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BRIDGING RA AND SCIENCE: ARE YOU PREPARED TO JOIN THE BIOSIMILAR RACE?

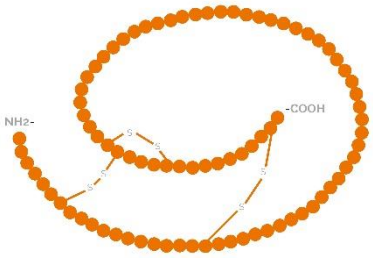
INTRODUCTION

It's an exciting time for companies joining the Biosimilar race.

As we get more experienced to apply more advanced technologies, as well as new production processes for biologics, the regulatory landscape and recent strategies for the development of Biosimilars are rapidly evolving at the same time. In Biosimilar development, it isn't easy to keep track of best development practices and regulatory expectations. Additionally, trends can be observed within leading health authority agencies to become more open for discussions and accept new scientific- and product-tailored development strategies to establish and demonstrate Biosimilar comparability. As usual, it´s all about risk assessment, impact evaluation, and scientific-based justifications, but agencies are actively paving the way for Biosimilars with new regulatory procedures and guidelines. In general, biological manufacturing processes show an inherent variation in terms of process and product. It's important to look at the development of Biosimilars from an integrated standpoint that includes the essential quality, non-clinical and clinical elements. Obviously, there is a high demand for Biosimilar CMC development as it plays a critical role in demonstrating comparability to the reference product.

THERE IS A WAVE OF BIOSIMILARS AT THE HORIZON

Since the first approval of the therapeutic biologic/Biosimilar Humulin (recombinant human insulin) by the FDA in 1982, biologics have gained significant importance in the pharmaceutical industry. More than 80 biologic molecules have been launched globally over the past decade. According to a report by Deloitte[1], $150 billion in global sales for biologics in 2013 are projected to almost double by 2020 to $290 billion, which comprises 27 percent of the pharmaceutical market. A 2016 IMS Institute report[2] on the potential market for Biosimilars (funded by Novartis) predicted that the global market for biologics would be even larger and reach $390 billion by 2020. The economic interest in Biosimilar development can be explained as 48% of the revenues come from 11 biologics that face the loss of exclusivity over the next seven years; consequently, the race for Biosimilar development is on.



Since the first Biosimilar approval (Omnitrope, Sandoz) in the European Union (EU) in 2006, there are now over 700 Biosimilars in the development pipeline (according to the website Biosimilar pipeline[3]) and more than 660 companies involved in that rush. Today, it's clear that Biosimilar products are set to play a vitally important role in the virtuous circle of pharmaceutical innovation and healthcare system sustainability. With a global Compound Annual Growth Rate (CAGR) for Biosimilars of 60.8%, Europe makes 25% of global biologics sales, but 87% of the Biosimilar sales. More than 20 Biosimilars have already been approved by the European Medicines Agency (2015).

Without a doubt, the potential financial benefit of Biosimilars is recognized and this is driving their development increasingly.

HOW CLOSE IS CLOSE ENOUGH? - DEVELOPMENT CHALLENGES AND BIOSIMILAR COMPARABILITY

That is (literally) the billion-dollar question. A Biosimilar must be systematically engineered to match its reference product and comparability studies are the key to a successful Biosimilar development program. Biosimilars are biological products with a high-molecular-weight and complex structure and are produced in living cells through genetic engineering. As this process is inherently variable, the main effort in the development pathway of a Biosimilar compared the originator product is the increased quality part to establish a suitable production process and to demonstrate analytical and preclinical comparability before entering clinical trials. Due to the complexity of biologics and their manufacturing processes, a product can only be made similar to the innovator drug, not identical. It is impossible for two different manufacturers to produce two identical products even when identical host expression systems, processes, and equivalent technologies are

used. Therefore, one needs to rely on analytics to establish similarity to the marketed innovator product. Comparability studies provide the totality of evidence that a biologic can be considered a Biosimilar.

