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Access to Biosimilars in Federal Hospitals in Addis Ababa: Assessment of the National Medicines Regulatory Framework and Healthcare Professionals' Perspectives.

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May, 2025
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We certify that we have read and evaluated the thesis prepared by Shimelis Ayele, entitled Access to Biosimilars in Federal Hospitals in Addis Ababa: Assessment of the National Medicines Regulatory Framework and Healthcare Professionals' Perspectives. We confirm that it fulfills the requirements for submission in partial fulfillment of the degree of Master of Science in Regulatory Affairs (Medicine Regulation Track).

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Declaration

I declare that the thesis submitted for the Degree of Master of Science in Regulatory Affairs (Medicine Regulation Track) to the Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University is my original and independent work. It has not been submitted previously by me or any other person to another university. All materials obtained from external sources are fully acknowledged in the thesis.

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Abstract

Background: The introduction of biopharmaceuticals brought remarkable clinical outcomes, particularly in the treatment and management of challenging chronic diseases. However, the high cost of originator biologics limits their accessibility. The adoption of biosimilars offers a cost-effective alternative, reducing healthcare expenditures and improving patient access to biologic therapies. Despite their potential benefits, the national regulatory framework and lack of understanding and confidence of healthcare professionals hinder the accessibility and uptake of essential biosimilars.

Objective: To assess the regulatory framework for biosimilars in Ethiopia and healthcare professionals' perceptions regarding their access and uptake in federal hospitals.

Method: The study employed a convergent parallel mixed design. Employing qualitative methods, the researcher performed interviews with 9 professional key informants and conducted document reviews. Thematic analysis was used to identify themes. In a quantitative study, 292 healthcare professionals participated in self-administered questionnaires. The researcher conducted analysis using SPSS for descriptive statistics and Spearman correlation.

Results: The qualitative findings revealed that the Ethiopian Food and Drug Authority follows biosimilarity principles and proof of biosimilarity that are largely consistent with international standards. However, the authority has approved only a limited number of biosimilars, and the healthcare facilities face significant challenges in accessing even the registered products. The findings showed that 56.4% of participants were unfamiliar with the term biosimilar, with median knowledge 2 (range: 0-6) and attitude scores of 31.00 (range: 14-44). The median scores of practices were 1 for physicians and 2 for pharmacy professionals. Barriers to biosimilar uptake in clinical practice included insufficient knowledge, lack of professional confidence, and the absence of reliable information sources.

Conclusion: The study highlights the insufficient availability of registered biosimilars, HCPs' knowledge gap, and absence of clear guidance for the switching and substituting of biologics. Policy instruments are urgently needed to address the gaps and ensure the balance between the demand and supply side of essential biologics.

Keywords: Access, Biologics, Biosimilars, Regulatory Framework, Healthcare Professionals' Perception

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List of Acronyms

ANVISA	Agencia Nacional de Vigilancia Sanitaria
ALERT	All-Africa Leprosy, Tuberculosis, and Rehabilitation Training Centre
CMC	Chemistry, manufacturing, and control
CPP	Certificate of Pharmaceutical Product
EFDA	Ethiopian Food and Drug Authority
EHIS:	Ethiopian Health Insurance Service
EMA:	European Medicines Agency
EPSS	Ethiopian Pharmaceuticals Supply Service
EHIS	Ethiopian Health Insurance Service
GMP	Good manufacturing practice
HCPs	Health care professionals
MoH	Ministry of Health
NCDs	Non-communicable diseases
NMRA	National Medicine Regulatory Authority
NRA	National Regulatory Authority
PBAC	Pharmaceutical Benefits Advisory Committee
RMH	Russian Ministry of Health
SBPs	Similar biotherapeutic products
SOPs	Standard operating procedures
SPSS	Statistics Package for Social Sciences
St PHMMC	St Paul's Hospital Millennium Medical College
TASH	Tinkur Anbessa Specialized Hospital
TMDA	Tanzania Medicines and Medical Devices Authority
US FDA	United States Food and Drug Administration
MHPRA	Medicines and Healthcare Products Regulatory Agency
WHO	World Health Organization

1. Introduction

1.1. Background

Changes in disease patterns and intensifying side effects of drugs from small molecules have triggered the growth of biological drug discovery and development research investment. Increasing morbidity and mortality from non-communicable diseases (NCDs) have become major challenges for the 21st century healthcare system (Sadek, 2020). According to World Health Organization (WHO) report, NCDs contribute to about 70% of deaths worldwide (Rasyid, 2014).

The global action plan 2013–2020 proposes that medicines are one of the interventions to target mortality and morbidity from NCDs (Dye et al., 2013). Biological medicines have been praised for their greater contribution in the treatment and management of difficult-to-treat diseases like cancer, diabetes, rheumatoid arthritis, multiple sclerosis, and other chronic NCDs (Priyarega & Natarajan, 2022). Biological medicines, also known as biologics or biological products, are medicines that contain biologically active substances produced from biological sources by using advanced biotechnological process. They are large, complex molecules, and may include proteins, nucleic acids, vaccines, cells, tissues or gene therapies (EMA, 2019).

Despite their presumed clinical and economic contribution, strong patent protection and higher prices are still major barriers to access to reference biological medicines by larger segments of the global population in resource-constrained regions. Following global and regional agreements towards balancing intellectual property rights and improved access to essential medicines and vaccines, increasing patent expiry of reference biological medicines encourages pharmaceutical companies to invest in the development and commercialization of biosimilars worldwide. The platforms created opportunities for middle- and low-income countries to expand patients' access to affordable biologics and increase cost savings for the health care system (Ghosh, 2016). Nevertheless, access to biosimilars has not been visibly enhanced in developing countries due to multifaceted reasons: (i) biosimilars may not be registered by local drug authority; (ii) registered ones may not be available in healthcare institutions; (iii) the products may not be affordable

because of high prices; (iv) lack of appropriate policies to encourage the use of biological medicines; and (v) healthcare professionals' knowledge and attitudes hinder uptake of biosimilars (Moorkens et al., 2016).

A comparative assessment of the national regulatory framework against worldwide norms aids in identifying limitations in regulatory processes and overcoming some of these deficiencies. Furthermore, understanding the situation of biosimilars' use in the health system provides a basis for policymakers and managers to improve equitable access to biological medicines. Therefore, this study tried to assess the national regulatory framework of biosimilars and healthcare professionals' perceptions regarding access and uptake of biosimilars in federal hospitals of Addis Ababa, Ethiopia.

1.2. Statement of the Problem

Access to essential medicines has been recognized as an essential indicator of the implementation of the universal commitment: the "right to health" (Halle, 2018). However, promising medicines like biosimilars are not adequately accessible in both developed and low-income countries because they are either not available, too expensive, or may not be prescribed and dispensed by healthcare professionals. Various studies indicated that the medicine regulatory framework of a country and healthcare professionals' knowledge and attitudes towards biosimilars are influencing factors to access biologics (Barbier et al., 2021; International Generic and Biosimilar Medicines Association IGBA, 2020; O'Callaghan et al., 2017a).

International and national regulatory environments and drug policies are fundamental determinants for the availability and use of biological medicines. Aligning technical standards across various countries accelerates the drug approval process both worldwide and in individual nations (Foreman et al., 2020). Although many countries have laws and guidelines to regulate biosimilars, they may still lack international standards for effective regulation. Studies indicated that the requirements for registration and approval of biosimilars vary in different jurisdictions; some lack comparability exercise, while others follow different regulatory procedures (Castañeda-Hernández et al., 2019; Rahalkar, Sheppard, & Salek, 2021; Rahalkar, Sheppard,

Santos, et al., 2021). These include selection of reference products, requirements of bridging or local clinical studies, and naming of biologics. Such divergent regulatory requirements do not favor pharmaceutical companies since they need to duplicate or require additional data for a single product to obtain market authorization (Heinemann et al., 2015; H. N. Kang et al., 2021; Narsai et al., 2012). In addition, lack of a transparent regulatory system and procedures for medicines registration and resource constraints for registration and inspection can have a significant effect on the availability of biosimilars (Kamwanja et al., 2011; Narsai et al., 2012).

Furthermore, the lack of government policies on international non-proprietary name (INN) prescribing, switching and automatic substitution, pricing, and reimbursement of biosimilars are other barriers to the clinical practices (Moorkens et al., 2017; Vogler et al., 2021). Healthcare professionals (HCPs) have an indispensable role in the promotion and rational use of biosimilars; however, lack of adequate knowledge and experience about the applications, clinical performance, and their attitude hinders the use of essential biosimilars (Aladul et al., 2018; Chapman et al., 2017; Cohen et al., 2017; Tomaszewski, 2016).

In Ethiopia, the economic and health burden of non-communicable diseases has been alarmingly increasing (Bollyky et al., 2017). Because of the historical epidemiological trends, economic imperatives, and policy direction, adequate attention was not given to the prevention, treatment, and management of NCDs. Despite the fact that biosimilars have significant contributions for the treatment and management of NCDs, the predominant out-of-pocket spending for pharmaceuticals and the low purchasing power by a larger segment of the population, coupled with the lack of a comprehensive health insurance system, contribute to the restricted access to biosimilars (Ali, 2014). The Ethiopian government has initiated healthcare financing reform and a social health insurance system. The national regulatory authority also developed a specific guideline for approving similar biotherapeutic products (Ababa, 2018b) in order to enhance access to essential medicines.

However, there is limited published evidence regarding the current state of availability and use of biosimilars in healthcare facilities. The interplay of national biosimilars regulatory framework

and healthcare professionals' knowledge and attitudes that could affect access and uptake of biosimilars have also not been investigated.

1.3. Significance of the Study

Theoretically, this study adds the understanding of biosimilars by centering low income setting, challenging assumptions derived from high-income contexts. Practically, the findings can have important implications for policy implementation and in cultivating a concerted effort from the major stakeholders, including the Ministry of Health, EFDA, healthcare facilities, healthcare professionals, pharmaceutical supply chain actors, patients, and research institutes. The findings highlight the existing context of access to biosimilars, the regulatory framework for biosimilar regulation, and major challenges for enhanced access in health facilities. The study tried to garner firsthand information from health professionals practicing in federal referral hospitals.

The mixed-methods study design helps to extract in-depth information from the experts in identifying the states of and influencing factors for the inadequate access and towards strategizing interventions to address the issue. The study tried to identify the challenges the healthcare professionals are facing in the prescribing and dispensing of biosimilars in their respective facilities in terms of knowledge, practice, and attitude.

The findings shall help to design mechanisms for training and capacity building for the health care professionals to improve their perception and skills for the rational use of biosimilars for the needful. Further, the study can be referred to as an information source for policy updates, regulatory system strengthening, resource allocation, workforce development, and for further studies in the area.

2. Literature Review

2.1. Theoretical Framework of Access to Medicines

In reference to the work of Penchansky and Thomas, the access framework by the World Health Organization and Management Sciences for Health (WHO-MSH 2000 model) identified five important components of access: availability, affordability, accessibility, acceptability, and quality of products. This model is centered at the health service delivery level. According to this framework, availability is defined by the relationship between the type and quantity of products needed and actually provided. Affordability is the relationship between product prices and the user's ability to pay. The quality of products is a cross-cutting determinant that specifically comprises their efficacy, safety, and cost-effectiveness. Acceptability is defined by the relationship between the users' attitude and expectations about products and the actual characteristics of those products (Bigdeli et al., 2013).

Literatures indicate that knowledge, attitude, and practice (KAP) can influence behavior directly (Chapman et al., 2017; Teixeira Rodrigues et al., 2016). Hence, the KAP model is helpful to assess the extent and association of knowledge, attitude, and practice in the context of the topic of interest. It covers the personal factors (healthcare professionals' related factors). However, the pharmaceutical sector (the external factors), such as registration, procurement, distribution, and medicines' prices regulation, also impact uptake of medicines in the delivery of health care (Gillet et al., 2013). Hence, both the WHO-MSH 2000 concept and the KAP model have limitations since both don't provide a view on determinants of access to medicines at the pharmaceutical sector and above level, where important barriers to access to medicines can exist.

On the other hand, the WHO 2004 access framework enables addressing the pharmaceutical sector, which considers four important components of access: rational selection and use, reliable health and supply systems, affordable prices, and sustainable financing (OMS, 2004; World Health Organization, 2007).

Rational selection and use can be pursued through national treatment guideline and national lists of essential medicines tools to ensure access. In a reliable supply system, regulatory control is one of the components in supporting access to essential medicines (OMS, 2004). Effective medication regulation assures drug safety, efficacy, and quality in addition to the accuracy and relevance of drug information made available to the public (Ndomondo-Sigonda et al., 2017).

Affordable price is a policy issue related to price competition through the tendering of generic products, promoting bulk procurement, reducing mark-ups, and implementing generics policies. Sustainable financing has implications for the level of subsidization for medicines or the extent to which patients are required to incur out-of-pocket (OOP) costs. This could be pursued through the mechanism of increasing health insurance coverage through national and employer-based programs (OMS, 2004). The model addresses the pharmaceutical policy formulation. However, none of these models, independently, capture the context of access to biosimilars as summarized in Table 1.

Table 1: Indicators and determinants of access and awareness of medicines

Dimension	**Determinant factors of each dimension and use**
Availability	Market authorization and medicine supply at facility
Affordability	Price regulation, procurement system, insurance scheme, and switching and substitution policy
Acceptability	Knowledge and attitude of the providers and consumers
Awareness	Effective communication and information strategies

2.2. Biosimilars

Biologics are medicines that are derived from living systems such as microorganisms, plants, and animal cells and their metabolites using the principles of biotechnology. Compared to conventional small molecule medicines, biologics are characterized by unique features in terms

of design, manufacturing process, mechanisms of action, and clinical outcomes, as summarized in Table 2 (Patel et al., 2015).

Biosimilars are defined differently by various regulatory agencies. European Medicines Agency (EMA) defines as "biological medicine highly similar to another already approved biological medicine. The Food and Drug Administration (FDA) defines a biosimilar as "a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product". According to the WHO definition, a similar biotherapeutic product (SBP) is a biotherapeutic product that is similar in terms of quality, safety, and efficacy to a previously registered reference biotherapeutic product (EMEA, 2005; US FDA, 2015; World Health Organization (WHO) TRS 977, 2009). Tanzania Medicines and Medical Devices Authority use the same term and definition of WHO (Authority & Authority, 2020).

Table 2 : Main differences between chemical and biological medicines

Chemical	**Biological**
Produced by predictable chemical synthesis	Produced by living cell cultures, which are intrinsically variable
Low molecular weight	High molecular weight
Well-defined structure	Complex
Mostly process independent	Process-dependent strongly
Stable	Sensitive to an external condition
Mostly non-immunogenic	Immunogenic

Biosimilars offer considerable advantages to healthcare systems, including cost savings, competitive prices, improved patient access, incremental innovation, and contribute to the prevention of drug shortages (Aitken, 2002; Batran et al., 2022; Vandenplas et al., 2023). The prices of biosimilars are lower than those of their reference biologics due to the reduced costs of researching, developing, and marketing. They provide savings to the pharmaceutical budget that support the sustainability of the healthcare system due to their affordable price compared with

their originator biologic (Barbier et al., 2020; Manova et al., 2018). Furthermore, studies showed money saved from biosimilars utilization was used to treat additional patients with the same

disease or different diseases that increase patient access to biologic therapy (Dutta et al., 2020). The launch of biosimilar Trastuzumab in the South Africa would result in a 50% price reduction, allowing 670 more people to be treated (Council, 2017). On the other hand, they have certain disadvantages, such as risks of eliciting an immune response that could decrease or neutralize their own biologic activity. This can reduce the efficacy or lead to adverse effects of biosimilars, which may not have occurred with reference biologics (Kuriakose et al., 2016).

