Evolving U.S. Biosimilars Landscape

A Medical Affairs Perspective

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Introduction

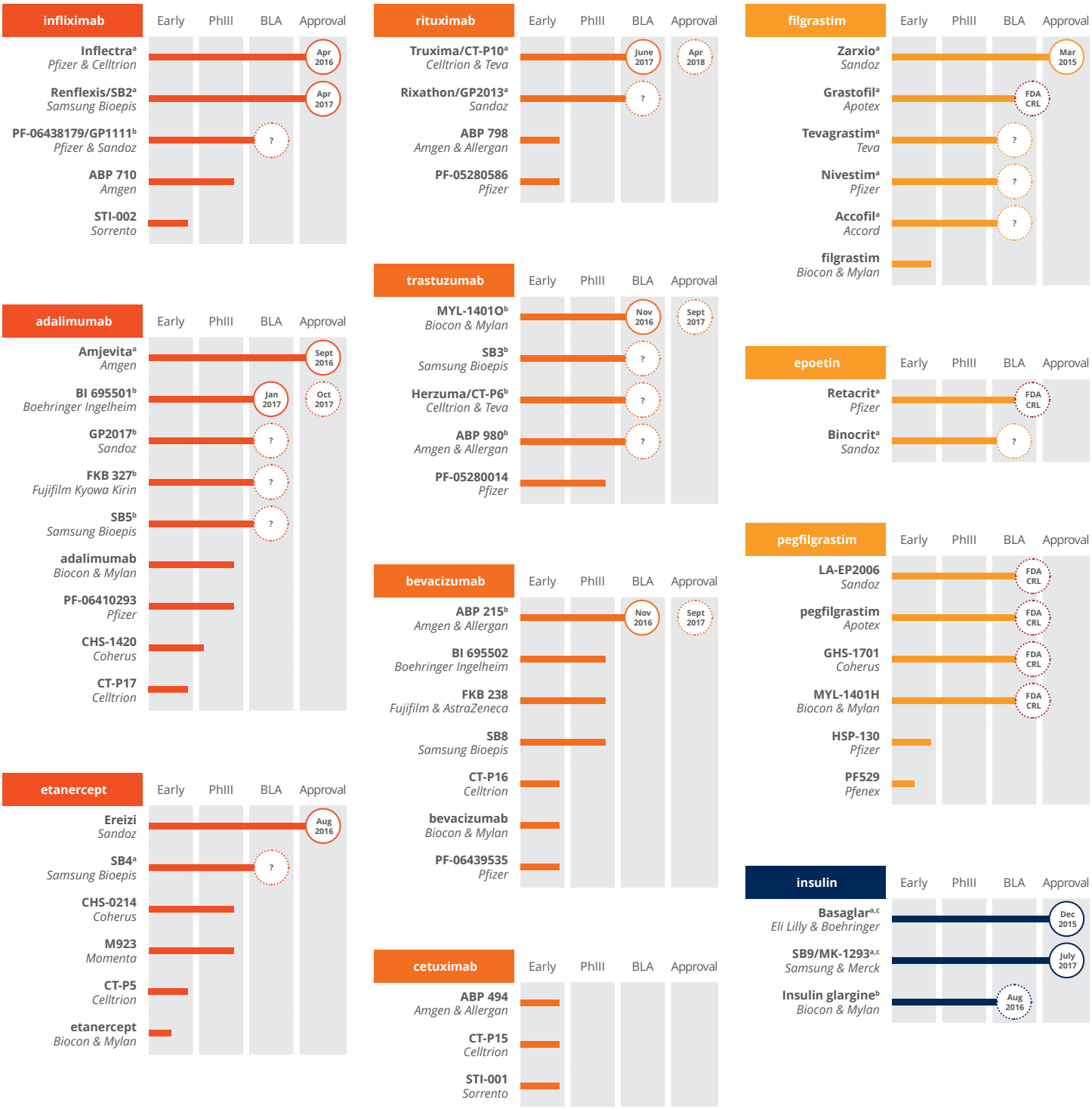
The U.S. biosimilar landscape is evolving rapidly, with three biosimilar products already available (Zarxio, Inflectra, Renflexis) and two more expected to launch by the end of 2018 (Amjevita and Erelzi). By 2020, there may be as many as 30 biosimilar products on the market in the U.S., targeting key indications in immunology, oncology, endocrinology, ophthalmology and pulmonology (Figure 1). Nearly half of biosimilar candidates in the pipeline are oncology products, including oncology therapeutics (bevacizumab, cetuximab, rituximab and trastuzumab biosimilars) and supportive care (biosimilar filgrastim, pegfilgrastim, and epoetin). The foundation for how the U.S. market will react to future biosimilar launches is being laid now, creating an opportunity for companies to shape the trajectory of biosimilars in the U.S., including their uptake, impact on corresponding innovator products and competition among multiple biosimilar versions of the same reference product. For example, there may be as many as five biosimilar versions of AbbVie's Humira (adalimumab) approved in the U.S. by 2020, vastly complicating the therapeutic landscape. No matter what position a company plays in the biopharmaceutical market (innovator or not), biosimilars will bring new challenges. The key challenge companies must face is how they will adapt their product development and commercialization strategies to be successful.

