturers with the intent of making the same product available to patients in multiple countries. **Lack of convergence in regulatory systems can mean that the same product may face different evidence requirements for regulatory approval across jurisdictions.** In some cases, local clinical data requirements can impose an unnecessary – and unethical – obligation to duplicate clinical studies without any scientific justification. Such requirements are also significant drivers of additional cost to bring a biosimilar product to market.

Regulatory timelines can also differ by country and are often lengthy and unpredictable, further complicating wide availability of the same product. Current review and approval timelines across jurisdictions can extend from 24 to 36 months with little transparency into application status. Once an application is approved, ongoing work is needed to keep the registration updated and compliant with evolving requirements (i.e. regulatory maintenance). Post-approval amendments (typically referred to as variations or supplements depending on the jurisdiction), for example to update the product label or transfer the manufacturing site, can take an additional 12 months. Maintaining approvals in each jurisdiction also comes at substantial cost, both in fees and in regulatory personnel to manage divergent requirements and timelines.

Manufacturing facility inspections can also serve as a substantial source of delay in approval of medicines, including biosimilars, and represent a tremendous opportunity for reliance on trusted partners to expedite access. While inspections are an important element of ensuring the robustness of manufacturing practices and the quality of registered medicines, compliance with international standards is required in most markets, with limited jurisdiction-specific requirements that deviate from globally accepted good manufacturing practices. Duplication in inspections is particularly inefficient when the same facility has recently been inspected for the same product by a mature, trusted regulatory authority.

Not only can a lack of regulatory convergence introduce additional cost to product development, it may also disincentivize companies from seeking product registration in all countries, further challenging the opportunity for equitable global access. Countries with lengthy or unpredictable regulatory procedures, or unique local requirements, may not support the same **degree of market availability and competition** as other countries with more streamlined processes. Ultimately, regulatory fragmentation limits the number

cohort includes 30 countries within Europe Economic Area <https://www.medicinesforeurope.com/wp-content/uploads/2020/12/BIOS5.pdf>

of companies able to bear the investment needed to make a product widely available and impacts their ability to actively compete in the markets they can access.

These challenges are broadly relevant for medicines in general, but are compounded for biosimilar medicines, including biosimilar insulins and analogs. While **regulatory pathways for registration of biosimilar medicines** have increased in prevalence over the last decade, there remain many countries that do not have biosimilar pathways offering an abbreviated registration option maintaining a robust head-to-head comparability exercise with the reference product in line with the WHO SBP guidelines. In some cases, due to the lack of a biosimilar pathway, sponsors of a product that is approved in other markets as a biosimilar must choose between registering the product as either a novel biologic, with the additional data requirements associated, or as a generic drug, which can have implications both for dossier requirements and market access of the approved product.

There are **many opportunities for greater convergence of regulatory requirements**, including through expansion of established mechanisms and platforms. The WHO is uniquely placed to facilitate greater reliance, for example **through increased use of the collaborative procedure for accelerated registration or by advancing the WHO Listed Authority mapping** to enable countries to make decisions around trusted sources for approval or inspection information to reduce duplication. WHO is also positioned to improve **capacity building and support for national implementation** of biosimilar pathways aligned with the WHO Similar Biotherapeutic Products ('SBP') Guideline. Specific to insulin and analogs, considering the Global Diabetes Compact, WHO is well-placed to disseminate guidance related to regulatory and clinical experience with insulin and analogs, including biosimilar insulins and analogs.

The WHO can also advance **greater regulatory reliance** to overcome local regulators capability and/or capacity constraints. A good example would consist in the **expansion of the WHO Pre-Qualification procedure to biosimilar insulins and analogs**. Facilitating broad registration of analog versions of insulin may improve the competitive dynamics of this market, allowing greater access for patients to more insulin therapeutic options, including some requiring less ancillary equipment and improving convenience, such as long-acting formulations and self-injecting pens.

Regulatory efficiency can be advanced not only through greater reliance between authorities, but also through greater alignment in requirements across regulatory frameworks. Achieving **single global development for biosimilar medicines** is increasingly realistic given greater recognition of common experiences with biosimilar medicines across regulatory jurisdictions. Two main areas where regulatory alignment would have outsize impact on the efficiency of biosimilar development are the **acceptability of a global comparator product**, and thus the waiving of bridging studies between local and foreign-licensed reference products, and the **advancement of a tailored approach to clinical trial requirements** in light of scientific, technical and analytical progress over the last decade⁵.

Aligning regulatory requirements across jurisdictions to truly allow for single global development of biosimilar medicines, without imposing local requirements for bridging between reference products or for comparative clinical efficacy trials, particularly those requiring testing in local populations, would improve access to biosimilar medicines for patients around the world.