2.3. Determinant Factors for Access to Biosimilars

Determinant factors for access to biosimilars occur at the individual level, such as income, to the international level. Low-income families experience excessive out-of-pocket payments or a lack of health insurance. The regulatory framework significantly influences access to biosimilars in several ways: approval process, clinical trial requirements, interchangeability designation, naming convention, post market surveillance, aligning regulation across countries, and providing education and awareness. Policies in prescribing, dispensing, and reimbursement in the healthcare system are other determinants of access to healthcare. Other important determinants are healthcare professionals' knowledge and acceptance towards the medical products and their use (Bigdeli et al., 2013; Lybecker, 2016; Rémuzat, Kapuśniak, et al., 2017).

Policies can significantly impact access to biosimilars by harmonizing regulatory standards and fostering global collaboration. Harmonized regulatory standards ensure that biosimilars meet consistent quality, safety, and efficacy benchmarks across different regions. This streamlining reduces the time and cost associated with bringing biosimilars to market, ultimately increasing their availability to patients worldwide. Furthermore, it encourages innovation by allowing manufacturers to focus on developing new therapies rather than navigating varied regulatory landscapes (Rahalkar, 2021). Policy interventions, including streamlined evidence requirements and regulatory approvals, and early biosimilar manufacturing licenses aim to increase uptake and access of biosimilars in South Africa (Kumar & Sigala, 2016).

2.3.1. Regulatory Framework of Biosimilars

The regulatory framework is a set of laws, regulations, and rules enacted by government bodies. Regulation gives guidance for regulatory functions; it interprets the law. Regulatory tools such as standards and guidelines equip drug regulatory authorities with the practical means of implementing those laws. The absence of regulatory tools may lead to variations in the implementation of the law or even lead to questions about the transparency of law enforcement. Regulatory agencies establish guidelines for biosimilar approval, affecting the time and cost required to bring these products to market (Good Regulatory Practices for Regulatory Oversight, 2014).

In Europe, the legal framework for granting market authorization for so-called "biosimilars" was established by Directive 2001/83/EC in article 10 (4) (Community, 2004). Then, the legal requirements for application and procedures can be found in Article 6 of Regulation (EC) No 726/2004 (EMA, 2014). EMA has the primary role of being a pioneer in establishing a regulatory pathway for guidance in market authorization of biosimilars in 2005 (EMEA, 2005). Then Omnitrope, a biosimilar version of Genotropin, got its first approval in 2006 (Schiestl et al., 2017).

The US Congress passed the BPCI Act 2009, which amends the Federal Food, Drug, and Cosmetic Act and creates an approval pathway for biosimilar and interchangeable biological products. The 351(k) pathway is an abbreviated pathway for licensing of products shown to be biosimilar to an FDA-approved reference product. The Act permits the FDA to issue guidance related to the approval of biosimilar and interchangeable biological products, but the FDA released its first guideline in 2012 (Lu, 2014).

Although the WHO is not a regulatory organization, it supports 194 member countries by setting and promoting global standards for biologics. This organization released the guideline on the evaluation of similar biotherapeutic products in 2009 (WHO TRS 977, 2009).

In South Africa after the guidelines were released in 2010, the first non-originator biological for filgrastim was approved by the Medicine Control Council (Kumar & Sigala, 2016).

2.3.1.1. Regulatory Requirements for Market Authorization

Market authorization is one of the determinants for the dimension of medicines access. A clear and globally consistent approval process and decision-making would facilitate a less-complex regulatory landscape for biosimilars. This enables manufacturers to save substantial time and resources and improve access to treatment for patients (Lybecker, 2016).

However, marketing authorizations of biosimilar medicines are often delayed as manufacturers face challenges of multiple regulatory requirements to register their products in different countries. The major regulatory inconsistencies in the approval process are about the choice of reference products, data requirements, extrapolation, lack of transparency in interchangeability, and naming and labeling of products (Pharmacovigilance et al., 2016; Rahalkar, 2021).

The selection of reference products is one of the concerns in biosimilar development and market authorization requirements. Regulatory authorities set mandatory requirements for locally authorized reference products. Some agencies require additional criteria for acceptability of RBP if countries lack nationally licensed originator products. For instance, Tanzania, Egypt, and Ghana accept foreign licensed and sourced RBP (H. N. Kang et al., 2021). Such a lack of flexibility in terms of sourcing the RBP is a hurdle for manufacturers.

The requirement for bridging studies between foreign and locally licensed reference biological are required by EMA and US FDA. Countries like China, India, and Korea have decided that they need local clinical development (LCD) in order to protect their populations (Rahalkar, 2021). However, there is growing debate that these studies impose redundant costs without added patients benefit (Webster & Woollett, 2019).

The legal basis for market authorization for different nations globally is based on demonstration of similarity, although slight differences of requirements are applied (Rahalkar, Sheppard, Santos, et al., 2021; World Health Organization (WHO) TRS 977, 2009). Another important component of the less lengthy regulatory pathway is indication extrapolation, which eliminates the need for a biosimilar manufacturer to complete clinical studies in all indications for which authorization is sought (European Medicines Agency, 2014). Some regulatory authorities, such as Swissmedic, the UK Medicines and Healthcare products Regulatory Agency (MHRA), and Agencia Nacional de Vigilancia Sanitaria (ANVISA), have introduced streamlined evidence requirements for biosimilar indication expansions. This can avoid unnecessary duplicated comparison trials and provide a way to expand access to biosimilars for more patients (Tesser et al., 2017).

A transparent policy on interchangeability is a crucial factor in accessing biosimilars. The national authorities are responsible for the legislation on switching and substitution. In Italian, the official position of the Italy medicine agency (AIFA) is that biological medicines and biosimilars cannot be considered in the same way as other generic medicines, excluding therapeutic substitutability. The choice to treat a patient with an originator biological medicine or a biosimilar is a clinical decision to be made by physicians (Sercic, 2019). In Russia, biosimilar drugs are legally interchangeable with the reference product. However, in India, Brazil, Mexico, and China, interchangeability is not regulated by law, allowing prescribers to make decisions based on the needs of patients (Rahalkar, 2021). TMDA clearly defines interchangeability and indicates in does not imply substitution (Authority & Authority, 2020).

Moreover, the ways pharmacovigilance and the naming of biologics are implemented also influence the utilization of similar biotherapeutic products. Thus, robust pharmacovigilance systems can enhance trust in biosimilars, potentially leading to increased adoption as stakeholders feel more confident in their safety and efficacy equivalence to original biologics. Similarly, regulatory decisions on biosimilar naming can affect HCPs and patients perceptions,

potentially influencing uptake. Hence, clear guidelines and consistent naming conventions are essential to ensure proper identification and reduce the risk of medication errors. The US FDA designates a proper name combining both the core name and a distinguishing 4-letter suffix. This naming convention was introduced to help providers and dispensers to distinguish and identify different versions of similar or interchangeable products (Banda et al., 2022; Hadoussa et al., 2020; Services, 2018).

Review model

National regulatory authorities, particularly in countries with limited sources, struggle to individually regulate existing and new medical products. An appropriate strategy to address this difficulty is to continue increasing the acceptance of effective regulatory reliance models while utilizing complementary convergence efforts (Roth et al., 2018).

Regulatory reliance refers to "the act whereby the NRA in one jurisdiction may take into account and give significant weight to evaluations performed by another NRA or trusted institution in reaching its own decision". It is a strategy that requires seeking a better use of resources to improve capacity, and it should be considered for any regulatory body in search of efficiencies (Durán et al., 2021; Padua et al., 2020).

The use of assessment reports from other trusted regulatory authorities in all or some parts of the drug approval process reduces approval time and reduces time to market. For instance, Hong Kong uses a certificate of pharmaceutical product (CPP) as a reliance tool, which helps as evidence of robust assessment to reduce time to market while Asia-Pacific Economic Cooperation (APEC) economies against the use of CPP in order to reduce wastage in redundant document review activities (Chong et al., 2021). Six countries participating in East African Community Medicines Registration Harmonization also require CPP for market authorization (Ngum et al., 2024).

2.3.2. Pricing, Purchasing, and Reimbursement Policies toward Biosimilars

National healthcare systems in terms of pricing, procurement, and reimbursement policies are potential drivers and barriers to the use of biosimilars (Rémuzat, Dorey, et al., 2017). The objectives of pricing policies should explicitly focus on achieving affordable and equitable

access to quality-assured pharmaceutical products for consumers and health systems (World Health Organization, 2020). In principle, there are two different approaches with regard to the pricing of biosimilar and generic medicines: 1. to allow for competition, and 2. to allow free pricing for off-patent medicines (Vogler & Schneider, 2017). WHO recommends that countries use multiple pricing policies to achieve low prices for biosimilar medicines (World Health Organization, 2020).

Egypt's Ministry of Health mandates a price reduction for biosimilars to improve their affordability. South Africa's pricing is based on a Single Exit Price that must be agreed upon between applicant and pricing committee (Batran et al., 2022). A study indicates that the influence of policies governing drug regulation and financing are principal determinants of medicines access in Ghana. Accordingly, participants of the study raised high medicines costs due to drug registration-related costs and a minimal or lack of drug pricing controls. In order to address high price-related challenges, the Ghanaian government discounted registration fees, and its FDA decided to register expensive medicines within 3 months (Boateng et al., 2020).

In procurement policy, tendering is an approach where competition is essential and the goal is to achieve lower prices. The lowest price often drives the award criterion, although other factors, including medication training, may also be considered. The other consideration that affect the quality and supply of a drug received through bidding processes is whether the tenders are granted to a single entity or shared among numerous suppliers (Farquharson et al., 2011).

Public procurement at the national or regional level could control the uptake of biosimilars as it disconnects physicians' prescription habits and the procurement (Gillet et al., 2013). WHO suggests countries should regulate mark-ups in the pharmaceutical supply and distribution chains

to ensure affordability in the procurement system. Accordingly, countries should regulate mark-ups in retail chain and consider implementing regressive mark-ups instead of fixed percentage mark-ups(World Health Organization, 2020).

Insurance formulary requirements might potentially provide a significant obstacle to the market entry of a biosimilar. For instance, if the payer favors or demands the use of the reference product over the biosimilar, there will be less entry in the market. Furthermore, lack of health insurance has been cited contributes to health-care inequity (Merga et al., 2022). Implementation of automatic reimbursement after regulatory approval enables immediate or rapid access to biosimilars in nations where health technology assessment is not mandated. Depending on the nation, reimbursement/coverage can vary from 100% to partial (Wilsdon et al., 2022).

Rwanda's health insurance system includes three main schemes: Community-based Health Insurance (CBHI), Medical Insurance Scheme (MIS), Medical Military Insurance (MMI), and Employers and Private Insurers. CBHI covers 94% of the insured population, aiming to improve health outcomes. By prioritizing inclusivity, Rwanda's health insurance system seeks to promote equity in health access across different socioeconomic groups (Assessment of Medicine Pricing and Reimbursement Systems in Health Insurance Schemes in Selected African Countries, n.d.).

2.3.3. Policy Intervention toward Prescribers and Dispensers

It is essential to understand factors that encourage or hamper the adoption of biosimilars in order to provide valuable insight for policymakers. Physicians and pharmacy professionals' practices are conditioned by demand-side policies. These policies were measures directed towards stakeholders who prescribe, dispense, and ask for medicines. They include INN prescribing and dispensing policies that allow biosimilar substitution and incentives for physicians, pharmacists, and patients (Gillet et al., 2013; Moorkens et al., 2016; Rémuzat, Kapuśniak, et al., 2017).

The official guidance regarding INN prescribing and interchangeability impacts the use of biosimilars in clinical practices. For example, in Belgium, INN prescribing and switching for biological products are not recommended. If switching is taken, it should be exercised under the supervision of the physicians (Gillet et al., 2013). Restriction is another barrier in the prescribing and dispensing (Sirjana Pant, Louis de Léséleuc, 2018). In Greece, pharmaceutical drug regulation obliges physicians to prescribe biosimilars strictly in accordance with indications and dosages approved in their marketing authorization (Rémuzat, Kapuśniak, et al., 2017).

Physicians are allowed to switch patients' medicines in the UK, but the guideline does not allow pharmacy-level substitution. In Germany, biosimilars are interchangeable at the pharmacy level when the products are 'bio-identical. Bio-identicals are biological products manufactured by the same supplier on the same production line but sold under different trade names (Gillet et al., 2013). France allowed switching and substitution based on certain criteria: switching based on patient consent and monitoring treatment closely (Sirjana Pant, Louis de Léséleuc, 2018).

The US FDA law allows pharmacists to substitute innovator biologics with biosimilars without prescribers' involvement, while in Australia, pharmacists are able to substitute brand equivalents if endorsed by the Pharmaceutical Benefits Advisory Committee (PBAC). However, the decision involves the prescriber, pharmacists, and patients (O'Callaghan et al., 2019). Data from 20 African and Middle Eastern countries shows a trend of 'no substitution,' with the majority categorized as such due to lack of guidance or regulations in local pharmacy practices(Larkin et al., 2017).

The naming of biosimilars has a direct influence on the physician's ability to prescribe an intended biologic medicine. In addition, it has a strong impact on the product's traceability and interchangeability. For instance, a study indicated the four-letter suffix implemented by US FDA suffixes assisted clinicians to ensure that patients received the right product and facilitated the tracking of adverse occurrences. The other perspective was that suffixes made prescriptions difficult and unclear (Narsai et al., 2012).

Similarly, understanding incentives as drivers of biosimilar uptake is a critical issue to inform policy decision-makers. A study by Rémuzat, Kapuśniak, et al. (2017) found that incentive policies were positively connected with biosimilars uptake in Europe. In order to enhance the uptake of biosimilar medicines, the government implemented professional education regarding the quality, safety, efficacy, and price of biosimilars.

2.3.4. Healthcare Professionals' Knowledge, Attitude, and Clinical Practices

Knowledge:

Evidence has revealed that healthcare providers in different countries lack understanding of the efficacy, safety, and interchangeability of biosimilars (Hadoussa et al., 2020). Assessment of physicians' perceptions revealed knowledge gaps about biosimilar definitions, the biosimilarity concept, and the safety and efficacy of biosimilars compared to innovator medicines (O'Callaghan et al., 2017b). The majority of health professionals incorrectly described biosimilars as generic medicines. A study indicated that only 22.9% of physicians and 38.8% of pharmacists had complete or strong understanding of biosimilars (Pasina et al., 2016). Similarly, 59% of clinicians couldn't define biosimilars or hadn't heard of them, and only 6% of clinicians were familiar with the concept of biosimilarity (Cassar et al., 2016). Likewise, study conducted in Tanzania indicated that almost half of participants were familiar with biologics with basic understanding while 40.9% of the respondents never heard the word biosimilars. The other problem is a lack of awareness of the items available in the country. For instance, rheumatologists (55%) and gastroenterologists (32.8%) were unaware that biosimilar filgrastim was available in the market (Cohen et al., 2017).

Attitude:

The main benefits of biosimilar medicine use identified by physicians and payers were improving patient access to biologics, cost-saving potential in healthcare budgets, and increasing the number of treatment options for clinicians (Barbier et al., 2022). Chapman et al. (2017) also noted that 77% of healthcare professionals thought biosimilars were extremely or very important in terms of cost savings. In contrast, Danese et al. (2014) reported 6% of physicians thought their potential savings were offset by their additional cost of regulation and pharmacovigilance

activities. A survey of oncologists and hematologists in Tunisia revealed a double vision of biosimilars, treating them as generics and raised question for their interchangeability. However, most physicians support the policy encouraging biosimilars use in Tunisia due to its high economic potential (Hadoussa et al., 2020).

Healthcare providers also had clinical concerns regarding biosimilar safety, efficacy, extrapolation, interchangeability, and pharmacy-driven substitution (Shakeel et al., 2020). Due to safety and efficacy doubts in extrapolated indications, 64% of pharmacists (Adé et al., 2017) and 39% of rheumatologists (van Overbeeke et al., 2017) opposed the practice. The healthcare providers also expressed concerns about interchangeability. According to Danese et al. (2016), 44.4% of physicians considered interchangeability. When switching patients to biosimilars, rheumatologists had concerns about safety (53%) and efficacy (55%). There was disagreement among providers about who was responsible for interchanging intended medicines. In line with this opinion, 58% of pharmacists and 61% of physicians thought that switching should be primarily the prescriber's discretion. However, according to Adé et al. (2017), 95% of pharmacists stated that exchanging biosimilars with originator biologics was a mutual responsibility between physicians and pharmacists (Adé et al., 2017).