Demonstrating Biosimilar comparability can be challenging because data for the innovator product is lacking. Another important aspect to keep in mind during comparability studies is that there is not only inherent variability in Biosimilars, but also in the innovator product. In an ideal scenario, the heterogeneity of a biological would be clearly understood, with variants easily isolated and characterized. In addition, no process and analytical changes would occur during the product life cycle. However, the reality requires an integrated set of analytical methods to establish ranges for the quality attributes of the innovator product and the Biosimilar to prove similarity.

Regulatory agencies evaluate Biosimilars based on their level of similarity, rather than the exact copy of the innovator drug. Considering the pivotal “totality of the evidence” when assessing a Biosimilar, this approach requires sponsors to demonstrate robust comparability data to the innovator product. However, compared to the innovator compound the development of a Biosimilar does have a few developments in their favor as technology has advanced to characterize biologic molecules and the analytics used to evaluate and prove Biosimilarity. Additionally, a Biosimilar does not have to use a similar production process as the originator drug and improvements are being made in the manufacturing and purification process of biologics.

The need for increased analytics and the request for a shorter time to market in Biosimilars development demands in particular that developers must invest early (and most likely more) in analytics/QC to establish and demonstrate comparability to the reference molecule at every stage of development, particularly during manufacturing when applying new processes Advances in current state-of-the-art analytical methods enhance the likelihood that the quality target product profile (QTPP)of a follow-on product will be highly similar to the innovator product through better targeting of the original product’s

physicochemical and functional properties. Sponsors with comprehensive comparability data combined with best practice of orthogonal approaches to prove similarity are likely to observe a reduced regulatory burden.[4]

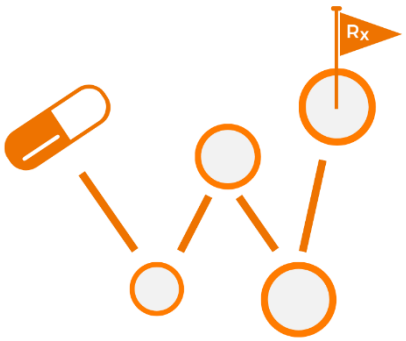
BEST-PRACTICE AND ORTHOGONAL APPROACHES FOR THE DEVELOPMENT OF BIOSIMILARS

Understanding the structure-function relationship of a biotech product is vital to the development of a Biosimilar. Awareness of this is important, and by selecting the right assays at the right time, it is possible to significantly reduce the costs and risks in the production process. The diversity of therapeutic biologics and their complexity also poses a challenge for robust manufacture and comprehensive characterisation of these molecules.

By applying orthogonal methods and approaches for characterization, information regarding the structure, binding interactions, and functional properties of the biological product are linked – providing a greater understanding and interpretation of the determined characteristics (related to CQAs). These data support a first-time right approach, allowing a streamlined Biosimilar development process and, at the same time, avoiding costly mistakes. Applying a QbD approach, CQAs can be identified at the molecular level and corrective procedures can be introduced at an early stage. Using correlating and orthogonal methods provides a complementary picture to correlate the molecular structure of the Biosimilar with its mode-of-action (MoA) and effector function, in terms of the CQAs of the innovator drug.[5] Understanding these characteristics in addition to the other quality attributes of a Biosimilar and how they related to your development strategy is worth the invested money and pays off at the end by reducing costs, risks and regulatory hurdles.

ARE YOU ON TRACK? - RAPIDLY EVOLVING REGULATORY LANDSCAPE FOR BIOSIMILARS

Europe has the longest track record for assessment and regulatory framework of Biosimilars, with which the U.S. is now becoming aligned. In February 2012, the FDA issued a formal draft guidance on Biosimilars in which it states that, since a one-size-fits-all pathway is not possible, it will "consider the totality of evidence" when assessing follow-on products. In addition, the FDA has the discretion to determine that certain studies are unnecessary in a 351(k) application, the approval pathway for Biosimilars, which is one of the reasons that early engagement with regulatory authority is vital to ensure expedited approval.



