ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

CENTER FOR INNOVATIVE DRUG DEVELOPMENT AND THERAPEUTIC TRIALS FOR AFRICA

CHALLENGES AND PROSPECTS OF REGIONAL BIOEQUIVALENCE STUDY INITIATIVE IN ETHIOPIA: A QUALITATIVE STUDY

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in Partial Fulfillment of the Requirements for a Degree of Master of Science in Clinical Trials

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Declaration

I, the undersigned, declare that the thesis is my original work and has not been presented for a degree in any other university and that all sources of material in the thesis have been acknowledged.

Declared by Yajeb Melesse

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Approved by Board of Examiners

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External Examiner _____ Signature _____Date_____

Internal Examiner _____Signature _____Date_____

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Abbreviations/Acronyms

AHRI:	Armauer Hansen Research Institute
ANDA:	Abbreviated New Drug Application
ARVs:	Anti-retroviral drugs
BA:	Bioavailability
BE:	Bioequivalence
CDSCO	Central Drugs Standard Control Organization
CDT-AFRICA:	Center for innovative drug development and therapeutic trials for Africa
CRO:	Contract Research Organization
EFDA:	Ethiopian Food and Drug Administration
GCP:	Good Clinical Practice
GLP:	Good Laboratory Practice
MoH:	Ministry of Health
MoI:	Ministry of Industry
NSPA:	National Strategic Plan of Action
RBEC:	Regional Bioequivalence Center
WHO:	World Health Organization

Operational definitions

Bioavailability (BA): The rate and extent to which an active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

Bioequivalence (BE): The absence of a significant difference in the rate and extent to which an active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Brand-name drug: A brand-name drug is a drug marketed under a proprietary, trademark-protected name.

Generic drug: Generic drug is one whose patent protection has expired, and which may be produced by manufacturers other than the innovator company. A generic drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use.

Pharmaceutical equivalents: Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredient(s), have the same dosage form and route of administration, and are identical in strength or concentration.

Pharmaceutical alternatives: These are drug products that contain the same active moiety but contain different chemical forms such as esters or salts of the active moiety or they may differ from the innovator's product in the dosage form or strength.

Reference /comparator product: The comparator product is a pharmaceutical product with which a multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established.

Abstract

Background: *Evaluation of the interchangeability of multi-source generic drug products or bioequivalence study has become a crucial activity since the share of generic medicines in healthcare has enormously grown over the past few decades. Among four East African Countries, namely, Ethiopia, Kenya, Uganda and Tanzania, there has been an initiative to establish an accessible and affordable BE center for the regional pharmaceutical manufacturers. This study aims at assessing the challenges and prospects of the bioequivalence center initiative in Ethiopia.*

Methods*: In-depth interview was conducted with individuals who were Ethiopian affiliates of the Regional Bioequivalence initiative; local pharmaceutical manufacturers, Ethiopian Food and Drug Administration, Regional Bioequivalence Center and other key stakeholders who are involved in the center capacity building. Data were collected using digital voice recorders, and transcribed. These data were analyzed using an inductive thematic analysis using Nvivo software and the findings were presented in narratives using the respondent's own words as illustrations.*

Results*: Based on the findings, four major themes, one as an opportunity and three as challenges, were identified. The mere presence of the Regional Bioequivalence Center by itself was considered as an opportunity by most of the participants. In addition, a number of favorable conditions including awareness and demand for product quality and diversity, the presence of attractive incentive packages for local pharmaceutical manufacturers and the proliferation of the generic medicines market in the region were mentioned as opportunities. On the other hand, lack of resources and stakeholders' commitment as well as lack of regulatory enforcement were identified as challenges.*

Conclusions*: The Bioequivalence center initiative has not functioned well as initially planned. The findings of this study suggest the need for government and key stakeholders to actively engage in the program to make the initiative viable. The significance of supporting this initiative could positively contribute to the creation of a competitive local manufacturing sector that will engage in the production of therapeutically interchangeable generic products and ultimately safeguard the health of the society at large.*

Keywords: Bioavailability, Bioequivalence, Generic drugs, Ethiopia

1. Introduction

1.1 Background of the study

The concept of bioavailability (BA) and bioequivalence (BE) have been recognized globally by the pharmaceutical industry and national regulatory authorities for over 30 years and are applied to new brand name drugs as well as generic products (Midha, 2009). Based on this central idea, thousands of high-quality generic drug products have become available at much-reduced costs in every corner of the world.

As per the World Health Organization (WHO), two pharmaceutical products are bioequivalent "if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailability, in terms of rate (described in terms of peak plasma concentration (C_{max}) and time for peak plasma concentration (T_{max})) and extent of absorption (area under the plasma drug concentration-time curve (AUC)), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same" (WHO, 2016). Thus, the BE study provides indirect evidence of the efficacy and safety of multi-source (generic) pharmaceutical products. Accordingly, it should be conducted by fulfilling the minimum standards outlined by the WHO (Hammami, 2017).

A generic drug is defined as "a drug product that is comparable to brand/innovator drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use. It has also been defined as a term indicating to any drug marketed under its chemical name without promotion (Sindhuja, 2018).

In the United States, generic drugs have a market share of more than 65% of the global market and account for 80% of prescriptions filled but for less than 18% of the cost (Cristancho, 2015). Thus, because of the importance of generic drugs in health care, the pharmaceutical quality, safety, and efficacy of generics should be reliably compared with the corresponding innovator or brand-name drugs (Mastan, 2011).

While there is a burden of disease in most developing countries, to reduce the cost of medicines to both governments and patients, their pharmaceutical policies encourage the use of generic drug products, which are therapeutic equivalents to the innovator or brand-name drugs (Moran, 2011).

According to WHO, the standard for approval of a multisource generic medicine is based on the demonstration of interchangeability or therapeutic equivalence to the innovator through bioequivalence studies (WHO, 2016).

However, the assessment of BE is not a simple issue for most African countries. According to previous studies, local manufacturers need to improve the quality of products and have to show the efficacy and safety of the generic products to access a broader market (Kaplan, 2016). But, the cheapest BE centers in South Africa and India have a cost of around $50,000 per study. These prices are too high for comparatively small local companies, and thus they need to have access to affordable BE center.

To address this problem, with the help of the German Ministry of Economic Cooperation and Development, Capacity Building Program of GIZ, the Regional Bioequivalence Center (RBEC) in Ethiopia was established in 2012 aiming to serve Ethiopia, Kenya, Tanzania and Uganda. Concurrently, the bioequivalence clinical center at AHRI was established in September 2013 as a clinical affiliate to the Regional Bioequivalence Center. RBEC aims at having a locally accessible, GCP/GLP compliant and WHO qualified BE testing center in East Africa.

The RBEC was started under public-private partnership model. This model was chosen to be realistic as an initial investment are not required for premises and buildings. Thus, from public wing Addis Ababa University, School of Pharmacy and from private side four pharmaceutical companies from member countries were the partners. In addition to this, the center was assumed to be independent in its decision and financially autonomous after two years of establishment.

While the center was led by the board and to overview centers' activity steering committee was formed with private sector representation from participating companies in the region, the public sector Addis Ababa University, School of Pharmacy and other key stakeholders.

Currently, in Ethiopia, there are 24 plants (small and large scale) involved in the manufacturing of pharmaceuticals and related products of which only 10 are manufacturers of generic finished pharmaceutical dosage forms whose local market share is around 15% (Alemayehu, 2018). In Ethiopia around one-hundred and twenty generic drugs are manufactured and most of these products are solid oral dosage forms, which requires bioequivalence testing. So, strengthening this bioequivalence center initiative is important for several reasons. First, it brings quality prod-

uct into the health system. Second, it helps to comply the local products in a diverse market authorization requirement for different countries and raises generic market access. Finally, it might promote local production of new off-patented generic products corresponding to the national essential medicines list. Therefore, this study deals with the challenges and prospects of bioequivalence center initiative in Ethiopia since the national drug registration guideline shows that bioequivalence study is a requirement for generic products registration under module five 5.1.3 (FMHACA, 2014).

1.2 Statement of the problem

Based on the literature, many pharmaceutical manufacturers in Africa are facing various problems in relation to conducting bioequivalence studies (Sultan 2016). Among these, lack of access to research organization, lack of capacity to conduct the clinical studies and low production capacity of the local manufacturers are frequently mentioned (Kaplan, 2016). To address this problem, four East African countries adopted an initiative for the establishment of an affordable and accessible Regional Bioequivalence Center with the financial and technical support of the German Federal Enterprise for International Cooperation (GIZ) capacity building program. In 2012, RBEC was established in Ethiopia. After the GIZ capacity building program has been terminated, RBEC was supported by WHO and USP/PQM.

The center was established eight years ago and some pilot and pivotal studies were conducted. This center has been in progress and awaiting WHO prequalification. But some limitation existed in relation to conducting commercial studies to generate income and ensure its sustainability. Therefore, it was necessary to examine the challenges and prospects of the bioequivalence center initiative in Ethiopia.

