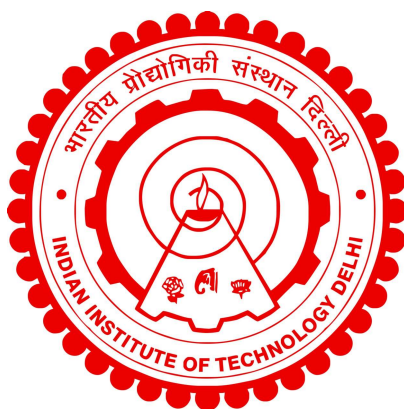


A FAIR PRICE DETERMINATION MODEL FOR THE AFFORDABILITY OF BIOTHERAPEUTICS

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by

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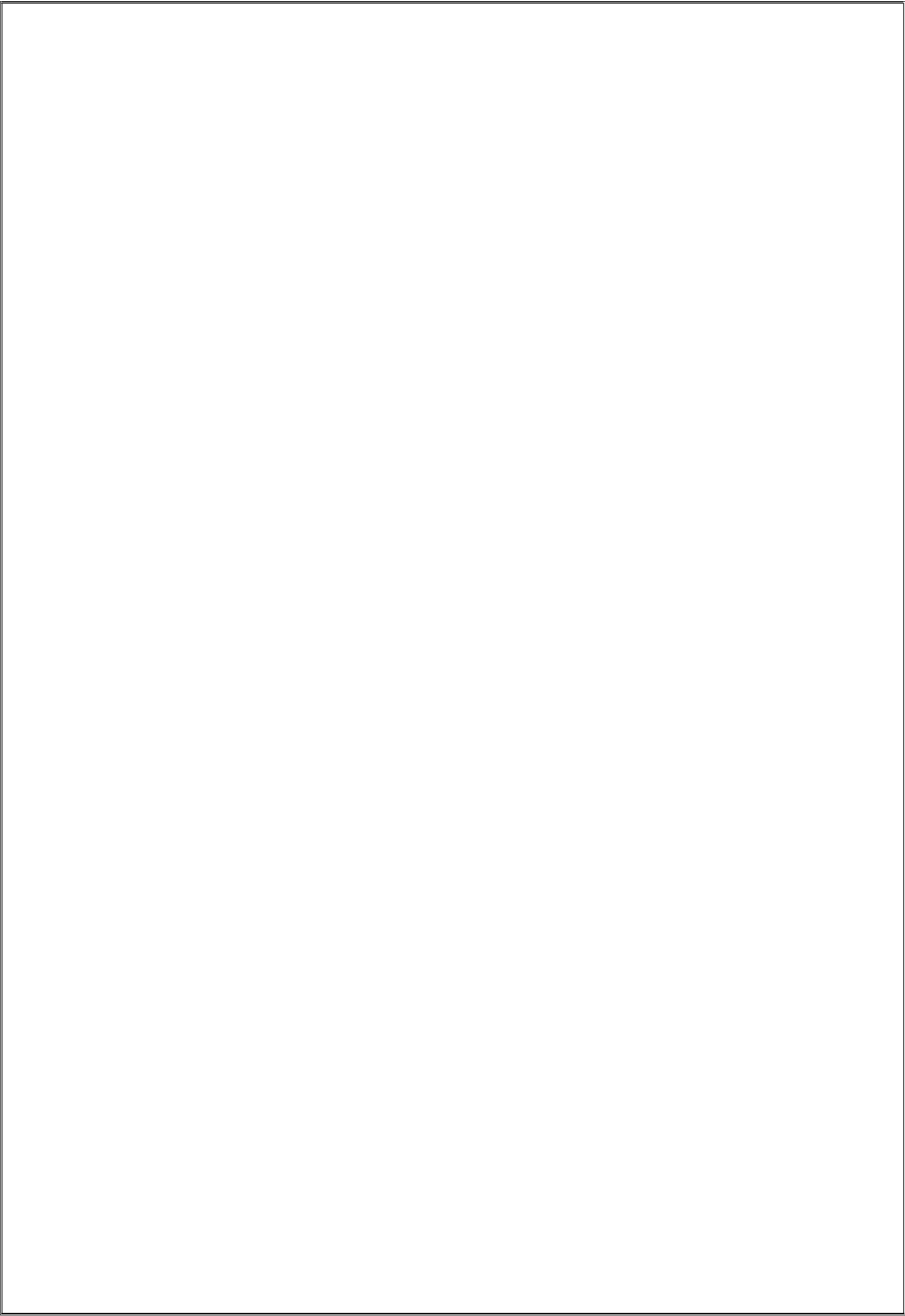
Submitted

in fulfillment of the requirements of the degree of Doctor of Philosophy to the



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Dedicated to My Dad, My Inspiration

Your guiding hand on my shoulder will stay with me forever...

Certificate

This is to certify that the thesis entitled “**A Fair Price Determination Model for the Affordability of Biotherapeutics**”, submitted by **Sonia Gandhi** to the Indian Institute of Technology Delhi, for the award of the degree of **Doctor of Philosophy**, is a record of the original, bona fide research work carried out by her under our supervision and guidance. The thesis has reached the standards fulfilling the requirements of the regulations related to the award of the degree.

The results contained in this thesis have not been submitted in part or in full to any other University or Institute for the award of any degree or diploma to the best of our knowledge.

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Abstract

Purpose

This study investigates the need for revision in the price determination mechanism used in India for biotherapeutics. The National Pharmaceutical Pricing Authority (NPPA), the medicines price regulating body in India, has adopted the market-based pricing policy for determining the prices of medicines. As criticised by multiple bodies, this mechanism is not an ideal approach to control or cap the prices of medicines, especially for the biosimilars, wherein the oligopolistic market is dominated by a few manufacturers. This study advocates for a new model for affordability of biotherapeutics and examines the (1) cost of development of a biosimilar from lab to market (2) the various factors influencing the prices of biotherapeutics, (3) hierarchy and interdependency of the determinants of prices, and (4) model for capping price limits for high cost lifesaving medications like biosimilars.

Design/Methodology/Approach

A sequential approach is adopted in the study design wherein data or findings generated from one objective feed into the other for further development. Firstly, a cost reference of biosimilar development is generated through a multiple-case study approach based on the “Eisenhardt Method”. The research design used is an adaptive, inductive, and holistic case study of six biopharmaceutical companies. Secondly, a modified bibliometric technique is deployed to identify the most significant factors influencing the biosimilar prices in India. These factors are further knitted into a hierarchical framework through Total Interpretive Structural Modelling (TISM) and MICMAC analysis in objective 3. Multiple rounds of questionnaires and interviews are conducted at various stages to validate the data. Finally, a mathematical equation

for biotherapeutics price determination is developed, which is validated through historical data on four in-market biosimilars.

Findings

One of the important outcomes of the research work is a reference or gold standard for the cost of translating a biotherapeutic from lab to market in Indian settings. The multiple case study on six biopharmaceutical companies based in India reveals that biosimilar development through the microbial system costs ~ 18 million USD and the mammalian system ~ 21 million USD. Additionally, 45 – 50 million USD is required as a one-time capital investment. Further, US/EU authorisation can cost ~ 25 million USD per product. Clinical studies are the most expensive and account for 60 - 70 % of total development costs.

A Biotherapeutics Price Determination Model (BPDM) is the second major contribution, conceptualised through this study. The model reveals that patent expiry period, partnerships/acquisitions, and the country's economy should be considered along with market dynamics for an effective pricing policy for biosimilars in India. The expense of biosimilar development is negligible in relation to the Maximum Retail Price (MRP) of the product. The price equation created in this study can be used by health or pricing authorities to set price caps for biosimilars in India. Its main purpose is to help develop a new policy for establishing biosimilar prices in the country.

The biotherapeutic price indicators are the third significant finding of this study. Policymakers can use these as national price indicators and map them for quantitative studies to inform policy decisions. The government policies, incentives and regulatory framework are country-specific factors that are mandatory to develop a conducive ecosystem for regulating the exorbitant cost in India.

The comparative study of BRICS countries reveals that Brazil's pricing mechanism is the most advanced among the BRICS nations. India can develop a mechanism to assess innovation levels, clinical evidence, and economic analysis. NPPA might set up a dedicated pricing system for high-cost biosimilar therapies, following the example of Brazil and Russia. Additionally, state-level pricing approaches, such as those used in Russia, could aid in effectively managing and enforcing price controls.

Key Implications

The price model developed in this study has the potential to pave the way for a new pricing regime for biosimilars. The characteristics of the price determination model outlined here can capture the full value of the product rather than relying on biased market values to determine prices. Due to ongoing legal challenges to the MBP policy implemented by the Indian government, developing an effective pricing mechanism for biotherapeutics is expected to have a significant impact.

सारांश

लक्ष्य

यह अध्ययन भारत में जैवचिकित्सा के लिए उपयोग की जाने वाली मूल्य निर्धारण प्रणाली में संशोधन की आवश्यकता की जांच करता है। भारत में दवाओं की कीमत को नियंत्रित करने वाली संस्था, राष्ट्रीय औषधि मूल्य निर्धारण प्राधिकरण (एनपीपीए) ने दवाओं की कीमतें निर्धारित करने के लिए बाजार आधारित मूल्य निर्धारण नीति को अपनाया है। कई निकायों द्वारा आलोचना की गई है कि यह प्रणाली दवाओं की कीमतों को नियंत्रित करने या सीमित करने के लिए एक आदर्श दृष्टिकोण नहीं है, विशेष रूप से बायोसिमिलर के लिए, जिसमें अल्पाधिकार बाजार पर कुछ निर्माताओं का प्रभुत्व है। यह अध्ययन जैवचिकित्सा की सामर्थ्य के लिए एक नए मॉडल की वकालत करता है और (1) प्रयोगशाला से बाजार तक एक बायोसिमिलर के विकास की लागत (2) जैवचिकित्सा की कीमतों को प्रभावित करने वाले विभिन्न कारकों, (3) कीमतों के निर्धारकों के पदानुक्रम और अन्योन्याश्रयता, और (4) बायोसिमिलर जैसी उच्च लागत वाली जीवनरक्षक दवाओं के लिए मूल्य सीमा तय करने के मॉडल की जांच करता है।

डिजाइन/कार्यप्रणाली/दृष्टिकोण

अध्ययन के डिजाइन में एक अनुक्रमिक दृष्टिकोण अपनाया जाता है जिसमें एक उद्देश्य से उत्पन्न डेटा या निष्कर्ष आगे के विकास के लिए दूसरे में फीड होते हैं। सबसे पहले, "आइजनहार्ट विधि" पर आधारित कई-केस अध्ययन के माध्यम से बायोसिमिलर विकास का लागत संदर्भ तैयार किया जाता है। उपयोग किया गया शोध डिजाइन छह बायोफार्मासिटिकल कंपनियों का एक अनुकूली, प्रेरक और समग्र केस अध्ययन है। दूसरे, भारत में बायोसिमिलर की कीमतों को प्रभावित करने वाले सबसे महत्वपूर्ण कारकों की पहचान करने के लिए एक संशोधित ग्रंथसूची तकनीक का उपयोग किया जाता है। इन कारकों को उद्देश्य 3 में कुल व्याख्यात्मक संरचनात्मक मॉडलिंग (TISM) और MICMAC विश्लेषण के माध्यम से एक पदानुक्रमित ढांचे में बुना गया है। अध्ययन के आंकड़ों को मान्य करने के लिए विभिन्न चरणों में

प्रश्रावली और साक्षात्कार के कई दौर आयोजित किए जाते हैं। अंत में, बायोथेराप्यूटिक्स मूल्य निर्धारण के लिए एक गणितीय समीकरण विकसित किया गया है, जिसे बाजार में उपलब्ध चार बायोसिमिलर्स पर पूर्वव्यापी डेटा के माध्यम से मान्य किया गया है।