⁵ Schiestl et al. The Path Towards a Tailored Clinical Biosimilar Development - BioDrugs 2020;34, 97–306; <https://doi.org/10.1007/s40259-020-00422-1>

Progress towards greater regulatory reliance between national competent authorities may reduce access delays attributable to the fragmented and disharmonized global regulatory landscape. Achieving greater alignment and convergence in regulatory frameworks supportive of single global development of medicines can facilitate expedited access more equitably across countries, with the possibility for lower development and operating costs and greater economies of scale, translating to more affordable prices reliably available for patients and health systems around the world.

IMPROVING MARKET PREDICTABILITY & RESILIENCE FOR TIMELY AND STABLE ACCESS

Securing timely and stable access to medicines for patients is a critical element of reliable health systems. This is particularly relevant for chronic, life-saving medicines like insulin and analogs. Continuity of availability of insulin and analogs is essential for people living with diabetes. Regulatory efficiency is an important element of access but is not in itself sufficient to enable availability for patients. Ensuring reliable patient access to insulin and analogs, including through biosimilar use, requires the confluence of **several factors enabling healthy market competition**.

Predictability is an essential component of ensuring consistent market availability. **Demand visibility** is critical for all medicines, but particularly so for medicines, like biologics, with complex manufacturing processes, longer lead times and higher investment costs. Manufacturing high-quality biologic medicines, including biosimilar medicines, is a complex and resource-intensive process. Insulin and analogs, as biologic medicines, are no exception. Enabling manufacturers to reach sufficient economies of scale to lower costs for health systems and patients requires predictable **volume planning**.

There are many mechanisms to enable better market predictability, allowing manufacturers to achieve the economies of scale necessary to offer a consistently priced and reliable supply of medicines. For insulin and analogs, a **globally aligned mapping of actual demand** would help set a baseline for manufacturers and procurers. This demand mapping would need to **translate concretely into long-term procurement forecasts** to allow manufacturers to plan for adequate production capacity to meet demand in all markets in which regulatory approvals are secured. As noted above, facilitating regulatory approval for registrations across a broad number of markets can enable planning to maximize production capacity.

Purchasing and procurement mechanisms have tremendous impact on supply availability. The appropriate method of procurement will likely vary per market based on the health system context, but shared principles focused on predictability can facilitate reliable medicine availability: purchasing and procurement models allowing for **multiple suppliers** to sustain competition in the market and mitigate against shortages resulting from supply disruption; **long-term agreements** enabling capacity planning and more competitive pricing; **purchasing and procurement criteria incorporating elements other than price** to allow for a holistic view of supply reliability, etc. Conversely, short-term fragmented orders without a consistent view of overall demand can lead to supply constraints. Overly punitive terms such as short lead times or high penalties for supply disruptions can limit the ability of manufacturers to respond to orders and counter-productively undermine the sustainability of supply.

Beyond predictability, which is relevant for the operation of healthy markets across many types of medicines, **biosimilar medicines require additional supportive mechanisms** to enable successful competition and maximize patient access. A baseline of trust in biosimilar medicines is required to ensure a level playing field in acceptability compared to established brand biologics. Beyond trust, however, market

dynamics must recognize the **systemic challenges to biosimilar utilization** that require additional intervention to ensure competition in the short, medium, and long term.

Despite substantial global experience with biosimilar medicines, gaps remain in acceptability of biosimilar medicines by patients and healthcare professionals. In many cases, this is due to a fundamental lack of awareness and understanding of biologic medicines in general but arises for the first time when confronted with the ‘new’ concept of biosimilar medicines. Educational initiatives supported by regulatory authorities and policymakers are needed to build trust in biosimilar medicines as a prerequisite for successful market competition. This is particularly relevant in situations of transition to biosimilars, such as in chronic therapy with insulin and analogs.

Due to the complex nature of biologic medicines, the development, market authorization and manufacture of biosimilar medicines can cost hundreds of millions of dollars and take up to ten years. This is a substantial investment that can only be borne with the expectation of sufficient utilization and can prevent biosimilars from actively competing with the original brand biologic unless adequate volumes are guaranteed. The absence of a general expectation of utilization will challenge biosimilar companies to make the investment needed to bring widespread access to biosimilar competition referencing additional original brand biologics.

Unfortunately, some payers have viewed the advent of biosimilar medicines as a lever to secure greater **price reductions from the original brand biologic in the short term**, with no corresponding utilization of the biosimilar medicine and with little consideration of the impact this practice will have on actual market competition dynamics or future investment in biosimilar competition. **This practice de facto prolongs originator monopolies and interferes with competitive dynamics.** In some cases, original brand biologics can more easily provide steep short-term discounts than a new biosimilar competitor given their many years of market experience. There are global repercussions for such decisions; if biosimilars cannot gain sufficient utilization in large markets, this impacts their ability to achieve economies of scale and remain competitive in other markets.