1.3 Significance of the study

Generic drug products are the main source of essential medicines in Ethiopia. Ensuring bioequivalent generic drug products is central to the national drug policy (Health, 1993). More than 80 percent of essential drugs are imported and the remaining 15 percent is supplied by local manufacturers (Alemayehu, 2018). Accordingly, for the product registration of those imported and locally manufactured generic products, bioequivalence study data is a requirement.

Therefore, this study will be beneficial to all local pharmaceutical companies as it will open up the avenue for the implementation of bioequivalence studies for their generic products which would have a multitude of benefits to patients, the public and the economy. More importantly, the outcome of this study will help policymakers within the public sector and stakeholders in the public and private sectors to identify the challenges as well as the opportunities of establishing the RBEC in Ethiopia that would help to provide support for the initiative.

1.4 The Objectives of the study

1.4.1 The General objective of the study

To assess the challenges and prospects of the bioequivalence center initiative in Ethiopia

1.4.2 Specific objectives

- To identify existing challenges in the bioequivalence center initiative

To outline the prospects of the bioequivalence center initiative

1.5 Conceptual framework

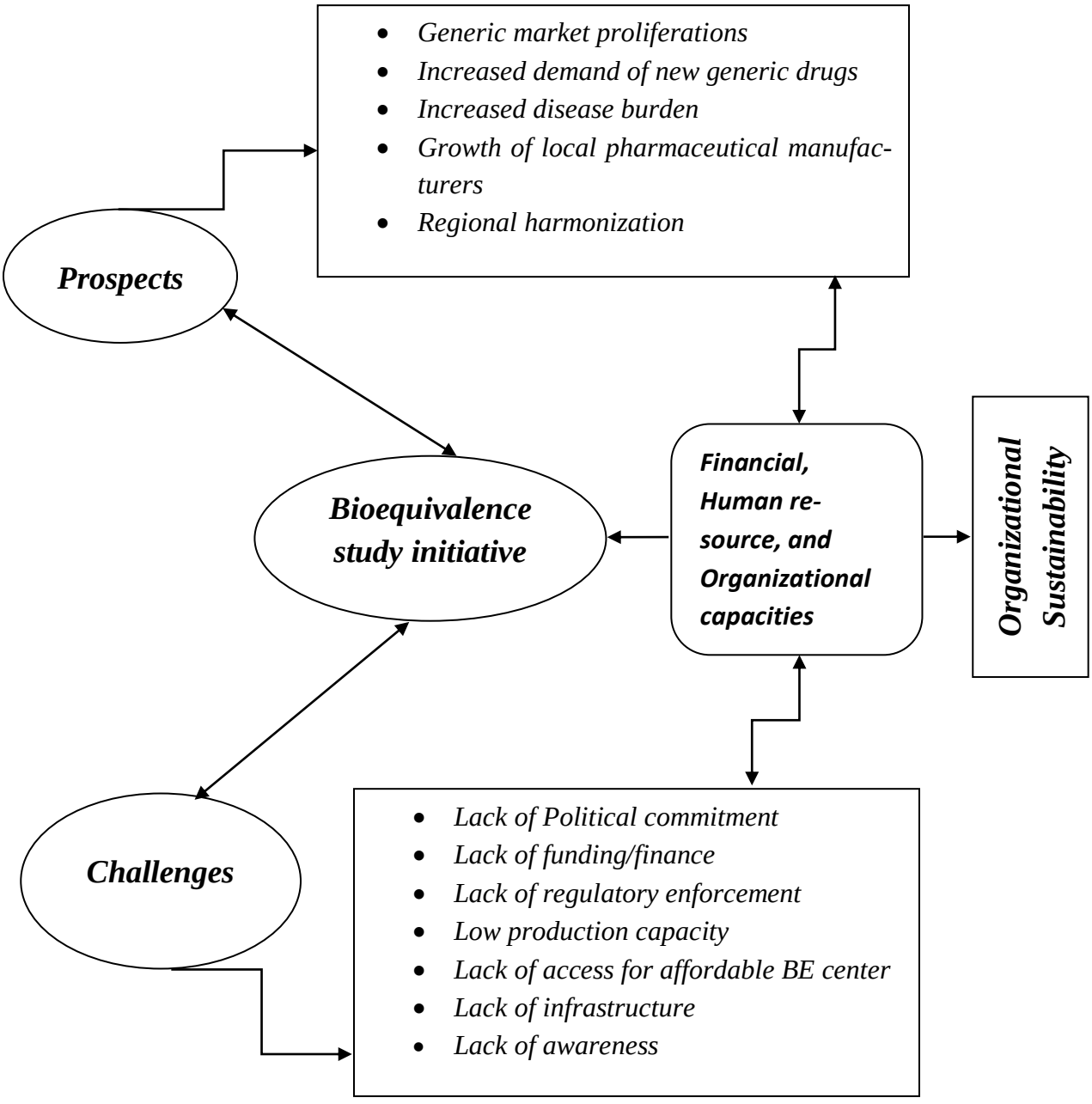

Figure 1: Conceptual framework of the challenges and prospects of bioequivalence center initiative.

2. Literature Review

2.1. History of the bioequivalence study

In the late 1960s, the "United States Food and Drug Administration" (FDA) became concerned regarding the equivalent therapeutic quality of generic drugs that had been approved under existing approaches for assessing bioequivalence. During this period, both the scientific community and the regulatory authority were continuing efforts to understand and establish valid approaches to the assessment of BE. At the time, the Office of Technology Assessment (OTA) established a drug bioequivalence study panel to realize the chemical and therapeutic equivalence relationships of drug products (Midha, 2009).

Preceding to Hatch Waxman Act enforcement in 1984, generic drugs were approved based on scientific literature since data to support safety and efficacy of the product was already filed by the innovator company. However, most of the innovator products apart from antibiotics were not exposed to this data filing requirement. Since the generic drugs have been marketed, the regulatory body enforced different legislations to ensure that the integrity and safety of drug products was assured. Lastly, the bioequivalence study panel confirmed the difference between chemical and biological availability and provided recommendation to the FDA on the BA/BE report to be part of regulatory and drug development requirements (Boehma, 2013).

Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act) was one of the essential regulations passed by US Congress and it helped to maintain balance between generic and brand drug manufacturers. It was fundamental in further defining manufacturing procedures and ensuring healthy competition for generic prescriptions. Thus, list of approved drug products was available with therapeutic equivalence evaluation and potentially benefiting other countries wishing to start generic drug industry (Sindhuja, 2018).

As a result of the passage of the Hatch-Waxman Act, generic drug companies rushed to develop products and gain first approval for certain products since this act granted 180 days marketing exclusivity. Due to this competition, some fraud was committed. FDA and some generic companies acted aggressively to prevent this fraud and enforced penalty measures. Besides, several different product specific and general guidelines were published by the regulatory body for the industry on conducting BA/BE studies and generic drug approval was allowed on the bases of bioequivalence data. Further-

more, statistical guidance to document BE for generic drug products' marketing approval were developed. Similarly, new drug patent term restoration which is the time lost during clinical development and regulatory review up to maximum of five years extension after patent expiry were initiated (Midha, 2009).

In the United States and Europe, the use of generic medicines has been generally supported by a series of policies promoting their utilization and these policies have been subject to monitoring and evaluation. It is far less clear which policies should be enacted by low- and middle-income countries (LMICs) interested in lowering their health care costs by increasing therapeutically equivalent generic medicines' utilization (Kaplan, 2016).

Subsequently, middle-income countries like India are known producer of generic drug products which accounts for 20% of global exports in terms of volume as well as domestic market and have an experience of conducting bioequivalence studies with little limitation in the uniformity of the infrastructure throughout the country (Dan, 2018).

Through time, different approaches to determine BE of pharmaceutical products have been largely standardized. This has occurred due to discussion and consensus among various stakeholders at numerous national and international meetings, conferences, and workshops to facilitate product registration across the globe (Dunne, 2013).

However, in many African countries, the demonstration of interchangeability remains nonexistent or is not fully enforced. Similarly, the majority of pharmaceutical manufacturers in these countries are inexperienced in conducting bioequivalence studies to the required regulatory standard (Kaushal, 2016).

2.2 Current landscape of bioequivalence in LMICs

Currently, the combination of economic growth and the prevalence of diseases is driving demand for medicines across Africa. As the pharmaceutical industries throughout the world are moving ahead to become more and more competitive, ensuring product quality towards the international standard has become compulsory (Juhi, 2018).

From the continent, South Africa has more advanced clinical research infrastructure including bioequivalence study centers. In addition, there is adequate regulatory capacity in line with the best international medicines regulatory practice (Senthil 2015).

Recently, two North African countries, Egypt and Morocco, established bioequivalence study centers. On the other hand, the majority of manufacturers in west Africa and the Sub-Saharan Africa produce a limited range of products and bioequivalence studies are almost non-existent (Kaplan, 2016).

Some LMICs health systems require incentives to ensure that generic medicines are of assured quality. Variations in price and availability have a great impact on the affordability of medicines, particularly for the poor and disadvantaged who mostly pay out-of-pocket. Increasing the accessibility of therapeutically equivalent generic medicines is not a simple task, neither from the perspective of the generic medicine's manufacturers, nor from the health system itself (Cristancho, 2015).