Based on key learnings from the first U.S. biosimilar launch[1], manufacturers have started to realize that biosimilars require not only a unique development pathway but also a more tailored go-to-market approach.[2] While much has been said about the need to modify the Commercial support required for biosimilars, the role of Medical Affairs and how it needs to evolve to guide biosimilar product development strategy is yet to be defined. Similarly, the role of Medical Affairs in shaping defense strategies in the face of biosimilar competition has not been explored. Syneos Health Consulting has leveraged its subject matter expertise in Medical Affairs as well as its experience in the biosimilar space to develop a perspective on the evolution of Medical Affairs in the era of biosimilars. The perspective is captured in this position paper and will be further validated via industry benchmarking research with key industry thought leaders.

Biosimilar Complexity Raises New Challenges that Medical Affairs Is Uniquely Positioned to Help Address

The development and commercialization of biosimilars presents new challenges for manufacturers of both biosimilar and innovator products. For biosimilar sponsors, regulatory uncertainty and development complexity continue to represent the main development challenges, while ensuring that payers, physicians, policymakers and patients understand key aspects of biosimilar development and approval is critical to supporting informed decisionmaking when selecting between biosimilar and innovator products or between two biosimilars indicated for the same condition.

FIGURE 1. EVOLVING U.S. BIOSIMILARS LANDSCAPE



a) Approved in the EU
b) Filed in the EU
c) 505(b)(2) regulatory pathway
Sources: company press releases and industry publications (e.g., FiercePharma) – all information is public

Biosimilar Complexity Raises New Challenges that Medical Affairs Is Uniquely Positioned to Help Address

CHALLENGE #1 | REGULATORY UNCERTAINTY

Regulatory guidance in the U.S. is evolving, with key questions centering around burden of evidence for interchangeability. Pharmacists would be able to substitute biosimilars designated interchangeable, thus facilitating switching from originator to biosimilar.

CHALLENGE #2 | DEVELOPMENT COMPLEXITY

Although the burden of clinical evidence is reduced for biosimilars, development still requires a significant time and resource investment. Biosimilar manufacturers need to manage development costs without compromising the totality of evidence required for approval and adoption.

CHALLENGE #3 | LACK OF STAKEHOLDER CONFIDENCE

Payers are generally covering biosimilars but lack the financial incentives to promote their use over originator brands. Physicians and patients remain skeptical of biosimiars; additional education will be required to increase their comfort.

Over the past decade, Medical Affairs has continued its evolution as a strategic partner with its ongoing seat at the table during the creation of product development and commercialization strategies. The strength of Medical Affairs relies on its ability to deliver insights that help shape evidence generation strategies to best align with multiple stakeholder evidentiary requirements. In a biosimilar context, this translates to ensuring the right data are generated to support reimbursement adoption, in addition to as well as approval of biosimilar products. Medical Affairs can also contribute to stakeholder understanding of key concepts related to biosimilars as well as the specific merits of individual biosimilar products through strategic education and stakeholder engagement. In order to be effective, Medical Affairs leaders must consider how the novel characteristics and requirements of biosimilar products drive changes in the traditional areas of focus for Medical Affairs: evidence generation, stakeholder education and medical engagement.