With over 15 years of biosimilar purchasing and procurement practice, the wealth of experience garnered across the world is immense and good practice sharing has proven a powerful tool to help late biosimilar adopters in making significant leaps towards greater biosimilar utilization. **Good practice and experience sharing** on tackling structural market barriers and designing adequate utilization incentives should constitute a basic pillar in support of national policy framework advances.

Purchasing and procurement systems that recognize the sustained need for biosimilar competition and advance policies that support biosimilar medicines are an important component of improving access. Policies that explicitly support biosimilar medicines and foster healthy competition between biosimilars and original brand biologics may look different based on varying health system contexts, but fundamentally require a focus on removing existing barriers to biosimilar medicines use and alignment in incentives across all stakeholders to use biosimilars as an access lever. The path of least resistance in a ‘level playing field’ is to stick with the status quo (in this case, use of the original brand biologic); health systems must correct this structure to ensure long-term competition from biosimilar medicines remains viable. Good practice and experience sharing is a cornerstone to significantly advancing biosimilar policies in countries where access to biologic insulins and analogs remains challenging.

ADVANCING UNDERSTANDING AND TRUST IN BIOSIMILAR INSULINS AND ANALOGS FOR SUSTAINED ACCESS

Ensuring stakeholders across the health system, from payers to healthcare providers and patients, have **access to accurate information about biosimilar medicines** and receive **appropriate educational support from trusted sources** can have an outside impact on the ability of a competitive biosimilars market to flourish. While pharmaceutical companies have an important role to play in ensuring accurate product information is available, many stakeholders look to health regulatory authorities, academic institutions or civil society groups as credible information providers instead of relying on private sector entities with the potential for conflicts of interest.

Important differences between biologic medicines and small-molecule chemical drugs are not widely understood, and in many cases these differences form the root of mistrust experienced with biosimilar medicines. For example, the concept of ‘similarity’ versus ‘sameness’ has at times created confusion among healthcare providers and patients accustomed to the chemical drug generic framework and skeptical of a seemingly lesser standard, without realizing that the inherent variability in biologic medicines that necessitates **‘similarity’ of biosimilars compared to originator brands equally applies to existing originator brand biologics as well.**

Advancing shared understanding of key concepts related to biologic medicines, also applicable to biosimilars, is an important role of health authorities. As the ultimate guarantor of the quality, safety, and efficacy of medicines available to the population, health authorities are a trusted resource for all other health system stakeholders. Bringing together stakeholders to share knowledge and experience, including **by co-creating educational materials targeting real questions and in language easily understood at various levels of familiarity**, can be a critical aspect of health authorities’ work in ensuring patient access to biologic medicines.

There is a growing pool of **cumulated clinical and pharmacovigilance experience** which is – to date – often not shared pro-actively with stakeholders. Given it is overwhelmingly positive, a publicly accessible set of resources on this important aspect, collaboratively updated, would be a steppingstone for stakeholders not yet familiar with the concept and a reassuring message on the robustness of the biosimilar regulatory pathway.

Trust in biosimilar medicines is particularly relevant for patients who are experienced with chronic use of biologic medicines, including insulin-dependent people living with diabetes. Changing medicines can be a stressful experience, especially if multiple medicines have previously been tried. The concept of switching to a biosimilar medicine while responding well to the originator brand biologic can be particularly challenging to accept.

However, **a treatment-experienced patient is the appropriate candidate to switch to a biosimilar because success with the biological medicine is a likely indication of success with the biosimilar since both are the same molecule.** This is a vital concept that trusted authorities should educate patients and health care providers about to combat the tendency to not change biologic medicines when appropriate and to encourage access through the uptake of biosimilar medicines. Good practice sharing on the many switching policies and switching studies carried out to date provide for an unambiguous resource on the clinical experience gathered thus far.

Biosimilar medicines, including insulin and analogs, contribute to broader and more equitable patient access to biologic medicines. Ensuring that lack of stakeholder understanding and trust in biosimilar medicines does not thwart access gains is an important aspect of the work that uniquely falls to trusted, credible resources like health authorities, academic institutions, and civil society groups. Equally important is the communication towards stakeholders on the cumulated global experience with biosimilars, including insulins and analogs, and the reassurance of post-approval safety signals gathered over time.