निष्कर्ष

शोध कार्य के महत्वपूर्ण परिणामों में से एक भारतीय परिवेश में जैव-चिकित्सा को प्रयोगशाला से बाजार तक पहुँचाने की लागत के लिए एक संदर्भ या स्वर्ण मानक स्थापित करना है। भारत स्थित छह जैव-औषधि कंपनियों पर किए गए बहु-मामले अध्ययन से पता चला है कि सूक्ष्मजीव प्रणाली के माध्यम से जैव-समान विकास की लागत लगभग 18 मिलियन अमेरिकी डॉलर और स्तनधारी प्रणाली के माध्यम से लगभग 21 मिलियन अमेरिकी डॉलर है। इसके अतिरिक्त, एकमुश्त पूंजी निवेश के रूप में 45-50 मिलियन अमेरिकी डॉलर की आवश्यकता होती है। इसके अलावा, अमेरिकी/यूरोपीय संघ प्राधिकरण की लागत प्रति उत्पाद लगभग 25 मिलियन अमेरिकी डॉलर हो सकती है। नैदानिक अध्ययन सबसे महंगे होते हैं और कुल विकास लागत का 60-70% हिस्सा इनका होता है।

बायोथेराप्यूटिक्स मूल्य निर्धारण मॉडल (बीपीडीएम) इस अध्ययन के माध्यम से परिकल्पित दूसरी प्रमुख खोज है। यह मॉडल दर्शाता है कि भारत में बायोसिमिलर दवाओं के लिए एक प्रभावी मूल्य निर्धारण नीति के लिए पेटेंट की समाप्ति अवधि, साझेदारियों/अधिग्रहणों और देश की अर्थव्यवस्था के साथ-साथ बाजार की गतिशीलता पर भी विचार किया जाना चाहिए। उत्पाद के अधिकतम खुदरा मूल्य (एमआरपी) के संबंध में बायोसिमिलर विकास की लागत नगण्य है। इस अध्ययन में निर्मित मूल्य समीकरण का उपयोग स्वास्थ्य या मूल्य निर्धारण प्राधिकरण भारत में बायोसिमिलर दवाओं के लिए मूल्य सीमा निर्धारित करने के लिए कर सकते हैं। इसका मुख्य उद्देश्य देश में बायोसिमिलर कीमतों को स्थापित करने के लिए एक नई नीति विकसित करने में सहायता करना है।

जैव-चिकित्सीय मूल्य संकेतक इस अध्ययन का तीसरा महत्वपूर्ण निष्कर्ष हैं। नीति-निर्माता इनका

उपयोग राष्ट्रीय संकेतकों के रूप में कर सकते हैं और नीतिगत निर्णयों को सूचित करने हेतु अर्थमितीय अध्ययनों के लिए इनका मानचित्रण कर सकते हैं। सरकारी नीतियाँ, प्रोत्साहन और नियामक ढाँचा देश-विशिष्ट कारक हैं जो भारत में अत्यधिक लागत को नियंत्रित करने हेतु एक अनुकूल पारिस्थितिकी तंत्र विकसित करने के लिए अनिवार्य हैं।

ब्रिक्स देशों के तुलनात्मक अध्ययन से पता चला है कि ब्राज़ील का मूल्य निर्धारण तंत्र ब्रिक्स देशों में सबसे उन्नत है। भारत नवाचार के स्तर, नैदानिक साक्ष्य और आर्थिक विश्लेषण का आकलन करने के लिए एक तंत्र विकसित कर सकता है। एनपीपीए ब्राज़ील और रूस के उदाहरण का अनुसरण करते हुए, उच्च-लागत वाली बायोसिमिलर चिकित्सा के लिए एक समर्पित मूल्य निर्धारण प्रणाली स्थापित कर सकता है। इसके अतिरिक्त, रूस जैसे राज्य-स्तरीय मूल्य निर्धारण दृष्टिकोण, मूल्य नियंत्रणों के प्रभावी प्रबंधन और प्रवर्तन में सहायक हो सकते हैं।

प्रमुख निहितार्थ

इस अध्ययन में विकसित मूल्य मॉडल में बायोसिमिलर दवाओं के लिए एक नई मूल्य निर्धारण व्यवस्था का मार्ग प्रशस्त करने की क्षमता है। यहाँ उल्लिखित मूल्य निर्धारण मॉडल की विशेषताएँ, कीमतों के निर्धारण के लिए पक्षपातपूर्ण बाजार मूल्यों पर निर्भर रहने के बजाय, उत्पाद के पूर्ण मूल्य को दर्शा सकती हैं। भारत सरकार द्वारा लागू की गई एमबीपी नीति को जारी कानूनी चुनौतियों के कारण, बायोथेरेप्यूटिक्स के लिए एक प्रभावी मूल्य निर्धारण तंत्र विकसित करने से महत्वपूर्ण प्रभाव पड़ने की उम्मीद है।

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List of Abbreviations

AB-PMJAY	Ayushman Bharat - Pradhan Mantri Jan Arogya Yojana
AIDAN	All India Drug Action Network
API	Active Pharmaceutical Ingredient
ARC	Adaptive Reduction Coefficient
ARV	Antiretrovirals
BIRAC	Biotechnology Industry Research Assistance Council
BPCIA	Biologics Price Competition and Innovation Act
CADTH	Canadian Agency for Drugs and Technologies in Health
CBP	Cost Based Price
CDMO	Contract Development and Manufacturing Organization
CDSCO	Central Drugs Standard Control Organization
CEE	Central and Eastern European
cGMP	Good Manufacturing Practices
CHO	Chinese Hamster Ovary
CMED	Câmara de Regulação do Mercado de Medicamentos
CPA	Central Pharmaceutical Procurement Agency
CROs	Contract Research Organizations
DBT	Department of Biotechnology
DP	Differential Pricing / Ramsey Pricing
DPCO	Drug Price Control Order
ERP	External Reference Pricing
ETP	Effluent Treatment Plant
FAS	Federal Antimonopoly Service

GCSF	Granulocyte Colony Stimulating Factor
GDP	Gross Domestic Product
HAI	Health Action International
HER 2	Human Epidermal Growth Factor Receptor 2
HHI	Herfindahl Hirschman Index
HTA	Health Technology Assessment
ICH	International Council for Harmonisation
IRP	Internal Reference Pricing
ISM	Interpretive Structural Modeling
JPO	Joint Procurement Office
LMIC	Low and Low Middle Income Countries
M&A	Mergers and Acquisitions
MBP	Market Based Price
MDR TB	Multi Drug Resistant Tuberculosis
MICMAC	Matrice d'Impacts Croisés Multiplication Appliquée à un Classement
MPS	Micro Physiological Systems
MSF	Medicine Sans Frontiers
mTISM	Modified Total Interpretive Structural Modeling
NDoH	National Department of Health
NEMLC	National Essential Medicines List Committee
NHSA	National Healthcare Security Administration
NLEM	National List of Essential Medicine
NME	New Molecular Entity
NPMPP	New Public Medicine Procurement Policy
NPPA	National Pharmaceutical Pricing Policy

OECD	Organisation for Economic Co’operation and Development
PAT	Process Analytical Technology
pCPA	pan Canadian Pharmaceutical Alliance
PEE	Pharmaceutical Economic Evaluation
PF	Prego Fabrica ou Prego Fabricante
PHS	Public Health Service
PLI	Product Linked Incentivisation
PPP	Public Private Partnerships
QOL	Quality Of Life
R&D	Research and Development
SEPA s	Single Exit Price Adjustments
SFDA	Saudi Food and Drug Authority
STGs	Standard Treatment Guidelines
TISM	Total Interpretive Structural Modeling
TNF	Tumor Necrosis Factor
TRIPS	Trade Related aspects of Intellectual Property Rights
UCPMP	Uniform Code for Pharmaceutical Marketing Practices
UHC	Universal Health Coverage
US FDA	United State Food and Drug Administration
VAT	Value-Added Tax
VBP	Volume-Based Procurement
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation
WHOCC	World Health Organization Collaborating Centre for Pharmaceutical
PPRI	Pricing and Reimbursement Policies

Background and Introduction

1.1 Background

Affordability and accessibility to high-quality lifesaving essential medicines are a basic right for equality. The cost-effective measures to promote fair prices are central to the implementation of any national or international healthcare program. Many international organisations like the World Health Organization (WHO), Organization for Economic Co-operation and Development (OECD) and Medicine Sans Frontiers (MSF), to name a few, have regularly highlighted the importance of developing strategies for monitoring, evaluating, measuring, and managing the prices of essential medicines to promote equitable access (Augustine et al., 2018; OCDE, 2019). Their collective efforts, particularly in the Low and Middle Income Countries (LMIC), resulted in the formulation of various guidelines and policy documents that facilitate policymakers and other stakeholders in the implementation of the pricing strategies to regulate the prices of essential medicines. However, the published literature reflects that no single approach is sufficient and/or is the right fit for implementation on both national and international scale (Manders et al., 2025). Hence, innovation is required at all levels of the healthcare ecosystem and should be aligned with the national regulatory policies and local factors impacting the prices of medicines. Further, most of the efforts in this direction are concerted towards the generic drugs for high burden diseases like HIV, Malaria and TB, while biopharmaceuticals, especially biosimilars, on account of the different value chain including R&D, production, procurement, distribution, and usage network (Ratih et al., 2021), demand separate research on pricing mechanisms and costing models.

At the 54th World Health Assembly in 2001, WHO member states passed a resolution that demanded a mechanism for voluntary monitoring of the prices of medicines and a global

system for drug price reporting. In response to the resolution, the WHO/Health Action International (HAI) project on medicine prices and availability was launched in 2001 (Cameron et al., 2009). Under the project, HAI has conducted surveys in more than 50 countries, including a few states of India (Rajasthan in 2003, West Bengal, Karnataka, Chennai, Haryana & Maharashtra in 2004 and Delhi in 2011) but no confirmatory study was conducted to check the effectiveness of the implementation of the proposed approach. The national reports, survey data, guidelines and related resources generated through the project are available in the public domain (NPPA, 2019). In continuation, WHO convened the fair pricing forums in 2017, 2019, and 2021 to enable deliberations on various aspects of determining the prices of pharmaceuticals (WHO, 2021).

1.2 Price control mechanism in India

India controls the prices of drugs through National Pharmaceutical Pricing Policy (NPPA), developed and implemented by the Department of Pharmaceuticals, Government of India (GoI). India introduced regulation of the prices of generic pharmaceutical formulations through the Drugs (Display of Prices) Order 1962 and the Drugs (Control of Prices) Order 1963. Thereafter, many amendments were notified through various orders by GoI. Currently, the National Pharmaceutical Pricing Policy, 2012, is in practice through the Drugs (Price Control) Order, 2013 (The Drugs (Prices Control) Order, 2013, 2016).

The three major principles of the 2012 policy are:

1. Essentiality of drugs
2. Control of formulation prices only (not bulk drugs) and
3. Market-based pricing

The methodology adopted to determine the ceiling price of National List of Essential Medicine (NLEM), is a simple average of the prices of all the brands available in the market with more than 1 % market share.

The following equation or method proposed by NPPA is currently in practice in India for scheduled formulations:

$$P(s) = \frac{\text{Sum of prices of all brands with more than 1\% market share}}{\text{Total number of manufacturers of such brands}} \dots\dots\dots(\text{Equation 1.1})$$

$$P(c) = P(s) * \left\{1 + \frac{M}{100}\right\} \dots\dots\dots(\text{Equation 1.2})$$

P(c) = The ceiling price of the scheduled formulation

P(s) = Average price to retailer for the same strength and dosage of the medicine

M = % Margin to retailer and its value is 16

Scheduled formulations are the list of formulations listed in the schedule of DPCO and their prices are controlled by the NPPA, aligning with the NLEM.