Even though generics in China are sold at a better price, they are not always as reliable and effective as the respective global innovator drugs. In response to data fraud findings in 2015 and 2016, the China Food and Drug Administration (CFDA) has insisted that its approved generic drugs be retested. Citizens need to be reassured that these generics are just as good as the innovator drugs and anyone using false data will be criminally punished. Currently, generic companies are being required to conduct new bioequivalence (BE) tests, and therefore there is a significant rise in BE trial activities (Davidson, 2017).

India amended the Drugs and Cosmetics Rules, 1945 via GSR-327(E) on 3rd April 2017, which mandates the Indian drug manufacturers to submit the result of the bioequivalence study for obtaining the license from the Indian Central Drugs Standard Control Organization (CDSCO) for drugs categorized as biopharmaceutical classification system class-II and IV. This amendment has been incorporated into a clause regarding the required documents dossier of BE study center for CDSCO registration. Meanwhile, the country has experienced numerous cases of falsification of data, breaches of confidentiality, violation of existing rules and regulations under various pressures. Thus, an amendment was made in this rule to ensure the credibility of the generated

data; meanwhile, CDSCO approved 82 bioequivalence study centers as of May 2018 (Dan, 2018).

2.3 Challenges of bioequivalence study initiatives

In low and middle-income countries (LMICs), there are local manufacturers most of whom cannot carry out bioequivalence studies. Therefore, access to a contract research organization is critical since these studies may require access to the proper reference product, the capacity to carry out studies in healthy humans that compare the proposed generic product with the reference as well as finding reliable analytical sites (Semde, 2012).

Bioequivalence requirements also generate extra cost for the generic manufacturers. In addition, local manufacturers are facing problems in finding affordable centers to conduct BE studies. Also available centers offering such a service are limited and hence the number of studies conducted by these centers per year is not able to meet demands. Moreover, there are also instances where a generic product has better bioavailability compared to the innovator (above the confidence interval of 0.80- 1.25), and thus fails to meet the BE criteria. In some cases, better bioavailability above the limit might lead to unwanted effect of the drug such as toxicity. Due to the above reasons, some smaller generic companies have stopped producing drug products that require BE testing, especially when their market share is small (Hanuja, 2016).

Apart from stressing the need for systematic quality and safety assessments for pharmaceutical products to achieve bioequivalence, the quality of pharmaceutical products available in the market in many developing countries varies, in part because of the lack of clear and specific requirements for generic pharmaceutical products (Davit, 2013).

Generally, in LMICs there are technical and financial challenges including deficiencies in human specialized skill, poor physical and managerial research platform, lack of contract research organizations and bioequivalence centers, lack of strong policy implementation and evaluation system (Kaplan, 2016).

Ensuring the accessibility of safe, effective and affordable generic products is a national responsibility. Registration of generic products and generic substitution policies are closely evaluated in

high-income countries, but are still under development in low- and middle-income countries (Tamboli, 2010).

WHO is providing norms and standards for medicines' quality assurance in member states, including resource-constrained countries. However, in many countries, the demonstration of interchangeability remains non-existent or is not fully enforced. Likewise, some pharmaceutical manufacturers in these countries are inexperienced in performing bioequivalence studies to the required regulatory standards (Gwaza, 2016).

2.4 Prospects of bioequivalence study initiatives

Generic products' compliance with BE requirement has led to an increase in the quality of healthcare products and increasing the export competitiveness of country-specific manufactured pharmaceuticals. This is evidenced by the increasing ability of developing countries' pharmaceutical products to be registered by regulatory bodies in many countries. It has also supported to increase the confidence of consumers about to their quality and efficacy (Pankaj, 2013).

Besides the large and diverse populations, LMICs have a large pool of pharmacists, scientists and engineers who have the potential to steer the pharmaceutical industry to a higher level. In the recent past, numerous discrepancies were brought into public and government notice which compelled them to become strict and frame stringent regulations for the testing of new drugs in these countries. As a result, pharmaceutical companies in various developed nations have moved their research to developing nations (Burt, 2014).

3. Methods

3.1 Study Design and Setting

In this study, we have employed a qualitative descriptive study design. This study design is suitable method to understand the participants' perspectives and experiences to provide insight and to build a sufficient dataset to look for emerging themes. This qualitative research assessed the challenges and prospects of regional bioequivalence study initiatives in Ethiopia. The study was conducted using an in-depth interview with key informants from the national regulatory authority, local pharmaceutical manufacturers, the Ministry of Health and the Regional Bioequivalence Center as well as other key stakeholders responsible for the availability and accessibility of essential medicines in Ethiopia.

The study was conducted in Ethiopia; it has a federal government structure with ten regional states and two autonomous cities. The total estimated population is around one hundred and ten million. The idea of RBEC was initiated in 2008 and the center was inaugurated in 2012 with the support of the Engineering Capacity Building Project (ECBP) of the GIZ, Germany. After the establishment of the center, pilot and pivotal BE studies have been conducted on generic products of regional and local manufacturers in comparison with the respective brand products. All the pilot and pivotal studies have been successfully completed with acceptable standards.

3.2 Eligibility criteria

- Individuals who were willing to participate in the study and gave informed consent;
- Individuals who were involved or being involved in the bioequivalence center initiative;
- Professionals in key health sector entities who are responsible for the availability and affordability of safe and effective drug products to the public;
- National regulatory authority professionals, who are responsible for policy enforcement;
- Senior professionals working in local pharmaceutical manufacturers;
- Professionals in Non-Governmental Organizations, who have provided support for the initiative and providing support to the RBEC; and
- Academicians working at the School of Pharmacy, Addis Ababa University.

3.3 Recruitment of participants

Study participants were purposively selected from different organizations based on their experience and involvement in the initiative. These professionals were experienced in the area and most of them had an involvement in the initiative and they could articulate their experiences as it relates to the challenges and prospects of the bioequivalence center initiative in the country. In the study, professionals who were members of the initiative and familiar with the practice, professionals who are currently involved in the bioequivalence study-related activities, key policy-makers, and academicians, local pharmaceutical manufacturers which are considered as immediate users of the center, Non-Governmental Organizations that have provided support for the initiative and who fulfilled the eligibility criteria were recruited.

At the time of participant recruitment, we contacted the management of respective organizations by explaining the purpose of the study. After getting permission from the organization, we communicated most of the participants in person and some of them only via telephone because of the restrictions imposed by the COVID-19 pandemic. Then, information sheets and informed consent forms were provided to them and the objective of the study was explained to the participants prior to the interview, and confidentiality of their identities was ensured. Before the interview, the researcher asked the participants to sign a consent form and completed relevant demographic data and also sought and got permission from the participants to be audio recorded. Each participant was given a code number and recorded to match up with the transcript of the interview afterward.

Among 7 local pharmaceutical manufacturers that are engaged in the manufacturing of oral dosage forms which may require bioequivalence study and were eligible for this study, four were not willing to participate in the study. Two participants from different organizations provided informed consent, but did not consent to the use of digital recorders. The researcher was able to take their detailed responses using field notes. All other participants participated in the study with full consent.

3.4 Data collection and analysis

Data collection was conducted from January 14/2020 to May 21/2020. Each interviewee was assigned a unique identifying code. This code was written on the notes taken, and was used to name audio files and transcript documents. So, notes were taken using participant code number, and this unique identifier was used to keep confidentiality at the time of transcription and referencing quotations. All recorded and written documents were presented only with the participants' codes, not the participants' names. Each interview lasted on average for 60 min. All paper and soft copies of field notes, audio files, and any other notes were kept in a password-protected computer.

Audio recordings were listened to carefully and then transcribed into word in the language of the interview (English). All typed records were kept in password-protected computers and a password-protected back-up drive. This included a summary of data describing the participant's demographic characteristics, and other key information to locate the discussion. This included word-for-word transcriptions, recordings of all hesitations, pauses, expressions, and incomplete sentences. The transcriptions were proof-read against the audio files by the independent researcher to check for accuracy and to identify any missed or misheard words and to clarify any areas of confusion or unclear terminology.

Data files were imported into NVivo software to be used for the study, where all transcriptions, demographic data summaries, and audio files were filed. Following the coding process, themes and sub-themes were developed from the interview transcripts. Transcripts were coded line-by-line, and then developed into themes and sub-themes by grouping similar ideas together. The themes were further refined to reflect any new emerging ideas and in line with the objective of the study. The on-going analysis was characterized by frequently going back to the original transcripts to ensure that text is coded within context.

Coding was conducted by reading the data line by line, trying to identify the underlying meaning or concepts behind the statement in each line, or few lines, and labeling according to the ideas in the transcript, using a short title to create a new tree node in the software. When the same idea appears again, this was coded to the same node, creating a list of repeating ideas. As coding develops and themes emerge, nodes were arranged in groups under a parent node labeled with the

theme. The codes were updated as new ideas, themes and sub-themes emerged. Once all transcripts had been coded, the coding tree containing repeating idea nodes, theme nodes, and some sub-theme nodes were analyzed.

3.5 Ethical issues

The study was approved by the "CDT-Africa Scientific and Ethics Review Committee" College of Health Sciences, Addis Ababa University (Approval number: CDT/077/20). We obtained written informed consent and permission from participants for audio recordings before each interview.