In February 2017, the EMA has launched a pilot for tailored scientific advice to support the step-by-step development of new Biosimilars. Through this new initiative, the EMA aims to provide developers of Biosimilars with advice on the studies/tests they should be conducting, based on the availability of quality, analytical and functional data for the product. Thereby the EMA expects to better support the stepwise development of

Biosimilars as recommended by the European Union (EU) guidelines. The EMA also states that according to this approach, the extent and nature of the studies/tests required depends on the level and robustness of data already accumulated[6]. Thus, it is vital to know and apply best practice analytics and approaches to the comparability exercise of a Biosimilar to reduce time and costs, as well as the regulatory burden.

Taking into account that the structural complexity of a biological also relates to the outcome of preclinical data, these studies have always been a critical part of the development program of biopharmaceuticals. With the advent of Biosimilars the traditional preclinical program has changed to a new paradigm that integrates the elemental concept of demonstrating comparability to the QTPP of the reference product. Recently, the recommended preclinical program espoused by the European Medicines Agency has been modified to an abbreviated one that now emphasizes in vitro studies instead of in vivo for monoclonal antibody Biosimilars. Likewise, the US FDA guidance on Biosimilars suggests a flexible approach rather than the 28-day comparative toxicology studies that have historically been conducted for worldwide marketing. For now, structure and function studies will continue to be the foundation of the overall analytical assessment to establish and demonstrate Biosimilarity. Traditional, comparative animal safety assessments will have limited value in determination of Biosimilarity and in an abbreviated design they may have most value in providing assurance of safety in first-in-human trials when structural attributes are not indistinguishable. Unless this value can be proven by the pivotal sum of evidence for similarity, by applying state-of-the-art analytics and orthogonal approaches, the need for these animal safety studies will diminish. Thus, the future lies in the ever evolving and sophisticated analytical studies that will replace the current in vivo studies for Biosimilar products. [7]

SUMMARY

The development of a Biosimilar could be as complex as the biological product and process itself is one of the best examples of bridging Science and Regulatory Affairs very early in drug development. Analytical methods as well as new production processes for biologics open the door to apply best-practice (orthogonal) analytics and process development to the comparability exercise and development of a Biosimilar product. As technology is advancing, the regulatory landscape for the development of Biosimilars keeps track. In-depth knowledge of the regulatory landscape and recent Biosimilar development strategies, strategic considerations for the nonclinical and clinical development program tailored to a product and in line with latest agency opinions will reduce development risks and time to market. Additionally, linking multiple orthogonal analytical methodologies will drive the reduction of costs, risks and contribute to the pivotal evidence to demonstrate comparability. Especially for small and medium enterprises (SMEs), these approaches will open the door to join the race.

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Christian Maasch is a Managing Consultant for Product Development at Xendo. He has more than 15 years of professional experience in drug discovery and development of biologics and chemical entities and a multidisciplinary scientific background and deep experience in translational medicine working with projects scenarios from various therapeutic areas, like inflammation, (immuno-) oncology, immunology and metabolic disorders. Prior joining Xendo, in the position as certified project manager in R&D and director of analytical sciences at NOXXON Pharma, he accompanied the discovery and development of three drug products from idea to clinical proof-of-concept in clinical phase II and the operational transition of a start-up to an established biotech company (incl. public offering).

Having a broad analytical expertise, Christian Maasch is an acknowledged expert for regulatory compliant analytical methods from drug discovery and companion diagnostics to clinical testing. He is a regularly invited speaker on the challenges/new approaches in R&D and QC, authored 28 publications and book chapters and (co)invented of more than 10 filed lead compounds.

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Dr. Franken works at the Isala hospital in the Netherlands as a consultant physician in internal medicine and endocrinology. During the past 12 years, he has been a Board Member of the MEB, specialized in the development and registration of Biosimilars. He was a board member of the Scientific Advisory Board Endocrinology and Diabetes of the European Medicines Agency (EMA) in London. He is a member of the Scientific Advisory Board at the Dutch National Healthcare Institute and is a co-founder and core member of the Initiative Biosimilars Netherlands (IBN).

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A cross-functional team of experts with in-depth knowledge of the Biosimilars regulatory landscape offers a seamless approach to support the development of your Biosimilar by strategic consultation and a customized program for your product. Xendo is funneling analytics, non-clinical development and the comprehensive comparability exercise of your Biosimilar product by tailored regulatory procedures, strategies and scientific advice.

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