Biosimilar's Growth in Pharmerging Markets: An Analysis of the Regulatory Environments

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A mini thesis submitted in the partial fulfilment of the requirements for the degree of

MSc Pharmacy Administration & Policy Regulation

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University of the Western Cape in collaboration with Hibernia College

November 2020

ABSTRACT

The introduction of biosimilars to health care markets across the globe has had some success in increasing competition and improving the cost of healthcare. While savings are important for driving the biosimilar uptake, this is not the only consideration for the growth of biosimilars onto emerging markets.

A systematic review of the literature to assess the growth of biosimilars onto the emerging market was conducted using the following data sources: PubMed, Website of the Generics and Biosimilars Initiative (GaBI) journal, ProQuest, Google Scholar. Studies that provided evidence of biosimilars onto the emerging market through surveys and other sources of existing data were included. The systematic review process followed Wichor et al. (2018) and the PRISMA checklist (PRISMA, 2009). The search strategy for the review provided a total of 71studies, which underwent title, abstract and full text review to give 20 articles that fit the inclusion criteria for the aimed study. A quality assessment was conducted on the 20 articles and by using the Hawker et al. (2002) quality tool and directed research questions to set variables, the data analysis of 13 articles emerged.

The included studies agreed on the growth of biosimilars onto the emerging market and on the switch to biosimilars to improve access to therapies. However, International Nonproprietary Name (INN) and physician confidence were still considered as hurdles. The two most successful drivers of the growth of biosimilars onto the emerging market based on this review was certainly the regulation of the process followed by the cost of biosimilars.

To conclude, data analysis of 13 articles determined that the general perception of using biosimilars in emerging markets is positive. However, for successful integration into routine healthcare and uptake into these markets, there must be a direct focus on the regulation of Biosimilars.

DECLARATION

I would like to thank the following people, without whom I would not have been able to complete this research, and without whom I would not have made it through my Masters' degree!

'My father who always supported me; my mother who always believed in me; my brothers and my kids, Ilyas and Adam who simply loved me'.

ACKNOWLEDGMENTS

My thanks go to Hibernia College (Ireland) and the University of the Western Cape (South Africa), School of Pharmacy, Pharmaceutics Discipline, for the support and encouragement throughout this MSc. Thank you to my dissertation supervisors, Dr Halima Samsodien and Mr Rafik Bapoo for their time and encouragement.

I would also like to expand my gratitude to all those who have directly and indirectly guided me in writing this thesis.

ACRONYMS

(ADAs)	Anti-Drug Antibodies
(BLAs)	Biological programs
(BPCIA)	Biologics Price Competition and Innovation Act
(BRIC)	Brazil, Russia, India, and China
(BRICS)	Brazil, Russia, India, China, and South Africa
(COVID-19)	Coronavirus disease 2019
(DNA)	Deoxyribonucleic Acid
(EMA)	European Medicines Agency
(EU)	European Union
(FOBs)	Follow-on Biologics
(FDA)	Food and Drug Administration
(INN)	International Nonproprietary Name
(JBSA)	Japan Biosimilar Association
(MENA)	Middle East and North Africa
(MIST)	Mexico, Indonesia, South Korea, and Turkey
(mAbs)	monoclonal Anti bodies
(PD)	Pharmacodynamic
(PK)	Pharmacokinetic
(PRISMA)	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
(PHS Act)	Public Health Services Act
(R&D)	Research and development
(SPA)	Program Specific Assessment
(NHS)	The National Health Service in UK
BsUFA)	The Organic Food Tariff Act of 2012 (
(SR)	The Systematic Review
(WHO)	World Health Organization

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CHAPTER 1 : INTRODUCTION

Chapter 1 presents a brief overview of biologics and biosimilars with insight into the economic evidence in emerging markets leading to the problem statement of the study, the specific research aim, and objectives.

1.1 Introduction to Biosimilars

The burden of chronic diseases is increasing worldwide; it is necessary for patients to receive safe and effective treatment (WHO, 2005). Biologicals are a unique group of effective drugs that have revolutionized cancer treatments, diabetes, autoimmune diseases, rheumatoid arthritis, and many other inflammatory diseases. Compared to traditional medicine often referred to as small molecule drugs, biologic drugs are inherently larger and derived from living cells through highly complex manufacturing processes (FDA, 2018a). Although they are highly targeted and efficacious, they are extremely expensive (Chen et al., 2018) and remain inaccessible to most patients in emerging markets. Alternatively, biosimilars offer the potential for lower-cost treatments and an attractive value for governments in many countries.

A biosimilar medicine is also known as a biologic drug, however it is a copy of a biologic medicine that is similar, but not identical, to the original medicine (EMA, 2019). In emerging markets the following key hurdles have to be considered when preparing a biosimilar medicine: quality concerns, technology hurdles, and lack of robust regulatory frameworks, development timelines and costs.

A biosimilar enters the market subsequent to a previously authorized version whose patent has expired and is approved only after showing that it is “highly similar” to an approved biological product, known as a reference product, in terms of safety, purity, and potency. It is estimated that nearly thirty-nine biologics representing almost 30% of the overall biologics market had more likely lost their marketing exclusivity between 2015 and 2019 (Wiatr, 2011). Factors such as the increasing demand for biosimilar drugs due to their cost-

effectiveness and patent expiry are expected to drive the growth of the emerging biosimilars market, however, questions remain over regulatory requirements (Cohen et al., 2017).

The absence of consistency crosswise over EU countries that have had entry to biosimilar drugs for ten years proposes that the basic components of accomplishing the maximum capacity from biosimilar drugs are not known at a policy level nor executed at a practical level successfully. As stated by Senior (2013), the availability of biosimilars will certainly not enhance competition as generics onto the market because the global players will not facilitate their introduction. They have learned from the generic experience; they will probably develop their own follow-on originator. On the other hand, Huzair, and Kale (2015) statethat the developing pharmaceutical marketplaces of Asia, Latin America, and Eastern Europe offer particularly attractive sites for biosimilar research and commercialization. They are increasingly important locations for biosimilar development as sponsors pursue multinational programs to gain access to appropriate patient populations. Not only are these emerging nations characterized by growing middle class and increasing healthcare expenditure they are also typically generic driven pharmaceutical market which provides a positive medical and commercial environment for biosimilars (Cazap et al., 2018).

1.2 Background tothe Study

Biologics have revolutionized treatment for many diseases; however their associated costs still pose a challenge to their use, more affordable medicines would be acquired by the patient and become indispensable in countries where regulations are less stringent as pharmaceuticals emerge. However, before delving into market projections, it is important to determine the differences between the generic and biosimilar markets.

Though both biosimilar and generic drugs have the same commercial goals and are only allowed to market when the patent of the original drug has expired they are two completely different products (Table 1.1). (McKinsey, 2019)

Table 1-1 Key differences between biosimilars and generics (McKinsey, 2019)

Biosimilars	***Generics***
Similar to and not identical to reference product	Bioequivalent and not identical to reference product
15-20% discount over reference product	40-50% discount over reference product
3 billion dollars investment	2-3 million dollars investment
8-10 years development timeline	3-5 years development timeline
No interchangeability or automatic substitution	Interchangeable with reference product

When it comes to their structure, development, and authorization, a biosimilar medicine must demonstrate no clinically meaningful difference in efficacy, safety, and potency with its reference product and must be highly similar to the original biological drug, while the generics are as the branded products (FDA, 2017). The cost of generic drugs generally stand at 40 to 50 percent less than the branded products. In contrast, biosimilars are closer to 15 to 20 percent cheaper than the original product due to the amount spent on testing by manufacturers. For generics, it is easy to produce exact copies of branded drugs and requires no complex modifications, making the manufacturing process easy and predictable. Biosimilars and reference drugs are not synthesized through a simple chemical synthetic reaction like generic drugs and require a complex process in a cellular environment like any protein from the body. Generic drugs require an approximate investment of around 2-3 million dollars for their development and due to the complexity involved, biosimilars require an investment of around 3 billion dollars (Mabxience, 2017).

Despite progress in the availability and use of generic and biosimilar medicines, there is potential for more competitive prices and greater uptake. A study comparing the cost of generic medicines in Europe in 2013 found wide variation in both prices and market share. For example, prices charged by manufacturers to wholesalers in Switzerland were more than six times those in the United Kingdom, based on the results of a commonly used price index. (Wouters et al., 2017)

While prices of medicines with generic competition have been shown to drop by up to 66% compared with the originator price (Vondeling et al., 2018), similar reductions have not been seen for biosimilars. On the one hand, this is, at least in part, as a result of the complex production process and greater regulatory requirements to obtain marketing authorization for biosimilars compared with generic medicines, which create barriers to market entry for competitors (Blackstone et al., 2013). On the other hand, less stringent or relaxed regulatory requirements for biosimilars are driving their growth in emerging markets as many emerging nations are establishing biosimilars regulatory pathways, and sponsors now have opportunities to select research sites strategically to optimize overall development timelines and achieve registration goals (McKinsey, 2019).

1.3 Problem Statement

One fundamental question is whether or not pharmaceutical and/or biotechnological companies should introduce biosimilar therapies based on the regulatory 'cost' associated with entry. Beyond just the monetary cost of drug evaluation, there is the regulatory system in emerging countries, which is new and not as stringent as in the US or Europe. These two burdens remain the most important challenges of the biosimilars' growth into the emerging market.

1.4 Purpose of the Study

The purpose of this study is to identify the main factors that contribute to the growth of biosimilars in emerging markets.

By definition, growth markets exist when the size of the market continues to grow at an increasing rate. The market growth is a key factor to be considered when calculating the development of a specific product in a particular market (Bhardwaj et al., 2005).

Many studies have identified several factors that are responsible for the biosimilar growth onto global markets and have suggested strategies to facilitate the entry of biosimilars

in emerging markets. However, due to differences in healthcare systems in each region and multiple geographical competitions there are still regulatory and operational hurdles to address. Uniform clinical studies remain an issue and harmonization between country regulations is concerning.

Thus, this study attempts to identify variables responsible for the growth of biosimilars in an emerging market with specific emphasis on cost of drug evaluation and the regulatory system in emerging countries.

1.5 Aim and Objective

The aim of the study is to identify the global challenges and opportunities (i.e. variables) impacting the growth of biosimilars in the pharmerging market and to examine in particular the cost of drug evaluation and the regulatory system. The specific objectives of this study are:

1) To identify the key variables affecting the marketing of biosimilars.
2) To identify the regulatory authorities for biosimilars globally and their role.
3) To identify the success criteria of biosimilars going onto the pharmerging market.
4) To identify the cost and regulatory issues for biosimilars emerging onto the market.
5) To identify the strategies for better costing and regulation of biosimilars in the pharmerging market.

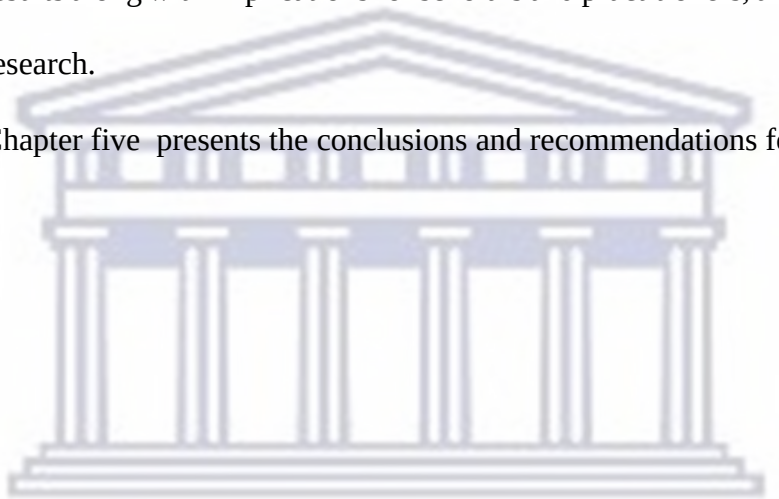
1.6 Research Structure

This dissertation contains five chapters:

- Chapter one presents an overview of the topic along with purpose of the study and its relevance to biosimilars' growth in pharmaging (pharmaceutical emrging) markets .
- Chapter two provides a review of the literature and explains how literature is relevant to the research topic. This chapter also contains scholarly literature

from Google Scholar and PubMed which describes the landscape of the global market of biosimilars and emphasizes the opportunities and regulatory strategies of the biosimilars' entry onto the emerging markets.