In case NPPA observes no reduction in the ceiling price of scheduled formulations due to less competition (less than five manufacturers with one percent or more market share), the following equations are used to determine the ceiling price:

$$P(s) = P_m \{ 1 - (P_{i1} + P_{i2} + P_{i3} \dots\dots) / (N * 100) \} \dots\dots\dots(\text{Equation 1.3})$$

P_m = Retailer price of the highest priced scheduled formulation

P_i = % reduction in retailer price of other dosage forms or strengths compared to the highest priced formulation taken for calculating the retail price of those strengths or dosage forms.

N = Number of other dosage forms and strengths in the list of scheduled formulations.

$$P(c) = P(s) * (1 + M/100) \dots\dots\dots(\text{Equation 1.4})$$

M = Percent margin to retailer, equals 16

P(s) = Average price to retailer of scheduled formulation

For Non-Scheduled Formulations, prices are not directly regulated but are overseen by NPPA to prevent price increases from exceeding 10% annually. For drugs already on the market, prices are determined according to scheduled formulations. For new medications not yet available, prices are based on pharmaceutical economics plus a 16% retail margin. New drugs may be exempt from price regulation for five years if they are covered by a product patent, developed through indigenous R&D, or for orphan diseases, subject to approval by the DCGI (Source: DPCO).

Although NPPA has established the methodology for determining the ceiling price $P(c)$ of medicines, various factors that may influence drug prices were not included in the formulas. Additionally, the same formulas are used to regulate the $P(c)$ for biologics, which indicates that biologics are treated as generic drugs synthesised through a chemical route. In contrast, biosimilars have different manufacturing processes (biological processes) compared to generic drugs (chemical synthesis). According to the US FDA, they are defined as:

“A biosimilar is a biological product that is highly similar to a US-licensed reference biological product not withstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product”.

1.3 Affordability of biotherapeutics in India – Current scenario

India currently has the maximum number of biosimilars approved in the world (151 biologics approvals by March 2024)¹. The domestic market for biosimilars is dominated by a few manufacturers, unlike the significant number of manufacturers in the generic drug manufacturing space. Few biosimilars approved in the Indian market along with their manufacturers in three oncology targeted therapy areas are detailed in Table 1.1.

¹ Source: CDSCO

Table 1.1: List of major Biosimilars approved for manufacturing & marketing in India for Anti-HER 2, Anti -VEGF and Anti – TNF therapy area

S. No.	Drug Name	Dosage Form & Strength	Name of Manufacturer	Indication	Date of Approval
1.	Trastuzumab emtansine bulk	Trastuzumab emtansine (r-DNA origin) Bulk drug substance; (Protein Concentration 18.00 – 22.00 mg/mL)	Cadila Healthcare Limited	NA	12 Jan 2021
2.	Trastuzumab	Lyophilized powder for concentrate for solution for injection. 150mg and 440mg vials	Intas Pharmaceuticals Ltd	HER2 positive metastatic breast cancer	06 April 2018
		150mg and 440mg vials	Dr. Reddy's Laboratories Ltd.		06 March 2018
		Lyophilized powder for infusion in single and multiple use vial. Strength: 150 mg single use vial and 440 mg multiple use vial.	Cadila Healthcare Limited		28 Oct 2015
		Lyophilized powder for concentrate for solution for IV infusion in 150 mg or 440 mg vials	Reliance Life Sciences Pvt. Ltd		02 Jun 2015
		lyophilized powder for concentrate for solution for Infusion in single and multiple use vials Strength: single use 150 mg trastuzumab multiple use vial 150 mg and 440 mg trastuzumab	Biocon limited		23 Oct 2013
3.	Ranibizumab	Solution for Injection in vial. Ranibizumab 0.5 mg -10mg/ml (2.3 mg/0.23ml) - Ranibizumab 0.3 mg - 6mg/ml (1.38 mg /0.23 ml) 1. Single Use Vial (Single vial containing of 0.5 mg or 0.3 mg Ranibizumab) 2. Combikit	Reliance Life Sciences Pvt. Ltd	Neovascular (Wet) Age-Related Macular Degeneration (AMD)	30 March 2020
		Solution for injection in single use vial of 0.23 mL contains 2.3 mg of Ranibizumab (10 mg/mL)	Intas Pharmaceuticals Ltd		20 Feb 2015

4	Bevacizumab	Bevacizumab Concentrate for Solution for Infusion Single use vial - 400 mg/16 mL, 100 mg/4 mL, (25 mg/mL)	Dr. Reddy's Laboratories Ltd.	Metastatic Colorectal Cancer (mCRC), Non-Squamous	04 Sep 2018
		vial for iv use (100mg/4ml and 400mg/16ml per vial)	Cadila Healthcare Limited	Non-Small Cell Lung Cancer (NSCLC),	12 May 2017
		Concentrate for solution in single use vial for iv use (100mg/4ml and 400mg/16ml per vial)	Biocon Limited	Recurrent Glioblastoma (GBM), Metastatic Renal Cell Carcinoma (mRCC), Metastatic Cervical Cancer, Recurrent Epithelial Ovarian, Metastatic Breast Cancer	01 May 2017
		Concentrate for solution in Single use vial for IV infusion Strength: 100 mg/4 mL and 400 mg/16 mL	Intas Pharmaceutics Ltd	Metastatic or recurrent non-small cell lung cancer	23 June 2016
		Concentrate for solution for IV infusion in Single use vial 100mg/4ml & 400 mg/16 ml	Hetero Drugs Limited	Metastatic colorectal cancer (mCRC)	13 May 2016
		Concentrate for solution for IV infusion in Single use vial 100mg/4ml & 400 mg/16 ml	Reliance Life Sciences Pvt Ltd		05 Jan 2016
5.	Infliximab	Lyophilized powder for intravenous infusion in vials contains 10 mg infliximab to be reconstituted with 10 mL WFI	Reliance Life Sciences Pvt Ltd	Rheumatoid Arthritis	21 March 2014
6.	Etanercept	Solution for subcutaneous Injection (single use) Pre-filled syringe:(i). 50 mg/mL in Prefilled Syringes (ii). 25 mg /0.5 mL in Pre-filled Syringes, Pre-filled Pen:(i). 50 mg/mL Pre-filled pen	Mylan Pharmaceutics Pvt Ltd	Rheumatoid Arthritis	07 Jan 2021
		Solution for subcutaneous Injection (single use) i. 50 mg/mL in Prefilled pen and Pre-filled Syringes ii. 25 mg /0.5 mL in Pre-filled Syringes	Lupin Limited		05 March 2019

		Etanercept injection lyophilized multi-use vial containing 25mg per vial	Reliance Life Sciences Pvt Ltd		07 May 2018
		Solution for injection in single use prefilled syringe contains Etanercept 25 mg/0.5 mL	Intas Pharmaceuticals Pvt Ltd		30 Sep 2014
7.	Adalimumab	Adalimumab 50 mg/mL. 10 mg/0.2 mL, 20 mg/0.4 mL, 40 mg/0.8 mL in single use prefilled glass syringe and 40 mg/0.8 mL in single use glass vial. Injections for SC use.	Hetero drugs Limited	Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis, Axial Spondylo	26 July 2017
		Solution for injection for SC injection in pre filled syringe contains 20 mg or 40 mg Adalimumab (50 mg/mL	Reliance Life Sciences Pvt Ltd	arthritis, Psoriatic Arthritis, Crohn's Disease.	26 Jun 2015
		Solution for injection in prefilled syringe contains 20mg and 40 mg	Cadila Healthcare Ltd.		25 Sep 2014

Source: Data collected from Company websites, CDSCO and other publicly available documents

It is worth noting from Table 1.1 that the number of manufacturers for most of the biosimilars used in cancer treatment ranges from one to four. Therefore, the dependency on market share alone for price determination (as per current practice in India) will give few companies a controlling stake in determining the ceiling price of the biosimilar. This provides an undue opportunity to the selected manufacturers (Bahl, 2018).

Furthermore, most of these biosimilars are supplied through the hospital network, and their adoption is heavily influenced by incentives and discounts offered by manufacturers to hospitals. In this highly regulated distribution system, the parameters of affordability and accessibility for the end-user, that is, the patient, are often overlooked, and most of the benefits are not passed on to them. According to a published report, a few biosimilars in India are among the lowest in cost compared to other parts of the world, yet they remain unaffordable for 80% of the Indian population (Bahl, 2018).

Table 1.2: Price variations of a few biosimilars in India

Name of biosimilar	Price of Brand 1	Price of Brand 2	Price of Brand 3	Price of Brand 4	Price of Brand 5
Etanercept	Enbrel; 17,170/PFS; 1mL	Enbrol; 28,740/Vial; 1 mL	Etacept; 6875/ vial; 3 mL	Intacept; 10,390/PFS; 1mL	--
Interferon α 2a	Alferon; 1000/vial; 3MIU	Exxura; 9175/vial; 0.5 mL	Inron-A; 970/vial; 3 MIU	LG Intermix Alpha; 2000/vial; 6MIU	Zavinex; 1175/vial; 3 MIU
Darbepoetin alfa	Darbotin; 2953/PFS; 40mcg	Dargen; 2506/PFS; 40mcg	Darbere; 2467/vial; 25 mcg	Darbecon; 2499/PFS; 0.4 mL	Darbelife; 2505/PFS; 40 mcg
Adalimumab	Adalipca; 25,000; 40 mg * 0.8 ml	Adalirel; 22,000; 40mg * 1	Mabura; 25,000; 40mg * 1	Plamumab; 16,071; 40mg * 1	Mabvinra; 23,999; 40 mg * 0.8 ml
Ranibizumab	Accentrix; 23,960; 100mg * 1mL	Lucentis; 70,160; 10mg * 1mL	Razumab; 17,000; 10mg * 1mL	--	--

Source: CIMS Database. Prices are in INR

The variations in the prices of a few biosimilar brands in India are provided in Table 1.2 and Chapter 7 of the thesis. This demands a detailed analysis of the biosimilar pricing ecosystem in India, including the factors that determine prices, their impact, government policies, regulations, distribution channels, stakeholder involvement, and ultimately the need for a dedicated costing mechanism for biologics.

1.4 Problem statement

In India, the National Pharmaceutical Pricing Authority (NPPA) amended the Drugs Price Control Order (The Drugs (Prices Control) Order, 2013, 2016) in 2013 and implemented a Market Based Price (MBP) for determining the prices of medicines. The Cost Based Price (CBP), in practice since 1979, was replaced as per the recommendation of a task force chaired by Pronab Sen (Recommendations of Task Force Chaired by Pronab Sen, 2005). The enactment of MBP by the Government of India initiated several debates and criticisms (Motkuri & Mishra,

2020; Narula, 2015; Renganathan et al., 2016; Shinde et al., 2023); the implemented method for drug pricing is different from the recommendations of the task force. As per the recommendation of the task force, the ceiling price of all drugs in the National List of Essential Medicines (NLEM) is to be fixed based on the weighted average price of the top three brands in the market by the value of single ingredient formulations. However, DPCO takes a simple average of price-to-retailer of all branded-generic and generic versions of a formulation with a market share of at least 1 percent and adds a national retailer margin of 16 percent.

The task force also recommended that all patented drugs and formulations should compulsorily be brought under price negotiation. The reference price in these cases will be the price of the closest therapeutic equivalent in the domestic market or the lowest price in the international market. This implies that the MBP for biosimilars can be influenced by the high prices of the originator and the biosimilars would be priced with reference to the originator cost. In addition, the number of manufacturers for most biosimilars is less (2 or 3) as compared to generic drugs (Pharmaceutical counterpart), leading to a manufacturer's monopoly. Moreover, fixing the average price to retailers (MRP) promotes high trade margins and incentives to distributors. Also, the clinicians and hospital procurement system can be lured by manufacturers through additional discounts. However, the discounts never reach the needy patients.

