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SAFETY ISSUES OF BIOSIMILAR PRODUCTS

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Biologics are complex molecules that are manufactured using living cells and used in the treatment of several chronic inflammatory diseases and cancer [1]. As biosimilars offer the potential for lower acquisition costs versus the originator biologic, evaluating the economic implications of the introduction of biosimilars is of interest [2]. As the costs of biologics are high, biosimilars offer the potential of greater choice and value, increased patient access to treatment, and the potential for improved outcomes [3]. By providing more-affordable treatment options and introducing price competition to the market, biosimilar medicines can generate significant savings. The cumulative savings between 2016 and 2020 in the EU5 and the USA are estimated to range between 49 and 98 billion Euros [4]. The Biologics Price Competition and Innovation Act (BPCIA) grants 12 years of exclusivity to originator or reference biologics; therefore, by law, the FDA cannot approve a biosimilar until this period has elapsed [2], [5]. Patents for many branded biologics will expire during the next few years, allowing biosimilars manufacturers to seek FDA approval for generic versions of these agents [2]. The Biologics Price Competition and Innovation Act (BPCIA), which is part of the Patient Protection and Affordable Care Act, was passed to facilitate the entry of biosimilar drugs into the market [6]. There has been an increasing trend toward the approval of biosimilars in the USA and the EU. The original goal of legislation to approve biosimilars through a fast-track process that would lead to more competition and price reductions is starting to be realized [7]. According to the BPCIA, a biologic product is deemed biosimilar to the already approved, originator biologic if the available data show that it is highly similar to the reference product, "notwithstanding minor differences in clinically inactive components, and there are no clinically significant differences between the biologic product and the reference product in terms of safety, purity, and potency of the product" [8-10]. Approval of biosimilars requires comprehensive assessment of all stages of the research and development process, including evaluation of analytical, preclinical and clinical data, to establish bio-similarity to their reference products. The goal of biosimilar comparability studies is not to re-establish efficacy and safety for the proposed biosimilar, but to demonstrate similarity to the reference product [11,12]. The biosimilar development pathway consists of a comprehensive comparability exercise between the biosimilar candidate and the reference product, primarily focusing on data from analytical studies. Clinical studies for biosimilar candidates follow a different design to those for a new biological, as the aim is not to independently establish clinical benefit, but to confirm bio-similarity between the two agents [4]. Physician awareness and perceptions towards biosimilars are important factors in their adoption to clinical practice [11]. A biosimilar applicant has to provide a considerably larger package of comparative data than a generic applicant to ensure that the biosimilar can indeed rely, for the purpose of licensing, on the efficacy and safety experience gained with the reference product. While for a generic, the demonstration of similar in vitro dissolution and in vivo bioavailability (so-called bioequivalence) is sufficient to conclude therapeutic equivalence with the reference product, for a biosimilar, comparable physicochemical, biological and functional characteristics as well as efficacy and safety/immunogenicity with the reference product must be demonstrated. In addition, unlike generics, any extrapolation to other indications of the reference product must be scientifically justified [12]. The approval of biosimilars is a highly regulated and detailed process. The European Medicines Agency (EMA) and the US FDA guidance documents stipulate that a biosimilar manufacturer must perform a series of extensive similarity assessments in order to demonstrate bio-similarity to the reference product, and

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to ultimately gain regulatory approval or licensure [13]. Difference between generic biotech and biosimilar products are: a) Biologic medicines are not made using a set of standard materials, but are developed using unique biological systems and living cells. Subsequently, the active ingredient is difficult to reproduce precisely and the chose cell lines from which the biologic prescription begins are interesting to every producer b) The assembling procedure for biologic medicines is commonly more perplexing than assembling forms for compound medications. Dissimilar to little particle drugs, biologic medicines are delivered in hereditarily built living cells that are supported in a very controlled condition. The protein delivered by the cells will be affected by individual cell attributes just as the earth and nutrients gave c) Each manufacturer has different processes that create distinctive characteristics in the product, which are specific to the manufacturer. This creates a unique relationship between a biologic's manufacturing process and the final product approved by regulators [14-21]. Despite the undeniable advantages of such procedure, some concerns (such as the absence of switching studies or the evaluation of efficacy and safety in all therapeutic indications) still exist about it. In particular, the European regulatory framework on biosimilars approval does not include the conduction of switching studies demonstrating the interchangeability to be carried out before marketing authorization. This is one of the main aspects that negatively affect healthcare professionals' clinical decisions on switch [22]. The FDA has accepted the concept of extrapolation of indications; we just need additional high-quality research on nonmedical switching and the risk of immunogenicity. FDA recently released a white paper indicating the types of trial designs that would be required before nonmedical switching of biosimilars in stable patients could be endorsed—in distinction to substitution by a pharmacist in patients starting therapy. These types of trials would involve multiple crosses between an originator biologic agent and a biosimilar. Thus, we need more studies on switching, especially multiple-switch studies [23-25]. A survey of 470 European physicians belonging to various specialties including rheumatology, nephrology, oncology and dermatology from five European countries (France, Germany, Italy, Spain and the UK) showed insufficient understanding of biosimilar. Only 22% responded that they were very familiar with biosimilars, and could define what it is. While a majority (54%) had a basic understanding of biosimilars, 24% of them answered that they had never heard of biosimilar before. Due to insufficient understanding of biosimilars, half of them thought that biosimilars have to use different International Non-proprietary (INN) Names from the originator biologic agents. However, this understanding of International Non-proprietary Name is misleading and is definitely different from regulatory authorities [26]. Biosimilar market take-up significantly relies upon healthcare supplier readiness to advance, endorse, and use biosimilars in clinical practice. U.S. furthermore, European social insurance suppliers still methodology biosimilar medicines with alert, refering to constrained biosimilar information, low recommending solace, and security and adequacy worries as primary obstacles for biosimilar use. To understand the full cost-sparing capability of biosimilar medicines, clinician-guided biosimilar instruction will be basic to address holes in biosimilar learning, encourage endorsing changes, and at last increment biosimilar use. A general absence of biosimilar commonality in U.S. also, European medicinal services settings went with worries about biosimilar wellbeing, viability, extrapolation, and compatibility [27]. A standout amongst the most critical wellbeing worries with biosimilars is the potential danger of safe based antagonistic responses. Due to their atomic size, biologics can legitimately actuate hostile to medicate antibodies which may have critical ramifications for both wellbeing and viability [28]. Libraries ought to be utilized to screen utilization of biosimilars and to recognize potential antagonistic impacts. The cost of biosimilars ought to be essentially lower than that of reference items to upgrade patient access. Bio-impersonates are not biosimilars and, in the event that they are to be marketed, they should initially be assessed and affirmed by set up administrative pathways for novel biopharmaceuticals [29]. It is imperative to be clear about whether a particular item has been assessed through a thorough assessment technique dependent on the criteria characterized in the EMA, FDA, or WHO biosimilar rules. It is also important for prescribers to understand what happens when a particular biosimilar receives a designation of 'interchangeable' with the originator and when substitution may occur, as these designations/policies may impact patient outcomes [30].

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