Practices:

Studies identified major potential barriers to the prescribing and dispensing of similar biological products at health facilities (Pasina et al., 2016; Sarnola et al., 2020). Leonard et al. (2019) indicated inadequate knowledge of biosimilars contributes to low prescribing or dispensing.

The other barrier is confidence in biosimilars among health care professionals in clinical practice. Numerous healthcare providers in Europe are hesitant to use biosimilars for patient treatment, although there is a clear legal pathway and specific regulation on data needed for their approval. Major concerns voiced relate to their pharmaceutical quality, safety (especially immunogenicity), efficacy (particularly in extrapolated indications), and interchangeability with the originator product (Weise et al., 2012). They also perceived biosimilars as still at a high price

due to an overall lack of competition. Conversely, Sarnola et al. (2020) identified motivators of prescribing biosimilars as lower price in comparison to originators. Most physicians disagreed with pharmacist-led substitution of biologic medicines. For example, 89% (n=118) of them disagreed with automatic substitution by a pharmacist (Danese et al., 2016).

The primary obstacles to the adoption of biosimilars in the Middle East and North Africa region include regulatory challenges, a knowledge gap resulting in safety and efficacy concerns, the influence of pharmaceutical companies, and a preference for brand-name products. In contrast, the acknowledgment of the advantages of biosimilars serves as facilitators (Alqawasmeh et al., 2025).

2.4. Conceptual Framework

There is no single model or theory sufficient to explain the state of access and the factors that influence biosimilar medicines uptake in hospital settings. Hence, these MSH 2000, MSH 2004, and KAP models were studied to comprehend the status of biosimilar accessibility and significant barriers in clinical practice (Figure 1). Many studies, have either quantitatively or qualitatively evaluated the opinions of regulators, knowledge, and attitudes of healthcare providers toward the uptake of biosimilars. However, there is limited literature that examines the collective perspective of different stakeholders through a mixed research approach to present a streamlined understanding of biosimilar adoption. This gap in research highlights the need for a comprehensive study that incorporates various viewpoints of regulators, suppliers, payers, physicians, and pharmacists.

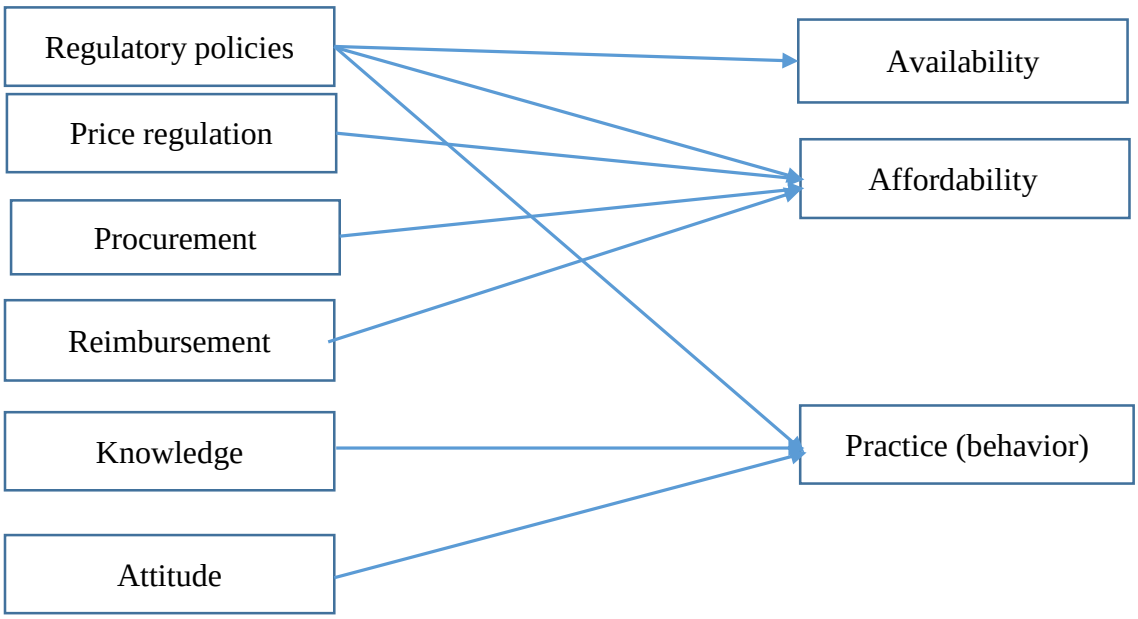

Figure 1: Conceptual framework of the study

3. Research Questions and Objectives of the Study

3.1. Research Questions

This study aims to answer the following research questions:

- How does the registration and approval process for biosimilars in Ethiopia compare to international practices?
- What is the current state of access to and use of biosimilars in the selected hospitals?
- What factors influence the adoption and use of biosimilar medicines in clinical practices?

3.2. Objectives

3.2.1. General Objective

To assess the regulatory framework for biosimilars in Ethiopia and healthcare professionals' perceptions regarding their access and uptake in federal hospitals in Addis Ababa.

3.2.2. Specific Objectives

- To evaluate the national regulatory framework for registration and authorization of biosimilar products in comparison to international standards and practices.
- To assess the current state of access to and use of biosimilars in selected federal hospitals.
- To identify factors influencing the adoption and utilization of biosimilars in clinical practices.

4. Methods

4.1. Description of the Study Setting

Ethiopia has a three-tier health service delivery system classified into primary, secondary, and tertiary levels. The tertiary level of care comprises specialized and teaching hospitals operated at the federal level. These hospitals are staffed by specialized healthcare professionals, providing comprehensive services that address complex health issues. There are five tertiary hospitals in Addis Ababa that are owned by the federal ministry of health. Among them, Tikur Anbesa Hospital (TASH), St. Paul Millennium Medical College (SPMMC), and All-Africa Leprosy, Tuberculosis, and Rehabilitation Training Centre (ALERT) are the three specialized hospitals where a high volume of patients attends emergency and outpatient clinics daily for advanced medical care and treatment. Each presumed to provide services to 3.5 million people. They act as referral points for general hospitals. The capacities for general and primary hospitals are 1 to 1.5 million people, while health centers serve 25,000 to 40,000 people (Ababa, 2018a).

The Ethiopian Food and Drug Authority (EFDA) is the national regulatory body responsible for approval and monitoring drugs. The regulatory framework for drugs in Ethiopia is provided through the national drug policy and the food and medicines administration proclamation number 1112/2019. The registration of similar biotherapeutic products in Ethiopia follows the requirements stated in guidelines for the registration of similar biotherapeutic products (FMHACA Guidelines for Registration of Similar Biotherapeutic Products (SBPs), 2018).

4.2. Study Design

The study used a convergent parallel mixed methods design, combining quantitative and qualitative data collection simultaneously (Bryman, 2013; Morgan, 2017). The qualitative component involved in-depth interviews with key informants and a comprehensive documents review related to regulatory framework for biosimilars, while the quantitative component consisted of a survey of healthcare professionals. The analysis was separately but integrated

during the interpretation stage, aiming to confirm findings through triangulation, and complete understanding of the research problem.

4.3. Study Population and Data Sources

The study population included healthcare professionals (physicians and pharmacists) working in three federal hospitals. Additionally, key informants from EFDA, EPSS, EHIS and hospitals were included to provide expert insights. Primary data was collected through structured questionnaires administered to healthcare professionals and key informant interviews from experts participating in medicine registration, procurement, and insurance procedures at their respective institutions. Secondary data was obtained from proclamations, directives, and guidelines of EFDA and international organizations.

4.4. Exclusion and Inclusion Criteria

The qualitative study assessed legislation, regulations, directives, and guidelines concerning biosimilars from publications by the EMA, US FDA, WHO, EFDA, and other pertinent literature. Key informants from EFDA, EPSS, the Ethiopian health insurance service (EHIS), and hospitals were considered. With regard to quantitative data, both physicians and pharmacy professionals practicing in the selected hospitals were eligible for inclusion, provided that they were willing to participate and available during the data collection. Healthcare professionals who were not directly involved in prescribing or dispensing were excluded.

4.5. Study Variables

The independent variables were regulatory policies, procurement systems, medicine prices, reimbursement modalities, and knowledge and attitude of healthcare professionals. The dependent variables included the extent of access to biosimilars in the selected hospitals and their use in clinical practices.

4.6. Sample Size and Sampling Procedure

For the qualitative study, a purposive sampling procedure was employed to identify participants who could provide the best possible information about the research problem. A total of nine key informants were interviewed: three experts from EFDA, two from EPSS, one from EHIS, and three from the selected hospitals.

For the determination of sample size for the quantitative study, the three hospitals were purposively selected based on the service they provide. The required sample size was calculated based on finite population correction for proportion (Morse, 2000) as equation 1:

$$n = \frac{\mathrm{n0}}{\left(1 + \frac{\mathrm{n0}-1}{\mathrm{N}}\right)} \quad \text{…….. Eqn.1.}$$

Where n and N are the sample size and population size for the study, respectively. The study population size (N = 1212) was obtained from human resource records of the three hospitals. While $n_0 = 385$, which was obtained from a single proportionate formula ($n0 = Z^2\, pq/d^2$). Since there were no previous studies related to the present study that would have been used to guide sample size determination, values of p and q were considered to be 0.5 each.

$$n = \frac{385}{\left(1 + \frac{385\_1}{1212}\right)} = 292$$

This calculated sample size was disproportionately distributed among health professionals, with physicians representing 60% of the population and pharmacy professionals accounting for 40%, reflecting the large proportion of physicians in the workforce. Accordingly, 175 physicians and 117 pharmacists were included for the study. Then, they were proportionally allocated across the three hospitals based on their representation in the population (Table 3).

Table 3: Distribution of the sample size by health facility and professionals.

Health facility	Physicians		Pharmacy professionals	
	Population	Sample	Population	Sample
TASH	366	65	80	42
SPHMMC	459	81	100	53
ALERT	165	29	42	22
Total	990	175	222	117
Population (N)	990+222= 1212			

4.7. Data Collection and Management

4.7.1. Study Instrument and Validation

For the preparation of the semi-structured interview, a thorough literature review was conducted to explore legal, procedural, and practical experiences from the US FDA, EMA, WHO and EFDA. Performance reports and published articles were also reviewed to identify sector challenges and prospects.

Separate semi-structured interview guides were prepared for experts from the regulatory authority, EPSS, EHIS, and three federal hospitals (Annexes III-V). The check list was also utilized to identify the availability of innovator biologics and biosimilars in the hospitals based on the list of market authorization from the EFDA website (Annex VII). The interview guides were prepared in English, then translated to Amharic and back-translated to English to check their accuracy and consistency. The tools were then reviewed and commented on by senior academic supervisors and two experts from EFDA and EPSS who were not included in the study; modifications were made as appropriate before being used for the final data collection.

For the quantitative study, a structured self-administered survey questionnaire was prepared by adopting from published literature sources and contextualizing to the local scenario (Annexes IX and X). The survey questionnaire was prepared in English to assess the knowledge, attitude, and

practice of physicians and pharmacists towards the understanding, availability, affordability, and use of biosimilars. The level of their agreements were measured using a five-point Liker Scale with a scoring system (5 = strongly agree, 4 = agree, 3 = neutral, 2 = disagree and 1 = strongly disagree). The confidence of healthcare professionals during their practices was rated from totally confident = 5 to not confident at all = 1.

To validate the data collection, a pretest was conducted on 22 health professionals (12 physicians and 10 pharmacists) working in Yekatit 12 Hospital Medical College, who were not included in the final study. This hospital was selected as it closely resembles the referral hospitals in terms of the service it provides. The value for reliability from the pre-test was 0.73, indicating good internal consistency; modifications were also made on some questions following the feedback during the pretest.

4.7.2. Data Collection Procedure

Data were collected between October 21 and December 25, 2021. First, it was commenced by searching the approved biosimilars including reference biologic products from EFDA's website by utilizing INN. In the second step, the EFDA was contacted for permission to conduct the study at its institution. Three KIs with experience in biological medicines registration activities were recruited after the study's objective was explained to the product registration directorate director. Thirdly, researching legislation, regulation, and guidelines established by EMA, US FDA, WHO, and EFDA to compare their regulatory frameworks. Then, six key informants from EPSS, EHIS, and store managers in hospitals were asked their opinion about access of, and related policies toward biosimilars in Ethiopia. Audiotape was used for those who were willing, along with taking notes as appropriate. Finally, checklists and self-administered questionnaires were distributed to store managers and HCPs, respectively.

4.7.3. Data Quality Assurance

Standard data quality assurance procedures, including daily cleaning, were regularly conducted. To establish the credibility, data from key informant interviews were triangulated with findings from the qualitative and quantitative studies. Interviews were obtained from audio tapes and were corroborated with notes taken during individual interviews. Further, the interviews were transcribed verbatim in Amharic and then translated to English and back translated to ensure accuracy.

4.7.4. Researchers' Position and Reflexivity

Reflexivity is recognizing the potential impact of the relationship between the researcher, the topic of study, and the subjects on the results. It is worth noticing that researchers are not neutral; they often make choices based on their role in interpreting what they find in their own reality (Darwin Holmes, 2020). Hence, it is essential to take into account researchers' own past experiences, biases, and prejudices, which can influence the investigation and interpretation of results (Olmos-Vega et al., 2023).

The researcher is a pharmacist by profession and has served in one of the tertiary hospitals of the study area. Professional practice could help the researcher to identify the research problem and construct the major research questions. While his professional network within the hospital could facilitate access to participants, it might also introduce bias if personal relationships affect the study's objectivity. This position allows the researcher to build trust more easily with participants, facilitating open and honest communication. Hence, the store managers perceived the researcher as an "insider' fostering trust but potentially withholding critiques of hospital supply inefficiencies.

Nevertheless, the research did not have any direct affiliation with the other institutions involved in the study; respondents and key informants could provide genuine information and freely express their opinions. Moreover, the lack of direct involvement in the other institutions positions researcher as an outsider, relying heavily on key informants' narratives. Maximum care was exercised throughout the data collection and analysis to minimize research bias.

4.7.5. Data Analysis

For qualitative data analysis, thematic analysis was utilized to identify themes relevant to the research question; a recommended method particularly for researchers novice to qualitative approaches, to compare and contrast opinions from different participants, and to adequately uncover unexpected findings (Braun & Clarke, 2006). A hybrid approach of inductive and deductive approaches with a predominant deductive approach was employed for data analysis (Swain, 2018).

Predefined sets of codes were generated from theoretical concepts in existing literature and aligned with research objectives and interview questions. After translation, the transcripts and all notes were read line by line to find excerpts from raw data that fit predefined codes. Simultaneously, those rows of data that did not fit any of the predefined codes were searched for meaning in order to generate posteriori codes. Early transcripts were reread and coded in this manner to ensure proper code application, and interviewees' responses to particular questions were summarized in the table. Further, the excerpt intended to be part of reports was copied and pasted in MS Word; the priori and posteriori codes were combined to create family codes known as family themes. Lastly, the predefined codes and themes employed in the interview transcripts were applied to the content of document analysis to address issues that go beyond KIs' experiences.

For quantitative data analysis, data were first checked for completeness and errors; incomplete questionnaires were excluded and counted as a non-valid. Verified data were entered into SPSS version 21.0; a correct answer for each item of knowledge was given a score of 1, while each wrong or do not know answer was marked as 0 (zero), and overall scores ranged 0 to 6 for knowledge, and 10 to 50 for attitude. In order to simplify the report of descriptive attitude, strongly agree and agree were combined to be labeled as agree; similarly, strongly disagree and disagree were added and labeled as disagree, while neutral remained as it was. In the same way, the responses of totally confident, very confident and confident enough were combined and labeled as confident, while little confident and not confident at all were classified as not

confident. The sum of scores of each participant for KAP aspects were used to rank the level of knowledge, attitude, and practice. The total score of more than or equal to three was labeled as good for both knowledge and practice, while the score of more than 25 for attitude indicated positive perception.