The Supreme Court of India constituted a three-judge bench led by Chief Justice Dipak Misra to evaluate the petition filed by All India Drug Action Network (AIDAN) challenging the MBP approach. In the 2015 verdict, the court asked the government to re-evaluate the shift from its earlier cost-based pricing policy to a new market-driven pricing² policy. As per the September 2023 proceedings of the Supreme Court,³ the union government has yet to place a mechanism for price control of essential drugs.

² <https://economictimes.indiatimes.com/news/politics-and-nation/sc-asks-government-to-explain-shift-in-drug-pricing-formula/articleshow/60967145.cms>

³ http://www.indiaenvironmentportal.org.in/files/file/price-control-life-saving-drugs-SC_Order_13-Sep-2023.pdf

1.5 Significance of the study

The affordability of medicine, specifically biotherapeutics, is one of the most complex and vexing challenges of the national and international healthcare system. The healthcare policies can be exploited by manufacturers, distributors, clinicians, and hospitals, hampering the accessibility of medicines to millions of people. The impact is not only restricted to the people at the bottom of the pyramid, but the uninsured patients of the developed world also suffer heavily from the financial burden of these high-cost lifesaving medicines (Augustine et al., 2018).

This research aims to untangle this complex yet critical problem and find implementable solutions for making biotherapeutics affordable in India. To be precise, the study attempts to develop a set of price indicators that can assist in measuring the prices of biotherapeutics in India. Having understood the most significant factors and global pricing mechanisms, the next logical step would be to suggest a framework for the factors affecting the prices of biotherapeutics in India.

Currently, there have been legal challenges to the MBP policy implemented by the NPPA, the government of India, and it is under evaluation (Mahajan, 2018; AIDAN Petition Proceedings, 2023). In this context, establishing an effective pricing mechanism for biosimilars is likely to have a significant impact on the affordability of these products.

Further, the research and development costs involved in biotherapeutics development are a grey area with limited literature. The cost reference developed through this study would help regulatory and international health agencies like NPPA, CDSCO⁴ and WHO in setting a harmonised pricing mechanism.

⁴ Central Drugs Standard Control Organisation is India's national regulatory body for cosmetics, pharmaceuticals and medical devices

1.6 Stakeholders for the study

The research attempts to bring the perspective of various concerned stakeholders including World Health Organisation, the Department of Health Research, biosimilar manufacturers, and the National Pharmaceutical Pricing Authority on this complex subject. The India specific recommendations might be useful for the WHO roadmap report, against the resolution WHA71(8), the pricing policy is one of the key milestones specified in the WHO roadmap. NPPA would directly benefit from the model developed for the determinants of prices. In general, the study attempts to elicit the opinion from national and international policymakers and provide a common platform for discussing fair pricing strategies and finding an implementable solution for the country.

The research employs a multidisciplinary approach and implicates interaction and cross-learning with different stakeholders of the Indian healthcare ecosystem. While the research is directly beneficial for NPPA, it engaged with WHO and manufacturers for guidance and consultation. Various stakeholders identified for the study are mapped in Table 1.3.

Table 1.3: Stakeholders for the proposed research

Organisation	Role / Purpose
NPPA	National Pharmaceutical Pricing Authority is an attached office of the Department of Pharmaceuticals (DoP), Ministry of Chemicals & Fertilizers and is responsible for pricing drugs and ensuring the availability and accessibility of medicines at affordable prices in India.
DBT	Department of Biotechnology, Ministry of Science & Technology, in collaboration with CDSCO developed a guideline on similar biologics. The guideline defined the process and regulatory requirements to bring similar biologics to India.
CDSCO	CDSCO is the national regulatory authority in India that evaluates the safety, efficacy and quality of drugs in the country.
DHR	Department of Health Research, Ministry of Health & Family Welfare is responsible for performing the health technology

	assessment, i.e the affordability, appropriateness and cost-effectiveness studies of the medicines.
WHO	WHO has proposed a mechanism for voluntary monitoring of the prices of medicines and a global system for drug price reporting. WHO/Health Action International project on medicine prices and availability was launched in 2001.
Biopharma Companies	Biotech companies manufacture and market biotherapeutic products in the country.
Niti Aayog	NITI Aayog is the policy think tank of the GoI. Opinions of policymakers will be taken for the study.
Medical Oncologists/ Clinicians	Medical oncologists and hematologists prescribe the medicine to the patients and are aware of the pricing and prescription-related behaviours of the customers.

1.7 Organisation of research work

The study design employs a sequential approach, in which data or findings from one objective are transferred to the other for further development. The final objective develops the mathematical model based on the inputs from previous objectives. The schematic of the research work is explained in Figure 1.1.

- Objective 1 develops the reference for cost estimates of biosimilar development in India, which is explained in Chapters 3 on Research Methodology and 4 of the thesis.
- Objective 2 determines the factors or antecedents that influence the prices of biotherapeutics and are detailed in Chapters 3 and 5 of the thesis.
- The hierarchy of the factors in the form of a framework is developed in Objective 3, which is explained in Chapters 3 and 6.
- The mathematical equation utilising the data from Objectives 3 and 1 is detailed in Chapter 7 of the thesis.

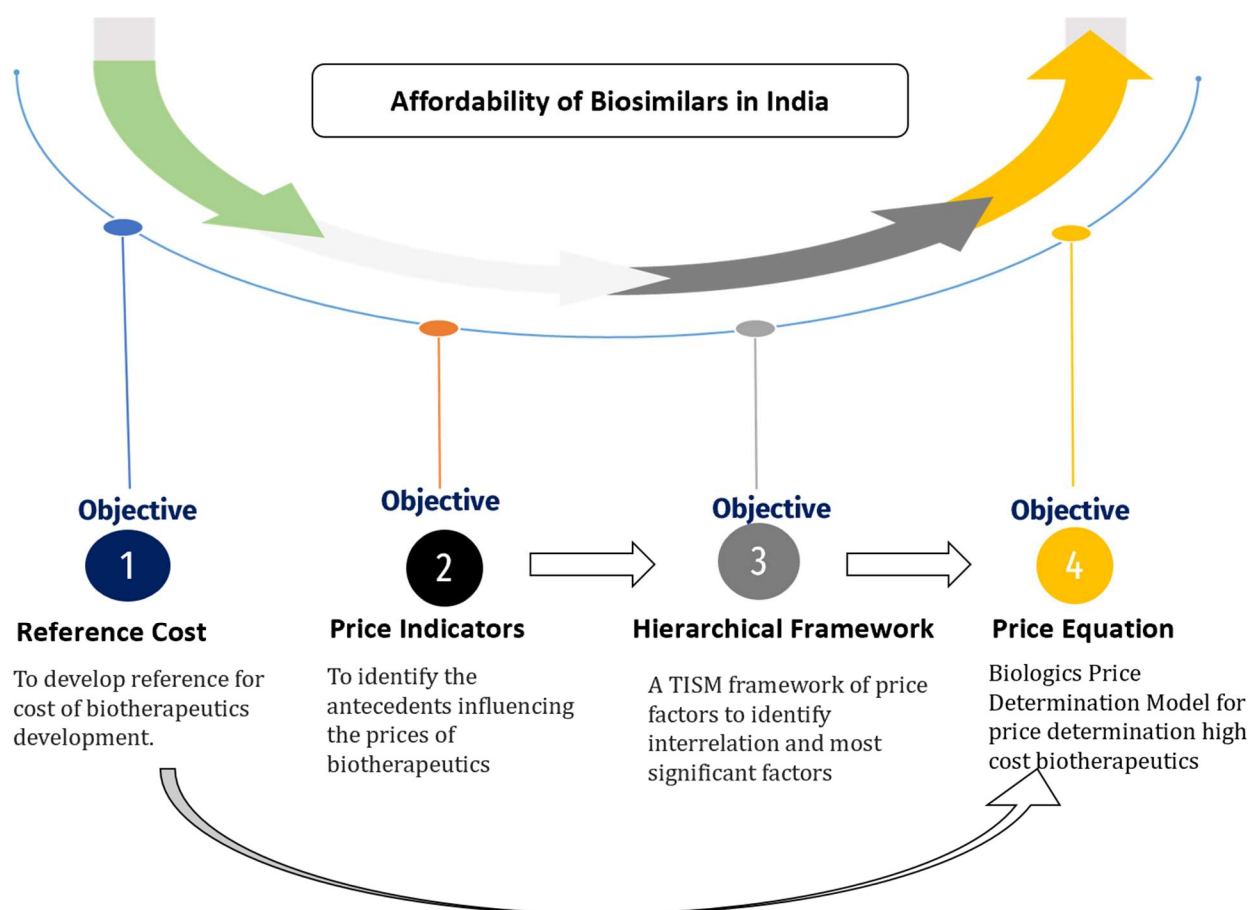


Figure 1.1: Research schematics

1.8 Key questions addressed through this research

Some of the critical questions to be answered by the study include:

- Which factors play a significant role in determining the prices of biologics in India?
- How are the prices of biotherapeutics defined at the firm and national levels?
- How does the stakeholders' network dominate the biosimilar adoption in India, and are there any loopholes in the healthcare system?
- What are the determinants of the prices of biotherapeutics? Is there a need for a harmonised global mechanism for regulating or monitoring the prices of biotherapeutics?
- What pricing and reimbursement approaches are used in India and internationally for biosimilars?

- Is it possible to develop an evidence-based tool for pricing biologics in India?
- Is the market share-based pricing mechanism a good option for determining the prices of biosimilars in India?
- How can we make biotherapeutics affordable and accessible in India?

1.9 Conclusion

The chapter lays the foundation for the thesis by describing the current price determination methodology in practice in India. The NPPA market-based price strategy suffers from major deficiencies, which are explored through the four objectives of the thesis detailed in Section 1.7. The Supreme Court of India has directed NPPA to explain the transition from cost based to market based pricing strategy. This research is a step towards developing a pricing approach for high cost biologics, which are not accessible to most of the Indian population. The affordability of biosimilars is a crucial research problem, and the variation in prices of brands in the country justifies this fact.

Review of Literature

2.1 Introduction

The argument related to the high prices of biotherapeutics, including similar biotherapeutics or biosimilars, is not new. Many researchers have highlighted the increasing trend in prices of biotherapeutic products and the various ways through which pharmaceutical companies indulge in profiteering from even outdated therapies (Blackstone & Fuhr, 2013; Rathore & Shareef, 2019; San-Juan-Rodriguez et al., 2019). Biosimilars in general dominate the market for oncology drugs; however, due to their high manufacturing and development costs, many end users are unable to afford these expensive prescription biologic drugs (Bachu et al., 2022). Biotherapeutics are a diverse class of complex molecules produced by living organisms, and their active ingredients mainly include cytokines, hormones, monoclonal antibodies, and insulin, which are mostly used for the treatment of various types of cancers (Similar Biotherapeutic Products, IFPMA). Due to different regulations, clinical norms, and distribution constraints, the price of these medications varies greatly between nations (Niazi, 2022). The various surveys also indicate that the public perceives drug prices to be unfair (Patricia Danzon, Andrew Mulcahy, 2015; Trujillo et al., 2020). Organizations including the World Health Organisation (WHO), Canadian Agency for Drugs and Technologies in Health (CADTH), and Organisation for Economic Co-operation and Development (OECD) have established standards and guidelines for this class of medications in response to the disputes sparked by the price variations (Knezevic & Griffiths, 2017; OECD, 2019; Rannanheimo Piia et al., 2018). However, biopharmaceutical companies frequently blame the expensive R&D and innovation costs linked to the molecule's discovery and development for the high price (Prasad et al.,

2017). The burden of these expensive medicines eventually restricts their availability to needy patients and calls for further deliberation.