- Chapter three outlines the methodology used to review the aim and objectives cited in chapter one.
- Chapter four presents the results and findings of the research. The themes are presented along with supporting textual data and quotes and a discussion of the results along with implications for scholars and practitioners, and areas of future research.
- Chapter five presents the conclusions and recommendations for future work.



CHAPTER 2 :LITERATURE REVIEW

Chapter 2 presents the scholarly background literature about the growth of biosimilars in the global market and the biosimilars' entry in the pharmerging countries.

2.1 Introduction

The development of the global market for biosimilars presents an opportunity for cost savings and improved health outcomes. Biosimilars continue to grow worldwide with emerging regions playing a larger role. As demonstrated by analysis of various countries, many emerging markets are establishing biosimilar regulatory pathways, providing increasing opportunities for biosimilar development. The global biosimilar market, which was valued at $5.5 billion in 2018, is estimated to grow at a compound annual growth of 38.21% during the forecast period of 2019 to 2025 (IMARC group report, 2019). Europe is currently the most lucrative region for the biosimilar market accounting for approximately 74% of the global market share. The market is also gaining traction in the North American region at a rapid pace (Industry ARC report, 2020). As stated by Mario Di Paola (2017), while Europe and the US have been the primary focus; biosimilars will also have a significant impact in the pharmerging market, primarily in India and China. Both countries have large populations and strong purchasing power, making them prime markets for biosimilar manufacturers. However, the use of biosimilars are debated globally due to many factors including the scientific complexity of biologics, safety/efficacy issues and political issues. To understand the more challenging factors of biosimilars entry into the global market, these factors could be divided into 4 key areas: (Commercial, Legal, Clinical and Political) and more specifically sub-areas defining the key factors affecting the entry of biosimilars onto the market (Figure 1) (Patrawala, 2010).

Figure 1: Key debate areas on global marketing of biosimilars (Adapted from Patrawala, 2010)

Commercial • Innovator and sponsors • Access to medicines • Education provider	***Legal*** • Interchangeability /substitution • Non propriety name/labels • Reimbursement system
Clinical • Clinical trials • Immunogenicity	***Political*** • Data/Market Exclusivity

2.2 Key factors affecting the marketing of biosimilars

2.2.1 Innovators and sponsors:

Developing and manufacturing biosimilars is challenging, so industrial players are adopting the strategies for investment and developing these into medicines (Moore, 2015).

Biosimilar sponsors are seeking market entry for their therapeutics and have to efficiently manufacture and develop biosimilars, whether working independently or with partners. Developers pursuing biosimilars must integrate capabilities in clinical development, regulatory compliance, advanced and safe manufacturing, and commercialization (Dunn, 2014). However, they face challenges from innovator such as the protection of brand portfolio.

For example, the case of Amgen vs Sandoz on the patent dispute between a biologics manufacturer and a biosimilar manufacturer respectively, negotiations failed between the two parties as the biosimilar applicant planned marketing before the 180 days approval by FDA. (Chen et al., 2020) In this case the court argued on the structure of the role of Biologics Price Competition and Innovation Act (BPCIA), which is to promote innovation and drug accessibility for patients while also recognizing that biosimilar products already face inherent challenges to gaining market access, so that the biosimilar applicant can provide the reference product sponsor with premarketing notice before license (Koya, 2019).

Although the innovator companies impose barriers to biosimilars manufacturer whose products act as cheaper alternatives, biosimilars have not been discounted 80-90% like

generics, but it is understandable, as Joseph Miletich (2012), Amgen's senior vice president R&D, has stated, 'the great economic advantage of biosimilar is that a manufacturer only needs to recreate the idea that has already been shown to work', This statement could be true by the innovator's point of view who is under pressure from biosimilar market entrants in most global markets. For this reason, they are developing a robust understanding of the broad competitive threat and clinical positioning of biosimilars, building defensive strategies, and taking substantive action in the marketplace.

On the other hand, companies do not focus on a single strategy but are involved in multiple investment and development strategies. A common strategy to market biopharmaceuticals is collaboration between companies. These collaborations can be used to gain access in regions where the company has less experience like pharmerging markets.

Historically, the challenges of entrepreneurship in biology have been largely limited and predictable. Many people now find it difficult to develop intellectual competition and understand such ecosystems' complexity. In addition, for some entrepreneurs who are inexperienced in implementing such complex business policies, the need for competitive pricing, profit pressure, and aggressive contracts can be a red flag. Cultural change must go hand in hand with expanding new opportunities for entrepreneurs to maintain their market share. Innovators must ensure that suppliers and patients who influence the market understand reliable data on the quality and reliability of supply and highlight new entrants' weaknesses in terms of production capacity and experience (Burchiel et al., 2019).

The company must also apply for patents related to production rights and intellectual property and continue to increase its production capacity. Faced with organic growers who can reduce suppliers' concerns about the safety and effectiveness of the differentiation, bio-innovators may also consider reducing cuts and bargaining methods. In this case, the entrepreneur needs to formulate a high probability of price patterns in the customer group and

establish action and thresholds. Biologists need to make decisions quickly before market share declines because it is difficult to regain lost market share. Biology and biological similarities production and purification processes can be more complex and expensive than those used in chemical drugs production. Although some studies have attempted to estimate production costs for specific biological information, there is generally no information on biology and drug production costs (Cazap et al., 2018). For example, a study looked at the cost of producing insulin and concluded: "Similar insulin could be produced for $ 72 or less for human insulin at $133 or less for analogs." The study identified several limitations, including registration fees, inspection and quality control fees, and others not specifically addressing fees. The second analysis looked specifically at the process of producing monoclonal antibodies, a class of biological substances that many chemotherapeutic drugs contain (Kang and Knezevic, 2018). According to an article written by biotechnologists Genentech, monoclonal antibodies are becoming a class of therapeutic products with unlimited production capacity and low production costs, and their price is not directly related to the API. Pricing reflects the investment of the innovative company together with the cost of product failure in processing.

2.2.2 Access to medicines:

There are many public health problems for which there are no treatments. Drug development pipelines are full but mostly focus on potentially profitable diseases that mainly affect high-income countries. In short, the free market does not effectively provide affordable access to medicines for all (United Nations Sustainable Development, 2018). Affordability and innovation can co-exist so that patients can sustainably access medicines. However, it is challenging to find agreement on a single definition of fair pricing, and health systems have struggled to achieve a balance between affordability and need.

A worrying gap exists between the promise of medical innovation and affordable access for all. When medicines are found to be truly effective, they must be made rapidly available to

both health systems and the individuals who need them at an affordable price. Unfortunately, some effective medicines remain unavailable to many patients or are available with out-of-pocket costs that make access impossible. In many low-income countries, the cost of treatment for diseases such as cancer can be devastating because it is the full financial responsibility of the patient (WHO, 2018). When a potential cure for hepatitis C recently became available even high-income countries found themselves rationing treatment and unable to treat all patients in need because of high prices (Iyengar et al.,2016).

There are still no treatments available for many public health problems, yet drug development pipelines are full for potentially profitable diseases that mainly affect high income countries, the free market simply does not work to effectively provide affordable access to medicines for all. Where there are limited markets and incentives to develop drugs for neglected diseases and populations there is also a pressing need for better coordination.

2.2.3 Provider Education

Biosimilar use is limited in some healthcare systems because they are not well understood by many healthcare professionals and patients. Trust is a critical component in the implementation of medicines, whether in cancer or other diseases. Furthermore, trust on the part of the patient is not related to the fact that a drug is approved by regulatory bodies; patients must trust that prescribed drugs are reliable and safe (Jacobs et al 2016). Acceptance of biosimilars by health care systems, health care professionals, and patients will be a key factor in the uptake of these therapies. As an example, the National Health Service in the United Kingdom(NHS), has released several resources for patients detailing the upcoming switch and The European Medicines Agency (EMA) released a video different European languages defining biosimilars. Furthermore, a survey has been conducted by Giuliani et al. (2019) which showed that 79.2% of prescribers indicated that they consider themselves to have an average to very high level of knowledge of biosimilars. In total, 74.6% of prescribers were able to identify

the most appropriate definition of 'biosimilar' ('highly similar to an approved biological medicine, with no clinically meaningful differences in safety and efficacy profile'). This definition was selected by 77.9% of European and 64.6% of Asia-Pacific prescribers. This survey found an encouraging level of prescriber use and general knowledge of biosimilars in oncology; however, the need for further education remains. Future educational initiatives should focus on improving prescriber understanding of extrapolation of indications as well as physicochemical data. Efforts should also be made worldwide to align definitions and regulatory standards for the development and approval of biosimilars. As Anna Rose Welch (2018), Chief Editor of Biosimilar Development, stated, t stakeholders still need more information on what the biosimilar concept is about with more general understanding and there are a number of ways information about biosimilars and biologics can be widespread, for instance, via leaflets, webinars, social media posts or free conferences accessible for a larger audience and continued education will lead to more informed discussion and decision-making regarding biosimilars market strategies.

Innovative marketing strategies should focus on recruiting target groups and knowledge groups to strengthen the differences between biologically similar entrepreneurs (Acha and Mestre-Ferrandiz, 2017). An inadequate knowledge and education on biosimilar development and manufacturing will lead to hesitancy in prescribing and/or switching patients to biosimilars.

2.2.4 Interchangeability/ Substitution:

The regulatory environment and scientific understanding of biosimilar medicines has advanced since initial establishment of biosimilar regulatory pathways over a decade ago. In the Europe (EU) and the United State (US), robust regulatory standards exist that ensure approval of biosimilars that are as safe and efficacious as the reference product. However, switching patients from the reference biological product to its biosimilar has been the subject of debate. A systematic review by McKinnon (2018) concluded that there are important

evidence gaps around the safety of switching between biologics and biosimilars and switching should remain a clinical decision made by the treating physician and the patient based on available evidence and individual patient circumstances. On the other hand, Ebbers and Schellekens (2019) stated that that there is now sufficient evidence to conclude on the robustness of the way biosimilars are developed and approved by regulatory agencies. Based on currently available data, biosimilars have to be shown to be interchangeable and that the risk of increased immunogenicity of switching to a bio-similar is no greater than switching between two batches of any biologic.

The lack of clear guidelines on substitutability and interchangeability with reference biologics will likely cause physicians to exercise more caution in prescribing biosimilars until they gain confidence with the quality and efficacy of biosimilars.

2.2.5 Non propriety name /Label

The complicated nature of biological molecules needs specific nomenclature guidelines and naming of biosimilars has heightened this complexity. So far, several inconsistent and different models have been applied in different parts of the world which has resulted in increasing concerns over the toughness of the World Health Organization's International Nonproprietary Name (INN) system currently in place. According to Mindy Prasad, a clinical pharmacist for Blue Cross Blue Shield of Michigan, biosimilars use proprietary names, which shows how different biosimilars are when compared to generic small-molecule drugs. This naming system can pose a strong challenge in environments that depend heavily on non-proprietary names when referring to drugs, like hospitals, and can puzzle patients since a biosimilar can apparently seem like a completely different drug compared to the reference product. Such challenges require a high level of education on the part of pharmacists, providers and patients.

2.2.6 Reimbursement

If greater benefits are to be gained from biosimilar medicines, a key issue is to increase trust in these products as well as their timely entry and uptake by markets. Authorities that are managing reimbursement should carefully evaluate the evidence on long term impact of pricing and purchasing policies. Internal reference pricing is a reimbursement policy used in several countries worldwide (Kaplan WA et al, 2017).

Insurers implementing this policy establish groups of interchangeable medicines, and a reimbursement price for all medicines in the group is set. The internal reference pricing group is made up of either medicine/s with the same active ingredient or medicines with different active ingredients but considered to have similar efficacy and safety profiles (Ferrario et al., 2020). The model works by making patients pay the difference if the price of the medicine dispensed at the pharmacy is higher than the reference price. There is mixed evidence on the impact of internal reference pricing on prices and use. However, a 2014 Cochrane review found that internal reference pricing may reduce medicine expenditure by insurers in the short term by directing patients towards medicines that cost no more than the reference price (Acosta et al., 2014).