The scores of KAP were tested for normality of distribution using the Kolmogorov Smirnov test. The samples were noted not to follow a normal distribution, and the median was calculated as a measure of central tendency. Spearman correlation was used to find relation between knowledge and attitude; attitude and practice; and knowledge and practice of respondents. Then, the results were interpreted based on correlation with Cohen's criteria (AlWahaibi et al., 2020). A p-value less than 0.05 was taken as statistically significant. Results from both qualitative and quantitative data were merged and integrated to provide interpretation of the overall findings.

4.8. Ethical Considerations

Ethical approval was obtained from the ethics review committee of the School of Pharmacy, College of Health Sciences, Addis Ababa University ERB/SOP/349/13/2021 (Annex XI). Support letters were written from the Department of Pharmaceutics and Social Pharmacy to the selected organizations for the research. In addition, written informed consent was received from all key informants prior to the interview. Personal information regarding participants was kept strictly confidential; codes were assigned for key informants comprising KI and interview number (for instance, the first interviewee was assigned as KI1). The raw data was only accessible to the investigator and used only for academic purposes.

4.9. Operational Definitions

In connection to this particular study, the following operational definitions were provided for the listed terminologies for proper understanding of the study context and result interpretation.

Access: the availability, affordability, and acceptability.

Availability: the existence of biosimilars in the study facilities during the study period.

Affordability: how feasible it is for an individual or society as a whole to pay for a biosimilar.

Acceptability: the degree to which HCPs agree that biological medicine is good enough to use.

Uses/uptake: the prescribing and dispensing practice of healthcare professionals

Opinion: one's view, appraisal, or attitude toward something.

Knowledge: understanding of something or a situation or a state of having been informed.

5. Results

5.1. Qualitative Study

5.1.1. Demographic Characteristics of Key Informants

Nine interviews were conducted with participants from the EFDA, EPSS, EHIS, and the selected hospitals (Table 4). The interviews lasted for a total of 1 hour and 36 minutes (range 13 to 21minutes).

Table 4: Socio-demographic characteristics of key informants.

ID	Gender	Age	Qualification	Position	Organization
KI1	Male	37	MSc in clinical pharmacy	Team leader	EFDA
KI2	Male	34	MSc in regulatory affairs	Team leader	EFDA
kI3	Male	35	B. Pharmacy	Officer	EFDA
KI4	Male	40	MSc in supply chain	Team leader	EPSS
KI5	Male	38	B. Pharmacy	Team leader	EPSS
KI6	Male	36	MSc. Pharmacy	Officer	EHIS
KI7	Male	31	B. Pharmacy	Store manager	SPMMC
KI8	Female	28	B. Pharmacy	Store manager	BLH
KI9	Female	27	B. Pharmacy	Store manager	ALERT

5.1.2. Opinions of Key Informants on Market Authorization of Biosimilars

From key informants' interviews, three major themes emerged along with the corresponding sub-themes (Table 5). The themes and subthemes were aligned with specific research questions and objectives.

Table 5: Themes and subthemes

Research questions	Themes	Subthemes
Research Question 1 (RQ1)	**Theme 1**: Approval pathways of biosimilars	**Subtheme 1**: Market authorization requirements of EFDA alignment with international practice **Subtheme 2:** Status of approved biosimilars **Subtheme 3**: Challenge in market authorization
Research Question 2 (RQ2)	**Theme 2**: Availability and affordability of biosimilars	**Subtheme 1**: Opinion on availability and affordability **Subtheme 2**: Status of availability in selected hospitals
Research Question 3 (RQ3)	**Theme 3**: Policy measures for biosimilar use	**Subtheme 1**: Procurement **Subtheme 2**: Insurance Scheme **Subtheme 3**: Communication and Education

Theme 1: Approval pathway of biosimilars

This theme emerged from interviews with key informants from the EFDA. Subsequently, three subthemes emerged: requirements for market authorization of biosimilars, the current state of registered and approved biosimilars in the healthcare system, and challenges in market authorization, as briefly summarized below.

Subtheme 1: Market authorization requirements of Ethiopian Food and Drug Authority alignment with international practice

The key informants reiterated the importance of the legal basis for the regulation of biopharmaceuticals because of the high level of risk associated with quality and safety issues and the complexity of formulation, manufacturing, distribution, and use. However, one of the key informants reported a lack of an effective legal framework for effective regulation, as illustrated below:

[...] *This is the main problem because biological medicines do not have a clear legal framework* (KI1).

On the other hand, other key informants described the similarity of safety, efficacy, and quality requirements of similar biotherapeutic products (SBPs) to already registered innovator biological products. They cited the similarity of the Ethiopian SBP registration guideline with those of the EMA, WHO, and US FDA guidelines for biosimilars registration and substantiated their claims as follows:

> *Biosimilars are similar to innovator biologics, with no significant difference in their clinical outcome. The only visible difference could be the minor structure of the molecules […]. Our registration guideline for SBPs has been adopted from the ICH, US FDA, EU, and WHO guidelines (KI2).*

This view was echoed by other key informants that biosimilars are different from generic drugs.

> *Biosimilars are not the same as their counter innovators in their structure. Thus, bioequivalence demonstrations are not as such enough during market authorization (KI3).*

Further analysis showed that the data for biosimilarity demonstrations followed stepwise approaches. The KIs indicated that comparability exercises are requirements in the market authorization process and substantiated their claim as follows:

[…] Unlike generic drugs whose bioequivalences are demonstrated to their innovator counter, similar biological products need additional clinical trials (KI1).

While discussing the application fee and timeline for the market authorization process, KI from the EFDA noted that the same amount of regulatory service fees and timelines are applied for SBPs as those for small-molecule medicines. This view was echoed by one of the KIs:

[…] *Application fees and times for the registration of biosimilars are similar to those for conventional drugs (KI3).*

Subtheme 2: Current state of approved biosimilars

During the interviews, KIs from the regulatory sector stressed that the current state of approved SBPs in Ethiopia was insufficient, as accounted for below by one of the key informants.

> *"Like other countries, we suffer from cancer, diabetes, and other diseases, but since Ethiopia is a developing country, I don't believe that these drugs are registered enough (KI3).*

Subtheme 3: Challenges in market authorization

Under this subtheme, lack of resources was frequently indicated as the major challenges. Thelack of specific a legal framework, limited technical expertise and lack of testing laboratories were reported as persistent challenges.

> […] *there is no person qualified to work with biological medicines in this regulatory authority, and there is no person who has received special training for this purpose (KI1).*

5.1.3. Availability and Affordability of Biosimilars

Subtheme 1: Opinions on availability and affordability

All key informants were asked about their opinions about access to biosimilars in Ethiopia. Acknowledging poor access, the key informants cited the reasons for limited availability: high medicine prices, low economic status of the population in need, shortage of foreign currency and supply disruption mainly because of the current situation of pandemic is a challenge for manufacturers. All of them agreed with inadequate availability and unaffordability as major concern in their country, as explained by the following quotes:

[...] I don't think biological medicines are adequately available and affordable due to their complex manufacturing nature and our country's economic status (KI1).

*These drugs are imported from abroad. I think only a few products have gotten market authorization, which may be due to foreign companies having no interest in exporting to our countries due to our communities' low capacities to afford them (KI2)***.**

[…] The current situation of COVID is also a challenge for manufacturers and for our supply system (KI4).

[…] We import around 80% of medicines from abroad, making our supply vulnerable to global disruption caused by COVID-19 and shortage of foreign currency (KI5)

Subtheme 2: Status of availability of biosimilars in selected hospitals

The hospital key informant indicated that certain biologics were somehow accessible, as explained by the following quote from one key informant:

[…] biological drugs for cancer are available in our stock (KI7).

Although certain biosimilars were available, there was inconsistent availability, with frequent stock outs attributed to inefficiencies in the supply chain managed by EPSS. One of the key informants claimed:

We usually do not get the products and quantities we demand from EPSS. For instance, Rituximab has been out of stock for four months. Our hospital didn't procure from private suppliers as it is too expensive (KI8).

In contrast, another key informant stated that biosimilars were not available in the hospital.

To my understanding, there are no biosimilars in this hospital. It might be a problem of our hospital formulary (KI9).

The availability of registered biologics in the selected health care facilities was assessed using a structured checklist. The findings indicated that biosimilars of Bortezomib, Rituximab, and Filgrastim were available in at least one of the selected hospitals included in the study.

Table 6: The availability of biosimilars in the selected hospitals

Biosimilars	**Available in the hospital (Yes/No)**		
	SPHMMC	**TASH**	**ALERT**
Bortezomib	Yes	No	No
Bevacizumab	No	No	No
Rituximab	Yes	Yes	No
Filgrastim	Yes	No	No
Pegfilgrastim	No	No	No
Epoetin	Yes	No	No

5.1.4. Policy Measures for the Uptake of Biosimilars

Subtheme 1: Procurement

It is well recognized that price is among the major influencing factors for access to and use of medicines in a given country. In this study, key informants from EPSS and EHIS emphasized the medicine price policy as a major challenge for the access and use of biosimilars in health facilities. The following account by a key informant substantiates this claim.

> *[…] I don't think we have a clear drug price policy; this is our main challenge. On the other hand, public health facilities add 20% to 25% to drug cost (KI6).*

In contrast, the key informants from EPSS presented practices of the implementation of preference pricing policy in tendering, as accounted by the following quote:

EPSS launched a call for tenders, and then the list price bidders would be awarded. However, other criteria were also considered (KI4).

Subtheme 2: Insurance Scheme

The requirements regarding insurance coverage might affect affordability. Accordingly, the key informants indicated full-cost coverage for premiums excluding brand medicines, while insurance for the formal sector is still not implemented. In addition, the lack of EHIS in price decision and the unavailability of a list of drugs covered by insurance were the main challenges reported. These were supported by the following excerpts.

Insurance organizations collect premiums from their members to fund medical expenses…The cost coverage for insured patients are 100%. The payers take drug prices from healthcare services providers. We don't have a list of drugs covered by insurance. Now, it is in preparation and may be nearly released. However, brand drugs are not reimbursed (KI6).

Subtheme 3: Education and Communication

It was reported that EFDA had already prepared guidelines for registration and list of essential drugs to provide regulatory-related information for stakeholders. Moreover, transparent approval procedures were in places that favor importers to register drugs. However, gaps in timely and effective communications during drug shortages have often been reported by stakeholders and substantiated by one of the key informants:

The mandate of EFDA is to assess drug quality, safety, and efficacy to be marketed in Ethiopia. There was no communication with manufacturers on the state of products shortage in the future or tracking stocks in the EPSS (KI2).

5.1.5. Document Analysis on Market Authorization Requirements

A review of regulatory documents complemented the finding of theme 1 that emerged from interview analysis. To better understand the differences and similarities in approval processes

across different jurisdictions, regulatory guidelines from the EMA, USFDA, WHO, EFDA, and other related literature were studied (Table 7).

Table 7: List of regulatory guidelines and related documents

Agency name	***Reference guidelines***
EMA	-Guideline on similar biological medicinal products CHMP/437/04 Rev 1. 44 (October 2014), 1–7. -Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: quality issues (revision 1). -Information guide for healthcare professionals. Prepared jointly by the European Medicines Agency and the European Commission.
US FDA	-Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act, Guidance for Industry
WHO	-Annex 2: Guidelines on evaluation of biosimilars. WHO Technical Report Series, No. 977.
EFDA	-Guidelines for Registration of Similar Biotherapeutic Products

Subtheme 1: Alignment of EFDA market authorization requirements with international practices

The European legislation and overarching guidelines open up a legal framework to get market authorization. The three overarching guidelines related to biosimilar development are: guideline for biosimilars in general; guideline for quality guidance; and for non-clinical and clinical guidance. There are also eight biosimilar product specific guidelines. The Biologics Price Competition and Innovation Act created an abbreviated licensure pathway. Similarly, the US FDA published three guidelines to provide details on scientific and quality considerations and to respond to questions asked by industries.

In Ethiopia, there has not been a separate directive for biological medicines as the time of the study was conducted. However, the guidelines for registration of similar biotherapeutic products indicated the requirements for biosimilars development and registration process. Table 8 shows the similarities and differences of the regulatory framework among jurisdictions.

Subtheme 2: Current state of approved biosimilars

In order to collect the status of market-authorized of biosimilars, including reference biological products, an official EFDA website was assessed. The results are presented in Table 9.

Table 8: Comparison of regulatory framework of EFDA with matured regulatory agencies

Requirements	**EMA**	**US FDA**	**WHO**	**EFDA**
Legal basis	Directive 2003/63/EC, overarching guidelines, eight product-specific guidelines	BPCI Act 2009, guidelines (references)	Unavailable	Food and Medicines Administration Proclamation 1112/2019, Similar biotherapeutic products guideline
Terminologies	Similar biological medicinal products	Follow-on biologics	Similar biotherapeutic product	Similar biotherapeutic product
Reference product selection	RP must be authorized in EU	RP shall be authorized in the USA. EU-authorized product is also acceptable	RP must be licensed in country/ region	Request for a nationally licensed reference product. Plus recognized authority should license

Biosimilarity demonstration	Stepwise comparability studies	Totality-of-evidence approach: Analytical studies, nonclinical studies, clinical studies, and post marketing surveillance	Stepwise comparability exercise: quality, non-clinical and clinical studies, and post market surveillance	Stepwise comparability exercise: quality, non-clinical and clinical studies, and post market surveillance
Extrapolation of indications	Possible with scientific justification	Possible with scientific justification	Possible with scientific justification	Possible with scientific justification
Interchangeability	It means switching/ substitution. No guidance since it is mandate to individual countries of EU; automatic substitution not always permitted	Similar to automatic substitution. Specific regulatory pathway for interchangeable biosimilars	Absent of guidance. National authorities have their own guidance	Absent of guidance; status of interchangeability is unclear
Naming and pharmacovigilance	RP and its biosimilar share the same INN. Use proprietary name plus lot number	Nonproprietary name with unique suffix	RP and its biosimilar have the same INN. INN plus lot number	RP and its biosimilar have the same INN Follow WHO approach

Table 9: List of biologics registered and authorized by EFDA

Ser. No.	Active substance	Biosimilars/RBP	Approval date	License holder
1	Bevacizumab	Abevmy (100,400mg)	2021-03-25	Mylan Laboratories Limited
		Avastin (100,400mg)	2018-05-22	Roche Pharma (Schweiz) AG Ltd.
		BEVAAS (100mg, 400mg)	2020-11-20	Hetero Biopharma Limited
2.	Bortezomib	Mibzo 3.5mg	07-03-2021	MSN Laboratories Pvt. Ltd
3	Rituximab	Mabthera 100mg	2018-08-10	Roche Pharma(Schweiz) AG Ltd.
		Mabthera 1400mg	2019-01-22	Roche Pharma (Schweiz) AG Ltd.
		Mabthera 500	2018-07-31	Roche Pharma (Schweiz)
		Rilast 100mg, 500mg	2020-11-27	Hetero Biopharma Limited
4.	Trastuzumab	Herceptin 600mg	2018-05-22	Roche Pharma (Schweiz) AG Ltd.
		Herceptin 440mg	2019-01-16	Roche Pharma(Schweiz) AG Ltd.
		Herceptin 440mg	2018-09-25	Roche Pharma(Schweiz) AG Ltd.
		Hertraz™	2021-03-25	Mylan Laboratories Limited
5	Darbepoetin alfa	Derise (25,40)	2020-11-27	Hetero Biopharma Limited
6	Epoetin beta	Recormon (2000IU/O.3ml)	2019-12-05	Roche Pharma(Schweiz) Ag Ltd.
7	Pegfilgrastim	Fulphila	2021-03-25	Mylan Laboratories Limited
8	Insulin glargine	Lantus	2021-02-16	Sanofi-Aventis Kenya Limited

Ser. No.	Active substance	Biosimilars/RBP	Approval date	License holder
9	Insulin aspart	Novomix 30 Flexpen	2013-04-25	Novo Nordisk A/S
		Novorapid Flexpen	2013-04-25	Novo Nordisk A/S
10	Follitropin alfa	Gonal-F 450 IU	2021-07-25	Merck Europe B.V

5.2. Quantitative Study

5.2.1. Demographic Characteristics of Participants

A total of 292 physicians and pharmacy professionals were invited to participate; 238 questionnaires were returned (response rate = 81.5%). Among them, 225 questionnaires were valid for analysis, of which 120 (53.3%) and 105 (46.7%) were physicians and pharmacy professionals, respectively. The mean age of respondents was 30.95 (SD = 4.96; ranged, 24 - 58). Among the 120 physicians, 70% were general practitioners (GPs). Similarly, 105 pharmacy professionals (85.7%) were graduates of Bachelor of Pharmacy. Table 10 depicts the detailed socio-demographic characteristics of the participants.