4. Results

4.1 Socio-demographic characteristics of study participants

The study involved a total of 15 participants in the interview: three from local pharmaceutical manufacturers, three from Ethiopian food and drug administration, three from the School of Pharmacy of Addis Ababa University, two from the Regional Bioequivalence Center, and four from other key stakeholders. Of the total participants, 3 were female. Two participants had PhD, while three participants were PhD candidates, nine of them had Masters' degrees and one had a bachelor's degree. The data collection was stopped when the data saturation was reached.

The findings by sub-groups or from different organizations have been integrated within each theme and presented as a whole. However, particular differences identified between participants are explained under each theme as appropriate.

Table 1: Demographic characteristics of study participants

Sex	Profession	N of study participants	Academic level	Responsibility	Experience
M	DVM	1	PhD Candidate	Bioequivalence Principal Investigator	>5 years
F	Pharmacist	2	MSc	Plant Manager Team leader	>10 years >5 years
F	Pharmacist, Biochemist	1	MSc	General Manager	>1 year
M	Chemist	1	PhD Candidate	Quality Manager	>5 years
M	Pharmacist	6	MSc	Project/Plant Manager Team leader/Advisor Program manager	>10 years >5 years >10 years
M	Pharmacist	2	PhD	Academic	>10years
M	Pharmacist	1	PhD Candidate	Academic	>5years
M	Pharmacist	1	BPharm	Expert	2-5years

4.2 Thematic analysis

Based on thematic analysis, four major themes, one as a prospect and three as challenges were identified:

1. Prospects of the bioequivalence center initiative
   - Theme one: The presence of a conducive environment to conduct BE studies
     - Availability of RBEC
     - Awareness and demand for product quality and diversity
     - Government incentives for the local pharmaceutical manufacturers
     - Generic market proliferation
     - Regional harmonization
     - National Pharmaceutical manufacturing strategic plan of action targets
2. Challenges of the bioequivalence center initiative
   - Theme two: Stakeholders' involvement and limitations in the initiative's activity
     - Lack of Stakeholders' involvement and integration
     - Limitations in the initiative's activity
   - Theme three: National regulatory policy enforcement and international standards
     - Lack of national regulatory policy enforcement
     - Failure to meet international standards
   - Theme four: Institutional organization, modelling, infrastructure and setting
     - Lack of clear institutional organization
     - Lack of business model
     - Lack of competitive infrastructure / Facility, Skilled Human Power and Equipment
     - Separate placement of the facilities
     - Lack of marketing capacity
     - Lack of finance

4.3 Prospects of the bioequivalence study initiative

4.3.1 The presence of conducive environment to conduct BE studies

4.3.1.1 Availability of RBEC

All participants agreed on the significance of the availability of a BE center in general. It might ensure the large public affordable, safe and effective generic medicines option as effective as the imported expensive innovator medicines. Currently, this center has been operating with certain limitations. But some opportunities may demand this service and the presence of a strong viable center will be one of the inputs to strengthen the local pharmaceutical manufacturing sector.

> *"… There is a center established to conduct BE studies at an affordable price when compared to BE centers elsewhere. Even though they are limited, some people are trained on the general aspects of bioequivalence study and these persons are mostly committed so there is knowhow and the technology are already available." (CPBI-002)*

Some participants pointed out that the mere presence of the BE study center is not enough. What is more important is having a strong and viable center because of various pushing factors in the country as well as in the region.

> *"…Currently, overall global generic market, particularly African market, is more than 60% of the pharmaceutical supply from the generic industry which means there is an increasing demand in generic supply that requires rigorous quality control. One of the quality tests that is required for specific molecules is BE study. In that regard, having a competent standard BE center that can provide accessible and affordable BE service to the local and regional manufacturers might generate huge market for the local and regional generic medicine manufacturers" (CPBI-001)*

In addition to the accessibility of affordable BE study centers, some participants noted that local pharmaceutical manufacturers can have extra services, for example, technical guidance and other analytical laboratory tests by those experienced professionals and validated methods from the BE center. Together, key stakeholder's strong engagement and all-rounded support to the regional bioequivalence center are seen as creating a strong functional testing center that ensures public health care.

Development of local pharmaceutical manufacturing is the priority area of the government policy and correspondingly that might create BE center demand by the local manufacturers in the country. Hence, such policy measures have facilitating role for the availability of standard BE center. As mentioned by few participants, this priority development area, as a developing country and having an infant pharmaceutical manufacturing sector, availing strong support and creating a base for strong quality infrastructure by the government is important to confirm overall development.

> *"… BE service can support the local manufacturers while providing a standardized accessible and affordable services and that promotes the local investment for the export market in addition to local and regional supply. Thus, we do have an opportunity because the market is large and the industry is growing" (CPBI-010)*

> *"… The country has an ambitious manufacturing plan. The plan requires a well-functioning and strong BE center. As BE studies are expensive, it would be a barrier for local manufacturers. Thus, the government, as well as the manufacturers, should provide support to make the center functional*" *(CPBI-009)*

Some participants thought that the availability of a functional BE center in the country and the implementation of BE data requirements for product registration may put additional cost on the local manufacturers. However, most respondents reported that getting this service nearby and doing BE test for the product at affordable price is an opportunity for the local firms to be competent in any market.

It was also indicated that the BE center could be a good opportunity to generate hard currency for the country. It is not just only the manufacturing industry, but also the BE center that would be used to generate and save much-needed foreign currency.

> *"…if you consider Africa and the Middle East in general, we do have the service from South Africa and Egypt …, as long as we can kickoff and we can fulfill the minimum requirements, we can provide that service to the region as well as the Middle East and Europe market" (CPBI-001)*

There is an assumption of having a full-operational BE center in the country and also expectations from the center to do commercial studies in full-capacity.

> *"…the government needs to seriously look into this and either work towards restructuring or reforming the current BE center or establishing new one. So, it will become full-fledged BE center and can conduct BE studies" (CPBI-013)*

4.2.1.2 Awareness and demand for product quality and diversity

When we are claiming supply of safe, effective and quality generic products, it usually implies testing the interchangeability or the BE of the product against the innovator. Confirming interchangeability is primarily a regulatory requirement for the product registration and it will also add consumer's confidence towards their product quality. Even though BE testing is not the only parameter to ensure quality, it gives much more trust and evidence than the *in vitro* testing that we routinely conduct.

> *"…awareness of quality product consumption is increasing. In my opinion, individuals are informed and attention to their health service is advancing". (CPBI-012)*

> *"… you know consumers have real concerns. They have concerns that the medicines which are available to them especially from generic manufacturers are not of good quality. I think this is very much important as we are in an epidemiological transition and more and more people are becoming chronic patients with cardiovascular, endocrinology and related problems and they are not that much confident about the generic products" (CPBI-011)*

Many of the study participants felt that there is a need for diversified products to address the high burden of health problems that are prevalent in Ethiopia and sub-Saharan Africa. Besides, the local pharmaceutical manufacturing has limitations in the supply of new off patented generic products aligning with the National Essential Medicines List.

> *"… We have limited generic products and old molecules manufactured locally.… And, most of the society can't afford brand products. So, we have to avail quality generic products in line with disease prevalence in the country" (CPBI-013)*

Similarly, some of the participants believed that any medicines produced locally or imported from abroad must fulfill minimum requirements for quality, safety and efficacy. The ultimate goal should be ensuring the availability of quality treatments for the society.

> *"… any medicine, be it produced locally or imported from overseas, must fulfill minimum requirements for quality. There is no excuse for not fulfilling the minimum requirements. … the manufacturers who produce these medicines must fulfill the minimum GMP requirements and the products produced must also fulfill minimum requirements; one of which is being bioequivalent … This is not a requirement that is open for negotiation; it is mandatory." (CPBI-013)*

> *"… Regarding the national drug registration process, there shouldn't be a double standard. The regulatory body in our country requires a bioequivalence study report for the registration of imported products. The same should work for local companies because the products are ultimately going to the population. … We are talking about medicines they should fulfill three requirements: safety, efficacy and quality. In vitro release studies might be indicative but can never substitute BE studies" (CPBI-002)*

On the other hand, the regulatory authority is attempting to balance access and ensuring the safety, efficacy and quality of locally manufactured products. Even though the few local manufacturers are weak in their production and financial capacity, the regulatory authority has been pushing them to come up with the full registration requirements by giving them a grace period to build their capacities.

> *"In pharmaceutical products, accessibility should incorporate quality components. There is a quotation in dispensing that says 'don't dispense the medicine that you wouldn't take'. Generally, health system thinking doesn't support accessibility with compromised quality" (CPBI-015)*

The majority of participants pointed out that since the regulatory authority is lenient and gives room for capacity building, the local manufacturers might care more about their product range and their production capacities instead of carrying additional burden like conducting BE studies on their products as far as they don't have a local market problem.

Some participants assumed that in addition to maximizing customer's awareness, big companies with better financial capacity are investing in Ethiopia and they might supply bioequivalent generic products to the market at reasonable prices. If and when this happens, those products that have poor quality will be out of the market.