Studies comparing price decreases in internal reference pricing systems versus non-regulated markets found larger price decreases in non-regulated markets (Kanavos et al., 2008). In internal reference pricing systems, once a certain reference price has been set after patent expiry there is little incentive for manufacturers to offer prices below the reference price whereas competition for market share led to lower prices in free markets. Similar findings were reported for use of internal reference pricing versus tendering for outpatient prescription medicines (Casanova-Juanes et al., 2018). While in most countries internal reference pricing includes only off-patent products, in Germany, for example, on-patent products which have no

additional benefit to existing medicines are included in reference pricing groups (Vogler et al., 2018).

2.2.7 Clinical trials:

Clinical trials of biosimilars must demonstrate safety and efficacy comparable to the reference product regarding pharmacokinetic (PK), pharmacodynamic (PD), and immunogenic properties. Comparative PK studies are a basic requirement for development of a biosimilar. In the presence of suitable PD endpoints and a clear mechanism of action, a PK/PD study may be sufficient clinical work for marketing approval (Webster et al., 2019). The main factors to be considered in clinical development include study population, design, end points, sample size, duration, and analytical methods. If phase 3 studies are successful and a biosimilar is approved for one indication, it is approved for all other indications for which the reference product is approved, provided there is adequate scientific justification (EMA, 2014). The guidelines state that the aim of clinical data is to address slight differences observed at previous steps and to confirm comparable clinical performance of the biosimilar and the reference product (EMA, 2019).

The immunogenicity assessment of biosimilars and their reference biologics should, therefore, be a critical component of a biosimilar's clinical development program. Various bioanalytical platforms may be used to detect and characterize immune responses, each having relative strengths and weaknesses (Schreitmüller et al., 2018).

2.2.8 Immunogenicity:

The goal of biological product development is a gradual approach to defining the level of available data and analyzing specific types of data to address the remaining uncertainties (Arkells et al., 2018). The first step in this process is to perform a comprehensive structural analysis of biological and control drugs. Planning experiments must explain the primary,

secondary, tertiary, and quadratic structure of the molecule and changes (such as glycosylation and phosphorylation) and deliberate chemical changes (such as PEGylation regions).

The difference between the composition of biological corpses and innovative formulations (for example, one uses human albumin and the other does not) is a factor that determines the scope and conduct of subsequent experiments on humans or animals (Buske et al., 2017). Supporters of in vitro practical tests, including binders and biological tests and in vivo disease models, often provide further evidence of similarities in biological activity, function, and mechanism of action. These practice tests are comparable and can provide information that confirms the similarity of the two products and assesses the impact of building nuances. Compound structure and function data can be used to guide biological development in clinical and animal studies. Animal experiments can be used in similar biotechnology applications to support the safety assessment of new products and to support the incorporation of general biodiversity (Dey et al., 2020).

Animal studies often involve toxicity studies, although the amount of data required for these studies vary according to the structure and utilization quality. However, animal studies can be quite extensive when diagnostic test data are limited, including PK/PD assessment, histopathology, and immunogenicity. In general, biological probabilities do not require pharmacological studies on animal safety, reproductive toxicity, or carcinogenic potential if the planning, efficacy, and toxicity tests performed are adequate. The safety of biological drugs is highly dependent on many different variables, but primarily on production and immunogenic effects.

Because of the structural complexity of biologics, a considerable problem for establishing an abbreviated regulatory path for biosimilars is immunogenicity. Immunogenicity is recognized as a possible clinical risk due to the development of anti-drug antibodies (ADAs) that can adversely impact drug safety and efficacy. Although robust assays are currently used

to assess the ADA, there is a debate on how best to generate the most appropriate immunogenicity data. There are several factors that can trigger ADA formation including the immunity status of the target population and the severity of the disease indication. Immunogenicity testing has defaulted to the most conservative approach regardless of the inherent risk of the molecule or the patient population (Arkells et al., 2018). For low risk biotherapeutics such as human monoclonal antibodies, ADA data that provide clinically relevant information should be prioritized when establishing immunogenicity monitoring plans.

2.2.9 Data Market/ Exclusivity:

Biosimilars undergo rigorous testing before being approved to ensure the safety of biological organs. However, any question of efficacy or safety has catastrophic side effects. Although rare, the immunological effects and potential consequences are key factors that healthcare professionals should inform patients about before switching to biometrics (Barlas, 2019). Patents can play an important role when developers apply for their biologically similar applications in the US. Historically, sponsors have tried to target biological probabilities due to pathological abnormalities. Many people call this act the "patent dance." The patent dance contains two waves of possible litigation. The "first wave" of the lawsuit allowed the reference product's licensees to claim that a similar organic producer had infringed one of their patents. The BPCI Act states that manufacturers of biochemical extracts "deliver" a copy of the 351 (k) application to the sponsoring company. However, some companies have tried to claim that the sponsorship application is free (Aladul et al., 2017a). This situation disturbs the balance that the BPCI Act sought between competition and innovation. "Second wave" litigation allows advocates to question procedures that biologically similar producers could not follow.

Biologics are characterized by higher discovery costs, longer development times and higher capital investment in manufacturing plants. Development times for biologics, moreover, have more than doubled in the past 25 years and development progression is fraught with

uncertainty because it often relies on venture capital. Biotechnology companies must have some certainty that they can protect their investment in the development of breakthrough therapies for a substantial period to secure the necessary resources from venture capital firms and other funding sources. (Grabowski, 2010) Thus, to preserve incentives for biomedical innovation, any statutory pathway for follow-on

Follow on Biologics (FOBs) must include a substantial period of data exclusivity. Such non-patent exclusivity is necessary because, due to the very nature of a FOBs regime, the patent system may not provide innovator biologics with effective protection against follow-on manufacturers prematurely entering the market. For biologics to receive the same length of effective market protection as small molecule drugs receive under the Hatch-Waxman Act, years. Anything less could skew investment away from biologics research and development (Brougher, 2010). In Conclusion of the key factors affecting the marketing of biosimilars are summarized in Table 2.2. The period of data exclusivity in any FOBs framework must be no less than 14 years.

Table 2-1 Summary of key areas of biosimilars debate (amended from Doyle 2009)

Area of debate	***Key Factors***	***Debate***
Commercial	Innovator and sponsors	Biosimilars requires strict and careful manufacturing practices in order to maintain safety and satisfy regulatory authorities.
	Access to medicines	The availability and use of fairly priced, quality assured generic and biosimilar medicines.
	Provider education	There are several different types of disparagement and misinformation directed against biosimilars, individually and collectively, that are impeding their ability to contribute to a sustainable multiple-source biologics market.
Legal	Interchangeability/substitution	Choice between patient and physician, the variation in the clinical impact of biosimilars and its reference product influences the choice of what should be used for medical treatment
	Non-Propriety name and labels	Biosimilar retain name of original product for safety reason –Issues of pharmacovigilance.
	Reimbursement system	Health plan coding is critical for determining product coverage and reimbursement.
Clinical	Clinical trials	Human clinical trials must be mandated to establish that biological product is safe pure and potent because it is not the same as its reference product.
	Immunogenicity	Immunogenicity required for each indication and post-marketing studies should be required.
Political	Data/ market exclusivity	Patent disputes over biosimilars are just one area of contention involving biopharma intellectual property protection.

2.3 Global regulatory authorities for biosimilars and their role:

Europe, the US, and Japan have been some of the first movers in the global regulatory landscape to establish biosimilar pathways and develop a rationale for establishing bioequivalence. When many potential manufacturers emerge for the regulatory guidelines need to be developed to ensure biological analogy, comparability, and acceptable variability in product safety and efficacy. The main dictators in this field are the European Medicines Agency (EMA), the World Health Organization (WHO), and the US Food and Drug Administration (FDA).

The EU was the first to propose guidelines for examination and approval for biosimilars with the creation of The European Medicines Agency (EMA) Biosimilar Regulatory process, enacted in 2005. As reported by Prof Guido Rasi, EMA Executive director, since the EU approved the first biosimilar in 2006, healthcare professionals have gained increasing experience with their use. Today, biosimilars are an integral part of the effective biological therapies available in the EU, supported by adequate safeguards protecting patient safety. (EMA guideline, 2019)

By providing specific solutions for treating diseases rather than symptoms, biological units are larger than chemical units. Still, there are smaller units that have a significant impact on patients around the world. As technology advances, people gain new insights into the molecular and cellular bases of diseases (such as cancer, arthritis and Multiple Sclerosis MS), and biotechnological therapies become more popular. The term "biodiversity" can include a variety of molecules such as therapeutic proteins, supplements, hormones, monoclonal antibodies, antibodies, pelagic proteins, anti-albumin binding domain antibodies, and vaccines with deoxyribonucleic acid (DNA) (Dey et al., 2020). In absolute size, these molecules are usually 100-1000 times larger than chemical molecules. All biological units of protein contain several amino acids. These amino acids are sometimes linked by disulfide bonds or other similar

or different alpha α -fold subunits, which generally form the first, second, third and fourth structures. The γ gamas and β beta sheets create pockets and spaces necessary for their actions. Recombinant proteins are generally obtained by genetically plotting living cells (cytotoxic drugs or eukaryotes) with genes of interest and culturing them in a liquid medium to select an expressed protein of interest. The protein is separated by chromatography, and the protein is surrounded by other proteins, sugars, and lipids such that the purity is higher than 98% and thus forms a drug. The drug is equivalent to the drug molecule's active drug component and is then combined with appropriate bumpers and excipients to obtain the closed syringe product called the drug product (Kabir et al., 2019). Due to sophisticated production methods that involve the use of living organisms in a highly controlled environment, ensuring continuous production is a challenge that cannot be ignored. Although there is a fundamental difference in the quality of a product in each batch, batch differences must be monitored to ensure a specific range by default for obvious reasons.

Significant changes such as glycosylation, oxidation, and degradation variants are often important quality characteristics that have a major impact on the molecule (Buske et al., 2017). Detailed descriptions of translation changes and other organizational possibilities not found in small molecules are scientifically difficult. Other impurities related to processes, such as host cell proteins, DNA host cells, and toxins, must be safely controlled. Product quality discrimination between batches should be carefully controlled in regular applications and linked to clinical trial results to avoid consumer safety risks.

Consequently, one appropriate approach to the revision of the Small Molecules Regulation is inappropriate for biology. In a sense, biological models are injected because they utilized are copies of expensive originals at affordable prices that provide high-quality medical care. Much of this availability stems from the reduced need for clinical trials that can be accepted if sufficient analogy can be demonstrated (Armuzzi et al., 2020).

As biological models are the end product of the biotechnology process, the system is a key element in genetic modification and the physiological environment and makes the active substances similar to the original biological environment but not in the same way. Unlike generic drugs, the duplication of generic drugs expected is dependent on the process and the product and subtle internal changes are inherent in the entrepreneur who knows the process or the initial cell of the system (Kang and Knezevic, 2018). Recombinant fingerprint protein has a cell line and handles impurities related to products and processes because it is a highly controlled production environment. Because of this complexity, beginners must meet clinical, pre-clinical, and diagnostic requirements to compare these shades. These regulatory requirements for similar applications are more important than standard drug applications but lighter than newer biological applications. Overall, there is ample evidence for quality, purity, and biological balance. However, in the case of biological body substances, in addition to chemical, production, and control analyses, the emphasis has also been placed on biological-like, pre-clinical, immunogenic, and limited clinical trials. Due to the lack of molecular selection, sponsors worldwide are trying to produce these drugs based on recombinant proteins. From a business point of view, many factors (such as development plans, product costs, drug offerings, lack of users, and customer satisfaction) drive the market to varying degrees in different areas (Armuzzi et al., 2020). When many potential manufacturers emerge, regulatory guidelines need to be developed to ensure biological analogy, comparability, and variability in product safety and efficacy. The main dictators in this field are the European Medicines Agency (EMA), the World Health Organization (WHO), and the US Food and Drug Administration (FDA). Some regional versions of the manual are based on the template above. It aims to compare the supervisory position of emerging markets in the developed European Union (EU) and the United States (Cohen et al., 2017). In 2009, the WHO developed a collection of globally recognized standards for the safety, efficacy, and quality of Similar Biotherapeutic Products

(SBPs). Its main purpose is to help local regulators ensure compliance with international standards. Following the rapid development of the guidelines, most countries adopted the EMA or WHO guidelines, while others have developed their national guidelines based on these models.