Challenge #1

Regulatory Uncertainty

Regulatory policies governing biosimilars are still in flux, especially in the U.S., where the approval pathway for biosimilars was not defined until 2009 with the passage of the Biologics Price Competition and Innovation Act (BPCIA). Since then, the FDA has issued a series of guidances to clarify key aspects of the BPCIA, including scientific[3], quality[4] and clinical pharmacology[5] considerations in demonstrating biosimilarity as well as draft guidance on interchangeability.[6] In addition, practical regulatory experience with biosimilars has grown along with the increasing number of applications submitted to the FDA by biosimilar sponsors. FDA decisions on the first six biosimilars approved in the U.S. provide insights into how the agency sets the bar for biosimilarity, indication extrapolation and interchangeability.[8,9,10] A key open question is how the agency will approach indication extrapolation across disparate therapeutic settings, especially when extrapolating from chronic disease management (e.g., rituximab in rheumatoid arthritis) to treatment with curative intent (e.g., rituximab in oncology indications). Another key question is what the impact of the FDA's draft guidance on interchangeability will be and how the agency will ultimately define requirements for interchangeability. Interchangeable biosimilars can be substituted for the reference product by the pharmacist but so far, none of the approved biosimilars have been deemed interchangeable. Regulatory uncertainty impacts manufacturers of innovator products as well as biosimilar sponsors. For example, how an innovator company may respond to biosimilar entry would vary depending on whether the biosimilar was deemed interchangeable. A non-interchangeable biosimilar would compete more like another brand, while a biosimilar that is interchangeable would drive a different competitive response due to its ability to be substituted for the innovator product without input from the prescriber, much like a generic small molecule drug.

Evidence Generation: Role of Medical Affairs in Informing and Supporting the Biosimilar Value Proposition

The lack of definitive regulatory guidance on key aspects of biosimilar development and approval creates uncertainty about how key stakeholders are viewing and interpreting biosimilars evidence. As a result, biosimilar sponsors will need to align with multiple stakeholder groups on the totality of evidence necessary for a biosimilar product's approval, reimbursement and adoption. The type of evidence that must be generated for a biosimilar is fundamentally different from evidence that is typically generated for an innovator product (covered in detail under Challenge #2: Development Complexity). In practice, this means that creating an effective evidence generation strategy for a biosimilar will require a more integrated approach and increased coordination between Research and Development, Medical Affairs and Commercial functions. Since biosimilars follow a distinct development pathway, which emphasizes preclinical analytical assessments and seeks to minimize the burden of clinical evidence, ownership for biosimilar evidence generation strategy may not be centered in Clinical Development and may need to be more flexible, especially in organizations that continue to develop both innovative products and biosimilars (e.g., Amgen, Novartis and Pfizer).

This creates an opportunity to leverage Medical Affairs functions to drive biosimilar evidence generation strategy, including:

- Understanding stakeholder evidence requirements, which are unique for biosimilars
- Ensuring that evidence generated is sufficient to satisfy stakeholder requirements
- Driving key aspects of the biosimilar evidence generation strategy, including immunogenicity
- Optimizing evidence generation to inform and support the medical value of a biosimilar product
- Coordinating and enhancing evidence generation activities across key internal functions

In particular, in order to understand and gain stakeholder alignment on evidence requirements for a biosimilar product, Medical Affairs will need to prioritize early engagement with a number of key stakeholders, including regulators, payers and physicians. Engagement with regulators will focus on building a compelling case for biosimilarity as well as supporting evidence for indication extrapolation and interchangeability where applicable. Establishing a common understanding for indication extrapolation requirements will be especially important in therapeutic oncology, where differential effect of targeted therapies across indications and lines of therapy create a complex therapeutic landscape. Engagement with payers and physicians will need to focus on obtaining their input on early evidence generation strategy and on educating these key stakeholder groups on key aspects of biosimilar development and approval (covered in detail under Challenge #3: Lack of Stakeholder Confidence). In particular, medical insights on how the standard of care may be evolving for particular target indications would be valuable in determining which clinical evidence to pursue for biosimilars.