Table 10: Socio-demographic characteristics of respondents

		N	**%**	**Mean (SD) Age**
Profession	Physician	120	53.3	30.95
	Pharmacy professional	105	46.7	(4.96)
Gender	Male	139	61.8	
	Female	86	38.2	
Work experience (years)	<5	110	48.9	
	5-9	89	39.6	
	11-14	22	9.8	
	20 and above	4	1.8	
Level of qualification of physicians	General practitioner	85	70.8	
	Specialist	34	28.3	
	Missing	1	0.8	
	Total	120	100.0	

		N	%
Specialty of physicians	Internist	14	41.2
	Oncologist	5	14.7
	Nephrologist	3	8.8
	Hematologist	2	5.9
	Others	9	26.5
	Total	34	100
level of qualification of pharmacy professionals	MSc in pharmacy	13	12.4
	Bachelor's in pharmacy	90	85.7
	Diploma in pharmacy	2	1.9
Area of specialty of pharmacy professionals	Pharmacologist	3	23.1
	Clinical pharmacist	5	38.5
	Pharmacist in supply chain management	4	30.8
	Pharmacist in pharmacoepidemiology and social pharmacy	1	7.7

5.2.2. KAP of Healthcare Professionals in the Selected Hospitals

5.2.2.1. Knowledge and Attitude towards Biosimilars among Healthcare Professionals

Respondents were asked to assess familiarity with biological medicines and biosimilars. Out of 225 participants, the majority (64%) reported that they were familiar with biological medicines. On the other hand, over half of the respondents (56.4%) were unfamiliar with the term biosimilar, while 4.4% and 39.1% were very familiar and familiar, respectively. The frequency distribution is depicted in Figure 2.

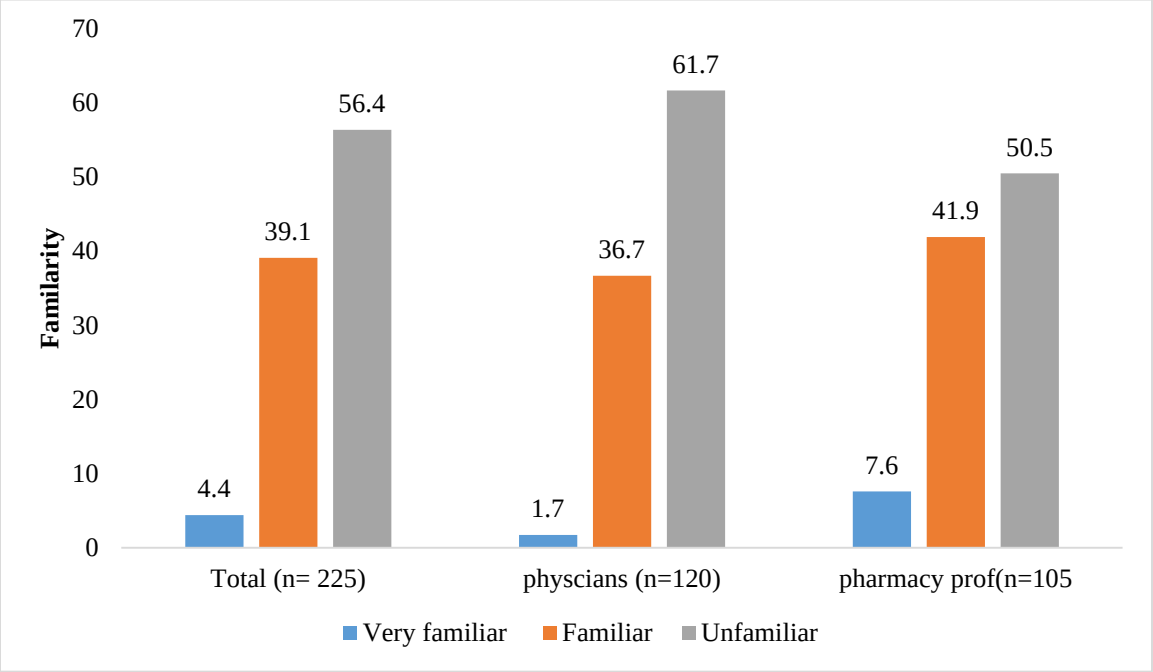

Figure 2: Respondents' familiarity with biosimilars.

Only 18.6% of respondents reported that biosimilar medicines have been included in the standard treatment guidelines of their respective hospitals, while over half of them (55.2%) do not have information about the issue. Further analysis indicated that 37.7% of respondents reported biosimilars were not available at all in their facilities. When sources of information were analyzed, internet browsers and medical scientific literature were mainly used, as illustrated in Table 11.

To evaluate the knowledge of the HCPs, six questions were used to measure the definition of biological medicines and biosimilars, the concept of biosimilarity, interchangeability, and the approval process of biological medicines. The median knowledge score for respondents was 2 (range: 0-6). The accuracy rate for each question was shown in Table 12. When knowledge scores of professionals were measured separately, only 23.3% of physicians and 59% of pharmacy professionals had a good level of knowledge.

With regard to attitude, the median score of Likert scale items was 31.00 (range: 14-44) out of a total score of 50. With a cut point score of 25, the findings of the survey indicated that 81.8% of

respondents have a positive attitude. However, 44% of respondents agreed that biosimilars are essentially the same as generic drugs, while 32.44% were neutral and 23.56% disagreed with the description. Further, 35.55% of participants believed biosimilars have comparable quality, efficacy, and safety profiles to those of their innovator brand counterparts. Considering confidence, almost half of physicians (54.2%) and two third of dispensers (66.7%) were not confident in prescribing and dispensing biosimilars, respectively (Table 13).

5.2.2.2. Prescribing, Dispensing, and Recording

The median scores of practices were 1 (range: 0-5) for physicians and 2 (range: 0-5) for pharmacy professionals, out of a maximum 5 of scores. The results showed that 83.3% of physicians and 76.2% of pharmacy professionals scored less than or equal to 3 on biosimilar prescribing and dispensing. The majority of prescribers (75.8%) stated they had not prescribed biosimilars to their patients. Similarly, 55.2% of dispensers had not dispensed biosimilars.

When considering switching practices, more than 80% of physicians reported that they hadn't made the switch. On the other hand, about three-fourths of dispensers also hadn't substituted reference biological medicines for their biosimilar medicines or one biosimilar for another equivalent biosimilar medicine. Further, one-third recorded biosimilars by only nonproprietary name (INN) after dispensing (Table 14).

Table 11: Availability and information sources about biosimilars

	Selected responses	
Are biosimilar medicines included in standard treatment guideline of your hospital?	Yes	18.2%
	No	26.6%
	I don't know	55.2%
Select biosimilar products currently available where you practice (More than one answers possible)	Monoclonal antibodies	28.3%
	Hormones	40.6%
	Enzymes	8%
	Cytokines	8.4%
	Peptides/ protein drugs	22.2%
	Others	6.7%
	Not available at all	37.7%

Information sources:	N	Percent	Percent of Cases
Medical scientific literature	70	18.2%	32.4%
Biosimilar Company	43	11.2%	19.9%
Medical professional association	28	7.3%	13.0%
Ethiopian Food and Drug Authority (EFDA)	19	4.9%	8.8%
Summary of product characteristics/leaflet	35	9.1%	16.2%
Treatment guideline	42	10.9%	19.4%
Hospital formulary	12	3.1%	5.6%
Internet browser	116	30.2%	53.7%
Others	19	4.9%	8.8%
	384	100.0%	177.8%

Table 12: Frequency of respondents (%) who correctly answered knowledge questions

	Correct responses	
	n	%
1. Biological medicines are products of biological origin prepared by recombinant DNA technology (Yes).	153	68.0
2. The requirements for registration of biological medicines are the same with chemical medicines (No).	83	36.9
3. Biosimilar medicines are similar copies of originator biological medicines (Yes).	78	34.7
4. Approval of biosimilars requires data demonstrating biosimilarity to the reference biological product which includes analytical, non -clinical and clinical studies (Yes).	64	28.4
5. Interchangeability is the process of transitioning from the reference biological product to the biosimilars and back and forth or between two biosimilars (Yes).	74	32.9
6. Currently biosimilars are marketed in Ethiopia (Yes).	77	34.2
Median: 2.00; Range: 0-6		
Good knowledge = 40%		
Poor knowledge = 60%		

Table 13: Assessment of respondents' attitudes toward the use and regulation of biosimilars.

	SD	D	N	A	SA
	N (%)	N (%)	N (%)	N (%)	N (%)
A1. Biosimilars are essentially the same as generic drugs.	24 (10.67%)	29 (12.89%)	73 (32.44%)	59 (26.22%)	40 (17.78)
A2. Biosimilars have a comparable quality, efficacy, and safety profile to that of their innovator brand counterpart.	20 (8.89%)	40 (17.78%)	85 (37.78%)	57 (25.33%)	23 (10.22%)
A3. I trust a company highly experienced in manufacturing generic drugs as a producer of biosimilars.	13 (5.78%)	40 (17.78%)	79 (35.11%)	76 (33.78%)	17 (7.56%)
A4. The Ethiopian Food and Drug Authority is sufficient to evaluate the efficacy and safety of biosimilars during the approval process.	18 (8.00%)	54 (24.00%)	90 (40.00%)	52 (23.11%)	11 (4.89%)
A5. Biosimilars increase patients' access to a variety of treatment options.	19 (8.44%)	28 (12.44%)	65 (28.89%)	83 (36.89%)	30 (13.33%)
A6. Biosimilar medicine prescriptions allow reducing healthcare costs.	24 (10.67%)	47 (20.89%)	87 (38.67%)	55 (24.44%)	12 (5.33%)
A7. I am comfortable with indication extrapolation.	51 (22.67%)	43 (19.11%)	87 (38.67%)	36 (16.00%)	7 (3.11%)
A8. Pharmacists can substitute biologics to a biosimilar drug without the physician's permission.	54 (24.00%)	47 (20.89%)	78 (34.67%)	31 (13.78%)	15 (6.67%)

A9. A standard guideline is needed for both physicians and pharmacists on the biosimilar substitution process.	5 (2.22%)	9 (4.00%)	42 (18.67%)	86 (38.22%)	83 (36.89%)
A10. In prescribing, having the rule of designation of a biologic medicine as “dispense as written” or “do not substitute”.	30 (13.33%)	27 (12.00%)	74 (32.89%)	60 (26.67%)	34 (15.11%)

Median=31.00

Positive attitude = 81.8%

Negative attitude = 18.2%

	Physicians		Pharmacy professionals	
Confidence assessment:	Confident	Not confident	Confident	Not confident
1. Prescribing the reference biological medicines for patients	67.5%	32.5%	76.2%	23.8%
2. Prescribing biosimilar medicines	54.2%	45.8%	33.3%	66.7%
3. Confidence in switching a patient from brand biological medicines to biosimilar medicines	44.7%	55.3%	23.4%	76.6%
4. Confidence in Ethiopia’s medicine regulatory processes during biosimilars registration	59.10%	40.9%	41%	59%

SD=Strongly Disagree, D=Disagree, N=Neutral, A=Agree, SA= Strongly Agree

Table 14: Assessment of the current state of biosimilars prescribing and dispensing practices

Questions	**Yes**	**No**
	n (%)	**n (%)**
P1. Have you ever prescribed reference biological medicine (brand biologic) to a patient?	36 (30%)	84 (70%)
P3. Have you ever prescribed biosimilar medicines to a patient?	29 (24.2%)	91 (75.8%)
P9. Have you ever switched reference biological product to its biosimilar medicine or one biosimilar to another equivalent biosimilar medicine?	20 (16.7%)	100 (83.3%)
P4. If your response is "Yes" for question number 3, how often do you prescribe biosimilar medicines?	Every day	4 (13.8%)
	once a week	6 (20.7%)
	once a month	7 (24.1%)
	once a year	12 (41.4%)
P12. In general, while you prescribe biosimilars, which of the following mostly indicates your behavior?	Prescribed by their brand name	6 (20.7%)
	prescribed INN only	8 (27.6%)
	prescribed by INN or brand	13 (44.8%)
	never prescribed biosimilars	2 (6.9%)
D1. Have you ever dispensed a reference biological medicine to a patient?	40 (38.1%)	65 (61.9%)
D3. Have you ever dispensed biosimilar medicine to a patient?	47 (44.8%)	58 (55.2%)

D9. Have you ever substituted reference biological medicine to its biosimilar medicine or one biosimilar to other equivalent biosimilar medicine?	27(25.7%)	78(74.3%)
D4. If your response is "Yes'' for question No. 3, how often do you dispense biosimilars?	every day	9 (19.1%)
	once a week	10 (21.3%)
	once a month	20(42.6%)
	once a year	8(17.0%)
D12. In general, while you dispense biosimilars, which of the following mostly indicates your behavior?	Record by brand name	4 (8.5%)
	nonproprietary name(INN) only	16 (34.0%)
	INN Plus Suffix of letter designated	4(8.5%)
	INN or brand name with batch number	14 (23.4%)
	Totally not record	5(10.6%)
	never dispensed biosimilars	4(8.5%)
	0thers	3(6.4%)
Median (Range)	Physicians: 1(0-5)	Pharmacists: 2(0-5)
Score of practice less than or equal to 3	83.3%	76.2%

5.2.2.3. Correlation of Knowledge and Attitude with Practice

The Kolmogorov-Smirnov normality tests of knowledge and attitude scores were $p<0.05$. Spearman's correlation analysis indicated that knowledge has a significant positive correlation with practice and attitude for both physicians (Rho = 0.59) and pharmacists (Rho = 0.40) (Table 14).

Table 14: Correlation of knowledge and attitude with Practice

	Variable	Correlation coefficient (Rho value)	P value
Physicians	Knowledge- practice	0.59	0.000
	Knowledge-attitude	0.19	0.04
	Attitude-practice	0.16	0.07
	Knowledge-confidence	0.34	0.00
Pharmacists	Knowledge- practice	0.40	0.000
	Knowledge-attitude	0.36	0.000
	Attitude-practice	0.18	0.07
	Knowledge-confidence	0.36	0.000

5.2.3. External Factors Affecting Prescribing/Dispensing

Opinions on factors related to prescribing and dispensing biological medicines, particularly biosimilars, were identified. The identified factors were insufficient information, unavailability in the hospitals, unaffordability, and unregistered biosimilars by EFDA (Table 15). Respondents also identified major factors that encourage/motivate them to prescribe/dispense biosimilars (Figure 3).