4.2.1.3 Government incentives for the local pharmaceutical manufacturers

The government has given priority to the pharmaceutical manufacturing sector in its Grand Transformation Plans and has developed a10 years National Strategic Plan of Action (NSPA) (MoH&MoI, 2015). In the NSPA, attractive investment incentive packages have been proposed for those investing in the sector.

Some respondents felt that strong support and favorable policy environment for local pharmaceutical manufacturing including the incentive packages, price preferences and tax exemptions are stimulating factors for the implementation of the BE center initiative.

> *"…Ethiopia is investing a lot in this (pharmaceutical) sector development. We can see the 10 years strategic plan of action. It is expected to be a pharmaceutical manufacturing hub. This may lead to generic production. For this reason, BE center will be demanded and this can be considered as an opportunity in the near future" (CPBI-014)*

> *"…Yes, the Ethiopian government, I think, has taken a huge step forward and political commitment to build local manufacturers' capacity in medicines production and the national strategic plan of action is evidence for this. Following that, there are a lot of incentive packages available for investors; the government has gone extra steps to attract investment in the sector" (CPBI-013)*

4.2.1.4 Generic market proliferation

Another remarkable opportunity mentioned by some participants to strengthen BE study center in Ethiopia is the generic market growth in the region. We don't have pre-qualified products that are locally manufactured yet and this pre-qualification is a requirement to export our products to the international market even to the regional market. So, this pre-qualification usually means that the product has to be ensured to be bioequivalent to the innovator products.

"*…most products manufactured in Ethiopia are generic solid dosage forms which require BE study. So there is a great market not only for Ethiopia but also for the Sub-Saharan Africa region.". (CPBI-002)*

Moreover, regional trade agreements such as Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) were mentioned as a trade-related advantage. This agreement is very essential and contains provisions that allow a degree of flexibility for the country to enter into the regional market and continental market but the country's capacity has to be strengthened before the TRIPS agreement coming into force. Our generic manufacturers need to prove that their products are bioequivalent to the innovator products. This agreement allows for member states a certain degree of freedom in modifying their regulation and requires to ensure minimum standards for the various rights. Some participants reported that the main concern is to prove this requirement for the local pharmaceutical manufacturers.

4.2.1.5 Regional harmonization

We have to make our local products ready for regional competition by meeting the required international standards. According to some participants, the regional regulatory harmonization could be realized very soon. Moreover, the inter-continental free trade agreement will soon be reached and this is expected to create a big market for the country.

The realization of this inter-continental free trade agreement is also expected to enhance competitiveness at the industry level through the exploitation of opportunities by creating a single continental market for products with free movement for better production and reallocation of resources.

"…Regional harmonization is on the way so we have to strengthen our capacity before it is realized. Because the member countries should follow the same requirement and this BE data is the minimum and critical standard, it should be mandatory for all countries. So, we have to think in larger scope" (CPBI-014)

"…There are regional and global initiatives. For instance, the regulatory harmonization, regulatory convergence issues are coming and the country is ratifying the inter-continental free trade agreement. Thus, we have to use this opportunity. If we are not

able to enforce such a very important requirement of the market, at least to East African market, this country will be just a damping site for others". (CPBI-010)

4.2.1.6 National Pharmaceutical manufacturing strategic plan targets

The study participants consider the national strategic plan of action for the pharmaceutical manufacturing development as a huge move by the government to support the pharmaceutical manufacturing sector. Accordingly, the objectives of this strategic plan of action take for all- rounded development includes creating a research and development platform to fulfill the main objective, i.e., to ensure access to safe, effective and quality product.

"…if we build local manufacturing capacity, there will be a huge demand for BE study and most importantly, the national strategic plan of action is aspiring for 50% of products to be exported. For export, BE study is mandatory. To conduct BE study, manufacturers should conduct these studies at reasonable prices. Having this is not only a resource for Ethiopia but also for all African countries, especially to East Africa. If we manage and develop it properly, it can be the source of income." (CPBI-013)

"…as part of this 10 years plan to strengthen local pharmaceutical manufacturing, the government should appreciate the role that the regional bioequivalence center can play towards meeting the quality objectives. Thus, it should be supported further by fulfilling all the required facilities, personnel and other requirements.…This is because having such BE tests would cost much more money if we do the test, for example, in South Africa or Egypt or other places." (CPBI-011)

4.3 Challenges of the Bioequivalence Study Initiative

4.3.1 Stakeholder's involvement and limitations in the initiative's activities

4.3.1.1 Lack of Stakeholders' involvement and integration

The Regional Bioequivalence Center was a joint initiative among four countries, namely, Kenya, Uganda, Tanzania and Ethiopia, and it was supported primarily by GIZ and was planned to serve the East African Region. The interviewed participants believed that the RBEC initiative was a grand initiative but key stakeholders including government institutions lost their interests and commitments through time.

"…*There was a competition regarding where to set up the center among the East African countries, i.e., Kenya, Tanzania Uganda and Ethiopia. After considering different criteria, I think the consultants have decided to place it in Ethiopia. This was largely because of the political commitment of the Ethiopian government to give support for the initiative*" (*CPBI-001*)

"…I think they (shareholders) were very active at the beginning but later on, lost their momentum. This could have partly contributed to the failure of the center because they contributed their shares as expected initially. However, after that, meetings and other things (financial contributions) were halted" (*CPBI-002*)

Moreover, key stakeholders did not play their roles in strengthening the center as anticipated initially. Some of the participants believed that there was lack of coordination among stakeholders and didn't provide optimal and tangible supports for the center. As a result, having a fully operational RBEC was delayed.

"…Especially, from the government's side, there was no proper follow-up and coordination. ... Since it is a matter of health, the Ministry of Health should have played a stronger coordinating role" (CPBI-012)

Some of the participants reported that key stakeholders for this initiative lacked proper integration among them. This activity is mainly collaborative work and stakeholders should have incorporated some activities in their organizational plans to support this BE center. Agreement among key stakeholders on the plan was important.

"… They (RBEC) have the board but this board didn't discharge its responsibilities; even it didn't undertake regular meetings." (CPBI-014)

4.3.1.2 Limitations in the initiative's activities

The responses of the majority of the respondents about RBEC's activities were similar and they mentioned some of the reasons that the center was not effective as planned initially. Among those reasons, lack of infrastructure, lack of financing mechanism, lack of awareness about BE study, lack of international accreditation and human power were the major ones. It was also im-

portant that those who were involved in the establishment of the center including the government and key stakeholders should have secured adequate resources to establish a functional BE center before its official launch and declaring to the public.

> *"… if you go back to the time it started, one of the major mistakes made in this BE center was that it was launched prematurely as if it was operational. When it was announced on the media and launched in the presence of higher officials, it was declared that an operational BE center was opened in Ethiopia. This set everyone's expectations that they have now BE center which is expected to do BE studies."* (*CPBI-013*)

An additional factor which was not considered by some stakeholders might be understanding the relevance of building the capacity of the BE center because of its technical nature. As mentioned by some participants, this is a profitable business in other countries. But in our case, few people are familiar with what it takes to establish a BE center and the overall health care contribution. For instance, the major stakeholder, the Ministry of Health, has limited involvement in the technical, financial as well as other policy-related issues to strengthen this center and did not take it seriously.

> *"… The role of this service isn't directly visible to the large public but if we couldn't assure this activity in the public health product, the consequence will have an impact in the future. Even at the higher government official level, there may be concepts that are difficult to appreciate easily especially for those stakeholders that are not familiar with the issue." (Code CAPA004)*

Moreover, local pharmaceutical manufacturers are not willing to test their products. Some participants felt that the establishment of RBEC was primarily to address the issue of BE center availability and affordability to the local and regional pharmaceutical manufacturers.

> *"…local manufacturers are not will to provide their molecules even for pilot studies. The regulatory enforcement is not yet in place. Moreover, they are manufacturing for local consumption and the local consumption doesn't demand BE testing. Therefore, they do not want to incur more cost for BE testing" (CPBI-001)*

4.3.2 National regulatory policy enforcement and international standards

4.3.2.1 Lack of regulatory policy enforcement

The regulatory system of the country requires a bioequivalence test as a requirement for product registration. But it is not implemented for locally manufactured products yet.

> *"… The challenge, I think, is from regulatory authority's protection due to the concept of access to medicines gaining a priority. Even though the few local manufacturers are weak in their financial capacity, they are using these relaxed systems to avoid extra costs" (CPBI-012)*

> *"… From the manufacturers' side, the number one concern is lack of adequate resources, but that couldn't be a reason for not meeting the minimum requirements. The local manufacturers are at times reluctant just because BE data is not a requirement by the regulatory authority to get registered. The regulatory authority doesn't put this as a prerequisite for manufacturers. They are doing their business so why should they invest 100,000 USD for during one product just to do BE study? They don't have the market problem; they can still market it in Ethiopia." (CPBI-013)*

> "*…in the regulatory body of Ethiopia, EFDA, there is a guideline on bioequivalence studies but the guideline isn't yet implemented and this is the problem. … if you prepare a guideline and don't put into action, it has no meaning.*" *(CPBI-015)*.