2.2 Biosimilars – an opportunity for cost reduction

As per a 2017 report by RAND Corporation, it is anticipated that biosimilars or similar biotherapeutics have a huge potential of saving healthcare costs, which may lead to the reduction of \$54 billion in direct spending on biological drugs from 2017 to 2026 (Mulcahy et al., 2018).

As can be seen, biosimilars can be a game changer in reducing healthcare costs, but the pricing mechanism for biosimilars is a complex process and involves various stakeholders, including physicians, manufacturers, distributors, payers and policymakers (World Health Organisation, 2018). Biosimilars, a class within the larger group of biotherapeutics, are not the same as generic drugs. Generic drugs or generic medicines are manufactured synthetically or naturally and can be identically described or recreated using standard chemistry and pharmaceutical manufacturing techniques. A biosimilar or similar biotherapeutic or follow-on biologics or similar biologics; different terms used for biosimilars by regulatory agencies of different countries; cannot be duplicated to the same extent as generic drugs because they are produced using living cells; these proteins are more susceptible to structural variability and post-translational modification changes (Harvey, 2017). Globally, it has been demonstrated that generic drugs have significantly decreased the cost of healthcare, but there is currently insufficient data to determine how biosimilars will affect the rising cost of biologics. Additionally, it is difficult to extrapolate from one country's experience to other countries due to differences in how biotherapeutics are regulated/approved, bought, priced, and distributed (S. R. Mehr & Brook, 2017; Rugo et al., 2019). Hence, to employ this cost-saving potential of biosimilars, it is important to understand the various factors influencing the prices of these similar biotherapeutics.

2.3 Dimensions of the pricing ecosystem

This chapter is divided into two parts. The first part discusses six key dimensions of the pricing ecosystem, while the second part provides a systematic literature review (SLR) using image viewing software and SLR tools, including bibliometric analysis. The six dimensions were chosen based on subject knowledge. This section details these dimensions, and section 2.4 explains the systematic literature review.

2.3.1 An overview of price control measures

To support equitable access, numerous international organisations, like WHO, UNICEF, and Médecins Sans Frontières (MSF), to mention a few, have consistently emphasised the significance of creating mechanisms for reviewing, measuring, and controlling the pricing of vital medications, including high-cost biosimilars (Afzali et al., 2019; Kanavos & Vondoros, 2011; World Health Organisation, 2007). Their combined efforts, particularly in developing nations including Low-Middle- Income Countries (LMICs), have led to the creation of several guidance and policy documents that aid policymakers and other stakeholders (Abdel et al., 2017; OMS, 2020). Studies show that different countries control their pharmaceutical economies in different ways, but affordability is higher in countries where prices are regulated (Abdel et al., 2017; Babar, 2022). Many countries in the world regulate medicine prices either directly by setting prices through price control policies at the government level or indirectly by using pharmacoeconomic ways; Malaysia prefers little interference, allowing for a balance based on economic interactions between patients, suppliers, and the healthcare industry (Anggriani et al., 2013). In developed countries of the West, like New Zealand and the UK, the governments provide subsidies for medicines in both public and private sector hospitals and pharmacies, leading to low out-of-pocket expenditures for patients. Further, the medicine prices are negotiated by drug procurement agencies that are separate from regulatory authorities. In Canada, setting policies and regulating drug costs is a responsibility shared by

the federal government, jurisdictional governments, and their agencies. For its member jurisdictions, the pan-Canadian Pharmaceutical Alliance (pCPA) bargains for lower prices for patented, generic, and biosimilar medications. The pCPA requires biosimilars to be priced transparently, often with a reduction of 25 – 50 per cent (GaBi, 2022). While in countries like India and Pakistan, the prices of medicines are controlled at the selling point through the Maximum Retail Price, i.e., market-based pricing mechanism. The government-sponsored health insurance scheme is available only for the most vulnerable section of the population, and a large portion of the population relies on private insurance or out-of-pocket expenses (Renganathan et al., 2016). A few countries, like the United States and Malaysia, do not directly control the prices of medicines, leading to high prices of medicines in these countries (Babar, 2022). In the US, Medicare policy for cost-saving similar biotherapeutics is evolving and is based on average sales prices, discounts and rebates that are approved by the government. Because the markup on a lower price is smaller in monetary terms, providers would typically be punished for selecting a less expensive medicine. After the intervention by the Biologics Price Competition and Innovation Act (BPCIA); which defines a pathway for the approval of interchangeable biologics and biosimilars while retaining the incentives for the development of the product; Medicare's current payment policy for biosimilars provides an average sales price for all biosimilars with the common reference biologic; in addition, a fixed percentage of the originator is mandated (Mehr & Brook, 2017; A. Mulcahy et al., 2018). The impact of the BPCIA is not yet established, and it is not clear that the private insurers are incentivising biosimilars.

Currently, the major pricing mechanisms used by different nations are health technology assessment; using legislation to establish default rules that strengthen the insurer's negotiating position; capping prices close to those in other European nations (external reference pricing); setting a maximum retail price for comparable drugs (reference group

pricing); restricting price increases; purchasing drugs through competitive bids; contracting to obtain discounts as sales volume rise; and mandating manufacturers to provide refund payments when spending goes over a predetermined limit. It should be noted that despite different countries adopting different price strategies, there are still a lot of controversies regarding the appropriate pricing structure for expensive therapeutics.

2.3.2 Medicine pricing mechanism at the national and international level

The pricing mechanisms and regulations for pharmaceuticals have been under discussion for more than thirty years. Many international organisations, especially the WHO, through different forums, have highlighted the importance of pricing policies for affordability and equitable access to essential medicines (OMS, 2020).

Specific regulatory and pricing approaches are proposed by various organisations, but significant disagreement exists in finding the appropriate solution for the high prices of therapeutics. The TRIPS agreement allows access to patent medicines in the interest of public health, but the affordability and adoption remain issues for discussion in many countries. Further, scant literature on the pricing mechanisms of biotherapeutics makes the study challenging (Rao, 2011).

Various types of medicine pricing mechanisms adopted across the globe and their impact on affordability are described in Table 2.1. Multiple global studies have emphasised the need for an efficient mechanism for fixing the prices of medicines (Ferrario et al., 2020; WHO., 2021; Moon et al., 2020). But only a few deep dived into the specific requirements of high cost biosimilars. (PWC, 2019) The report describes the six financial risk-based pricing models adopted by biopharmaceutical companies to make biologics affordable and accessible. A comparative study from Brazil on biologics prices describes the disparities created by various pricing policies and highlights the necessity of political and regulatory debate (Pontes et al., 2023). Saudi Arabia implemented full control of the prices of biosimilars through the Saudi

Food and Drug Authority (SFDA) due to the excessive prices of biopharmaceuticals. (Alhomaïdan et al., 2016). WHO recommends a combination of pricing policies for the affordability of biosimilars (World Health Organization, 2020), as the general price capping mechanisms cannot be adopted as such for biosimilars. Developing nations apply a number of globally known pharmaceutical price policies, although their adoption is not optimal (Abdel et al., 2017). Taking into account both macro and microeconomic aspects, policymakers should customise the country's pharmaceutical pricing approach. The ideal pricing policy should consider various variables that might influence the prices of biosimilars, such as the manufacturing process (Rathore & Shareef, 2019), product attributes, the country's economy, strategic partnerships, government incentives, and regulatory framework (Gandhi et al., 2023). The existing pricing mechanisms, along with their unique characteristics and publications regarding their impact on affordability are detailed in Table 2.1.

Table 2.1: Medicine pricing mechanisms

Mechanism Name	Key Parameters	Impact on Price/Affordability	Paper
Internal reference pricing (IRP)	• Reimbursement • A group of interchangeable medicines with set prices • Patients pay the difference in price if the price at a pharmacy is more than the reference price.	As per the 2014 Cochrane review, IRP leads to a reduction in the price	(Ferrario et al., 2020)
External reference pricing	• Reference-based on international price comparisons. • Comparison as per the prices charged for the same medicine in other countries.	• Germany's case review reflects limited success. An initial reduction in the public expenditure was observed followed by an increase. • The use of branded products declined.	(Ess et al., 2003; Kawalec et al., 2017)
Differential Pricing / Ramsey Pricing (DP)	Different prices of the same medicines in different countries by a single manufacturer.	• DP can improve access for patients.	(Babar & Atif, 2014)

		• In the long run, it could benefit patients in both developing and developed countries.	(Chalkidou et al., 2020)
Value-Based Pricing	Prices in each country should be based on the actual, assessed value of the product within that health system. (Accounting for affordability and budgetary constraints)	• Increase the accessibility and affordability of health innovation in LMICs. • Reflect local opportunity costs	(Chalkidou et al., 2020)
Horizon Scanning	Pricing tool to prepare for the pricing and reimbursement of medicines that have not yet been launched	• Extremely time-intensive and costly. • Information on medicines in the pipeline is limited.	(Edwards, 2016)
HTA based Pricing	A technical evaluation tool that informs policy decisions on reimbursement and pricing by evaluating the clinical, economic, and other consequences of medicines	• Cannot work in isolation. • Need consideration of other parameters, like in orphan and cancer treatment; payers are sometimes willing to accept high prices for relatively low benefits.	(Edwards, 2016)
Central tender based pricing	The price of generic medicines can be reduced by creating economies of scale and pooling procurement across health facilities. Suppliers compete for contracts.	• It may decrease competitors. • The benefit is only to the winner. • Make the market vulnerable to shortages of essential medicines.	(Ferrario et al., 2020)

2.3.3 Indicators for measuring the prices

Currently, different kinds of indicators for various dimensions of the healthcare ecosystem are available and deliberated in the literature. WHO has defined three major indicators for accessibility namely physical, economic (affordability) and information accessibility. A review study by (Afzali et al., 2019) identified the indicators used for measuring the accessibility of medicines. A few economic accessibility or affordability indicators identified through the review study are total pharmaceutical out-of-pocket expenditure, Medicines' inflation rate, per

patient drug expenditure (monthly drug costs divided by the number of patients dispensed drugs), Affordability was measured as the number of days' wages required for the lowest-paid unskilled government worker to purchase standard treatments for common conditions, Affordability (GDP per capita), average household medicine expenditures as % of total health expenditures, type of insurance coverage, price variation of key medicines in public health facility dispensaries and private drug outlets and public medicines budget and per capita drug expenditures.

OECD has developed a set of health indicators (OECD, 2019) for measuring the health performance of 36 OECD member countries and partner countries. The health status indicators used are life expectancy – years of life at birth, avoidable mortality – deaths per 100,000 people (age-standardised), chronic disease morbidity – diabetes prevalence (% adults, age-standardised) and self-rated health – population in poor health (% population aged 15+).

The key health indicators for Indian states as described by (Patel et al., 2015) are social determinants like % of literate women, % of children younger than 5 years who are underweight, % of households that use open defecation, % of households with an improved source of drinking water, public spending on health per head, Average population size served by each government-run hospital bed, % of allopathic doctors who work in the public sector etc.

A study by (Borges Dos Santos et al., 2019) describes the various factors that can influence pharmaceutical pricing. The identified factors are grouped into themes like supply, demand and product-related market dynamics, trading strategies and regulatory approaches. The literature review highlights the gap in developing a set of indicators for measuring the prices of biotherapeutics as per the country-specific policies and regulations. (Walley et al., 2006) derived a few markers of the prices of medicine. They also highlighted the limitations of using them in price setting.

2.3.4 Factors impacting the prices of biotherapeutics

A literature review was performed to determine the factors associated with the prices of biosimilars; the research articles published in the time zone of 2010 to 2021 are collected in Table 2.2.