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Challenge #2

Development Complexity

The totality of evidence required to demonstrate biosimilarity is vastly different from the evidence required for approval of an innovator product. Due to the complexity of biologic medicines, small variations in their manufacturing process may lead to large differences in how well they work. As a result, biosimilars must undergo extensive characterization to demonstrate their similarity to the reference product both in structure and function. Characterization studies for biosimilars typically include analytical, nonclinical and clinical studies (Figure 2), with highly similar analytical and nonclinical data lowering the risk of clinical differences and reducing the burden of clinical data requirements. Clinical similarity must include pharmacokinetic (PK), pharmacodynamic (PD) and clinical immunogenicity assessments. Alignment on immunogenicity strategy is of particular importance during biosimilar development, as any changes in immunogenicity versus the reference product would raise questions about the biosimilar product's safety. Questions about immunogenicity were central to the FDA's Complete Response Letter recently issued to Coherus Biosciences in connection with its application for marketing authorization of CHS-1701 (pegfilgrastim), a biosimilar version of Amgen's Neulasta.[10] Extrapolation of approval to additional indications without the need for clinical data in each indication further lowers the evidence burden for biosimilars. On the other hand, demonstrating interchangeability would require additional switching studies (e.g., NOR-SWITCH) to show that there is no change in safety or efficacy when patients are switched between the biosimilar and its reference product. As a result, although the burden for clinical data is reduced for biosimilars compared to innovator products, development of biosimilars remains complex and costly, averaging a 7-8 year development timeline and $100-$250M in development costs.[11] One of the key challenges for biosimilar sponsors is managing development costs without compromising the totality of evidence required for biosimilar approval and adoption. In contrast, for manufacturers of innovator products, it is important to understand exactly how the totality of evidence supports biosimilarity and, more importantly, where key differences in the evidence base might be found.

Opportunity exists to leverage medical affairs to drive biosimilar evidence generation strategy and to coordinate execution.

FIGURE 2. EVIDENCE BASE FOR BIOSIMILARS VS. INNOVATOR PRODUCTS

Role of Medical Affairs in Addressing Development Complexity

In addition to a new approach to evidence generation strategy, biosimilar development places novel requirements on Medical Affairs from an operational perspective. Although clinical programs for biosimilar products are less extensive versus innovator products, some clinical studies are required to explore PK/PD, immunogenicity, efficacy and safety. However, investigator and patient interest in joining clinical trials of a biosimilar product may be limited by several factors, including the perception that biosimilars may be less safe, lack of enthusiasm for "copycat" products, and market availability of the reference product. As a result, Medical Affairs play a more important role in identifying and recruiting potential study sites, especially in the U.S. Since most U.S. sites have limited experience with biosimilar clinical trials, sites may require additional training and support from Medical Affairs. Depending on the number of sites and protocol complexity, Medical Affairs organizations may need to re-evaluate existing models for site support and reallocate resources assigned to this activity.

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Given the complexity of demonstrating biosimilarity and reliance on extrapolation for multiple indication approvals, biosimilar manufacturers will need to be prepared to address outstanding stakeholder questions about their products' safety and efficacy, following regulatory approval. In fact, a rigorous Phase IV program can be critical to differentiating a biosimilar product from other biosimilars in the same class and Medical Affairs will play an important role generating post-approval evidence for biosimilar products in order to create competitive advantages.

Post-approval switching studies can also be used to update labeling for an approved biosimilar product from "biosimilar" to "interchangeable." As the market for biosimilars in the U.S. continues to evolve, Medical Affairs will serve as a strategic partner to help create a strong evidence base for biosimilar products pre- and post-approval.

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Challenge #3

Lack of Stakeholder Confidence

Ultimately, the slow uptake of biosimilar products in the U.S. is driven by the lack of confidence in biosimilars on the part of key U.S. stakeholders, including payers, physicians and patients. With respect to payers, the first biosimilar approved in the U.S., Zarxio (filgrastim-sndz) was launched at a 15 percent discount to its reference product. However, it took U.S. payers roughly a year to grant preferred formulary status to Zarxio. In August 2016, CVS Health announced that it opted to exclude Amgen's Neupogen from its 2017 formulary coverage, in favor of biosimilar filgrastim.[12] These formulary exclusions subsequently coincided with a small acceleration in the rate of decline in Neupogen U.S. sales from -10 percent in Q4 2016 to -13 percent in Q1 2017.[13] It remains to be seen whether payers will take a similar approach with infliximab biosimilars, including Inflectra and Renflexis. Although changes in payer coverage policies led to a faster erosion of the reference product's U.S. sales in the case of filgrastim, the rate of decline remained far less than the 25 to 30 percent reductions observed in the EU, suggesting a lack of enthusiasm not only from U.S. payers but also from U.S. physicians and U.S. patients.