In contrast, as some interviewees indicated, it is hard to put blame on the regulatory authority's measures towards BE requirements. Since the local pharmaceutical companies are faced with a lot of limitations to fulfill this requirement, the government needs to place some kind of subsidy for the companies.

> *"…The BE guideline should be implemented and to implement that the regulatory authority should enforce it" (CPBI-010)*

> *"…the BE guideline is already there; what is left is enforcing it. But, before enforcing we have to avail strong BE center. For me, BE is mandatory and unquestionable. The local manufacturers are weak and most of them are manufacturing at 30-40% capacity. Some*

sort of subsidy on some selected products such as essential medicines should be given the first priority." (CPBI-005)

Most of the participants emphasized that the current BE initiative concept has public health sake rather than business interests. Hence, the government should provide special protection like market preference to the local pharmaceutical manufacturers who are engaged in this practice.

"... If you establish bioequivalence for one or two basic products, it will be safe for the society. However, if there is no special protection to prioritize those medicines which did BE studies, you will be making everything stringent on yourself and incurring additional costs. ... this will not encourage manufacturers to participate in BE studies" (CPBI-004)

"...local and regional manufacturers are aiming for local consumption as long as they aren't required to do or enforced to do the BE testing. They aren't in a position to test unless they do have a kind of subsidized or minimum payment service or affordable service" (CPBI-001).

4.3.2.2 Failure to meet international standards

Despite the availability of this service, the whole infrastructure of the center should be consistent with international standards. Some participants mentioned their concerns with limitations to meet these international standards in our setting.

"...Another challenge to conduct this (BE) study for our local products is that the local pharmaceutical companies aren't certified for good manufacturing practices and it is a prerequisite (for BE studies). This service should also fulfill international standards like infrastructure, personnel, premise and other facilities at the required standards". (CPBI-012)

"... Regarding accreditation, RBEC was (ISO-) accredited by the Ethiopian National Accreditation Office. Later on, the accreditation was suspended because inspection should be performed every six months or every year. ... but there were not activities to inspect for the third time. Due to this, they cancelled the accreditation" *(CPBI-002)*

"… The center has done one pivotal study. That was done as per the international norms. … Unfortunately, the protocol approval process took about a year… So, it wasn't justifiable to invite them (the WHO prequalification team) for inspection. Otherwise, as far as the personnel are available, the know-how is there, and the required facilities are fulfilled, I think there may not be problem with conducting BE studies. The problem is with the materials or instruments and the limited number of staff" (CPBI-002)

4.3.3 Institutional organization, modeling, infrastructure and setting

4.3.3.1 Lack of clear institutional organization

Another concern mentioned by the respondents was the ownership issue that comes from RBEC's structure. To be a strong and viable business entity and as an investment, it should have been structured with efficient monitoring and evaluation system right from the inception stage.

"*… In my opinion, the main challenge has been the lack of clear identification and allocation of roles and responsibilities to the respective stakeholders. For instance, allocation of budget, detailed implementation plans and the institutional structure were not clearly described." (CPBI-015)*

"… The other challenge, I have heard mentioned several times, is the organizational structure itself; how it is structured, I think PPP. They claim that it is public-private but who is involved? What is the share of everyone? What is the business plan if you want funding entity? To invest resources in this center, they (funders) want to see the business plan and evaluate if it is a viable organization in the first place. For me, to invest in it, this must be reviewed in detail to identify the gaps and resolve the issues." (CPBI-013)

"… As a business entity, is it functional? Is it responsible for what activities have been done? For whom the center reports? So, because of these unclear issues, the capacity building activity which is expected from respective stakeholders is weak. If these roles and responsibilities have been clearly defined, those responsible bodies may follow and strengthen its activities". (CPBI-012)

4.3.3.2 Business model

The other difference of opinion was the business model of the center. Some interviewees believed that public-private partnership could be appropriate for the current situation but it must be assessed based on the country's capacity. Various local situations that must be studied and suitable business models come from the actual assessment of the real situation that works best for Ethiopia.

According to some respondents' abroad experience, benchmarking the actual model that works for Ethiopian context is important. In most of the Asian countries and the Middle East, most of the BE services are hosted in public institutions like research institutions or teaching institutions so that resources can be shared. You can pull public resources and provide the necessary services not primarily as commercial entity such that the cost would initially be based on cost recovery and not on the basis of profit-making.

> *"… I think PPP can work for the RBEC but ownership issue has to be clear. Governance should be clearly defined and the partners' contributions should also be mentioned and general organizational structure has to be clear and open for all. And the roles of the partners should be clear. It could be PPP or private or public but some kind of roadmap is important to predict its destination". (CPBI-014)*

> *"… It can continue as PPP model. I don't think that is a big obstacle. The main thing is that a channel of communication should be put in place. From my abroad experience, most of the centers are private-owned but supported by the government budget but they are operated by individuals who don't have connection with the government body. They aren't profit-making organizations. Rather, they provide quality service for the public." (CPBI-002)*

Some participants did not support having government-owned BE study centers due to different reasons.

> *"… I don't personally recommend that. The government has enough headache because this is a very sensitive subject. This institution must follow internationally accredited procedures in terms of staffing, quality management system and equipment. There are a lot of services - equipment maintenance and calibration. There are a lot of uniqueness in*

this service which might not be really well handled and managed by governments due to lack of experience." (CPBI-013)

On the other hand, we can aspire for a private-owned BE center since BE study market is huge in the region and it might be also a possible option. In this particular area, giving incentives for those who want to involve in the clinical trial or BE studies may impact the overall health system.

"…Most clinical trial sites are private (internationally) so we can aspire for these options in this particular area giving incentives for those who want to actually involve in the clinical trial, BE studies because the market is huge. This is about Africa and we can even provide a better price for doing quality BE studies and the market might even expand at a global scale that could be very good business by itself. So, we should think over it". (CPBI-012)

4.3.3.3 Lack of Infrastructure / Facility, Skilled Human Power and Equipment/

Most of the respondents considered that we lacked infrastructure especially well-organized facility and up to date equipment to conduct BE studies. On the contrary, some of them believed that we can invest and establish a competitive BE study center if we are committed.

As far as we have the policymaker's commitment in the health sector, building a strong BE infrastructure with the capacity of the government might be possible. But the preceding step should be the common understanding of the need for this infrastructure. Most key stakeholders are believed to have a common aspiration to provide safe, effective and quality product to the large public.

"… *When we are talking about a full-fledged center, we need to have the infrastructure. ... Now, the required test specifications are very dynamic and they are getting stringent so we need to have equipment and systems that can actually comply with these requirements. These days, even HPLC is getting obsolete. I don't think we have sufficient facility right now, but as we said if the stakeholders are giving due attention and working together, I think it may not be that much. The other is human capital. The regulation is very stringent so qualified experts are very important for the clinical investigation as well as*

the bio-analysis. Giving training to human capital and employing additional experts are very important which are not sufficient at this juncture." (CPBI-010)

On the other hand, some participants mentioned the availability of minimum infrastructures that might support BE study initiatives, such as the availability of trainable human power and expansion of clinical facilities in the country.

"... generally, the capacity is growing because there are a number of postgraduate programs. Thus, whenever we need to trained manpower, we can easily access and hire them. The infrastructure, the clinical set up, is growing. Currently, the number of tertiary hospitals is increasing. We will have a better capacity in terms of recruiting participants and hosting such kind of facilities within these tertiary and teaching hospitals. In general, a number of opportunities are on the way" (CPBI-001)

4.3.3.4 Separate placement of the settings

The physical separation of the analytical and clinical settings cannot be a major problem as most participants mentioned. But as a beginner, with the given resource limitations and poor communication infrastructure in the country, it would be best to have the center within the same institution.

"... It is not the place really, or it is not because the two services are hosted in different institutions, that is the problem. Rather, the project plan on how the two services are supported and financed and how the relationship of the two institutions is or the two services can be integrated was the problem. It is not because the two services are hosted in different institutions. I think that is not a problem. It would be best if you have a clinical service and the bio-analysis center especially in terms of the management under one umbrella; it isn't physical separation that matters" (CPBI-001)

"... In terms of distance, I think they must not necessarily be at one site; especially, for counties like Ethiopia it might not be possible to have all of them at one site. However, there must be a system in place that ensures the proper transport of sample from the clinical trial site to the bio-analytical site in line with good clinical practice and good laboratory practice. In my view, if it is secured, it wouldn't be a problem, but the ideal option

is to have them all at one site. If you want to establish a brand-new facility, this must be taken into account". (CPBI-013)

Since both SOP, AAU and AHRI have well-organized systems, the two separate settings have better experience in conducting clinical trials not only for this BE activity but also for other clinical trials as well. They have skilled professionals in both settings that can be considered as an advantage to share different expertise. Instead, a serious concern is the system establishment. A strong system is important to ensure coordination of the different aspects of the study at the clinical and bioanalytical units. In contrast, few participants believed that since their systems are not well organized, things might be complicated and it might impact the outcome.