Australia adopted the EU guidelines without change, and Singapore and Malaysia have largely adapted their guidelines to the EMA guidelines. Brazil and Cuba have chosen the World Health Organization guidelines, and Canada has chosen their national standards. However, the definition, concepts, requirements for comparing data, criteria, and other factors are completely different. India previously approved 20 biological models for India under the temporary reduction process (Kang et al., 2020).

Regulators in several European healthcare institutions, including Germany, Finland, and the Netherlands, have stated that European-recognized organics can be considered interchangeable for their reference products and transfer patients from innovative products to biological images (and vice versa (for courses)) can be produced safely. In the United States, Biological License Applications (BLAs) are used to obtain approval for macromolecular products or living organisms such as hormones, enzymes, vaccines, and monoclonal antibodies (mAbs). BLA's legal basis comes from the Public Health Services Act (PHS Act) (Diependaele et al., 2018). An amendment to the PHS Act was approved in 2010 and paved the way for licensing biological bodies in the United States. This change is called the Organizational Price Competition and Innovation Act . The amendment establishes a legal definition of biological probabilities in the United States and introduces a regulatory approach to marketing authorization in Section 351(k). The statement said that biological similarities "although there is little difference in clinically inactive substances are very similar to the reference product" and that "biological similarities differ from the reference product in terms of life safety, purity and clinical differences between products" (Harsányi et al., 2019). A similar biological product

may be accepted under point 351 (k) for all, part or reference product has approved trademarks. It is important to keep in mind that products approved for use as biological and volatile must be approved for all indications of the reference product. The Organic Food Tariff Act of 2012 (BsUFA) amended the Food, Drug, and Cosmetics Act so that the FDA could assess and collect fees for similar organic products between October 2012 and September 2017 (Burich, 2018). The FDA uses this fee to fund a similar background check process. The bill also sets out the FDA's review objectives. It establishes five types of formal meetings that can be organized between product sponsors and FDA staff to discuss organic image development plans as part of the organic product development plan. BPD as it is called, biology was created to provide sponsors with specific biological images guidance. In the Accessibility Program Development Program, clinical trial programs may also meet the requirements of the Specific Program Assessment SPA to demonstrate biological imaging or substitution. Biosimilars are often considered generic versions of biological or biotechnological drugs (Kabir et al., 2019). The legal definitions of biological corpses in the EU and the US show that there are details and nuances in this heuristic approach. Low molecular weight products can determine their exact structure and properties by analysis and testing generic versions of the same product which can be demonstrated to have the same structure as the reference product or original product. Biological origin products are much larger and more complex and may or may not affect the molecule's clinical activity, causing subtle structural differences.

2.4 Biosimilars' entry onto the Pharmerging market

Biological product development for launch in multiple geographies with varied regulatory expectations would require a planned and focused strategy, involving the selection of the appropriate reference product, defining the extent of process and product characterization and design of non-clinical and clinical studies.

The development for established markets like the EU and the US, which have precedence in regulatory pathways, may face very different challenges compared to emerging markets, many of which are still in the nascent stages of regulatory guidelines.

2.4.1 Definition of pharmerging countries

Although EU, US, and Japan have the highest number of biosimilar molecules in development (Decision Resources Group, 2014), the pharmaceutical industry is expanding into developing countries at a rapid pace. This is because the growth pattern in developed markets continues to flatten. In addition, globalization is causing pharmaceutical industries to cut through traditional boundaries and push into developing countries—the so-called emerging markets (Meyer K et al., 2006). Countries with emerging pharmaceutical market have attracted attention in recent years by the fast growth of the local pharmaceutical market, especially by the investments made by national companies in the generic segment, through methods such as reverse engineering. Also, population aging favors the growth of the sector in pharmerging countries as it has a direct impact on the economic growth of these countries due to the change in consumption patterns (Ding M et al., 2014).

Jim O'Neil, retired chairman of asset management at Goldman Sachs, identified leading economies of emerging markets: Brazil, Russia, India, and China (BRIC) and later Brazil, Russia, India, China, and South Africa (BRICS) and then Mexico, Indonesia, South Korea, and Turkey (MIST), which followed years later as the second tier of nations. Sales of the pharmaceutical markets in BRICS and MIST countries doubled in 5 years, reaching a market share of approximately 20%.

Emerging markets represent an exceptional opportunity for the pharmaceutical industry. Qualifying a market as emerging is not merely based on the economic status of the country but on several criteria that render the definition applicable to each country. Official reports from the pharmaceutical industry indicate that of the 21 pharmerging countries, 5 countries (Brazil,

Russia, India, China and South Africa), BRICS members, rank among the top 10 in terms of sales, with China standing out for accelerated growth of the sector. Studies indicate that the sustainable growth of the sector associated with these countries is due to the increase in domestic demand. (Quintiles IMS, 2017)

The shift toward these new markets has been attributed to their large populations, growing prosperity, and increasing life expectancy. Emerging markets constitute 70% of the world's population, account for a 31% share of global gross domestic product and are predicted to account for approximately 30% of global pharmaceutical spending (Leintz et al., 2015; Mooraj et al,. 2017). Pharmerging markets currently account for 33% of the global growth in drug demand at the expense of the US and EU. In 2015, they accounted for 28% of the market worldwide spending. (Dimond, 2015; Liang, 2012)

In addition, companies are suffering from the flattened growth of developed markets, expiration of patents leading to the up-selling of less expensive generic drugs, and tight regulations enforced in mature markets. Particular attention must therefore be given to these emerging markets. The strategies adopted by pharmaceutical companies that want to expand in these markets must be tailored to the developing pace of each country. These countries need drugs against infectious diseases and communicable diseases such as STDs. They are readily exploitable territories for the innovative products of pharmaceuticals. Nevertheless, with the increase in wealth and longevity, a change of lifestyle is occurring. These changes accompany a shift in disease patterns. A disproportionally fast rise in the incidence of non-communicable diseases such as cardiovascular illnesses, diabetes, and oncologic diseases has been observed in emerging markets, mimicking their Western counterparts. This shows that pharmaceutical industries will also be able to market their global products in these new countries. (Tannoury et al., 2017)

2.4.2 Success Criteria of biosimilars onto the pharmerging market

Emerging countries are solid markets for drug formulae that have been selling for decades. This significantly boosts the chances of succeeding in launching new products tailored especially for these markets. The human data company IQVIA, formerly Quintiles and IMS Health, Inc, consulting expects that the competition between biosimilars and their biologics will reduce the spending on biologics by 10% to 30% ($50 billion to $78 billion) between 2018 and 2022 (IQVIA, 2018). The emerging countries are probably the most concerned by developing an alternative industry regarding the economic and demographic pressure to enable the access to the health in large, various and heterogeneous countries like China and India (IQVIA, 2018a). Moreover, the emerging pharmaceutical markets Latin America and Eastern Europe offer especially attractive locations for biosimilar research and commercialization. Not only are these emerging nations characterized by growing middle classes and increasing healthcare expenditures, but they are also typically generics driven pharmaceutical markets; this provides a positive medical and commercial environment for biosimilars where multinational clinical programs have the added advantage of supporting biosimilars product registration in emerging economies with growing biologics markets (Kabir et al., 2019). Multinational development strategies pose country-by-country challenges. Implementing studies across countries with varying regulations involves layers of complexity that demand in-depth knowledge of each local environment.

A survey in India done by the Economist Intelligence Unit Industry Report (2014) found that physicians were willing to prescribe a first-line critical therapy if it was offered at a 60%–70% discount, whereas in China, getting on the essential drugs list means usage by many hospitals at a 25%–50% price cut (The PharmaLetter, 2016).

India saw the launch of its first biosimilar in 2003 when it launched biosimilar rituximab at half the price of the biologic product. Today, 25 Indian companies are marketing close to 50 biosimilar products (Limaye, 2017).

2.4.3 Regulatory Barriers

The regulatory procedures used for generic drugs cannot be applied for biosimilars as they are large complex structures produced from living cells and can produce potential risks of immune-based adverse reactions. Out of several safety issues related to biosimilars, two main safety concerns are variable potency and immunogenicity, for which a robust long-term pharmacovigilance system is needed. Various guidelines have been issued for the regulatory approval and pharmacovigilance of biosimilars by the US FDA, EU, and pharma-emerging countries like China and India(Singh et al., 2019).

Emerging markets differ in regulatory pathways, payer perceptions, pricing, affordability, and competitive landscapes factors that biosimilar companies should consider when deciding which markets to enter (Table 2.3). A good first step is to assess a country's regulatory framework carefully to ensure that it sets a high standard for biosimilarity and has a clear approval pathway (McKinsey, 2019).

To gain access and develop a sustainable share, companies need to prioritize markets with a maturing regulatory environment and policy incentives that create a supportive environment for biosimilars. Most emerging markets that have such a regulatory framework have modeled it on those of the World Health Organization (WHO) or the European Medicines Agency (EMA) (Chen Y et al., 2019).

Brazil and China have created solid frameworks, including accelerated approval pathways and strict requirements for evidence of biosimilarity. In Brazil, more than 10 biosimilars have been approved since its biosimilar pathway was established in 2010. Although China did not experience an immediate uptake of approvals for biosimilars under its new

pathway, several them are expected to launch in the next few years, after the recent reforms of the Chinese healthcare market (Pategou, 2019). Other countries Egypt, India, Indonesia, Mexico, Russia, Turkey, and Vietnam—have also defined biosimilar comparability pathways, although they are yet to be implemented effectively everywhere. (McKinsey, 2019)

Some of the biologic alternatives commercialized in emerging markets have been developed without recourse not only to high standards for biosimilarity but also to analytical or clinical investigation. Dealing retrospectively with these products remains a challenge. In India, for instance, more than 70 approvals have been granted in the past 25 years, mostly to local manufacturers while quality standards were not yet fully harmonized. Such conditions make markets less attractive for entry and partnerships, as the barriers for entry may be too low to support adequate returns for companies investing in dossiers in several countries.

Table 2-2 Biosimilars' Regulations landscape country-by country (McKinsey 2019)

Country	Regulatory	Payers	Procurement
China 	Technical guidelines for development and evaluation of biosimilars in place since 2015	New national RDL effective since 2017 includes multiple monoclonocal Antibodies mAbs especially for cancer treatment	Focus on hospitals through engagement with formulary committees in large centers
India 	Pathway defined but not yet fully implemented	Limited reimbursement in mAbs and none featured RDL	Procurement through private segments: focus on hospitals
Russia 	Pathway established in 2014 following EMA guidelines	Public reimbursement of cancer and diabetes broader than immunology treatments	Central and regional Government procurement, focus on public hospitals
Brazil 	Pathway based on WHO and EMA guidelines in place since 2010	Mainly public biologics account for <5% of volume but -40%of health ministry spending on drugs	Central procurement focus on public hospitals through national public health insurance.
Mexico 	Comparability pathway defined	Mainly public through the health insurance system	Procurement through insurance company tenders offered through hospital channels
Indonesia 	Pathway defined, trial data accepted from other countries	Little for reimbursement for biologics and biosimilars	Procurement through private provider
Vietnam 	Abbreviated pathway in place, promotion of local manufacturer	Biologics/biosimilars covered at up to 50% by public healthcare system depending on molecule	Local manufacturer are also distributors: penetration into public hospitals via tender process
Turkey 	Comparability pathway defined, following EMA	Well covered in national healthcare system	Procurement via national or regional tender: focus on hospitals channels

2.5 Regulatory Strategies

The EU is currently the most advanced biosimilar market (54 biosimilars approved). While the European Medicines Agency (EMA) published a biosimilar framework in 2005, Japan and the US developed their guidelines in 2009, and the number of approved biosimilars in these countries remains relatively small (21 and 26, respectively). China entered the market in 2019 with the first biosimilar approved in line with the guidelines published in 2015. However, the copy-biologics, not meeting the criteria for biosimilars, have been available in China for a long time. (Skowron et al., 2020).