Table 15: Analysis of perceived influencing factors to prescribe and dispense biosimilars

	Physicians		Pharmacists	
	Yes	No	Yes	No
Do you think there are any potential barriers to you in prescribing/dispensing biosimilar medicines?	104 (86.7%)	16 (13.3%)	73 (69.5%)	32 (30.5%)
Identified barriers by respondents				
	n	%	n	%
1. Insufficient information on biosimilar medicines.	78	76.5	47	65.3
2. Shortage of biosimilars in the hospitals, i.e. frequently stock out.	62	60.8	46	63.9
3. Biosimilars are not registered by the Ethiopian Food and Drug Authority.	17	16.7	8	11.1
4. Concern about safety and efficacy of biosimilars.	14	13.7	8	11.1
5. Biosimilars are not affordable.	28	27.5	10	13.9
6. Biosimilars are uncovered by health insurance.	2	2.0	1	1.4
7. Absence of incentives for physicians.	2	2.0	2	2.8
8. Their packaging, dosages and devices are less attractive than reference biological product.	2	2.0	6	8.3
9. Biosimilars are not included in the hospital standard treatment guideline.	19	18.6	7	9.7
10. Patient preference.	2	2.0	4	5.6
11. Others.	1	1.0	1	1.4
Perceived reasons for the shortage of biosimilars in the hospitals:				
1. Lengthy period of Ethiopian Drug Authority to review drugs	9	14.5	7	16.3

2. Lack of communication among stakeholders(hospitals, EPSA, and Ethiopian Food and Drug Authority)	43	69.4	25	58.1
3. Covid-19 outbreak	28	45.2	14	32.6
4. Limited EPSS capacity	46	74.2	29	67.4
5. Limited private importers capacity	18	29.0	15	34.9
6. Insufficient hospital's budget	24	38.7	17	39.5
7. Biosimilars are excluded from tenders at hospital level.	9	14.5	14	32.6
8. Others	7	11.3	2	4.7
Reasons for switching/ substituting				
1. Unavailability of the first prescribed biological product	11	64.7	24	92.3
2. The initially prescribed biological drug is not affordable for the patient (cost issue).	12	70.6	9	34.6
3. Due to the safety issue of initially prescribed	1	5.9	1	3.8
4. Due to the efficacy issue of the initially prescribed	1	5.9	1	3.8
5. Lack of insurance coverage for initially prescribed biologic	3	17.6%	6	23.1
6. patient preference	3	17.6%	24	92.3
Reasons not to switch/substitution				
1. Switching is prohibited	5	5.4	6	7.9
2. There is no clear legislation on interchangeability of biologics	25	26.9	38	50.0
3. Fear of potential loss of clinical efficacy	21	22.6	11	14.5
4. Fear of potential for adverse events	22	23.7	8	10.5
5. Concern for potential for increased risk of immune reaction	20	21.5	4	5.3

6. Concern for traceability for post-market surveillance	12	12.9	8	10.5
7. Others	41	44.1	29	38.2

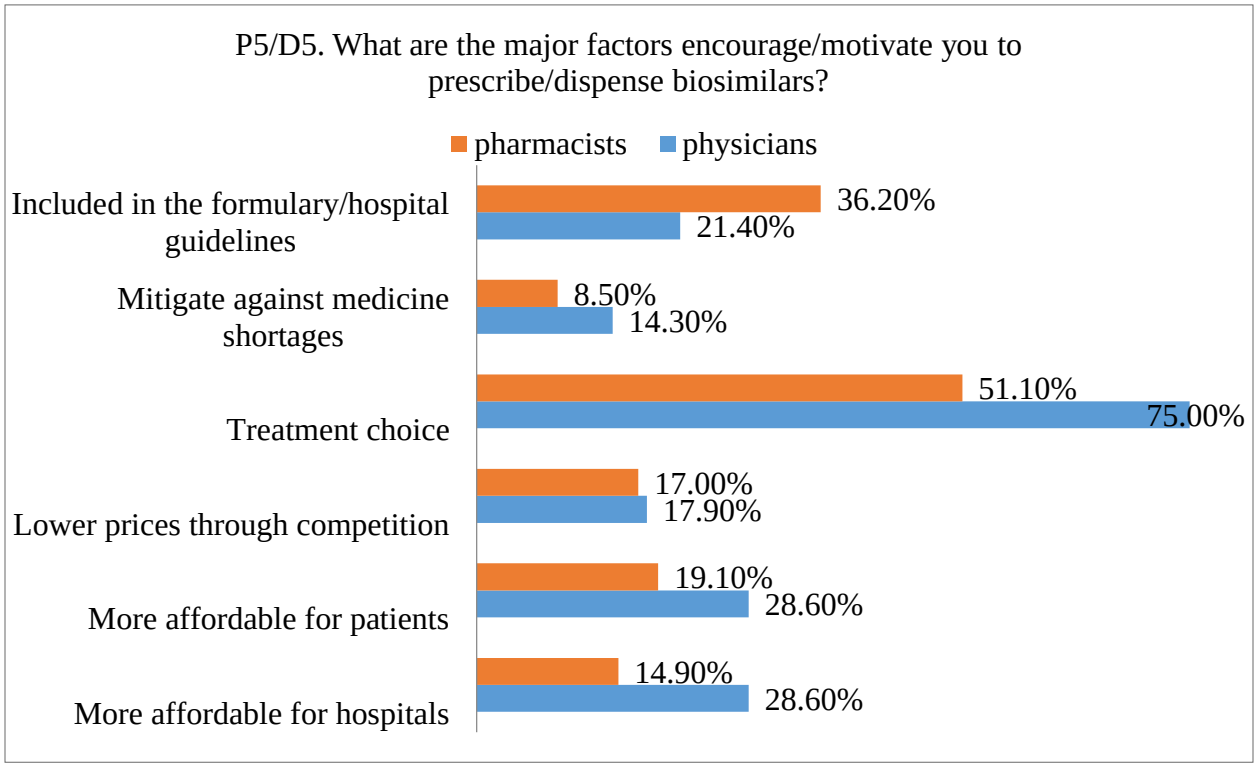

Figure 3: Factors that encourage/motivate prescribers and dispensers towards promoting the use of biosimilars.

6. Discussion

This study explored the state of biosimilar access and use in selected referral hospitals and their influencing factors using both qualitative and quantitative approaches. The study revealed that the biosimilarity principles, data requirements for biosimilarity, and extrapolation to indication followed by EFDA align with EMA, US FDA and WHO standards. It indicates that the Ethiopian Food and Drug Authority has established guideline that is consistent with international standards, which enhance the efficiency of biosimilar approval and promote their access. However, some divergences from global regulatory requirements have significant impacts on the access to and use of biosimilars in Ethiopia.

With regard to legal basis, the regulation of biosimilars in Ethiopia is founded on Proclamation 1112/2019, although core regulatory functions for biosimilars are lumped together with other small-molecule medicines. This lack of specificity is a challenge for approval and monitoring process of biosimilars. In contrast, the EU established a shortened process of licensing biological products in directive 2001/83/EC and Regulation 726/2004. Similarly, the BPCI Act created abbreviated approval pathways for biosimilars and products that are interchangeable with RBPs.

Considering the guidance for biosimilar manufacturers, the EMA has developed specific guidelines for eight product classes (products containing somatropin, low molecular-weight heparin, insulin, erythropoietin, recombinant granulocyte colony stimulating factor, follicle-stimulating hormone, interferon beta, and monoclonal antibody) in addition to three overarching guidelines that could simplify and ease the development and market authorization of these medicines. Except for particular guidance for biosimilar insulins, the US FDA primarily offers general guidance documents. The EFDA, on the other hand, prepared only one general guideline for the comparability exercise signaling a gap in guideline preparation for specific product classes. These suggest the regulatory environment in Ethiopia is least favorable for manufacturers as compared to EMA. However, the country follows reliance concept and joint review to speed up market authorization.

The key informants acknowledged that the scientific principles and regulatory requirements for biosimilarity followed by EFDA are basically similar to those of EMA, US FDA, and WHO guidelines. The document evidence corroborates that the regulatory procedures entail stepwise development approaches for demonstrating the biosimilarity. The EFDA follows an abbreviated approval pathway that reduces the time and cost of biosimilar development, an approach often adopted by most developing countries (H. N. Kang et al., 2021; Sani et al., 2020), which improves the speed of market entry of affordable biologics.

Most of the selection criteria for reference biological products are common among the EMA, US FDA, EFDA, and WHO. From document reviews, it was found that all of them considered locally approved RBP to be used as the basis of comparison to demonstrate similarity (BPCI Act FDA (2012), 2021; EMA, 2014). The EFDA also mandates the use of nationally licensed originator products.

Another worth-noticing issue is flexibility in obtaining RBP from other countries. Both EMA and US FDA have accepted reference products authorized outside the EEA (EMA, 2014) and in the USA (US FDA, 2015). Similarly, WHO states that if the reference product is not approved locally, the NRA may permit the use of a product that has been approved by a recognized NRA (World Health Organization, 2018). In addition, they advise conducting bridging studies if the reference product is not authorized locally but comes from a different country. The EFDA also considers RBP licensed or resourced in other jurisdictions, but it has not stated the requirement of a bridging study. These suggest that EFDA reduces duplication of clinical studies. However, such decision may lead concerns about the applicability of data to the Ethiopian population. Similar study by Rahalkar et al (2021) indicated that CDSCO, TITCK, and COFEPRIS allow for sourcing RBP from ICH/reference nations. Tanzania, Ghana, and Egypt also accept foreign licensed and sourced RBP (H. N. Kang et al., 2021).

Furthermore, the qualitative findings indicated the Ethiopian Food and Drug Administration and other international organizations require non-clinical and clinical studies to address uncertainty of biosimilarity. Ethiopian regulations also allow extrapolation of indications, reducing market

entry time and cost. In contrast to this finding, Castañeda-Hernández et al. (2019) found extrapolation between indications is not permitted in Argentina.

The key regulatory divergence lies in how interchangeability is defined and implemented. In the US, interchangeability means automatic substitution and requires switching studies, while in the EU it refers to switching and/or substitution. EMA relies on comparability without specific switching studies. Substitutions have been established by US FDA but the states laws govern their implementation. In the EU, member states decide regarding switching or automatic substitution. The EFDA's system lacks clear guidance on interchangeable use specifically for biosimilars. Similar findings have been reported by Kang et al. (2021) that the majority of nations lack guidelines pertaining to the interchangeability of biosimilars. However, Rahalkar et al. (2018) reported the decision for interchangeability is under reimbursement institutions in Turkey and Australia.

Furthermore, EFDA enforces requirements for biosimilars' naming, pharmacovigilance, and labeling in alignment with the WHO guideline but has taken divergent positions with the US FDA and EMA. Both biosimilars and their originators have the same INN in the WHO guideline. traceability (Anon., 2022). The US FDA demands that all originator biologics and biosimilars have non-trade names, and that a 4-letter suffix, devoid of meaning, is added to the names to separate them from one another (FDA, 2017). Such distinct identifiers can be identified correctly, and the safety of the drugs can be monitored. In contrast, the EMA requires biosimilars to have the same INN as their reference products but a unique brand name. INN along with the marketing authorization holder can be used if no brand name is provided. The agency suggests in its pharmacovigilance system to use INN, trade name, and batch number as identification tools (EMA, 2019).

Drug labels are one of the inconsistencies in regulatory approval pathways. For instance, the inclusion of the word "biosimilar*" followed by US FDA and "biosimilar" according to EMA implies the products are biosimilars (Services, 2018). The US FDA uniquely addresses interchangeability designation if approved. On the other hand, WHO recommends labeling with

biosimilarity but no interchangeability concept, while EFDA relies on WHO guidelines with an emphasis on local language. These findings are similar to those of Heinemann et al. (2015) and Kang et al. (2021), which indicated the additional data requirements or duplication do not favor companies to get market authorization. Furthermore, Kaplan et al. (2016) demonstrated that adding a BQ for the INN would send a wrong signal regarding trust in biosimilars.

Submitting non-essential documents, such as a certificate of pricing, has the potential to delay the review and approval process. Unlike the practice in Egypt, in which the applicant should submit pricing dossiers (Directorate General Drug Administration, 2018; Guideline for Registration of Biosimilar Products in Egypt, 2023), Ethiopia does not require the assessment of biosimilars' prices but mandates the affixing of retail prices. This facilitates a more efficient market entry.

While Ethiopian regulatory requirements are reasonably aligned with international standards, EFDA has already licensed a few types of biosimilars. These include classes of granulocyte colony-stimulating factor, erythropoiesis-stimulating agent, and monoclonal antibodies. This limited number of approved biosimilars with single brands indicates inadequate availability and lack of competition that impacts their affordability in Ethiopia. It is comparable to the situation in Ukraine (Kang et al., 2021). EFDA key informants highlighted a delay in the market approval process due to a shortage of trained personnel with expertise in biosimilar evaluation. This necessitates investment in training and capacity-building initiatives.

With regards to availability within the health facilities, the qualitative study indicated a few types of biosimilars were available in SPHMMC and TASH. Rituximab (Mabthera) and a biosimilar of Bortezomib were available in only one of the three hospitals. Rituximab was stock out in one hospital for more than 4 months; signaling the serious impact of the shortage and prolonged stock out on access to essential biosimilars in the country. The EPSS and hospitals' stores managers emphasized inconsistent biosimilar availability, attributing this to Covid-19 pandemic and fragmented logistics. The key informants emphasized biosimilars' cost issues as a pressing barrier to equitable healthcare access. A survey of healthcare professionals also revealed

concerns of access, with over 60% of physicians citing inadequate availability in hospitals, while 27.5% of prescribers and 13.9% of dispensers highlighted affordability as a critical barrier.

The availability of biosimilars does not guarantee access. Acceptability critically influences their adoption, while knowledge and perceptions shape this acceptability. The current quantitative study demonstrates that most HCPs are more familiar with biologics in general than biosimilars, comparable to the findings from Zambia (Banda et al., 2022). About 60% of participants have poor knowledge related to understanding of biosimilars. The data illustrated more than half of survey participants were unfamiliar with the term biosimilar. Further, assessment of knowledge questions indicated the majority of respondents have poor knowledge concerning the standard definition of biosimilar, the concepts of biosimilarity and interchangeability, requirements for registration, and awareness about their availability in the country. A similar question was asked in Ireland, and 42 % of respondents were unfamiliar (O'Callaghan et al., 2017a), indicating lower awareness in the present study.

On the other hand, the study participants reflected their concern about biosimilars' quality, safety, efficacy, extrapolation to indications, and automatic substitution. These support the issues raised by Danese et al. (2016) and van Overbeeke et al. (2017). Substitution of prescriptions by pharmacists has been one of the sources of disagreement among healthcare professionals in many countries. This study showed that the majority of physicians disagreed or remained neutral about automatic substitution of biosimilars without physicians' permission. Similarly, Danese et al. (2016) reported that 89.8% of participants disagreed with pharmacy-driven automatic substitution biological medicines. In another study, most doctors and pharmacists thought that switching medications ought to be decided by the doctor prescribing the medication, although the majority of pharmacists expressed comfort in changing innovators to biosimilars with the agreement of prescribers (O'Callaghan et al., 2017b). Nevertheless, both groups of professionals had similar opinions on the need for 'having the rule of designation of a biologic medicine as "dispense as written" or "do not substitute" during prescribing.

Data regarding participants' perceptions about the potential advantages of biosimilars were varying; half of the respondents agree that biosimilars increase patients' access to a variety of treatment options, but only 30% of them have a positive attitude about the advantage of cost savings. The reason for this could be attributed to the fact that respondents are judging the costs of biosimilars in relation to generic drugs, as 44% of respondents agreed that biosimilars were essentially the same as generic drugs, similar with the finding in Tunisia (Hadoussa et al., 2020). Furthermore, the result is in line with the report by Mohd Sani et al.(2023), where 90% of pharmacists were in favor of potential cost savings. Contrary to this opinion, nearly to 65% of respondents cited lower price as the main driver for clinicians to prescribe biosimilars (Farhat et al., 2016).

Despite generally poor knowledge about biosimilars, healthcare professionals still a positive disposition towards them, possibly due to perceived benefits for patients. The important underlying factors for limited knowledge were the lack of appropriate information channels. The regulatory body plays a role in educating healthcare professionals and patients about biosimilars, influencing their acceptance and use. However, prescribers and dispensers utilized less EFDA and professionals' associations as their source of information. The study indicated a strong need for educating healthcare providers to enhance knowledge about biosimilars, which might increase acceptance and use of biosimilars.

In terms of practices, the findings showed that more than 80% of prescribers and 75% of dispensers have poor practices. Around one-fourth of physicians had prescribed biosimilars. This implies poor prescribing practices in the study settings as compared to a survey by Farhat et al. (2016), where 41% of participants reported that they had prescribed biosimilars. With regard to dispensing practices, less than half of respondents (44.8%) reported that they had dispensed biosimilars that could be better than the study conducted by Barbier et al. (2021), in which 32% (n=45/139) pharmacists indicated such experiences. It was found that pharmacy professionals reported better exposure to biosimilars than physicians. This may be attributed to prescription flow from different wards.