"…if you sub-contract one activity to another, it will not be easily manageable. And there is a great delay because that organization might have its own organizational system and the one who subcontract the activities might have its own separate rules and so on. So, the location should be brought into one if possible" (CPBI-002)

"… There may be focus area difference if the leadership is separate. There may be a problem and definitely there will be an effect on the whole outcome. But, if they are under the same leadership and the discussion is made within the same leadership, I don't think there will be a problem. Physical separation doesn't have any effect if the leadership and management component, decision making, budgeting and making priority could be under the same management. As far as these issues are smooth, it helps to use human resources and other infrastructures effectively for the same objective" (CPBI-015)

4.3.3.5 Lack of marketing capacity

As any service provider entity, BE industry needs proper marketing strategy to maximize their service capacity.

"*… Lack of marketing experience also contributes to this because it (RBEC) should approach the different companies to conduct BE studies on their products. However, there is a gap in the marketing aspects for the local manufacturers and even for the regional. This is because the center was established to conduct bioequivalence studies not only for Ethiopia but the whole of sub-Saharan Africa. So, the marketing shouldn't have a border*

and ultimately it will be an international service provider organization. It should have some products from elsewhere and for this, marketing is critical" *(CPBI-002)*

Marketing strategy should be started at the beginning of the project planning. As the participants indicated, due to lack of human and financial resources availability in the RBEC, marketing activities were not properly done.

4.3.3.6 Lack of finance

Manufacturers that produced generic products must also fulfill minimum requirements which are being bioequivalent with the innovator. One of the major limitations raised by our participants was the local manufacturer's financial and production capacity to fulfill this requirement.

In addition, maximizing local pharmaceutical manufacturers production capacity might increase company's financial strength and encourage them to conduct BE tests for their products. Hence, majority of participants thought that availing working capital to manufacturers as well as strengthening RBEC by the responsible key stakeholders should be done parallel to regulatory enforcement.

"…Our local manufacturers aren't strong enough and adequately financed to fund bioequivalence study for their products in oversees CROs. If we capitalize on the existing BE center, progressing towards having a full-fledged BE center with good clinical and good laboratory practices and accreditation by relevant international organization might support local manufacturers". (CPBI-013)

"… There is no special protection for local pharmaceutical companies that can submit BE data for their products to compensate for their additional costs. For those products which are locally produced and tested for bioequivalence, the government should give special protection such as market incentive or price protection incentive in the local market" (CPBI-004)

5. Discussion

Generic drug consumption is growing due to its cost-saving measures in the health provision. Thus, demonstration of *in vivo* bioequivalence for those eligible generic products is one of the minimum requirements (Meersch, 2011). However, there was a lack of accessible bioequivalence study infrastructure in the region and BE data submission for product registration has been complex. In this study, there was consensus among participants regarding the availability and accessibility of affordable BE study centers in the country. It is fundamental to exploit local manufacturing capacity and ensure safe, effective and quality generic medicines to the public.

This study demonstrated the major challenges and prospects of bioequivalence study initiative in the country. Since bioequivalence study is an expensive venture by its nature, governments and key stakeholders' involvement is considered vital to make the initiative viable. Although orally administered products need application of interchangeability including comparative dissolution profile and clinical data that compare both products in the form of BE to measure clinical outcomes, these clinical trials rarely are carried out in developing countries (Hill, 2004).

Even though the RBEC is not fully functioning yet, its mere availability with certain limitations has its own advantage in advancing know-how. The study participants mentioned that the primary intention of the initiative was establishing affordable and accessible BE center for the region. At the time, the commitment of Ethiopian government's high officials to host the center in Addis Ababa seemed high. One of the major reasons for the limited activities of the initiative indicated by this study was the lack of key stakeholders' involvement and integration. Moreover, the lack of clear organizational structure or modeling and lack of proper follow-up systems were identified as the limitations of the initiative.

Besides, from the early project conception stage, its planning and budgeting were not properly performed. In addition, technical, financial as well as other policy-related issues hindered the BE center's performance.

Despite the public health issue, lack of awareness of the generic interchangeability in the society was playing a significant role in affecting their decisions and health care cost. This is supported

by a previous study in the country which found out that physicians and patients were scared regarding therapeutic equivalence of locally manufactured medicines (Alemayehu, 2018).

In addition, at this time, product diversity is very much important because there is epidemiological transition and more people are becoming chronic patients with cardiovascular and endocrinology problems which need prolonged treatment. But, majority of the society are not that much confident about the generic products' qualities which are used for the treatment of these chronic diseases and patients and healthcare professionals prefer innovator drugs with extra cost. Similarly South African consumers also acknowledge limitations in actual quality of generics and tend to use innovator drugs (Patel, 2012).

A frequently mentioned reason by local manufacturers not to submit BE data for their product registration was lack of access to affordable BE center. But as mentioned by some participants, after the establishment of the center, those local or regional companies were not willing to provide test materials. This is not surprising because local manufacturers do not have market problems; their products are registered and approved for domestic use. Moreover, since local manufacturers only cover 10-15% of the local need, whatever they produce is immediately taken up by the government distribution agency, PFSA, for distribution throughout the nation. The current study also identified the gaps around regulatory functions. There is no strict adherence to rules on the submission of BE data for the registration requirement of locally manufactured generic products. This is consistent with other studies conducted in Africa which exempted a wide range of products from *in -vivo* bioequivalence study regardless of their biopharmaceutical classification system (WHO, 2010).

It was also presumed that the BE center in Ethiopia, not only will be conducting bioequivalence studies, but it could provide additional advanced laboratory services to the industry as well as giving guidance for the local manufacturers. But, the finding of this study indicated that there is limited coordination among this center, the local manufacturers and other relevant stakeholders.

The government has taken important measures to attract investment in the pharmaceutical manufacturing sector. It has instituted attractive incentive packages for local manufacturers; it has also established a dedicated pharmaceutical industrial park. As a result of this, a number of interna-

tional companies are showing interest and some are already investing in the country. Thus, there will be a significant demand for the bioequivalence test. So, if the center becomes fully functional, the companies will have their products tested at an affordable cost at the center.

The findings of the study further indicate another opportunity, that is, proliferation of generic medicines market in the region. In addition to public health safety, strengthening this quality infrastructure is very essential for the country to enter into the regional as well as the continental market (Holt, 2015). Manufacturing quality products would be one sort to market products.

Ethiopia is building local pharmaceutical manufacturing capacity and the national strategic plan of action is aspiring 50% of products for export by 2025. Therefore, to be competitive in the international market, comprehensive industrial development including quality infrastructure should be in place. Another study that has been done in India indicated that generic medicines in different markets can be understood as defined by WHO, to mean pharmaceutical products interchangeable with the innovator (Pankaj, 2013).

Moreover, regional harmonization and inter-continental free trade agreement are on the process of realization (IGAD, 2016). Hence, Ethiopia needs to strengthen its capacity before harmonization initiatives are put in place. Otherwise, if the country is not able to enforce such a very important requirement, it will not have access to the East African market.

According to the finding, lack of stakeholders' involvement and integration, lack of resource, lack of regulatory policy enforcement, lack of clear institutional organization and modeling were mentioned as the major challenges of the BE study initiative in the country.

The regulatory authority needs to be stringent and policy enforcement has to be consistent and applicable for all imported and locally manufactured medicines. This study showed that in the policy enforcement, there is a double standard between the imported and locally manufactured generic products' registration process. Other study has found in Burkina Faso that evaluation of the registration application by the regulatory authority was weak and the bioequivalence compliance was not verified for registration of generic drugs (Semde, 2012). The most common reason mentioned by some participants for not pushing local manufacturers to fulfilling BE data requirement was to improve access to medicines through local production. But health care products

have to be as per the international standards and rather a strong capacity-building effort by key stakeholders is an important option to achieve those international norms and standards.

Bioequivalence study involves human subjects, requires clinical and bio-analytical facilities, experts and the testing facilities have to be WHO accredited as well because of regulatory requirements. So, having these certified and standard facilities is a challenge that the center has not yet accomplished. This finding is supported by other studies from developing countries such as strong involvement of the regulatory and all responsible stakeholders to fulfill the standard requirements and establish credibility to the center (Dan, 2018).

Some participants argued that public-private partnership model is suitable for the time being with government leadership. Because, the government interest is clear, that is, to safeguard the larger public rather than profit and the government could discharge this responsibility by allocating some subsidy, and also the private share will be defined as far as some amount of finance is allocated in this public-private partnership. Moreover, a proper channel of communication should be in place and the professionals should be able to work autonomously without interference from government. In the context of public-private partnership model, combined resource and knowledge with shared responsibility and risk is crucial (Reillon, 2017).

On the other hand, some study participants aspire for private options because the market is huge not only in Ethiopia but also in Africa and beyond as far as it can be competitive. Like any industry, the government should have a focus on this particular area and give incentives for those who want to involve in clinical trials to make a difference.

Besides, overall infrastructure limitations were identified. From the beginning, the initiative was hosted in already existing academic and clinical settings that made its own limitations related to physical infrastructure. By its nature, the standard requirements and test specifications are very dynamic while only basic equipment such as HPLC were procured by the GIZ project. Even though the project was initiated by performing pilot studies and to transform into commercial studies, it actually required huge amount of investment and the center needs to be equipped with modern and up to date testing instruments and facilities. Furthermore, for this type of clinical

investigation, only few qualified and experienced professionals are available that are not sufficient to conduct multiple studies at a time.