As stated by Calo-Fernández (2012), in the short term, it will be crucial for biosimilar companies to engage with healthcare professionals regarding the safety, potency and efficacy of biosimilars. Sales and market intake will be driven both by the brand of the product and the reputation of the company promoting it. Lobbying of healthcare institutions, governments and key opinion leaders, as well as accessing a global network of sales representatives, will be necessary at this stage. In the mid-term, it is expected that all the actors of the biosimilar market, including regulatory bodies, national health systems, healthcare professionals and patients, will feel increasingly more confident about the prescription of biosimilars. Lobbying of regulatory authorities could encourage the approval of legislation supporting the substitution of biologics. Sales at this stage may be more price sensitive, encouraging competition between all the players in the biosimilars market. Eventually, in the long term, we can expect a mature biosimilars market showing similar dynamics to the current generics market, where sales are entirely driven by price. Therefore, generating economies of scale in manufacturing to lower production costs per unit, andacquiring global coverage through excellent distribution channels, will be key capabilities required to succeed (Calo- Fernández et al., 2012).

The transition time between different stages will vary with the particularities of a geographical market, it's the generics culture and the strictness of its regulatory agencies. To

cut healthcare expenditure, it will be a priority for both public and private payers to try to shorten this transition time, ultimately lowering the prices of biosimilars. (IMS Health, 2015)

Emerging markets including the BRICS (Brazil, Russia, India, China, and South Africa) and MIST (Mexico, Indonesia, South Korea, and Turkey) provide the best future opportunity for manufacturers of biosimilars (Limaye, 2017). With millions of people in these developing countries, and unmet medical needs, the uptake of biosimilars is expected to be tremendous (GLOBOCAN, 2012).

As an example, McKinsey (2019), has suggested a strategy to access an emerging market in the summary below:

Assess country's regulatory framework:	Brazil and China have created solid frameworks, including accelerated approval pathways and strict requirements for evidence of biosimilarity. Other countries including Egypt, India, Indonesia, Mexico, Russia, Turkey, and Vietnam have also defined biosimilar comparability pathways, although they are yet to be implemented effectively everywhere.
Employ innovative pricing:	Roche's Herceptin in China provides a notable case of a company that tackled the affordability gap to expand opportunities for patients.
Unlock access to patients	Introducing support programs for patients and healthcare professionals using real-world evidence from early-launch markets in the EUand the US. In markets with limited experience of quality biosimilars, this approach helps companies to build trust in a treatment's safety and efficacy among payers, patients, and physicians.

Adapt business models to compete on factors other than price:	Competing in emerging markets means competing in a price-driven environment. Besides adopting innovative pricing strategies to address affordability, biosimilar companies must also seek to differentiate themselves to preserve profitability and encourage switching in markets with lower-priced alternatives. Biosimilar manufacturers, which have repeatedly experienced stock outs in emerging markets, could learn lessons from other market segments (such as vaccines).
Targeting sub-geographies and channels:	Maximizing uptake for biosimilars in emerging markets calls for a carefully crafted channel strategy that sets clear priorities. A company could choose to focus on, say, large hospitals in urban areas with greater patient flows for specialty care, physicians receptive to novel treatment methods, and patient segments that can afford complex treatments.

Overall, the main variables that are responsible of the growth of biosimilar onto the pharmerging market are the population size/ medical needs, lower-priced biosimilar, the government investment and the purchasing power of the country.

Furthermore, the pharmerging markets have developed their own regulations and laws related to biosimilars according to the European framework but with lower general requirements, fewer clinical trial requirements, and less regulatory control (IMS Health, 2011). Therefore, adequate tailoring strategy and timeline should be designed to match the emerging market of choice. For example, India has been at the center of controversy recently as a result of some of its renowned generics and biosimilar companies producing and marketing biosimilars of still-patented original products without any reliable comparative trials or

licensing. These factors, among other regulatory guidelines, will shape the actual market contributions of such products in the future (Kabir et al., 2019).

CHAPTER 3 : METHODOLOGY

This chapter introduces materials and methods for collecting relevant data from different sources according to research questions and research objectives.

3.1 Introduction

The Systematic Review (SR) method was conducted to review the main aims and objectives previously cited in Chapter 1. In addition, specified questions were added to determine the variables responsible for the growth of biosimilars onto the emerging markets.

3.2 Materials and methods

3.2.1 Literature and search

To guide this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009), Search strategy tool (Wichor et al., 2018) and Quality assessment tool (Hawker et al, 2002) were followed. Relevant English-language articles indexed in the literature were collected by hand search using academic sources: ProQuest (dissertations and theses), PubMed, Google Scholar (Published Academic Articles and Journals) and websites such as GaBI and Biosimilar Development (Market Reports). The systematic review of articles followed 3 steps to select the articles that can be useful for the study:

- **STEP 1**-Read and assess the title

The titles were assessed to eliminate the articles that did not meet the inclusion criteria (see Table 3.1)

- **STEP 2**-Read and assess the abstract

The abstracts were read to assess aims / objectives and conclusion in order to select the best match with inclusion criteria (see Table 3.1)

- **STEP 3**-Follow the search strategy tool

The systematic search strategy was constructed according to a methodology process adapted from Wichor et al. (2018); this method provides a stepwise approach that facilitates the search strategy development process from question clarification to final iteration and beyond.

The steps in the process of the systematic literature search are described below (see detailed description Appendix A):

1. Determine clear and focused questions (see table 3.1)
2. Describe the articles that can answer the questions
3. Decide which key concepts address the different elements of the questions
4. Decide which elements should be used for the best results
5. Choose appropriate database and interface to start with
6. Document the search process in a text document
7. Identify appropriate index terms in the thesaurus of the first database
8. Identify synonyms in the thesaurus
9. Add variations in search terms
10. Use database-appropriate syntax, with parentheses, Boolean operators, and field codes
11. Optimize the search
12. Evaluate the initial results
13. Check for errors
14. Translate to other databases
15. Test and reiterate

The initial search resulted in 71 articles that met the inclusion criteria (Table 3.1), As the PRISMA diagram (Figure 2) shows, after removal of duplicates (n=20), 51 articles remained. These articles were examined based on title, abstract and entire text. Eventually, full texts (n=20) were selected and distributed with a further structured analysis through the development of biosimilar drugs in the emerging market (see quality assessment Table 3.2).

The differentiation criteria include all data that are consistent with the study and the exclusion criteria include irrelevant or outdated data that could lead to deviations or inaction from the objectives of the study. The following study selection criteria are listed below (Table 3.1).

Table 3-1 Inclusion and exclusion criteria

Criteria	Inclusion Criteria	Exclusion Criteria
Time	Review studies conducted between 2010 and 2020	All studies before 2010 were rejected
Keywords	Biosimilar AND Emerging AND Markets AND Growth, Biosimilar AND opportunities OR challenges Biosimilar AND Regulatory AND strategy	Regulatory environment in developed countries markets were excluded
Response	All articles and markets reports which respond to the objective in item 7 of protocol were included.At least 2 questions have to be answered	All articles which have no answers to the questions cited in item 7 of the protocol were rejected
Language	Articles and reports written in English were included	Non-English articles were rejected
Type of data	Articles that provide quantitative or qualitative analyses on the variables responsible of the growth of biosimilar were included	Articles where qualitative or quantitative analyses of the variables were not provided
Sources	Cochrane library, Medline, Google Scholar, EMBASE, Biosimilar development website, GaBI website, McKinsey website.	All other sources were excluded

3.2.2 Quality assessment:

Each of the 20 selected studies were concisely reviewed and summarized in Table 3.2.

The quality assessment tool used for the study was drawn directly from Appraising the evidence: reviewing disparate data systematically by Hawker et al. (2002). This tool contains nine questions as follows:

1. ***Abstract and title.*** Did they provide a clear description of the study?
2. ***Introduction and aims.*** Was there a good background section and clear statement of the aims of the research?

3. ***Method and data***. Is the method appropriate and clearly explained?
4. ***Sampling*.** Was the sampling strategy appropriate to address the aims?
5. ***Data analysis***. Was the description of the data analysis sufficiently rigorous?
6. ***Ethics and bias*.** Have ethical issues been addressed and has necessary ethical approval been gained? Has the relationship between researchers and participants been adequately considered?
7. ***Results*.** Is there a clear statement of the findings?
8. ***Transferability or generalizability*.** Are the findings of this study transferable (generalizable) to a wider population?
9. ***Implications and usefulness***. How important are these findings to policy and practice?

Each question can be answered 'good', 'fair', 'poor' or 'very poor'. Having applied the tool to the studies, it was converted into a numerical score by assigning the answers from 1 point (very poor) to 4 points (good). To create the overall quality grades, the following definition have been used: high quality (A), 30–36 points; medium quality (B), 24–29 points; low quality (C), 9–24 points (Table 3.2).

Table 3-2 Quality assessment of the 20 articles adapted from Hawker et al, 2002

Study/Questions*	1	2	3	4	5	6	7	8	9	Total	Grade
Almaaytah et al., 2020	4	4	4	4	4	4	4	3	3	34	A
Bennett et al., 2014	4	4	4	4	4	4	4	3	3	34	A
Fadi et al., 2017	4	4	2	2	3	4	2	1	2	29	B
Ferrario et al., 2020	4	4	3	3	4	4	4	4	4	30	A
Knighton, 2018	4	4	4	4	4	4	4	3	4	35	A
Krishnanet al., 2015	4	3	3	4	4	4	3	3	2	30	A
Lammers et al., 2014	4	4	4	4	4	4	4	3	2	33	A
Patel et al., 2013	4	4	3	3	3	4	3	2	2	28	B
Gabi, 2020	4	4	4	4	4	4	4	2	2	32	A
Sonam, 2020	4	4	4	4	4	4	4	2	2	32	A
Liang, 2014	4	4	4	4	4	4	4	2	2	32	A
Tannoury et al., 2017	4	4	4	2	3	4	4	1	1	27	B
Fadi et al., 2016	4	4	4	4	4	4	4	3	3	30	A
Hamzi, 2019	4	4	4	4	4	4	4	3	3	34	A
El Zorkany et al, 2018	4	4	4	4	4	4	4	3	3	34	A
Bhupinder et al., 2011	4	4	4	4	4	4	3	1	1	29	B
Eva et al., 2019	4	4	4	4	4	4	4	3	3	34	A
Vesa et al., 2020	4	4	4	4	4	4	4	1	1	31	A
Eduardo et al., 2018	4	4	4	4	4	4	4	1	1	31	A
Freire et al., 2020	4	4	4	4	4	4	3	3	4	34	A

1. Abstract and title*, 2. *Introduction and aims*, 3. *Method and data, 4. ***Sampling*, 5. *Data analysis***, 6. ***Ethics and bias*, 7. *Results*, 8. *Transferability or generalizability*, 9. *Implications and usefulness***.

To complete the quality assessment of the 20 articles, a further evaluation was needed to measure the reliability factor of quality, in the following (Table 3.3). The main strength and limitations of each article is described and assessed, the evaluation of the quality is based on the questions asked in the aims and objectives (see PRISMA checklist Table 3.4 item 7).

After the quality assessment, full texts which had a grade less than (+++) in terms of quality and reliability were excluded i.e., n=7 (highlighted in grey color in Table 7) and 13 studies were selected using the PRISMA 2009 flow diagram (see Figure 3.1).