The other trend in clinical practice is the issue of interchangeability. This study revealed the majority of healthcare professionals didn't have switching or substituting behaviors. One of the reasons was the lack of clear legislation on interchangeability of biologics. Findings from document reviews substantiated this claim that Ethiopia does not have a clear legal basis for interchangeable use of biological products, unlike the situation in France that allows switching and substitution based on certain criteria: switching based on patient consent and monitoring treatment closely (Sirjana Pant, Louis de Léséleuc, 2018). Nearly half of the physicians prescribed biosimilars by INN or brand name and a few of them had done so by INN. However, the finding from policy reviews indicated that INN-based prescribing for biologics have not been clearly stated in national drug policy, indicating the gap of guidance for HCPs.

The findings have identified the adoption and use of biosimilars in hospitals depends on a combination of healthcare professionals' perceptions and regulatory policy. The primary reason for slow adoption of biosimilars was the lack of knowledge and acceptance among HCPs. The correlational analysis findings showed that knowledge has a strong relationship with practice for both physicians and pharmacists. Conversely, there was a weak relationship between practice and attitude. Furthermore, more than half of physicians and nearly a quarter of pharmacists were not confident in prescribing and dispensing biosimilar medicines. They perceived biosimilars are not comparable with their originator biologics in terms of quality, safety, and efficacy. In addition, 59.1% of physicians and 41% of pharmacy professionals lack confidence in EFDA's regulator process during licensing of the medicines. These findings coincide with previous studies that indicated knowledge gaps and lack of confidence are common barriers in prescribing and dispensing (Aladul et al., 2018; Dylst et al., 2014).

Survey participants illustrated factors such as treatment choice, affordability for patients, and inclusion in the national medicine's formulary and treatment guidelines as encouraging factors for the prescribing and dispensing of biosimilars. These comply with previous studies that biosimilars provide patients the opportunity to have access to less expensive, equally effective treatments and offer doctors more treatment options (Barbier et al., 2020; Simoens, 2021).

However, the major external factors that have a detrimental impact on the prescribing and dispensing of biological medications were unavailability and/or shortages in the health facilities, unaffordability, the state of market authorization, and policy framework. The qualitative analysis indicated that the national regulatory authority approved very few numbers of biosimilars. Among biologics that got approval from the authority, only Rituximab (Mabthera), Filgrastim, and Bortezomib were available in hospitals' stores during the survey period. While the quantitative analysis corroborated that the second barrier in clinical practice was unavailability or stockout in hospitals due to four reasons. These included EPSS's limited capacity, a lack of communication among stakeholders, an insufficient hospital budget, and the COVID-19 pandemic. This highlights inadequate supply systems influences patients' access to biological medicines.

Policy frameworks such as price regulation, the procurement system, and insurance benefit design affect the affordability of medicines. Proclamation 1112/19 article 53/7 requires manufacturers or importers to display a medicine's retail price to promote transparency, prevent price gouging, and foster a competitive marketplace for informed health choices. However, the interview analysis showed the country imported biologics based on free pricing (flexible market approach) by not mandating a prior price assessment, which allows manufacturers or sellers to set higher prices. In contrast, Egypt's Ministry of Health mandates a 35% price reduction for initial five biosimilars, followed by a 40% reduction for subsequent products (Batran et al., 2022). In the case of the EU, 15 out of 42 surveyed countries implemented a price link policy in which the price of a biosimilar is determined in relation to the price of the innovator medicine (Vogler & Schneider, 2017).

EPSS uses tendering to procure off-patent biological products at the central level based on EMLs. A call for international tenders in bulk is initiated, and the winning bidder is chosen primarily based on the least price, considering other criteria such as charges along the supply chain and supply reliability. It also distributes medicines to public health facilities at wholesale prices. On the other hand, the interviews of store managers indicated that hospitals add up 20% (at Budget Pharmacy) to 25% (Community Pharmacy) to set a retail price for all medicines,

including higher-priced medicines. The fixed percentage regardless of the base price the pharmacies added to drug costs could lead to the final price being high. Thus, these findings suggest the procurement at national level with an open tender and the least price, plus other criteria, have a positive implication to ensure affordability as well as sustainable availability. However, hospitals implement fixed marks that don't support WHO recommendations for regressive policy (World Health Organization, 2020).

Coverage and reimbursement of similar biological products have also been important determinants of access at patients' level. This study indicated that biosimilar is covered by community-based health insurance. However, two major gaps were identified, similar to the findings by the WHO assessment *(Assessment of Medicine Pricing and Reimbursement Systems in Health Insurance Schemes in Selected African Countries, n.d.)*. First, insurance coverage is limited to the informal sector because social health insurance still wasn't implemented. In contrast, almost all HCPs didn't perceive health insurance coverage as a barrier in their practice. This discrepancy demonstrates a wide gap between healthcare professionals' perspectives and the realities encountered by patients in the informal sector. Secondly, CBHI is a price-taker from contracted health facilities. It does not conduct medicine pricing and has no medicine list for reimbursement.

Policies directed at prescribers and dispensers also promote the use of biosimilars. They include prescribing by INN, switching, substitution, financial incentives, and education (Machado et al., 2024; Vogler & Schneider, 2017). The finding from the Ethiopian drug policy showed there is no clear position on biological medicines interchangeability. While in the USA, the FDA clearly stated pharmacists can substitute approved interchangeable without approval of the prescriber, and there are possibilities of switching in EU members through prescription guidelines (Rémuzat, Kapuśniak, et al., 2017). A KAP survey analysis also indicated that nearly half of prescribers prescribed by INN or brand name, while 29.6% of physicians and 50% of pharmacy professionals reported the absence of clear legislation for interchangeability as a hurdle in switching or substituting. Consequently, it implies the need of clear guideline like TDMA

(Authority & Authority, 2020) that could avoid confusion with generic drugs during switching and substituting in clinical practice.

The implementations of appropriate information channels determine the uptake of biosimilars. The analysis of KIs interviews indicated a gap in communication between EFDA and suppliers to avoid a shortage of products in the country. On the other hand, EFDA already prepared procedures for registration and guideline in order to facilitate market authorization. In addition, the authority listed those approved products on its website page. Apart from this guideline and information on the list of market-authorized products, there is limited educational material compared to the EU (Barbier et al., 2022). A survey result has also shown that the majority of physicians (76.5%) and pharmacy professionals (65.3%) perceived insufficient information as the first barrier to prescribing or dispensing.

Strength and Limitation of the Study

The study attempted to explore the research problem using mixed-method study approaches and involving key stakeholders in the area as its major strengths. Nevertheless, there are a few limitations. First, it is a cross-sectional study, which makes it impossible to determine causality among variables. Being a single-point cross-sectional study, it is also unable to reflect the average monthly or annual availability of medicines at individual outlets. Second, the survey study only involved three hospitals, potentially limiting the ability to apply the findings to other hospitals. The sample selection may reduce the representativeness of the results. In order to improve representativeness, a balanced sample of health professionals from hospitals was recruited by quota. Moreover, reported results correspond to the study setting at the time of the study done since the policy update, the status of registered and availability of biologics in hospitals can change over time due to various factors.

7. Conclusion

The study revealed that the regulatory framework of biosimilars in Ethiopia is closely aligned with international practices. EFDA has established a regulatory pathway and developed guidance for market authorization of biosimilars. It integrated requirements from EMA, US FDA, and WHO to improve access. However, disparities were observed in areas such as terminology, bridging studies, nomenclature, and interchangeability guidance.

The availability and uptake of registered biosimilars were found to be inadequate in the study facilities. The majority of physicians and pharmacists reported they had never prescribed or dispensed biosimilars to their patients. Furthermore, the switching and substitution practices for biologics were rarely observed in the study facilities. The key barriers identified include a limited number of registered biosimilars, limited capacity of EPSS, constrained hospital budgets, inadequate knowledge and lack of confidence among healthcare professionals, and the absence of reliable information sources.

The absence of a clear drug pricing policy and a reliable social health insurance system in the country has further compounded the challenges of accessing and utilizing biosimilars in healthcare institutions. Considering the essential clinical role of biosimilars as cost-effective interventions and the growing burden of NCDs, a concerted effort from major stakeholders is required to improve access to essential biosimilars, at least in tertiary-level health facilities.

8. Recommendations

Policy makers:

- Establish a dedicated organization responsible for managing the pharmaceutical pricing system.
- Integrate more information on biosimilars into the curricula of medical and pharmacy undergraduate programs.
- Implement a social health insurance system to address the healthcare needs of the population in the formal sector.
- Develop a clear and comprehensive national drug pricing policy.

Ethiopian Food and Drug Authority:

- Develop a clear position statement on interchangeability to build trust among physicians and pharmacists, which will encourage the prescription and dispensing of biosimilars..
- Create educational campaigns and programs to inform healthcare professionals about the safety and efficacy of biosimilars, their potential advantages, and address common concerns.

Hospitals:

- Provide in-service training on biologics, including biosimilars, through continuous professional development programs.
- Drug and Therapeutic Committees should review their hospital formularies and guidelines to promote the safety, efficacy, and affordability of biosimilars.
- Procure multiple brands of biosimilars for each reference biologic to foster competition and reduce stock outs.

Healthcare Professionals:

- Utilize EFDA, medical scientific literature, and professional medical associations as trusted sources of information.
- Electronically record product names, batch numbers, and manufacturers to ensure traceability of biologics.

Ethiopian Pharmaceutical Supply Service:

- Award tenders to multiple suppliers with predictable volumes for each to maintain healthy competition and avoid medicine shortages or stock out.

9. Suggestion for Future Research

To gain deeper insights into perspectives on access to biosimilars in Ethiopia, it is suggested to conduct a similar system-based study with a larger sample size. This study should include regional regulatory bodies, pharmaceutical importers, wholesalers, and health facilities for a more comprehensive understanding of the situation. Future studies should also consider longitudinal studies are needed to assess how any change in policy or efforts impact biosimilars accessibility over time.

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Annex I: Interview Participants' *information sheet (English version)*

My name is Shimelis Ayele. I am a postgraduate (MSc) student at Addis Ababa University, College of Health Sciences, School of Pharmacy, Department of Pharmaceutics, and Social Pharmacy. As part of this degree in Regulatory Affairs, I am conducting research entitled "***Access to Biosimilars in Federal Hospitals in Addis Ababa: Assessment of the National Medicines Regulatory Framework and Healthcare Professionals' Perspectives".*** The research could mainly serve for the country to identify modifiable factors concerning access to biosimilars and plan intervention accordingly. If you agree to take part in this study, you will be among those who will contribute towards strengthening access to biosimilars in hospitals (country). Your information and others participating in the study will collectively be used by policymakers in strengthening the system.

To obtain the necessary information, I am delivering an interview. The in-depth interview is prepared to assess the issues about access to biosimilars in the country. The interview will take 25-45 minutes of your time and the interview will be held at your convenient location and time. Your participation is purely voluntary and the information you provide will be kept completely confidential. Direct quotes might be taken from your response to be used in written and verbal reports of the paper but your name will never be written and aggregate responses from different respondents will only be identified by codes. However, voice recorded (tape recorder) may be used during the interview. Your honest response to the question is of paramount importance for the successful completion of the study. There is no right or wrong answer and you can have clarification for any doubt regarding the questions.

Are you willing to respond to the questions? Yes/No

Annex II: □□□□□□□ □□□□□□ □□□□□□□ □□□ **(Amharic version)**

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Annex III: Interview guide questions for EFDA employees (English version)

Instruction: the following general interview guide questions are intended to collect in-depth information from key informants regarding access to biosimilars

1. Code no: _____
2. Name of the Interviewer: _____
3. Date of interview: _____
4. Place of interview:_____

Part 1: Key informants' Profile

1. Gender A. Male B. Female
2. Age :_____(in years)
3. Profession: _____
4. Academic qualification: _____
5. Position: _____
6. Work experience :_____(in years)

Part 2: General Interview guide Questions

1. What is your understanding of biosimilars/similar bio-therapeutic product (SBPs)?
2. What do you think the advantages of biosimilars as compared to chemical medicine in the Ethiopian context?
3. What are the policies issues affecting access to biosimilars in Ethiopia?
4. In general, how do you regulate biosimilars?
5. Would you explain the registration process of biosimilar medicines at EFDA?
6. How do you describe EFDA's alignments in the authorization of biosimilars with international standards?
7. What do you think about the major challenges for EFDA in the market authorization process of biosimilars concerning overall capacity?
8. How do you describe the extent of availability of biosimilar in Ethiopia?
9. How do you see the affordability of Biosimilars?
10. How does your organization prevent and mitigate shortages of biosimilars in Ethiopia?

Annex IV: Amharic Version of the Interview Guide (□□□□□□□ □□□□ □□□□□□ □□□□□□□ □□□□□□ □□□□ □□□□□ □□□□□□)

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Annex V: Interview questions for expertise at EPSS, EPSS, and hospitals (English version)

Instruction: The following interview guide questions questionnaires are intended to collect information from expertise from the Ethiopian ministry of health on "***Access to Biosimilars in Federal Hospitals in Addis Ababa: Assessment of the National Medicines Regulatory Framework and Healthcare Professionals' Opinion".***

Code no: _____

1. Name of the Interviewer: _____
2. Date of interview: _____
3. Place of interview:_____

Part 1: Key informants' Profile

1. Gender A. Male B. Female
2. Age :_____(in years)
3. Profession: _____
4. Academic qualification: _____
5. Position: _____
6. Work experience:_____(in years)

Part 2: General Interview guide Questions

1. What is your understanding of biosimilars/similar bio-therapeutic product (SBPs)?

2A. How does the health insurance system promote patients' access to biosimilar medicines? (Question for only EHIA's expert)

2B. How does PFSA procure biologics, particularly biosimilars? (Question for only PFSA expert)

3. What are the policies issues affecting access to biosimilars in Ethiopia?

4. How do you describe the extent of availability of biosimilar in Ethiopia? (What about in your hospital setting? (Leading question for store managers))

5. How do you see the affordability of Biosimilars?

Annex VI: Amharic Version of the Interview Guide (□□□ □□□□ □□□□ □□ □□□□□□ □□□□□ □□□□ □□ □□□□□□ □□□□□□□ □□ □□□□**)**

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Annex VII: Check list for availability of biosimilars in hospitals' drug store

Ser. No	INN	Reference biologics	Biosimilars available in stock
1	Bevacizumab		
2	Bortezomib		
3	Rituximab		
4	Trastuzumab		
5	Darbepoetin alfa		
6	Epoetin beta		
7	Pegfilgrastim		
8	Insulin glargine		
9	Insulin aspart		
10	Follitropin alfa		

Annex VIII: *Consent form* for self-administered questionnaires

My name is Shimelis Ayele. I am a postgraduate (MSc) student at Addis Ababa University, College of Health Sciences, School of Pharmacy, Department of Pharmaceutics, and Social Pharmacy. As part of this degree in Regulatory Affairs, I am conducting research entitled "***Access to Biosimilars in Federal Hospitals in Addis Ababa: Assessment of the National Medicines Regulatory Framework and Healthcare Professionals' Perspectives".*** The research could mainly serve for the country to identify modifiable factors concerning access to biosimilars and plan intervention accordingly. If you agree to take part in this study, you will be among those who will contribute towards strengthening access to biosimilars in hospitals (country). Your information and others participating in the study will be collectively used by policymakers in strengthening the system.

To obtain the necessary information, I am delivering questionnaire. To complete the questionnaire, it will take 15 minutes. Your participation is purely voluntary and the information you provide will be kept completely confidential. Your honest response to the question is of paramount importance for the successful completion of the study.