This study also identified separate placement of clinical and analytical settings as a challenge for the initiative. This is confounded by the limited resources and poor communication system. Separating setting and sub-contracting one activity to another facility is common for most CROs. However, in this case, the system is not well organized and the units are under different managements with differing focus areas, decision makings, budgeting and priorities.

The other problems that deter local manufacturers from testing their products' interchangeability reported by the participants were financial problems. As any business entity, they have financial problems for capital investment, for running their businesses and especially hard currency to import raw materials, active ingredients and equipment. Local manufacturers are waiting until they are forced to do BE studies because there is a lot of costs which will be an addition to this with low production capacity. Similarly, approaches taken by Ghana showed that government facilitates credit with low interest rate directly for upgrading local pharmaceutical firms (UNDP, 2016).

Limitations of the study

This study broadly assessed the bioequivalence study initiative in the country and the current situation of RBEC in the view of different key stakeholders. One of the limitations was the occurrence of the COVID-19 pandemic. It limited free movement for data collection. The other limitation was low participation of higher officials particularly, Food and Drug Administration policy decision makers' participation in the study.

6. Conclusions

In conclusion, this study demonstrated different insights into the major challenges and prospects of the bioequivalence study initiative in the country. In depth interviews with participants identified that lack of resources is the major challenge for the initiative. It is not only that resources are lacking to conduct BE studies, there are also challenges of lack of regulatory enforcement, stakeholders' involvement and coordination, clear institutional structure and business model. Attractive incentive packages designed by the government for local pharmaceutical manufacturers and proliferation of the generic market in the region are the major opportunities for having a competitive BE study center. The majority of the study participants agreed on the presence of a strong BE infrastructure by any means to strengthen the local pharmaceutical manufacturing and to tackle the problem of limited access to essential medicines.

By its nature, bioequivalence study is an expensive venture, thus, the government's and key stakeholders' active involvement should be considered to provide support and to make the initiative viable. The significance of supporting this initiative is to create a competitive manufacturing sector which is engaged in the production of safe, effective and quality pharmaceuticals that safeguard the society. Hence, it is clear that coordinated efforts and commitment at the national level is required to ensure access to effective and safe medicines.

7. Recommendations

1. Based on our current situation, full-fledged bioequivalence testing center combined with all other quality infrastructures could be achieved in two ways.

- **On the existing initiative:** there is know-how and technology within the existing initiative. The center can be re-established but still the legal framework of how the RBEC was established is a cornerstone in general. It has been demonstrated that something can be done, information about what is actually lacking is available. Building on the already gained experience and the available expertise is a way forward. There should be aggressive investment with proper benchmarking on the required minimum infrastructure in terms of equipment, personnel and other infrastructure. It is also necessary to have a kind of core funding that should support and sustain this service until it becomes self-reliant.
- **Establishing a new one:** although not necessarily a cost-effective approach, it is possible to start with a new initiative. It is possible to start from scratch, and invest on the clinical as well as the bioanalytical lab functions. The important thing is understanding the impact of the service. Aggressive actions are needed with clearly mandated institutional leadership.

2. The BE center needs its own strategic plan and a clear plan of action and since the existing initiative's ownership is regional, they have to be involved and form a strong managing board to go forward. Currently, in our country and also in the region, there is a great opportunity in the pharmaceutical sector and this needs rigorous reform to make use of the huge generic market. It is of paramount importance to be on the same page or in harmonized system with regional, continental as well as global regulatory requirements. Otherwise, pharmaceutical manufacturing growth will be limited to domestic use as usual.
3. Ministry of Health should be at the forefront to support this initiative and should work very closely with other relevant local and international stakeholders. All stakeholders: the government, the regulatory body, the center itself and other responsible organizations such as MOH and MOI as well as international partners should come together and discuss the obstacles or challenges towards the development of the center and can work together to find out particular solutions to build local capacity on BE studies.
4. Regarding its modelling, RBEC needs benchmarking. If the PPP model continues, key stakeholders should be identified outside of the traditional way and with clear stakeholders' responsibilities and type of support required from them, be it technical or financial. Stakehold-

er analysis, clear communication strategy and documented action plans have to be developed. Moreover, clear governance should be in place with accountability and check and balance among stakeholders.

5. To safeguard our society, the drug registration policy should be implemented and all products that require BE studies should have that test done whether it is locally manufactured or imported. The manufacturers might be concerned about compliance of their manufacturing processes such as GMP certification and encounter established quality-attributes of their products. So, it is the regulatory body's mandate to identify products manufactured locally that need BE studies and the products that need biowaiver. There might be a guideline to support this process.
6. If the study setting's physical separation is mandatory, clinical and bio-analytical settings have to have some sort of communication framework, integrated planning, implementation, and monitoring as well as financing system. Furthermore, it should be equipped by all required inputs, and strong marketing strategy is important to promote their services as any business entity.

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Appendix A: Consent Form

Title: Challenges and Prospects of Bioequivalence Study Initiatives in Ethiopia

- The study has been explained to me in a language that I comprehend. All the questions I had about the study have been answered. I understand what will happen during the interview and what is expected of me.
- I have been informed that it is my right to refuse to take part in the interview today and that if I choose to refuse, I do not have to give a reason.
- I have been informed that anything I say during the interview today will audio recorded and remain completely confidential: my name will not be used nor any other information that could be used to identify me.
- It has been explained that sometimes the researchers find it helpful to use my own words when writing up the findings of this research. I understand that any use of my words would be completely anonymous (without my name). I have been told that I can decide whether I permit my words to be used in this way.

I agree to take part in the study:	Yes	No
I agree that my own words may be used anonymously in the report	Yes	No

Signature of participant:

NAME **(in capital letters)**	**SIGNATURE**	**DATE OF SIGNATURE** (in DD/MM/YYYY)

Signature of study staff taking consent:

I have discussed the study with the respondent named above, in a language he/she can comprehend.

I believe he/she has understood my explanation and agrees to take part in the interview.

NAME	**SIGNATURE**	**DATE OF SIGNATURE**
Yajeb Melesse		(in DD/MM/YYYY)

Appendix B: Demographic data

Please answer the following questions in the spaces provided, circle or tick the most appropriate options.

A. Personal Information

1. Are you: (please tick as necessary) □ Male □ Female

2. What is your professional background?

□ Medical Doctor/ Veterinary Doctor

□ Pharmacist

□ Biologist

□ Chemist

□ Other: (please describe) _____

3. Experience in bioequivalence study/bioequivalence document evaluation/manufacturing inspection/ pharmaceutical production/quality assurance/policy analysis/clinical research/others (underline your choice):

□ <1 Year □ 1-2 Years □ 2-5 Years □ 5-10 Years □ >10 Years

4. Respondent's responsibility in the organization ----------

B. Organizational Information

1. Name of organization_____
2. Year of Establishment _____
3. Location _____

   Region _____

   Zone/Sub-city _____

   City/Town _____

   Woreda/Kebele _____
4. Contact Address

   P.O.Box _____

   Tel _____

   Fax _____

   e-Mail _____

Appendix C: Interview guide

Title: Challenges and Prospects of Bioequivalence Study Initiatives in Ethiopia

General Objective

To assess the challenges and prospects of bioequivalence study initiatives in Ethiopia

Specific objectives

- To Identify existing challenges in bioequivalence study initiatives
- To outline the prospects of bioequivalence study initiatives

Guiding questions for the interview

1. Did you have any involvement in the Regional Bioequivalence Centre initiative? If yes, do you think it is working as planned initially? If not, what are the limitations/challenges/gaps?
2. In your opinion, why do we need to improve the availability (new generic molecules) and quality of locally manufactured essential medicines?
3. What opportunities are available in the country for conducting bioequivalence studies?
4. What challenges are existing in the country for conducting bioequivalence studies?
5. What should be done to strengthen the bioequivalence study initiative in the country and particularly related with the country's pharmaceutical manufacturing strategic plan?
6. In your opinion, what policy/regulation should be in place to ensure localgeneric products are bioequivalent to comparator/ original products?
7. Has your organization/personally ever been involved in strengthening the Regional Bioequivalence Centre in different capacities? If yes, in what way? Financial/Technical/Other?
8. In your opinion, is there a need to improve/change the business model of the RBEC (public private partnership)?
9. Do you think key stakeholders are contributing their share and disposing their responsibilities as expected to strengthen the BE study initiatives?
10. What were/are the strengths and weaknesses of the Regional Bioequivalence Center under the School of Pharmacy, CHS, AAU?
11. What were/are the strengths and weaknesses of the Clinical Unit affiliate of the Regional Bioequivalence Center at AHRI?

12. In general, do you think the infrastructure for the bioequivalence study - such as, skilled professionals, chemicals, clinical setting, reagents and analytical laboratories - are sufficient in quantity and quality?
13. What is your vision for the RBEC in particular and the bioequivalence initiative in the country in general?
14. Do you have any additional suggestions for the bioequivalence study initiative in the country?