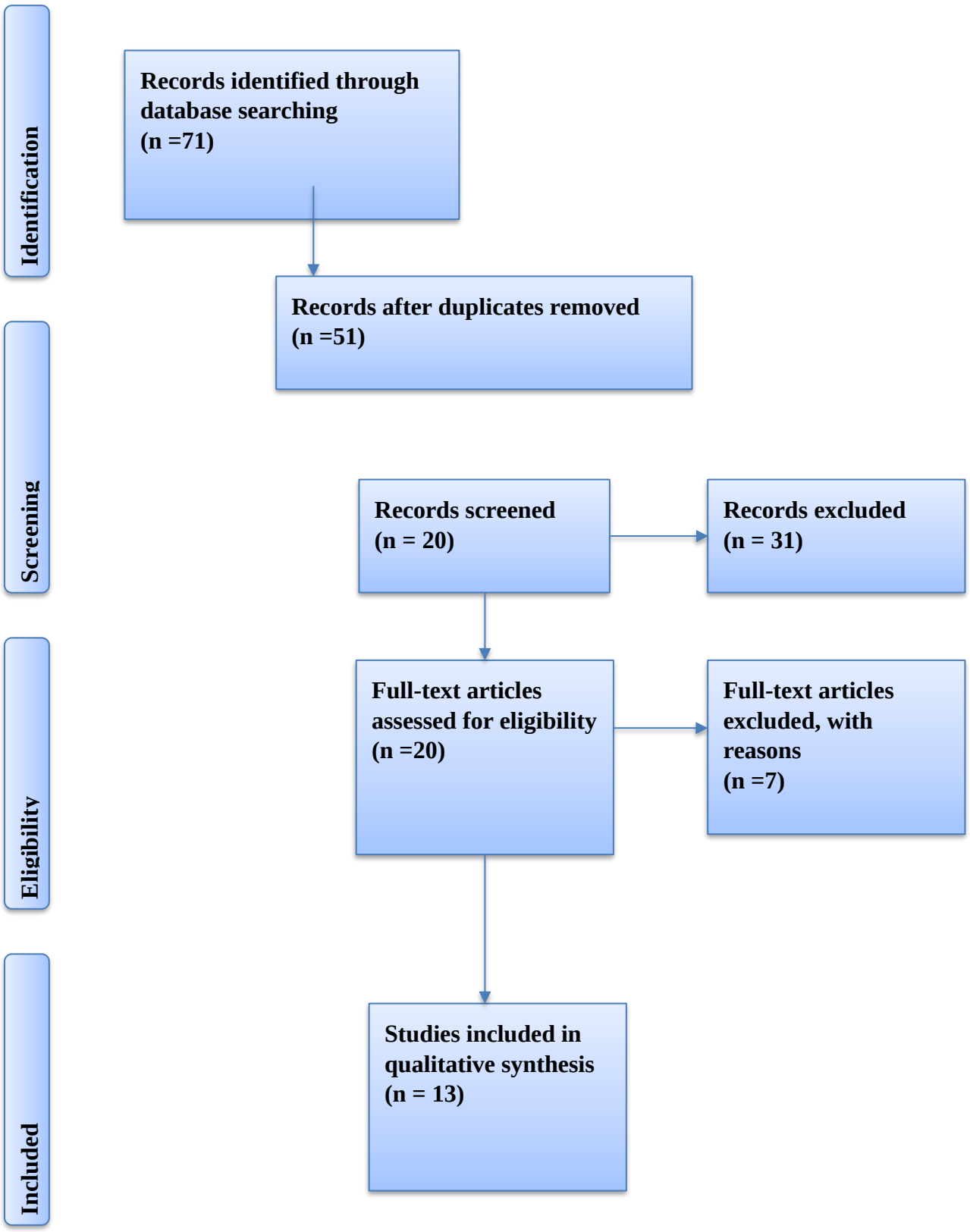
Table 3-3 Evaluation of the quality assessment

Reference	Main Strengths	Limitations	Reliability/Questions of aims and objectives
Almaaytah et al., 2020	This study highlighted budget impact onto 13 emerging countries to evaluate the access of biosimilars	This study focused on Middle East North Africa (MENA) countries and one therapeutic area: oncology	+++
Bennett et al., 2014	The study determined the factors impacting on regulatory frameworks globally and focused on emerging markets	The study was enrolled between 2008-2012 and focused on oncology	+++
Fadi et al., 2017	The study was focused on the emerging markets opportunities for biosimilar entry	The general information recorded in the study were reviewed qualitatively in the period from 1999 to 2014	++
Ferrario et al.,2020	The author suggested global strategies that can help into emerging market	Focus on both generics and biosimilar on the global market	+++
Knighton, 2018	The study methods and suggestions were different from previous research, they can be very useful for future researches	Focus more on US	+++
Krishnanet al., 2015	The study focused on pharmerging market regulatory pathways	The conclusion was not made on persuasive arguments	++
Lammers et al.,2014	The study identified the barriers to access Human Epidermal growth factor Receptor 2(HER2) in 4 emerging countries	The study focused on oncology therapeutic area recommendations	+++

		were not drawn up based on outcomes	
Patel et al., 2013	SWOT analysis of biosimilar entry onto the global market	The study is focused on the global market and it answered only to one question of the protocol / the INN concern.	++
Gabi, 2020	The article is a recent study which highlighted the development of biosimilar in Asian countries such as China, Japan, or India. In terms of manufacturing or regulations.	The article is focuses only on Asia pacific countries only	++++
Sonam, 2020	The main strength of this review is that the search was conducted in 2020 and aimed to study perceptions, knowledge, and attitudes of all the stakeholder groups and countries with different regulatory laws and policies that contribute towards the adoption of biosimilars.	Most of the studies included in the review were conducted in the UK and the US.	+++
Liang, 2014	The article outlines a possible solution to promote the biosimilar access in the emerging market which is the public-private partnership (PPP), the article answered to almost all the questions in aims and objectives	The author is focused on PPP as strength to penetrate the emerging market	++++
Tannoury et al.,2017	Challenges and strategies of the pharmaceutical growth in emerging markets	Focused on MIST and BRICS only Biosimilar is not highlighted in the research	++
Fadi et al., 2016	Regional survey to understand the impact of different parameters on the acceptance of future biosimilar prescription	Respondents were from Arab countries and Iran	+++

Hamzi, 2019	The authors proposed a strategy of the entry of biosimilar onto the MENA markets and added value to the research by business reviews, SWOT and Porter' five forces	The author focused on MENA countries	++++
El Zorkany et al., 2018	Researchers provided recommendations for the regulation and use of biosimilar medicines in the Middle East	Therapeutic area focused on Rheumatology Region studied: Middle East	++++
Bhupinder et al., 2011	Biosimilar medicine issues are being discussed dynamically around the world.	The emerging market was not considered in the study	++
Eva et al., 2019	Provided a visualization of essential steps that are required to be taken for global biosimilar acceptance.	Strategies provided are not focused on emerging markets	+++
Vesa et al., 2020	The purpose of this study was to evaluate the current knowledge and attitudes of health care professionals towards biologically similar solutions and to broaden their benefits.	The aims and objectives questions were poorly answered	++
Eduardo et al., 2018	This study provided an overview of the global biologically similar situation's progress and provides examples of imbalances in administrative requirements across regions.	The study focused only on developed countries	++
Freire et al., 2020	The study aimed to develop a quantitative study and prediction scenario based on patent data as an indicator of biopharmaceutical innovation in order to assess how emerging pharmaceutical markets are being explored.	Focused on BRICS	++++

Figure 2 PRISMA Diagram (PRISMA flow chart, 2009)



3.3 Protocol checklist (PRISMA, 2015)

The protocol was followed as per the PRISMA checklist (See the full checklist in Appendix A) and the registration was not included since this review was achieved for mini-thesis purposes. Some of the checklist parts were not included in the study as the method is not about a clinical study and not registered on PROSPERO, an international prospective register of systematic reviews which should be done before the start of data extraction process.

Table 3-4 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) Recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:	1	Protocol defining systematic review on the growth of biosimilar onto the pharma-emerging market
Registration	2	Not included in the study
Authors:		
Contact	3a	Ryma Batel, batel.ryma@gmail.com
Contributions	3b	Not included in the study
Amendments	4	Not included in the study
Support:	5	
Sources	5a	Not included in the study
Sponsor	5b	Not included in the study
Role of sponsor or funder	5c	Not included in the study
INTRODUCTION		
Rationale	6	The growth of biosimilars onto the pharmerging countries is still a debate as the introduction of biosimilar globally is not mature yet and requires stringent regulations. Multiples studies have been conducted to analyse the challenges versus opportunities of biosimilars. While the predictions on the economy of advanced countries are not promising, the possibility of biosimilars submersion onto the pharmerging market as small generics molecule is not excluded (Chopra et al., 2018). Moreover, the generics commercial expansion has been seen during the financial crisis of 2008. This critical period had a considerable impact on the budgets and the available funding for health services. So, if the biosimilars benefit from the Covid 19 crisis, its competition onto the market will probably resemble generics. However, the assumptions are not reliable; they are needed to be substantiated in a serious research project. Determining the variables responsible for the growth of biosimilars in emerging markets could provide useful information for policy makers to develop/determine appropriately tailored regulatory strategies for biosimilars in (targeted) emerging markets.

Objectives	7	1-Is the regulatory pathway of biosimilars' entry in emerging markets affected by their cost? 2-Is the cost the main driver of prescribing biosimilars? 3-Will the switch to biosimilars improve patients' access to therapies? 4-Does biosimilar naming/labelling influence patient safety in emerging countries? 5-Will biosimilars grow onto the emerging market?
METHODS		
Eligibility criteria	8	See table 3-1
Information sources	9	ProQuest, Google scholar, PubMed, EMBASE.
Search strategy	10	1. Determine clear and focused questions 2. Describe the articles that can answer the questions 3. Decide which key concepts address the different elements of the questions 4. Decide which elements should be used for the best results 5. Choose an appropriate database and interface to start with 6. Document the search process in a text document 7. Identify appropriate index terms in the thesaurus of the first database 8. Identify synonyms in the thesaurus 9. Add variations in search terms 10. Use database-appropriate syntax, with parentheses, Boolean operators, and field codes 11. Optimize the search 12. Evaluate the initial results 13. Check for errors 14. Translate to other databases 15. Test and reiterate
Study records:		
Data management	11a	• Maintain a searchable database of references related to the systematic review • Store all references selected for the systematic review • Remove duplicate citations • Store all discarded references • Create citations and bibliography when writing up the results of the SR
Selection process	11b	Hand search Selection as per inclusion criteria: see table 3-1 1-Date from 2010-2020 2-Keywords 3-Determine variables 4-Answer questions (see item 7 (Table 3.4))
Data collection process	11c	All the articles/ reports which meet the exclusion criteria to be rejected
Data items	12	***Variables (Extracted from literature review)*** • Population demand/ supply • Government investments in biopharmaceutical innovation/ purchasing power

		• Biosimilar pricing strategies/ profitability
Outcomes and prioritization	13	Finding and results compared to the results obtained from literature review extraction of new variable
Risk of bias in individual studies	14	Not included in the study
Data synthesis	15	The responses will be evaluated by calculating the number of Yes' or No's by the number of articles and summarized in a table

CHAPTER 4 : RESULTS AND FINDINGS

This chapter presents all the data extracted from the relevant references identified previously (in chapter 3), the analysis of the findings and their interpretation.

4.1 Introduction to Results

The potential strength of a systematic review lies in the transparency of each phase of the synthesis process, focusing on each decision made in compiling the information, but the main step of a systematic review is to formulate a research question. However, a question that is too specific will result into too few or even no search results, for this reason the questions were expanded from 1 research question (see chapter 1) to 5 research questions (see item 7 PRISMA protocol).

Traditional methods of SR search strategy development and execution are highly time consuming, reportedly requiring up to 100 hours or more (Erwin PJ, 2004). So, the first approach that has been used was the method of selection of Wichor et al. (2018) which have been used to select the relevant references; this method describes step by step the process of developing a systematic search strategy as needed in the systematic review. (See described steps in Appendix A). This method helps to focus on the search terms, instead of on the structure of the search query. It describes all steps of the search process, starting with a question and resulting in thorough search strategies in multiple databases. The methodology is intended to create thoroughness for literature searches. The optimization method identifies missed synonyms or thesaurus terms, unlike any other method that largely depends on predetermined keywords and synonyms. Using this method results in a much quicker search process compared to traditional methods. By using the Wichor et al. (2018) search strategy 71 articles were selected, assessed (table 3.1) and optimized to result 20 articles. Each of the 20 selected studies was reviewed and quality appraisal was conducted according to Hawker et al, (2002) for prevalence studies was used for the systematic review, while quality evaluation was used for

the study. There were 13 articles that had a high-quality score, and the rest scored a moderate score. The articles with a high-quality score had clearly defined reliable methods of data collection, and an appropriate method of analyses. Those with a moderate quality score did not have adequate answers to the research questions (see item 7 PRISMA protocol checklist)

Besides that, they also did not report percent response rate, and supporting evidence was not mentioned for the non-response population, their comparable characteristic differences, and how non-response was managed. Overall, the quality assessment revealed a lack of valid scales/ scores/ methods used in survey or interview studies. The assessment scores are presented in (table 4-1).