Table 2.2: Key factors impacting the prices of medicines

S. No.	Author /Year	Objectives of the study	Factor(s) (Study period)	Medicine & Geography	Key Findings
Market dynamics					
1.	(Dylst & Simoens, 2011)	Impact of market share of generic medicines on prices in European off-patent markets.	Market share (June 2002 to March 2007)	Medicines in oral, solid and immediate-release dosage forms. Austria, Belgium, Germany, Denmark, France, Netherlands, Italy, Sweden, Spain and UK.	The price varies as per the market share of generic medicines. Competition from generic medicines leads to price reductions. Generic market share is directly proportional to a decrease in medicine prices.
2.	(Meiners et al., 2011)	Antiretrovirals (ARV) price evolution and market dynamics	Market competition and demand (1996 and 2009)	ARV procured in Brazil	Chances of generic suppliers responding to factors influencing demand size and market competition are high. Originator suppliers set prices strategically to reduce compulsory licensing and generic competition threats.
Selection Strategy					
3.	(Zeng, 2013)	Comparison of the price and use of generic and originator	Originator vs generics (2006 to 2011)	12 cardiovascular drugs China	Switching originator drugs to generics results in savings of 65% for patients.
4.	(Takizawa et al., 2015)	Quantitative relationship of the selection between the originator and the generic drug	Selection strategy	Dispensing and hospital claims databases of out-of-hospital pharmacies and in-house pharmacies in Japan	The price of the originator varies with the selection strategy between branded and generic drugs in out-of-hospital pharmacies, but not in in-house pharmacies of medical facilities.

Economic drivers					
5.	(Helble & Aizawa, 2017)	To study the relation between prices and per capita income.	Per capita income (1995 to 2013)	Insulin prices for 186 importing countries	Per capita GDP is positively correlated with the unit price of insulin. The price of insulin drugs originating from OECD countries is higher than that imported from developing countries.
6.	(Rathore & Shareef, 2019)	Domestic manufacturing capabilities on the prices of biologics	Domestic demand and the paying capacity of the economy	Insulin, Erythropoietin, Human growth hormone, Interferon Emerging Economies like China, Japan, Korea, India, South Africa, and Nigeria	Developing domestic manufacturing capacity is important, but due to complexities, it is not a recommended option for emerging economies. It is recommended to expand the market and facilitate the import of biologics.
Pricing Mechanism					
7.	(Kawalec et al., 2017)	Comparison of the reimbursement requirements for biosimilars and generic medicines.	Reimbursement costs of biosimilars, Market share (November 2016 and January 2017)	25 Biosimilar brands for 10 biologic drugs: Enoxaparin sodium, Filgrastim, Epoetin alfa, Epoetin zeta, Follitropin alfa, Etanercept, Insulin glargine, Teriparatide, Infliximab, and Somatotrophin. Central and Eastern European (CEE) countries	No specific difference was observed between the reimbursement criteria for biosimilars and other generic products in the selected CEE countries. The price of biosimilars is usually reduced in comparison to original drugs, and huge price discounts are offered.
8.	(San-Juan-Rodriguez et al., 2019)	Change in list prices, net prices, and discounts of the originator products with biosimilar entry	List prices, Net Prices, Discounts (January 2007 to June 2018)	Filgrastim, Peg-filgrastim, Insulin glargine and Infliximab. USA	The price drop is observed for originators after the entry of biosimilars or other substitutes in the market. The entry of biosimilars stopped the increase in list prices but net prices commenced to decrease due to discounts offered by companies.

Process Innovation and M&A					
9.	(Richman et al., 2017)	The relation of mergers and acquisitions (M&A) with upstream and downstream factors of drug development	Innovation and competition in the market	Pharmaceutical Medicines. USA	Price does not correlate with market power based on Industry concentration (HHI Index). M&A induced market concentration may weaken competition. The potential danger of market concentration is at the stage of regulatory approval.
10.	(Gotham et al., 2017)	Pricing based on API, formulation, packaging, and profit margin	Costs/kg of chemical reagents, routes of synthesis and yield	Multi-drug resistant tuberculosis medicine	Competitive large-scale generic manufacturers can supply 5-10 times more MDR-TB treatment within current procurement budgets.
Psychological factors					
11.	(Weijters et al., 2018)	Comparing consumer behaviour towards generic price terms like cheap and not expensive	Consumer behaviour	No specific medicine	Cheap is associated with lower prices than the not expensive word. It is not related to higher preferences for cheap drugs as it may evoke negative quality perceptions.
12.	(J. Yang et al., 2021)	The financial impact of introducing pegfilgrastim biosimilar.	Impact of new biosimilar entry	Comparison of GCSF with pegfilgrastim (Nyvepria) in the French healthcare system	The introduction of new biosimilar pegfilgrastim resulted in substantial cost savings for French healthcare.
Product-specific factors					
13.	(Shiragami, 2015)	Variation in prices with the drug information	Information provided with the medicine	No specific medicine. 229 products in 13 different formulations in Japan	Information provided for generic drugs is less than for brand drugs. The difference in the quantity of information is based on

		sheet provided with generic and originator			differences in the manufacturer's policy on the information.
Pricing Policy					
14.	(Babar & Atif, 2014)	Differential pricing of pharmaceuticals – Literature review	Differential pricing policies	Research articles selected from the WHO website. No specific medicine and countries were targeted.	Differential pricing policies are feasible mostly for ‘global’ diseases, where drugs through worldwide sales recoup their R&D costs. The differential prices vary with the pharmaceutical industry and do not encourage sustainability or autonomy in developing countries.
15.	(Hu et al., 2019)	Impact of New Public Medicine Procurement Policy (NPMPP) on medicine prices	New Procurement Policy (2015 – 2017)	Emergency, paediatric and gynaecological medicines. Shaanxi Province, Western China	The introduction of the NPMPP policy led to an increase in the prices of emergency medicines and gynaecological medicines but a decrease in the prices of paediatric medicines.
16.	(Ferrario et al., 2020)	Role of strategies in determining the prices of medicines	Pricing policies	No specific sample size. Generic medicine and Biosimilars	Despite many efforts toward the implementation of policies to increase biosimilar adoption, a large difference remains in the price and uptake of medicines between countries.
Regulations					
17.	Zhang, Wei, et al. 2016	Price-cap regulations and generic firm exit	Price Cap Regulations (2003–2012)	Formulary listings of prescription drugs. The Ontario Drug Benefit program, Canada.	A continuous decline in the ceiling prices is associated with a high incidence of exit of generic firms from markets.

(Source: Collected by authors through literature review)

The review on price factors indicates that factors like market share, market competition, and pricing policies are extensively explored, but limited studies focus on innovation capability (R&D), regulatory framework, and mergers & acquisitions (M&A). Evidence-based studies can be undertaken to understand the important primary and secondary factors affecting the prices of biologics. Variables such as technological innovation, R&D costs, production yield, regulatory ecosystem, and patent protection could be further explored as potential factors impacting the prices of biotherapeutics. It is important to point out the studies on consumer behaviour, pharmacy type, and product information sheet, which are often overlooked. In addition, the inter-linkages between the factors leading to the complexities of the pricing mechanism are an interesting research area for further consideration.

2.3.5 Fair pricing models

Scant literature is available on the pricing models for biotherapeutics. The fair pricing zone model proposed by (Moon et al., 2020) describes a framework in which a fair pricing zone lies between a price floor (Minimum) and a ceiling (Maximum). The lowest price at which a supplier can sell a medicine sustainably is called the price floor. The price floor includes the full development cost, like research, manufacturing, distribution, regulatory costs, and a fair profit. The price floor should incentivise innovation and maintain competition. The price ceiling depends on the maximum cost the buyer can incur. Prices above the ceiling are defined as excessive and would justify the country-specific regulation and policies.

The framework is based on a concept that considers the needs of both sellers and buyers, and the end-user, i.e., the patient. While securing innovation, sustainable supply, and affordability. However, the proposed model is not based on any scientific method to justify the various factors that can impact the prices of biotherapeutics.

The indicators of the public- and private-sector contribution to biopharmaceutical R&D are proposed by (Simoens & Huys, 2022). The set of three indicators used for the price model

includes “Authorship of publications”, “Marketing Authorisations” and “Intellectual property rights” as the indicators of contribution. The identified indicators have limitations, as the private sector publishes fewer papers than the public sector, but is more likely to pursue marketing authorisations. The proposed indicators do not consider the unequal contributions of the authors. They do not account for unpublished manuscripts or medicines that do not gain marketing authorisation. The IP indicator does not recognise the non-patented contributions.

2.3.6 Research & development costs of biotherapeutics

The R&D cost refers to the cost involved in the development of any molecule from the very inception of the developmental process. In India, the Department of Biotechnology (DBT) and CDSCO released a guideline in 2016 (DBT CDSCO, 2016), which defines the various regulatory requirements to obtain the manufacturing authorisation of biosimilar or similar biotherapeutics in India. As per a report, 201 active biosimilars are in the pipeline of 52 Indian pharmaceutical companies (BIRAC, 2019). The various steps to develop a similar biotherapeutic and the key features of the regulatory guidelines are published and deliberated by many researchers (Ratih et al., 2021; Rugo et al., 2019).

Many reports⁵ and studies provide an estimate of R&D expenditure by a biotech company (country-wise or across countries). A study by Evaluate Pharma calculated that global private-sector expenditure on biopharma R&D increased from US\$136 billion in 2012 to US\$186 billion in 2019. OECD⁶ has developed two indicators to monitor R&D expenditures – “Business enterprise expenditure on Pharmaceutical R&D” and “Government budget allocation for health-related R&D”. Currently, these indicators are used as investments or R&D input cost data by the biopharmaceutical industry. These indicators act as proxies for

⁵ EvaluatePharma ([https:// www.evaluate.com/](https://www.evaluate.com/))

⁶ (https://stats.oecd.org/Index.aspx?DataSetCode=MSTI_PUB#)

investments, but the literature also identifies many factors that can impact the investment and developmental cost of a biosimilar.

Most of the available literature discusses the costs of one or two phases of developing biotherapeutics; a study by (Webster & Woollett, 2017) highlights the substantial costs required for performing the bridging studies between local and foreign versions of an originator biologic without providing any additional patient benefit or scientific data for the regulatory approval of the biosimilar. (Adwal & Baghel, 2019) evaluates the variation of cost among different brands of anti-cancer drugs available in the Indian market. The literature review led to research papers on cost variations, but none of them map the costs against the developmental stages as defined by the regulatory agencies.

The review revealed that the price difference of biosimilars from their reference product is not the same as that of generics and their originator product in the pharma domain. This is because of the complex manufacturing process of biosimilars. (Ditani et al., 2021) calculated the estimated cost of biosimilar therapy in the oncology sector. As per the analysis, the current expenditure on therapy is approximately 35% of the cost of targeted biological drugs. The use of biosimilars in cancer treatment reduces the cost burden of biologics. Similarly, the studies reflect the various aspects of biosimilar development, like affordability and accessibility (Trapani et al., 2021) but the gap is found in the literature for estimating the actual costs involved in the development of a biosimilar.

2.4 Systematic Literature Review

The Systematic Literature Review (SLR) is a tool used to evaluate available research content methodically. It collects multiple published papers based on the keyword search and generates a summarised evidence to answer a research question.