CONCLUSION

The opportunity to align globally on the value of biosimilar competition is starkly relevant for access to insulin and analogs. Overcoming lengthy, costly and at times inefficient regulatory approval pathways can be difficult and limit the number of companies able to bring biosimilar insulins and analogs to market in countries around the world. Once regulatory approval is received, however, the ability to reach patients is not guaranteed. Lack of market predictability and general challenges in purchasing and procurement practices can hamstring supply for all medicines, but particularly so for biologic medicines that are complex and costly to manufacture. On top of these general challenges, biosimilars are faced with additional hurdles: lack of acceptance and trust in biosimilar medicines among providers and patients can limit utilization, and continued preference by healthcare stakeholders, including payers, for original brand biologic medicines can challenge the viability of biosimilar competition.

Together, these factors lead to a situation in which biosimilar competition, while the ideal solution for improving access to insulin and analogs for patients regardless of geography, faces an uphill climb to achieve this goal. Importantly, these challenges are structural and not within the power of any single biosimilar company to address unilaterally. A given biosimilar company may commit to register their biosimilar products in a set number of countries, or to price their biosimilar products in a way that reflects a country's income level, but ultimately these commitments are limited by the policy environment -both the regulatory and market policy frameworks. Where biosimilar utilization is supported and encouraged, broader and more sustainable biosimilar competition across all countries will lead to a greater impact on patient access than any action a single company can commit to.

Collectively, the biosimilars industry can advocate for policies that pave the way for sustainable competition and reliable access, but fundamentally the industry relies on policymakers, regulatory authorities, and payers to make and implement these policy decisions. There is tremendous potential to unlock patient access through use of biosimilar insulins and analogs; stakeholders must join in recognizing the power of global alignment and good practice sharing in overcoming our common access challenges.

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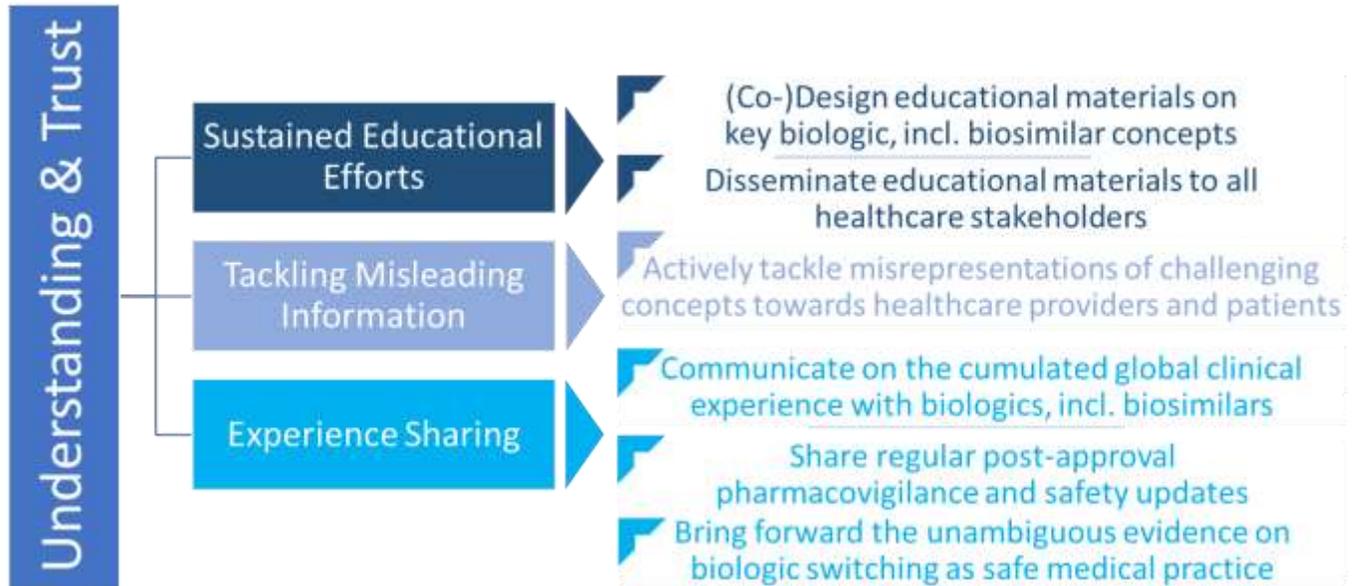
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ABOUT IGBA



INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

The International Generic and Biosimilar medicines Association (IGBA) was founded to strengthen cooperation between associations representing manufacturers of generic and biosimilar medicines from around the world. The IGBA is at the forefront of preserving sustainable competition within our industry, by stimulating competitiveness and innovation in the pharmaceutical sector; thereby, ensuring millions of patients around the world have access to high quality, pro-competitive medicines.

For more details, regarding IGBA and its member associations, see the IGBA website at:
www.igbamedicines.org

For IGBA Biosimilar resources, please see: <https://www.igbamedicines.org/committees/biosimilars-committee>