While the concept of biosimilars in the U.S. in not new, practical experience with biosimilars among U.S. prescribers remains limited; biosimilars have been on the U.S. market for less than two years, compared to more than a decade in Europe. On the eve of Zarxio's U.S. approval in March 2015, a survey of ~300 U.S. physicians revealed that only 17 percent of prescribing specialists who see patients with conditions commonly treated with biologics reported that they would be "very likely" to prescribe biosimilars to eligible patients.[14] A separate survey conducted at the end of 2015 confirmed a general lack of knowledge about switching, extrapolation, interchangeability, and overall safety of biosimilars among U.S. physicians.[15] For example, only 45 percent of surveyed physicians agreed that biosimilars would be "safe and appropriate for use in naive and existing patients," and only 12 percent of survey respondents indicated that they trusted the extrapolation process as the basis for approval of multiple indications. A third of respondents incorrectly thought that FDA approval meant a biosimilar could be substituted for a biologic by a pharmacist. All biosimilars approved in the U.S. to date have been approved as the only biosimilar, not as interchangeable, meaning pharmacists cannot switch prescriptions. Overall, insufficient understanding of key concepts related to biosimilars and a lack of clear guidelines (e.g., on switching, interchangeability, and substitution) contribute to uncertainty in the medical community and drive a confidence gap among U.S. prescribers (refer to sidebar).

Negligible impact on innovator U.S. sales to date suggest lack of confidence in biosimilars from key U.S. stakeholders.

Stakeholder Education and Engagement: Medical Affairs Well-Positioned to Address the Biosimilars Confidence Gap

Given that the underlying science is not fully understood and development pathway of biosimilars is complex, extensive education will be required to gain the confidence of payers, physicians, and policymakers and patients. In order to advance stakeholder understanding of key concepts and address information gaps that are specific to biosimilar products, Medical Affairs will need to develop and effectively execute on a robust and well-orchestrated education strategy. Medical Affairs education efforts will need to build on existing capabilities and focus on advancing the understanding of key concepts and terminology, such as extrapolation across indications and bioequivalence, related to the biosimilar development pathway. This effort will need to establish context for interpreting the totality of evidence necessary for biosimilar approval and adoption. For example, educating stakeholders on the fundamentals of interchangeability would facilitate their understanding of the outcomes of key switching studies.

Themes from the Biosimilar Forum Survey[15]

The results of the survey highlight a significant need for evidence-based education about biosimilars for physicians across specialities.

Five major knowledge gaps were identified:

1. Defining biologics, biosimilars and biosimilarity
2. Understanding the approval process and the use of "totality of evidence" to evaluate biosimilars
3. Understanding that the safety and immunogenicity of a biosimilar are comparable to the originator biologic
4. Understanding the rationale for extrapolation of indications
5. Defining interchangeability and the related rules regarding pharmacy-level substitution

Survey conducted November 2015 to January 2016. n=1,201 U.S. Physicians

In addition to education on biosimilar key concepts, an important component in building stakeholder confidence in biosimilar therapies will be the communication of evidence supporting the similarity in safety and efficacy. Medical Affairs will need to be able to develop and effectively articulate a compelling medical narrative that clinically differentiates the biosimilar product while maintaining its biosimilarity to the reference product; articulating those clinically meaningful concepts that are unique to biosimilars, the supporting clinical evidence required, and how it all translates into clinical practice and outcomes. Finally, stakeholder education would need to begin earlier in the product lifecycle and reach a broader set of audiences – implying early coordination across key internal functions to draft a biosimilar medical narrative that aligns and supports the broader biosimilar value proposition.

Medical Affairs will need to be able to develop and effectively articulate a compelling medical/clinical value story for a biosimilar product.