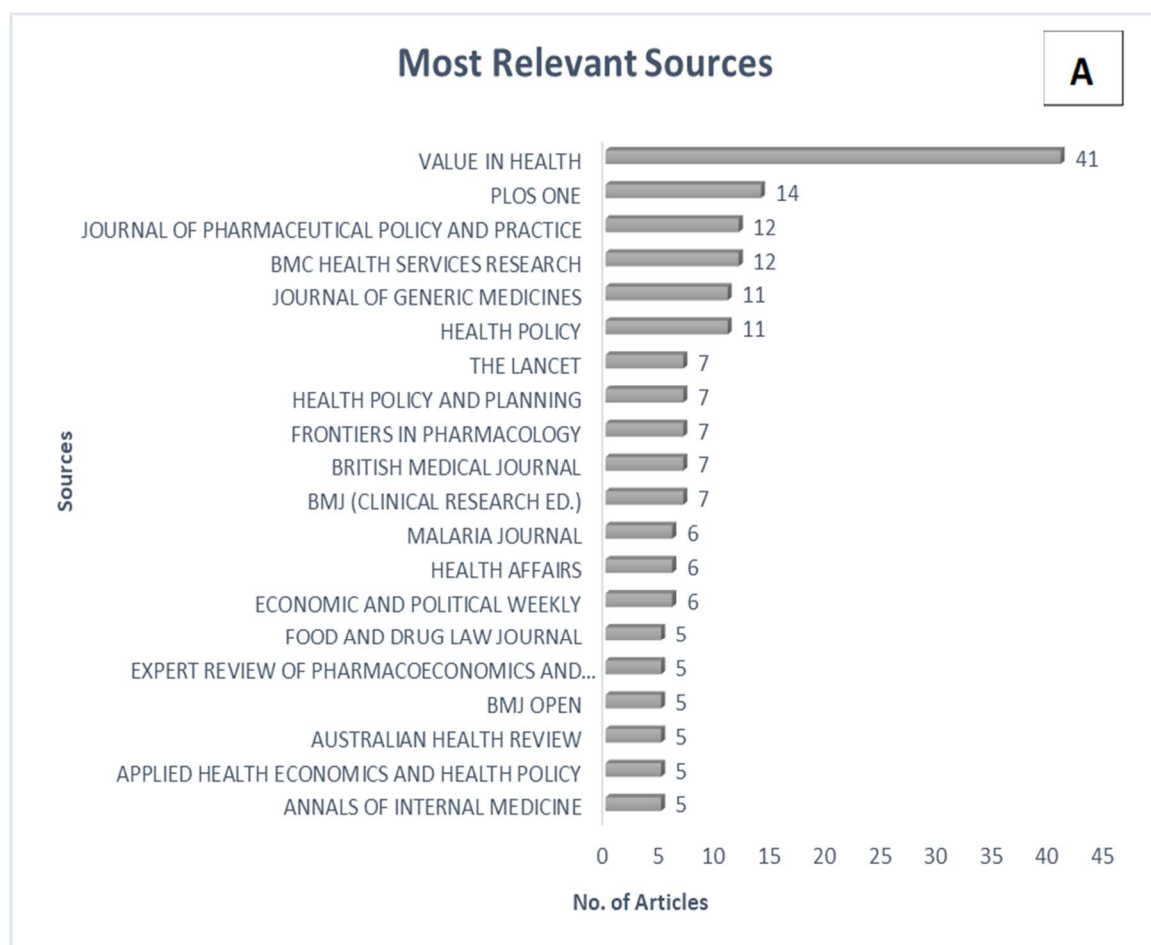
There are multiple methods and tools for conducting an SLR. It provides a comprehensive overview of the research landscape related to a theme and transforms qualitative data into quantitative evidence. The SLR generates extensive information on the authors researching a theme, the social interaction scores between them, collaborations, major institutions related to the theme, and journals publishing such research. This helps in developing historical trends and can be used to forecast and identify significant research gaps. The study design, including research objectives, keyword selection, three verticals, and the flow of information, is described in Chapter 3 (Research Methodology) of the thesis.

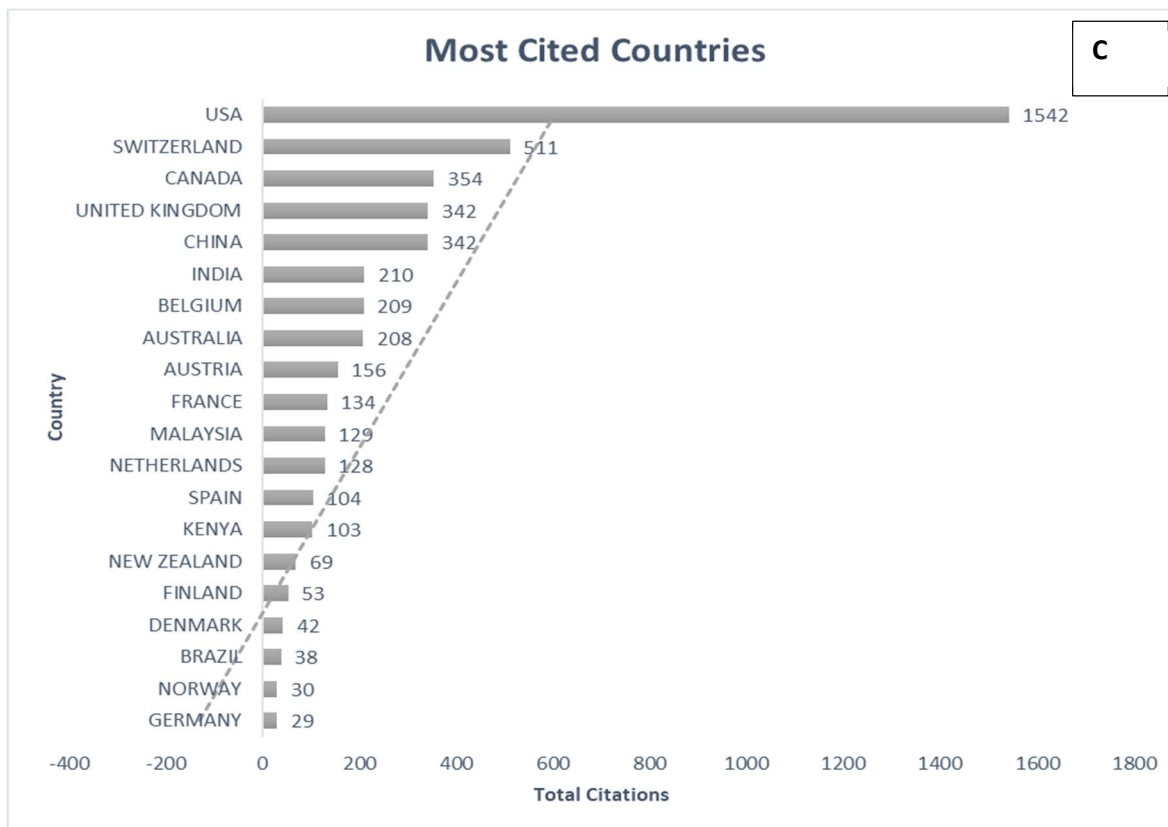
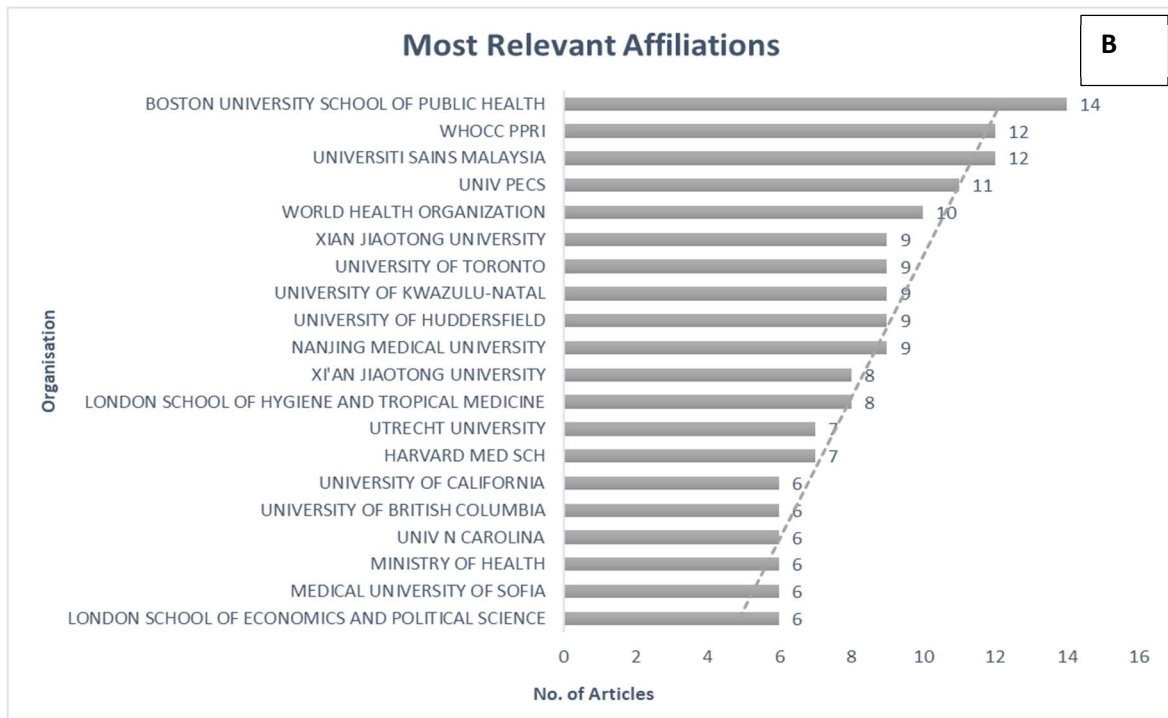
The SLR study has identified many elements that affect the cost of biotherapeutics, specifically biosimilars. The study began with a larger range of search terms, such as biotherapeutics, biologics, generics, and biosimilars. However, after bibliometric investigations revealed that biosimilars were an active topic of discussion, a specific study on biosimilars was conducted. As highlighted earlier, a biosimilar is a class of products under the larger group of biotherapeutics. The keyword ‘generics’ is also a crucial component of this review because biosimilars are frequently compared to generics, making it challenging to distinguish them. Moreover, a few policies and regulations about generics apply to biosimilars as well. The addition of generics in the first keyword search strategy has helped in identifying many research articles that are relevant for biotherapeutics and particularly biosimilars.

2.4.1 Overview of the pricing ecosystem

This section presents an overview of the performance of the entire pricing ecosystem of medicines and narrows it down to biosimilars. The results in Figure 2.1 indicate that Sabine Vogler of the World Health Organization Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies (WHOCC PPRI) has made a significant contribution to the domain of pharmaceutical pricing mechanisms and policies. The same is also evident from the most relevant affiliations section, wherein the WHO and its collaborating centres have published a

significant number of articles. Similarly, Laing R from Essential Medicines and Pharmaceutical Policies, World Health Organization, Geneva, Switzerland has worked extensively in the essential medicine domain. Country analysis indicates that the maximum number of cited papers is from the USA and Switzerland. In terms of the most relevant sources, the maximum articles are published in “Value in Health”, “PLOS ONE” and “Journal of Pharmaceutical Policy and Practice”.