Are you willing to participate? Yes/No

Annex IX: Questionnaire for Physicians

Section A: Socio demographic characteristics

1	Sex	A. Male B. Female
2	Your age(years):	_____
3	Your current workplace/ department/Unit	_____
4	Your level of qualification	A. General practitioner B. Specialist
5	If you are specialist, Please select your area of specialty	A. Internist B. Oncologist C. Rheumatologists D. Nephrologist E. Hematologists F. Gastroenterologist G. Endocrinologist H. Dermatologist I. Neurologist J. Other
6	Please, select your years of experience	A. <5 B. 5-9 C. 10-14 D. 15-19 E. 20 and above

Section B: Knowledge

Consider these descriptions of terms while you respond to question number 1 and 4:

- **Very familiar**= able to define appropriately, and aware of approval process
- **Familiar**= able to define appropriately
- **Unfamiliar=** heard the term but unable to describe properly

1	How familiar are you with biological medicines?	A.	Very familiar
		B.	Familiar
		C.	Unfamiliar
2	Biological medicines are products of biological origin prepared by recombinant DNA technology	A.	Yes
		B.	No
		C.	I don't know
3	The requirements for registration of biological medicines are the same with chemical medicines	A.	Yes
		B.	No
		C.	I don't know
4	How familiar are you with the term biosimilar medicines (biosimilars)?	A.	Very familiar
		B.	Familiar
		C.	Unfamiliar
5	Biosimilar medicines are similar copy of originator biological medicines	A.	Yes
		B.	No
		C.	I don't know
6	Approval of biosimilars requires data demonstrating biosimilarity to the reference biological product which includes analytical, non -clinical and clinical studies	A.	Yes
		B.	No
		C.	I don't know
7	Interchangeability is the process of replacing the innovator biological medicine to the biosimilars (or vice versa) or between two biosimilars	A.	Yes
		B.	No
		C.	I don't know
9	Currently biosimilars are marketed in Ethiopia	A.	Yes
		B.	No
		C.	I don't know

10	Are biosimilar medicines included in standard treatment guideline of your hospital?	A. Yes B. No C. I don't know
11	Select biosimilar products currently available where you practice (More than one answers possible)	A. Monoclonal antibodies B. Hormones C. Enzymes D. cytokines E. peptides/ protein drugs F. Others G. Not available at all
12	In general, what are your main source(s) of information on biosimilars? (More than one answers possible)	A. Medical scientific literature B. Biosimilar Company C. Medical professional association D. Ethiopian Food and Drug Authority (EFDA) E. Summary of product characteristics/leaflet F. Treatment guideline G. Hospital formulary H. Internet browser I. Others

Section C: practice

1	Have you ever prescribed reference biological medicine (brand biologic) to a patient?	A. Yes B. No
2	If your response is "No" for question number 1, what could be the reason(s)?	A. Not available in the country B. Not available in our hospital C. Too expensive D. Health insurance doesn't cover reference biologic medicine E. Lack of confidence in safety and efficacy of biological products F. Others
3	Have you ever prescribed biosimilar medicines to a patient?	A. Yes B. No
4	If your response is "Yes" for question number 3, how often do you prescribe biosimilar medicines?	A. every day B. once a week C. once a month D. once a year E. never
5	If your response is "Yes'' for question No.3, what are the major factors that encourage/motivate you to prescribe biosimilars? (*Multiple answers are possible*).	A. More affordable for hospitals B. More affordable for patients C. Lower prices through competition

		D. Treatment choice E. Mitigate against medicine shortages F. Included in the formulary/hospital guidelines G. Others
6	Do you think there are any potential barriers to you in prescribing biosimilar medicines?	A. Yes B. No
7	If your answer is "Yes" for question number 6, select **potential barriers** to you in prescribing biosimilars*(many responses are possible)*	A. Insufficient information on biosimilar medicines B. Shortage of biosimilars in the hospitals i.e. frequently stock out C. Biosimilars are not registered by Ethiopian Food and Drug Authority D. Concern about safety and efficacy of biosimilars E. Biosimilars are not affordable F. Biosimilars are uncovered by health insurance G. Absence of incentives for pharmacists H. Their packaging, dosages and devices are less attractive than reference biological product I. Biosimilars are not included in the hospital standard treatment guideline J. Patient preference

		K. Others
8	If your response for question No 7 is "Shortage of biosimilars in hospital" what are the major reasons for it? (*multiple answers are possible*)	A. Lengthy period of Ethiopian Drug Authority to review drugs B. Lack of communication among stakeholders (hospitals, EPSA, Ethiopian Food and Medicine Authority and manufacturers C. COVID-19 outbreak D. Limited Ethiopian pharmaceutical Supply Agency(EPSA) capacity E. Limited private importers capacity F. Insufficient hospital budget G. Biosimilars are excluded from tenders at hospital level H. Others
9	Have you ever switched reference biological product to its biosimilar medicine or one biosimilar to other equivalent biosimilar medicine?	A. Yes B. No
10	If your answer is "Yes" for question No 9, why you have made the switch? (*please select as many responses as applies to you*)	A. Unavailability of first prescribed biological product B. initially prescribed biological drug is not affordable for patient (cost issue) C. Due to Safety issue of initially prescribed

		D. Due to efficacy issue of initially prescribed E. lack of insurance coverage for initially prescribed biologics F. patient preference G. other reason
11	If your answer is 'No' for question No 9, what are your reasons? (*Multiple answers possible*)	A. Switching is prohibited B. There is no clear legislation on interchangeability of biologics C. Fear of potential loss of clinical efficacy D. Fear of potential for adverse events E. Concern for potential increased risk of immune reaction F. Concern for traceability for post market surveillance G. Others
12	While you prescribe biosimilars, which of the following mostly indicates your behavior? (*Only Single Answer)*	A. Prescribe by their brand name B. prescribe by non-proprietary name(INN) only C. prescribe by non-proprietary name or brand name D. I have never prescribed biosimilars

Section D: Attitude

1. For each of the following statements, please encircle a number which best describe how confident you are **(**5= Totally Confident, 4= Very Confident, 3= Confident Enough, 2= Little Confidence, and 1= Not Confident at all)

		Totally Confident	Very Confident	Confident Enough	Little Confident	Not Confident at all
1	Prescribing the reference biological medicines (brand biological medicines) for patients	5	4	3	2	1
2	Prescribing biosimilar medicines	5	4	3	2	1
3	Confidence in switching a patient from brand biological medicines to biosimilar medicines	5	4	3	2	1
4	Confidence in Ethiopia's medicine regulatory processes during biosimilars registration	5	4	3	2	1

2. For each of the following statements, please encircle a number which best describe the level of your agreement **(5= Strongly Agree (SA); 4= Agree (A); 3= Neutral (Neither agree nor disagree) (N); 2= Disagree (D) and 1= Strongly Disagree (SD)**

		SA	A	N	D	SD
1	Biosimilars are essentially the same as generic drugs	5	4	3	2	1
2	Biosimilars have comparable quality, efficacy and safety profile to that of their innovator brand counterpart	5	4	3	2	1
3	I trust a company highly experienced in manufacturing generic drugs as a producer of biosimilars	5	4	3	2	1
4	Ethiopian Food and Drug Authority is sufficient to evaluate efficacy and safety of biosimilars during approval process	5	4	3	2	1
5	Biosimilars increase patients' access to variety of treatment options	5	4	3	2	1
6	Biosimilar medicines prescription allows reducing healthcare costs	5	4	3	2	1
7	I am comfortable with the use of biosimilar medicine in all indications of its innovator brand	5	4	3	2	1
8	Pharmacists can substitute biologics to a biosimilar drug without the physician's permission	5	4	3	2	1
9	Guideline is needed for both physicians and pharmacists on the biosimilar substitution process.	5	4	3	2	1
10	In prescribing having the rule of designation of a biologic medicine as "dispense as written" or "do not substitute"	5	4	3	2	1

Thank you

Annex X: Questionnaire for Pharmacy Professionals

Section A: Socio demographic characteristics

1	Sex	A. Male B. Female
2	Your age(years):	_____
3	Your current workplace/ department/Unit	_____
4	Your level of qualification	A. Ph.D. in pharmacy B. MSc in pharmacy C. Bachelor's in Pharmacy D. Diploma in pharmacy
5	Please select your area of specialty if you have a Ph.D. or MSc in pharmacy	A. Pharmacologist B. Clinical pharmacist C. Pharmacist in supply chain management D. Pharmacist in pharmaco-epidemiology and social pharmacy E. Regulatory pharmacist F. Other
6	Please, select your years of experience	A. <5 B. 5-9 C. 10-14 D. 15-19 E. 20 and above

Section B: Knowledge

Consider these descriptions of terms while you respond to question number 1 and 4:

- **Very familiar**= able to define appropriately, and aware of approval process
- **Familiar**= able to define appropriately
- **Unfamiliar=** heard the term but unable to describe properly

1	How familiar are you with biological medicines?	A. Very familiar B. Familiar C. Unfamiliar
2	Biological medicines are products of biological origin prepared by recombinant DNA technology	A. Yes B. No C. I don't know
3	The requirements for registration of biological medicines are the same with chemical medicines	A. Yes B. No C. I don't know
4	How familiar are you with the term biosimilar medicines (biosimilars)?	A. Very familiar B. Familiar C. Unfamiliar
5	Biosimilar medicines are similar copy of originator biological medicines	A. Yes B. No C. I don't know
6	Approval of biosimilars requires data demonstrating biosimilarity to the reference biological product which includes analytical, non -clinical and clinical studies	A. Yes B. No C. I don't know
7	Interchangeability is the process of replacing innovator biological medicine to the biosimilars (or vice versa) or between two biosimilars	A. Yes B. No C. I don't know
9	Currently biosimilars are marketed in Ethiopia	A. Yes

		B. No C. I don't know
10	Are biosimilar medicines included in standard treatment guideline of your hospital?	A. Yes B. No C. I don't know
11	Select biosimilar products currently available where you practice (More than one answers possible)	A. Monoclonal antibodies B. Hormones C. Enzymes D. cytokines E. peptides/ protein drugs F. Others G. Not available at all
12	In general, what are your main source(s) of information on biosimilars? (More than one answers possible)	A. Medical scientific literature B. Biosimilar Company C. Pharmacy professional association D. Ethiopian Food and Drug Authority (EFDA) E. Summary of product characteristics/leaflet F. Treatment guideline G. Hospital formulary H. Internet browser

Section C: Practice

1	Have you ever dispensed biologic reference medicine to a patient?	A. Yes B. No
2	If 'No' for question number 1, what could be the reason(s)?	A. Not available in the country B. Not available in our hospital C. Too expensive D. Health insurance doesn't cover biosimilars (similar biotherapeutic product) E. Lack of confidence in safety and efficacy of biosimilars
3	Have you ever dispensed biosimilar medicine to a patient?	A. Yes B. No
4	If your response is "Yes'' for question No.3, how often do you dispense biosimilars?	A. every day B. once a week C. once a month D. once a year
5	If your response is "Yes'' for question No.3, what are the major factors that encourage/motivate you to dispense biosimilars? (*Multiple answers are possible*).	A. More affordable for hospitals B. More affordable for patients C. Lower prices through competition D. Treatment choice E. Mitigate against medicine shortages F. Included in the formulary/hospital guidelines G. Others
6	Do you think there are any potential barriers to you in dispensing biosimilar medicines?	A. Yes B. No

7	If your answer is “Yes” for question No 6, select potential barriers to you in dispensing biosimilars*(Please select as many responses as apply to you*	A. Insufficient information on biosimilar medicines B. Shortage of biosimilars in the hospitals i.e. frequently stock out C. Biosimilars are not registered by Ethiopian Food and Drug Authority D. Concern about their safety and efficacy E. Biosimilars are not affordable F. Biosimilars are uncovered by health insurance G. Absence of incentives for pharmacists H. Their packaging, dosages and devices are less attractive than reference biologicals I. Biosimilars are not included in the hospital standard treatment guideline J. Patient preference

8	If your response for question number 7 is "Shortage of biosimilars in hospital" what are major reasons for it? (*Multiple answers are possible)*	A. Lengthy period of Ethiopian Drug Authority to review drugs B. Lack of communication among stakeholders(hospitals, EPSA, and Ethiopian Food and Medicine Authority C. COVID-19 outbreak D. Limited Ethiopian pharmaceutical Supply Agency(EPSA) capacity E. Limited private importers capacity F. Insufficient hospital budget G. Biosimilars are excluded from tenders at hospital level
9	Have you ever substituted reference biological medicine to its biosimilar medicine or one biosimilar to other equivalent biosimilar medicine?	A. Yes B. No
10	If your answer is 'Yes' for question No 9, why have you substituted? (*please select as many responses as applies to you*	A. Unavailability of first prescribed biological medicine B. Initial prescribed biological product is not affordable for patient (cost issue) C. Due to Safety issue of initially prescribed D. Due to efficacy issue of initially prescribed E. lack of insurance coverage for initially prescribed biologics F. patient preference

11	If your answer is 'No' for question No 9, what are your reasons? (*Multiple answers possible)*	A. Substitution is prohibited B. There is no clear legislation on interchangeability of biologics C. Potential loss of clinical efficacy D. Potential for adverse events E. Potential for increased risk of immune reaction F. Concern for traceability for post market surveillance G. Others
12	In general, while you dispense biosimilars, which of the following mostly indicates your behavior? (Only Single Answer)	A. Record biosimilars in the patient registry book by brand name B. Record biosimilars by nonproprietary name(INN) only C. Record by nonproprietary Plus Suffix of letter designated D. Record biosimilars by nonproprietary name or brand name with batch number E. Totally not record after dispensing F. I have never dispensed biosimilars

Section D:

1. For each of the following statements, please encircle a number which best describe how confident you are (5= Totally Confident, 4= Very Confident, 3= Confident Enough, 2= Little Confidence, and 1= Not Confident at all)

		Totally Confident	Very Confident	Confident Enough(	Little Confidence	Not Confident at all
1	Dispensing the reference biological medicines (brand biological medicines) for patients	5	4	3	2	1
2	Dispensing biosimilar medicines	5	4	3	2	1
3	Confidence in substituting patients from brand biological medicines to biosimilar medicines	5	4	3	2	1
4	Confidence in Ethiopia's medicine regulatory processes during biosimilars registration					

2. For each of the following statements, please encircle a number which best describe the level of your agreement (5= Strongly Agree(SD); 4= Agree(A); 3= Neutral (Neither agree nor disagree)(N); 2= Disagree(D) and 1= Strongly Disagree(SD))

		SA	A	N	D	SD
1	Biosimilars are essentially the same as generic drugs	5	4	3	2	1
2	Biosimilars have comparable quality, efficacy and safety profile to that of their innovator brand counterpart	5	4	3	2	1
3	I trust a company highly experienced in manufacturing generic drugs as a producer of biosimilars	5	4	3	2	1
4	Ethiopian Food and Drug Authority is sufficient to evaluate efficacy and safety of biosimilars during approval process	5	4	3	2	1
5	Biosimilars increase patients' access to variety of treatment options	5	4	3	2	1
6	Biosimilar medicines prescription allows reducing healthcare costs	5	4	3	2	1
7	I am comfortable with the use of biosimilar medicine in all indications of its innovator brand	5	4	3	2	1
8	Pharmacists can substitute biologics to a biosimilar drug without the physician's permission	5	4	3	2	1
9	Guideline is needed for both physicians and pharmacists on the biosimilar substitution process.	5	4	3	2	1
10	In prescribing having the rule of designation of a biologic medicine as "dispense as written" or "do not substitute"	5	4	3	2	1

Thank you!

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Addis Ababa University

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School of Pharmacy
Ethical Review Committee

ቀን Date: August 31, 2021

ቁጥር Ref. No.: ERB/SOP/349/13/2021

To: **Shimelis Aycle**
School of Pharmacy

Re: Ethical Clearance

It is to be recalled that you submitted a research proposal entitled "**Access to Biosimilars in Federal Hospitals in Addis Ababa: Assessment of the National Medicines Regulatory Framework and Healthcare Professionals' Opinion.**" The committee thoroughly reviewed the proposal based on its operational guidelines and found that it fulfills all the ethical requirements stipulated in the guidelines. This is, therefore, to inform you that the proposal is ethically approved for implementation.

With best regards,

Shemsu Umer (PhD)
Chairperson, ERC
School of Pharmacy
College of Health Sciences
Addis Ababa University

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