The need to engage a broader set of stakeholders, from payers, physicians, and policymakers, early in the product lifecycle also drives the need to re-examine the medical engagement model and identify opportunities to expand engagement to reach a more diverse audience. According to the physician survey conducted by the Biosimilars Forum[15], the most trusted source of information about biosimilars was specialty societies (cited by 25 percent of respondents), followed by peers (19 percent) and key opinion leaders (18 percent). As a result, medical engagement strategies for biosimilars might focus on new types of audiences such as professional societies as well as broader audiences since peer-to-peer learning appears to be equally as important as learning from KOLs. In order to engage with a broader and more diverse audience, Medical Affairs organizations may need to accelerate their current trends towards multichannel and digital-based engagement. In fact, 80 percent of prescribing specialists surveyed by the Biosimilars Forum reported that they would want to learn about biosimilars through expert-led digital content.[15]

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From a stakeholder engagement perspective, an assessment of stakeholder needs and knowledge gaps with respect to biosimilars is necessary to help inform the development of engagement strategies. Biosimilar manufacturers will need to assess how they need to adapt their customer engagement model for biosimilars and what new competencies, skill sets and tools are needed for Medical Affairs customer facing roles, including field medical teams, medical information and medical communication. Medical Affairs teams supporting biosimilars will need to be well-versed and knowledgeable on key biosimilars concepts and terminology to effectively engage in a deeper discussion with stakeholders and address their questions and concerns with regards to biosimilars. Medical Affairs teams, especially field medical teams, will also need to have access to a robust set of tools to help them communicate key messages and complex biosimilar datasets. Another aspect of Medical Affairs capabilities that would become more prominent is the collection of medical insights. A more sophisticated insights process may be required, with tighter coordination between insights collection, internal alignment on insights, and external response. It will also be important for companies to establish a baseline for external stakeholder perceptions on biosimilars, in order to effectively track how medical engagement is moving the needle with external stakeholders.

FIGURE 3. KEY CONSIDERATIONS FOR MEDICAL AFFAIRS SUPPORT FOR BIOSIMILARS

	Evidence	Education	Engagement
Challenge 1: *Regulatory Uncertainty*	• Own/drive evidence generation strategy, including immunogenicity • Optimize evidence to generation to inform and support the broader biosimilar value proposition	• Educate payers and HCPs on key regulatory concepts (e.g., extrapolation, interchangeability)	• Early engagement with regulatory agencies to align on evidence needs • Engagement with payers and HCPs to vet EG plan
Challenge 2: *Development Complexity*	• Integrated real-world data (e.g. innovator insights) and stakeholder evidence requirements into clinical strategy and study design	• Educate investigators and patients on the value proposition of biosimilars • Educate sites on the conduct of biosimilar trials	• Engage with investigators to create "pull" for biosimilars • Support robust patient advocacy strategy
Challenge 3: *Lack of Stakeholder Confidence*	• Understand stakeholder evidence requirements (i.e., strong medical insights) • Ensure evidence meets stakeholder requirements	• Educate stakeholders on key aspects in biosimilars (collaborative initiatives) • Develop and communicate a compelling biosimilar medical narrative – "Similar but different"	• Engage earlier in the product life cycle (preclinical) • Expand engagement to more diverse audiences (multichannel, digital)

In Summary

As the U.S. biosimilar market matures and becomes more competitive, it will be increasingly important for manufacturers to ensure that Medical Affairs functions as a strong strategic partner in biosimilar product development and commercialization. Medical Affairs is uniquely positioned to address key challenges facing biosimilar sponsors: regulatory uncertainty, development complexity and lack of stakeholder confidence. Medical Affairs can achieve this by focusing in the following key areas: evidence generation, stakeholder education and stakeholder engagement (Figure 3). Medical Affairs can help alleviate regulatory uncertainty and development complexity associated with biosimilars by informing and supporting the broader biosimilar value proposition through evidence generation and scientific communication. In order to do this, Medical Affairs must play a more prominent role in defining and developing the evidence base for a biosimilar product pre- and post-approval. Further, Medical Affairs is well positioned to address the biosimilars confidence gap across a wide range of stakeholder types, including patients, physicians and payers, through robust stakeholder education and engagement. With respect to education, Medical Affairs will need to drive the development and communication of a compelling biosimilar medical narrative that resonates with a wide range of audiences and is aligned to the broader biosmilar value proposition. With respect to engagement, Medical Affairs will need to evolve its engagement model to include new competencies, skill sets and tools that support a stronger emphasis on broad multichannel/digital engagement, as well as more well rounded and targeted engagement by customer-facing Medical Affairs teams.

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