4.2 Data Collection Process

4.2.1 Literature Search Results:

The PRISMA Checklist helped in the definition of the protocol and research questions which resulted in 5 specific questions (see protocol above in page 45). The flow of information through the different phases of the process is seen in diagram (in page 44).

The PRISMA checklist focused on the way the review was conducted and did not address directly nor in a detailed manner the evaluation or assessment of the systematic review for which Wichor et al. (2018) search strategy tool was used. This was then used to define the inclusion and exclusion criteria, optimize the search and finally reducing the number of articles by 71.83% where only 20 articles remained. The most important criteria for PRISMA were the objective questions designed to be answered by a 'YES', 'NO', or 'NOT SURE' to facilitate the evaluation of the biosimilar's growth in emerging markets. If the article didn't respond to at least two questions it was excluded from the search.

Next, the Hawker et al. (2002) quality assessment tool was used to assess the quality of each article by evaluating the 20 articles with a score. The purpose of this rating tool was to evaluate the quality of systematic reviews related to the aim and objective determined

previously in chapter 1. It was not intended to measure the literary quality, importance, relevance, originality, or other attributes of the scientific quality of the articles.

Four articles, Fadi et al. (2017), Patel et al. (2013), Tannoury et al. (2017) and Bhupinder et al. (2014) were graded B, mostly due to being poorly answered to question 8: Transferability or generalizability and question 9: Implications and usefulness. (See table 3.2) The findings of their study were not transferable to the emerging market. However, the scoring method by Hawker et al. (2002) was not sufficient to evaluate the articles as per the questions of the aims and objectives which were chosen concisely to answer the main research question in Chapter 1.

4.2.2 Quality Assessment:

The 20 articles were assessed by using the following factors of reliability:

1. The number of countries included in the study; the total number of regions included will reflect the reliability and accuracy of information presented, i.e. more regions will lead to more dependable results.
2. The year the study was completed; the newest most recent is the most up to date and therefore was viewed as the most accurate.
3. Focusing on one therapeutic area is a limitation to the information provided.
4. The number of factors that drive the entry of biosimilar onto the emerging market.

   Keywords: cost, switch, prescribing, access, labelling, naming and growth

5. The argument in the conclusion of the article must be easy to understand and focused on the aim and objectives of the main research questions.

   Keywords: growth, emerging markets

Factor 4 and 5 are the most relevant when it comes to making a decision regarding analyses of data.

Table 4-1 Exclusion of 7 articles

Reference	Limitations	Reason of exclusion	Reliability/ Questions of aims and objectives	Results
Fadi et al., 2017	The general information recorded in the study were reviewed qualitatively in the period from 1999 to 2014	Two articles from the same author were assessed one was more reliable in terms of factors that drive the entry of biosimilar onto the emerging market	++	Excluded
Krishnanet al., 2015	The conclusion was not made on persuasive arguments	The conclusion did not mention the emerging market as potential market for the biosimilar	++	Excluded
Patel et al., 2013	The study is focused on the global market and it answered only to one question of the protocol / the INN concern.	Only one keyword was included naming could not answer to the 5 questions for the data analysis	++	Excluded
Tannoury et al., 2017	Focused on MIST and BRICS only Biosimilar is not highlighted in the research	The articles are focused on the potential of the emerging g market in the pharmaceutical industry but the factors 4 and 5 of reliability were not emphasized	++	Excluded
Bhupinder et al., 2011	The emerging market was not considered in the study	Factors of reliability 4 and 5 were very poor	++	Excluded
Vesa et al., 2020	The aims and objectives questions were poorly answered	Only one keyword was included from the factor of reliability number 4	++	Excluded
Eduardo et al., 2018	The study focused only on developed countries	Factors of reliability 4 and 5 were very poor	++	Excluded

Consequently, 13 articles were retained for the data analysis and werefinally reviewed by answering the questions previously cited in the protocol in Table 4.1 / Item 7.

The 5 questions applied were as follows:

1. Is the regulatory pathway of biosimilars' entry into emerging markets affected by their cost?
2. Is cost the main driver of prescribing biosimilars?
3. Will the switch to biosimilars improve patients' access to therapies?
4. Does biosimilar naming / labeling influence patient safety in emerging countries?
5. Will biosimilars grow onto the emerging market?

4.3 Data Analysis

4.3.1 Data presentation

The answers of the selected 13 articles to the above questions were measured on the number of 'Yes/No/Not sure' answers. 'Yes', meant agree, 'No' meant disagree and 'Not sure' meant varied arguments or not specified (See table 4-2).

Table 4-2 Scoring of included articles to item 7 (PRISMA)

Reference	Q1	Q2	Q3	Q4	Q5
Almaaytah et al., 2020	No	No	Yes	Yes	Yes
Bennett et al., 2014	No	Yes	Yes	Yes	Yes
Ferrario et al.,2020	Not sure	No	Not sure	Yes	Not sure
Knighton, 2018	Not sure	Not sure	Not sure	Not sure	Yes
Lammers et al., 2014	Yes	Yes	Yes	Not sure	Not sure
GaBI, 2020	Yes	Yes	Yes	Not sure	Yes
Sonam, 2020	Not sure	No	Yes	Yes	Not sure
Liang, 2014	Not sure	Not Sure	Yes	Yes	Yes
Fadi et al., 2016	No	No	Yes	Not sure	Not sure
Hamzi, 2019	No	No	Yes	Yes	Not sure
El Zorkany et al., 2018	Yes	No	Not Sure	Yes	Yes
Eva et al., 2019	Not Sure	No	Yes	Yes	Not sure
Freire et al., 2020	Not sure	Not Sure	Yes	Not sure	Yes

The responses were evaluated by the 'Yes', No' and Not sure' w.r.t questions on Table 4.1 / Item 7

There were only agreements and non-expressed opinions about the growth of biosimilar onto the emerging market where the number of 'Yes's' was 6

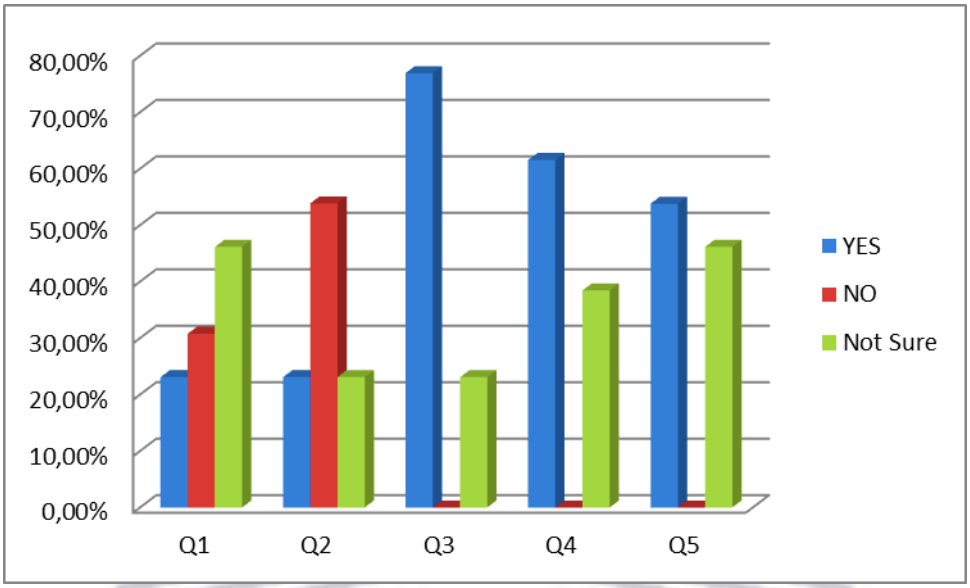
The number of included articles i.e. 13 represent 100%. Calculation of the percentage of 'Yes', 'No' and 'Not sure' based on the number of articles is seen in Table 4.3 and Figure 2.

Table 4-3 The percentage 'Yes', 'No' and 'Not sure' (n=13)

Answers/ Total (%)	Q1	Q2	Q3	Q4	Q5
Yes	23.07%	23.07%	76.92%	61.53%	53.8%
No	30.76%	53.84%	0%	0%	0%
Not Sure	46.15%	23.07%	23.07%	38.46%	46.15%

*The highest percentages are colored in orange to emphasize the majority

Figure 3 Graphical representation of answers in table4.3



4.3.2 Data Interpretation

The chart illustrates the results obtained in the table 4-3 where questions 3, 4 and 5 are in majority favorable, (76.92%) agreed that the switch improves patients' access to therapies.

This is in agreement with the literature review previously which concluded that affordable prices can improve the access to medicines, as the biosimilar are lower priced than biologics. However, inadequate knowledge and education on biosimilar development and manufacturing will lead to hesitancy on switching. 61.53% agreed that the naming / labelling are a big challenge and influence the patient safety; even in literature review it was noted that the naming system can pose a strong challenge while prescribing biosimilars. On the other hand, question 1 had a majority of diverse responses (46.15%) where authors were not sure about the price impact on regulatory decision, and (30.76%) were against it. In literature review, it was reported that the development for established markets like EU / US which have presence in regulatory pathway may face different challenges compared to emerging market. Regarding the question 2, (53.84%) disagreed on the fact that the price is the main driver for biosimilar prescription, in the literature review it was found out that physician are more comfortable to prescribe biosimilar depending on the quality and efficacy. Finally, the growth

of biosimilar on the emerging market had (53.8%) of agreement versus (46.15%) uncertain opinions, in the literature review it was mentioned that BRICS and MIST provide the best future opportunity for manufacturer of biosimilar. In the following discussion the results are more developed in terms of statement and arguments.

4.4 Discussion of Results

The discussion of the study findings was divided into 5 questions as follow:

Question 1

Is the Regulatory pathway of biosimilars' entry into the emerging market affected by their cost?

The answers were different regarding the impact of price on the biosimilar regulatory approval where 23.07 % agreed and 30.76% disagreed but the majority, 46.15% of the answers were varied.

Almaaytah et al. (2020) and Hamzi (2019) arguments were made on the fact that rather than focusing on price, biosimilar adoption should be correlated with stringent and rigorous guidelines that guarantee the quality and safety of the patient. Furthermore, Fadi et al. (2016) and Bennett et al. (2014) stated that the credibility is the main driver of any biosimilar in countries with emerging biosimilar industries,

On the other hand, GabI (2020), Lammers et al. (2014) and El Zokrani et al.(2018) agreed with the association of the cost to the regulatory approval where many examples have been cited like the South Korean government has been actively providing capital, generous tax breaks and regulatory guidance to local biosimilars companies (GabI,2020).

Hence, the public policies in emerging countries aim to empower innovation in the biopharmaceutical productive sector like Pfizer's $ 350 million investment to build a global biotechnology center in China in 2016. China, during the period showed a very forceful growth, especially due to the strengthening of its public policies aimed at the advancement of science

and technology and arrived with 5,098 patents in that year (Freire et al., 2020). This statement is not clearly supporting the cost association to the regulatory approval but could be more agreeing to it than disagreeing. Furthermore, Sonam (2020) and Eva et al. (2019) reported that the introduction of cheaper pharmaceutical products is needed in emerging countries despite the difficulty of biosimilar approval and the establishment of regulatory procedures that improve efficiency of the approval process which could provide significant traction and benefit to biosimilar adoption. Although the answers to question 1 were less confident, it could be understood from statements made by the authors that the answers were more directed towards the cost impact on regulatory approval.

Question 2

Is cost the main driver of prescribing biosimilars?

The cost factor is not seen as the main driver of biosimilar prescriptions where 53.84% of responses disagreed.

According to Sonam (2020), Almaaytah (2020), and Eva et al., (2019) the lack of confidence in the efficacy or safety profiles of biosimilars is the main barrier for prescribing biosimilars due to the lack of data from clinical trials .

Other authors stated that prescribing a biosimilar is related to the drug approval, for example, in a survey made by El Zokrani et al. (2018), it was reported that physicians from Lebanon, Egypt, Syria, Algeria, Iraq, Sudan, Jordan, Iran, Belgium, and Italy, only 41% of responders stated that they prescribe biosimilars and, in most cases, only drugs that have been approved by the FDA and EMA.

Furthermore, Fadi et al's survey (2016) in MENA countries and reported that the main driver for prescribing biosimilars is the drug approval (68.8% of respondents) followed by a lower price (64.6%). However, regulatory uncertainty and product complexity are the main challenges because of the unclear legislation and lack of awareness in these countries Hamzi (2019) reported that in Tunisia and the MENA regions, only 25 % to 30 % of physicians think

that price is a strong motivation to prescribe local or imported biosimilars; and doctors trust more the imported biosimilars approved by the EMA and FDA.

In conclusion, clinical data and previously approved drug are the main factors in prescribing biosimilars by physicians in MENA countries. In Pacific Asia, most of the research was supportive of the prescription of biosimilars depending on the price. For example, in 2016, the Japan Biosimilar Association (JBSA) was established to address biosimilar penetration challenges like encouraging prescribers/pharmacy/hospitals to use biosimilars and removing the high medical cost care benefit system (GabI, 2020). Bennet et al. (2014) stated that some countries hospitals have financial incentives to adopt biosimilars, because of their low price and Lammers et al. (2014) reported that the first intended biosimilar to the monoclonal anti-CD20 cancer agent, rituximab, was launched in India in 2007 at 50% lower cost than the originator biologic (MabThera™®, Hoffman-LaRoche, Basel, Switzerland). As a result, patient access to CD20 directed therapy increased six-fold within three years of launch due to lowering of its cost.

Other research was scored as 'Not sure' response because the prescription/cost factor was not clearly mentioned except Liang et al. (2014) who was more direct toward the fact that the major barrier to biosimilar growth is related to the lack of clinical data. Consequently, the majority of opinions are shared between two regions; Pacific Asia and MENA regions. For example, in MENA, the prescription of biosimilars is not influenced by the price compared to Asia Pacific regions.

Question 3

Will the switch to biosimilar improve patients' access to therapies?

The switch factor which can increase patient access had more agreed with 76.92% of positive arguments but in some research the responses were to 23.07 %. For example, Knighton et al. (2018), El Zokrani et al. (2018) and Ferrario et al. (2020) had no clear statements about switching impact on patients' access to therapies. El Zokrani et al. (2018) said that the decision

to switch should be made on a case-by-case basis supported by scientific evidence and must be patient, disease, and product specific. Thus, originator biologics and biosimilars are not allowed to be automatically substituted without physician involvement or patient awareness. From this statement, it could be understood that switching is not preferred.

On the other hand, the rest of the studies suggested that biosimilars are expected to bring significant budgetary savings to national health and increase patient's accessibility to biologic therapy. For example, Bennet et al. (2014) reported that in India, before the biosimilar rituximab approval, fewer than 1000 people received the originator rituximab because of its high cost. Since then, several thousand people have received the biosimilar rituximab and in Russia, biosimilar rituximab approval and price discounts are expected, and, presumably, overall use will increase. Furthermore, in Japan, biosimilars are priced at 70% of the reference products' prices which is expected to increase patient access (GabI, 2020).

Regulatory submissions for a biosimilar may sometimes consist of information on substitution of the reference product for the biosimilar and the quantity and type of this information may differ with each submission, but the 'switch' is likely to be related to the growth of the biosimilar market.

Question 4

Does biosimilar naming / labeling influence patient safety in emerging countries?

Several barriers to implementing international non-proprietary prescribing and generic substitution exist. However, implementation of international non-proprietary prescribing is the key enabler of greater uptake in countries at all levels of income according to Ferrario (2020). In question 4, 61.53% of responses agreed, where Almaaytah et al. (2020), Bennet (2014), Eva (2019), Liang (2014), Sonam (2020) and Hamzi (2019) stated that INN prescribing is challenging in terms of switching side effects and distrust in authorities, specifically in emerging countries where the pharmacovigilance is one of the important issues.

In the other articles 38.46 % responses were ‘Not sure’ because the issue of INN is not highlighted nor mentioned clearly.

Question 5

Will biosimilars grow onto the emerging market?

Several international pathways have been developed to expedite entry of biosimilars onto the global market. Emerging countries generally allow extrapolation to reference that previously received approval in Europe or the USA but most of the emerging countries guidelines are based on the EMA. However, the regulatory pathway of biosimilars in the pharmerging region is immature, so replication of European experience can be challenging due to the critical economic, political, and social gap between the two regions. The experience of the BRICS countries can be more suitable to copy according to Hamzi (2019) and Ferrario (2020). Because these countries have the highest number of biosimilar development and they have created a solid framework compared to other emerging countries and the replication of the European experience can be challenging due to the current and critical economic, politic and social gap between emerging countries and the EU.

Kinghton (2018) presumes that firms with previous generic drug experience drugs will enter the biosimilar market more frequently than those that do not have generic experience; for example, Teva and Sandoz are pursuing the biosimilar route. However, a counter discussion to this is that companies that have experience with only generic drugs may not have the deep biological and technical understanding to develop biosimilars.

Regarding the growth of biosimilars in the emerging countries, the review is more in agreement with 53.84% but 46.15% of opinions were varied and unclear with this matter. For example, Hamzi (2019) stated that the MENA countries have great opportunities for biosimilars as local regulations in these countries are encouraging biosimilars for their lower price which can be beneficial to the health expenditure growth. Moreover, government will adopt cost saving strategies in the healthcare sector where partnerships with local

manufacturers is recommended and policymakers implemented differential advantages to reduce healthcare expenditure by encouraging multinational to install or subcontract locally. The political environment in these countries is, however, unstable like the Arab spring which witnesses a huge depreciation in local currencies and increase of medicines importation.

On the other hand, 30% of the total biosimilar market today belongs to emerging markets with 60% of the global population based in Asia. The South Korea investment is 2.6 billion dollars in R&D and commercialization and Japan is attractive market for biosimilar sponsors as they are encouraging the prescription of biosimilars.

The Chinese government offers several initiatives to facilitate the development and adoption of biosimilars and the Indian government has also been actively promoting the production in India campaign to enhance R&D where more than 2700 biotechnology startup firms and 1600 biotechnological incubators are present in India. Market data research forecast estimated the size of the biosimilar market in Asia Pacific by 1.26 million dollars in 2019 to grow 4.99 million dollars by 2024, thus with a 31.6% growth rate (GaBI2020).

Most of the research defined the aging, growing population and government investments having a direct impact on the growth of biosimilars in emerging countries.

A report has been published recently by IQVIA on the potential of biosimilars in the Middle East and Africa (MEA). A comparison can be done on the outcomes that resulted previously and the outcome from that report (Table 4.4.).

Table 4-4 Comparative analysis of outcomes of biosimilars in the Middle East and Africa (PRISMA checklist – item 7)

Answers/ Total (%)	Q1	Q2	Q3	Q4	Q5
Review (13 articles)	Not Sure→→Yes	No	Yes	Yes	Yes
Review IQVIA Report	Yes	No	Yes	Not Sure	Yes

*The shared answers are colored in blue

The price was not the main driver of prescription from the two reviews. Achieving success in the biosimilar space requires a different approach compared to traditional generics. Regulatory framework, guidelines and pricing have been challenging because stakeholders (including regulatory agencies, payers, and prescribers) demand additional level of evidence to approve the use of biosimilars and to provide evidence for interchangeability of biosimilars, often resulting in delayed approvals. These characteristics are likely to impact biosimilar adoption in the MEA region. Given the regulatory differences across borders and internal delays in implementation, there is a need for a regulatory convergence and harmonization at an international/regional scale to facilitate biosimilar uptake.

The commercial environment of the MEA region is becoming more conducive for a strong uptake of biosimilars, considering increased government focus on expanding patient access to medicines, budget constraints and availability of a regulatory framework. In 2019, biologics accounted for nearly 15% of the total MEA pharmaceutical market (vs. 30% biologic share in the global market).

The markets that are best placed to capitalize the benefits are those (1) where biosimilar guidelines are established, (2) where manufacturers are motivated to participate over a longer period, and (3) where physicians are at the heart of decision-making, since they influence biosimilars' uptake and usage. For example, biosimilars have been able to gain market access in Algeria using generic approval pathways. Faster registration routes for local products are applied. In the IQVIA report, it was suggested that tailored strategies by pharmaceutical companies are necessary to navigate the markets successfully, and the main driver of the growth of biosimilars in MEA are improved stakeholder's awareness and an increase in per capita pharmaceutical spending.

CHAPTER 5 : CONCLUSION AND RECOMMENDATIONS

Despite the differences among regulatory bodies across emerging markets, there are some efforts occurring for greater harmonization. Many countries adopted a big step forward for the establishment of a global, harmonized regulatory framework, but the potential is huge, and the hope is that biosimilars will allow greater patient access to treatment through cost savings.

This research showed that the variables responsible for the growth of biosimilars onto the market are the large population compared to the non-existing or ineffective treatments for certain diseases, the amount that each country spends on pharmaceutical and health care services depending on economic or political factors, and the biosimilar guidelines already established. The study findings have also highlighted that the switch to biosimilar will improve patients' access to therapies, but the awareness of the physician is important for biosimilar prescribing decisions. Mostly, the price is not the main driver to prescribe biosimilar. So, the most successful driver of the growth of biosimilars onto the emerging market based on this review was found to be the regulatory process.

Recommendations

1. ***Establish a tailored regulation process for each country:*** literature noted that the emerging countries (BRICS, MIST) susceptible to growth in terms of biosimilar marketing are the ones which have already created a solid framework and comparability pathway based on the WHO or EMA guidelines, but in some countries like MENA the regulatory path have to be tailored due to factors such as the political instability or economic situation.

2. ***Evaluate the impact of the protection policies from the innovators***: Innovator biologics companies impose barrier to the manufacturer which can be an issue to gain

access in regions with little or no experience in biosimilar options exist for collaboration between companies to promote biosimilar accessibility in these countries.

3. ***Prioritize the therapeutic area/number of patients***: In some countries, the access to certain treatment is difficult and the number of patients is extensive in such cases, biosimilars can help to improve the cost-effectiveness of cancer drugs and make them accessible to more patients.
4. ***Identify and anticipate possible barriers to adoption, both by the doctor and the patient- Education is required:*** To ensure that patients and physicians have the required information about available treatment options and know what questions to consider when working healthcare providers to select the right treatment.
5. ***Lower development cost, shorter time to market fuels growth***: Lowering development cost via innovation to create a sustainable future, as well as working other companies to lower the costs--and the risks--around new product development. This is also known as open innovation, and it can take many forms ranging from idea competitions to longer-term partnerships or equity investments.
6. ***External partners for contract manufacturing services*****:** External manufacturing is a strategic operation. The share of production driven by cost and efficiency constraints coupled with the need to efficiently supply a diverse global patient population.
7. ***Local policies to facilitate approval access and marketing in the local markets to support multinationals:*** Manufacturers will need to work closely with policy makers and payers to implement reimbursement policies built on solid evidence. Furthermore, companies evaluating opportunities in particular countries pay attention to their market and regulatory maturity; therefore, to attract multinational in these countries, local policies should help by developing tailored policies.

8. ***Implement real world data incentives:*** There should be mandatory brand-name prescribing to avoid unintended switches as well as a robust pharmacovigilance system to report adverse drug reactions (ADRs).

Competing in emerging markets means competing in a price-driven environment. So, an extensive research on the impact of each recommendation and development of a business model of each country can be more informative and can have more targeted recommendations.

Overall, the biosimilar will probably grow onto the emerging market and the price will be one of the main drivers and this will undoubtedly be accentuated after the COVID-19 crisis. Jason Furman (Harvard Kennedy school, 2020) affirmed that the economic activity collapsed by 15%. The future economic crisis is expected to further accelerate the pragmatism of governments and measurements to promote the use of biosimilars (Ignacio Diaz, 2020).

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CHAPTER 6 APPENDIX – A PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Section/topic	**#**	**Checklist item**	**Reported on page #**

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097