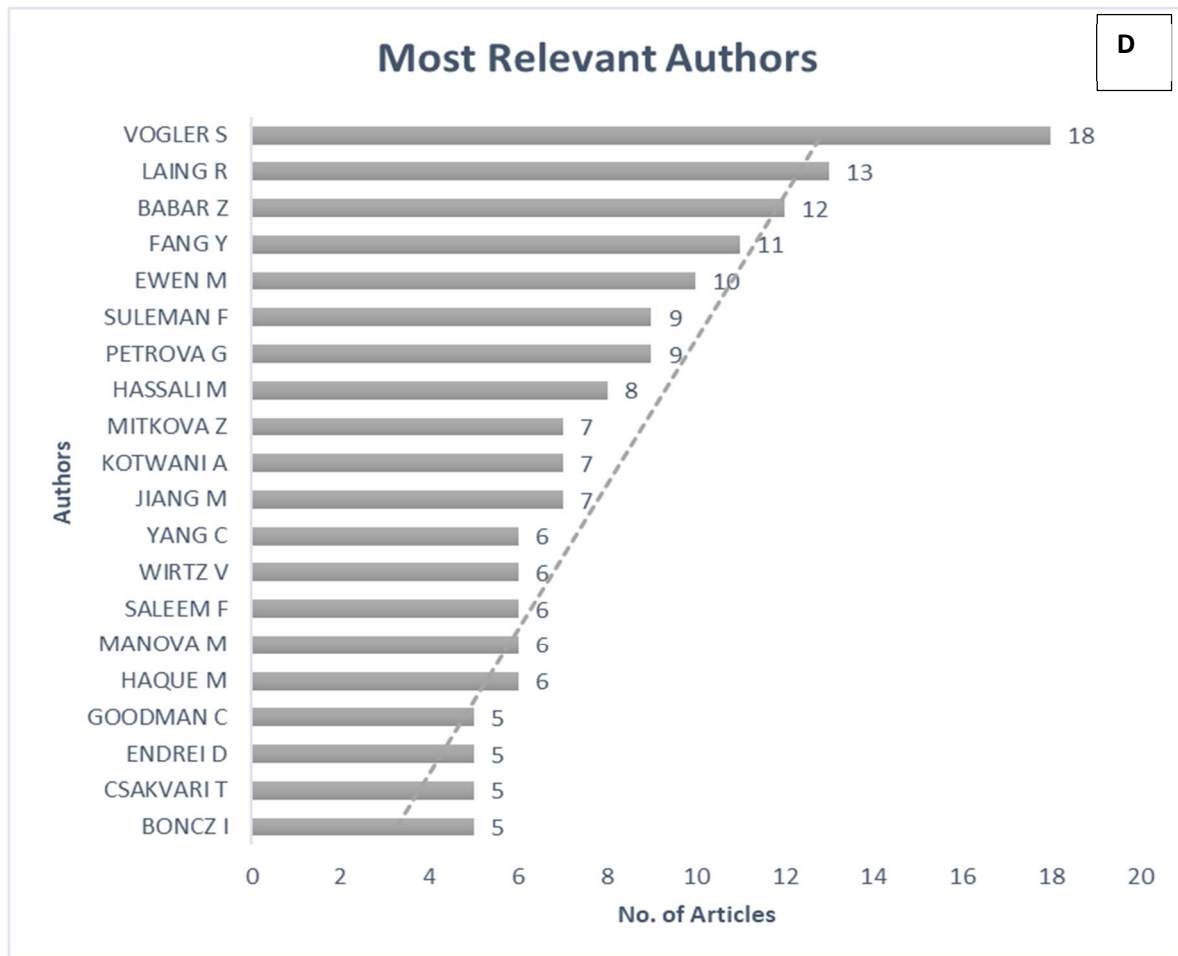


Figure 2.1: Performance overview of pricing ecosystem: A-leading sources, B-affiliations, C-countries, and D-authors

2.4.2 Chronological trends

Chronological Trends on the year-wise publications of the leading 20 authors reflect that most of the articles are published between 2011 to 2020. Additionally, the maximum number of papers was published in the year 2019. While the maximum articles are published by Vogler S, Ewen M, and Laing R remain the most consistent authors of this domain. Likewise, analysis of leading sources reflects the exponential increase in the number of publications from 2007 onwards. Journals like PLOS ONE, Lancet, BMC Health Services Research, Frontiers in

Pharmacology and BMJ are publishing consistently in this domain, but “Value in Health” emerged as the leader in the domain after 2005 (Figures 2.2 & 2.3).

The results of chronological trends are based on the author and source developments as depicted in Figures 2.2 and 2.3.

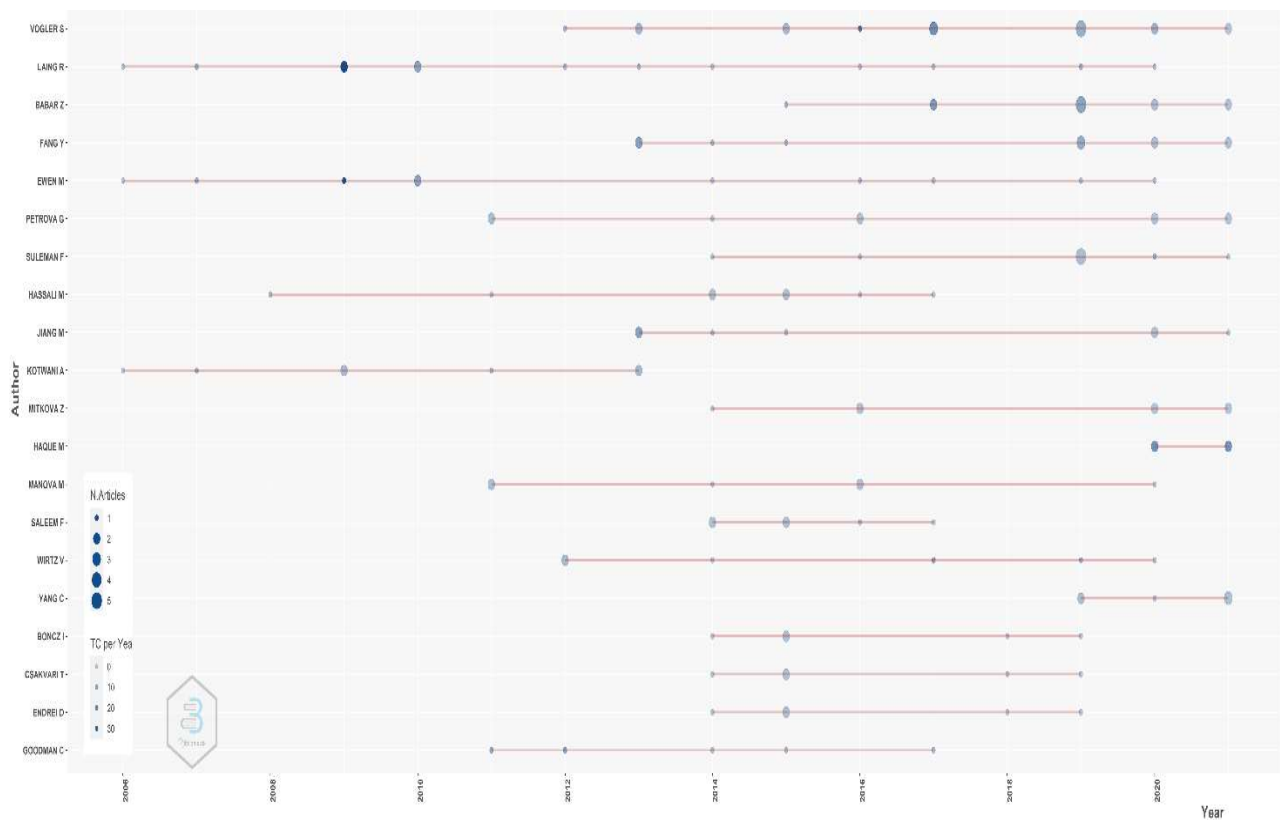


Figure 2.2: Historical trends for leading authors

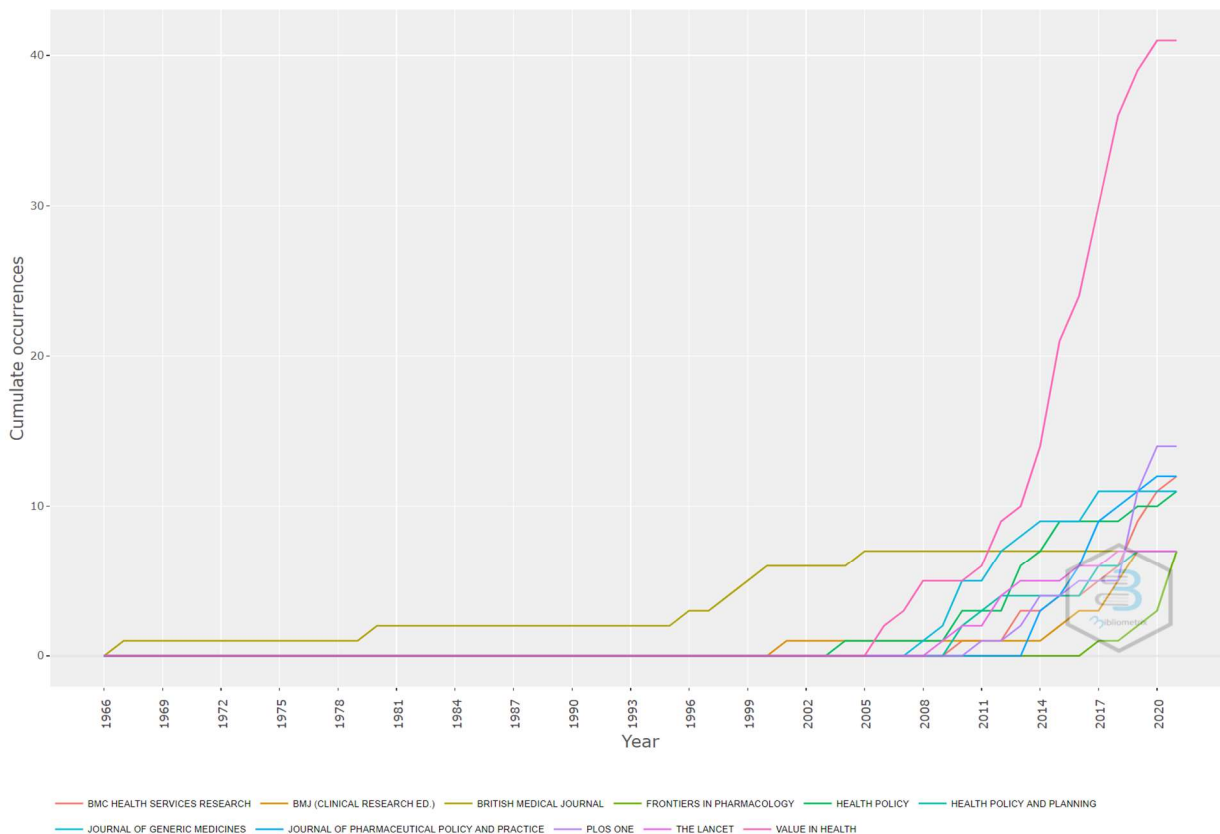


Figure 2.3: Leading journals - publication trends

2.4.3 Collaborative / Concerted trend

Collaborative / Concerted trend: Figure 2.4 presents a keyword co-occurrence map and depicts the relation between the keywords based on their co-occurrence within the dataset. It further highlights the nine clusters generated from 759 eligible items with a threshold limit of three. In-depth analysis indicates drug economics/cost control (N=649), human (N=508), article/journal (N=339), generic drug industry (N=333), health services accessibility/healthcare delivery (N=201), healthcare policy (N=132) and essential drug (N=114) have high occurrence scores.

Table 2.3: Co-authorship map depicting the strength of social interaction between the authors

S.No	Author	No. of documents	Total link strength
1	Vogler S	17	27
2	Babar Z.U.D	11	20
3	Fang. Y	10	24
4	Suleman. F	10	7
5	Ewen. M	9	11
6	Hassali. M.A	8	16
7	Jiang. M	6	16
8	Saleem. F	6	14
9	Petrova. G	6	12
10	Laing. R	6	10
11	Wirtz. V. J	6	8
12	Kotwani. A	6	2
13	Schneider. P	5	12
14	Mitkova. Z	5	10
15	Kesselheim. A. S	5	4
16	De Joncheere. K	4	13
17	Yang. C	4	11
18	Manova. M	4	10
19	Waning. B	4	6
20	Dave. C. V	4	4

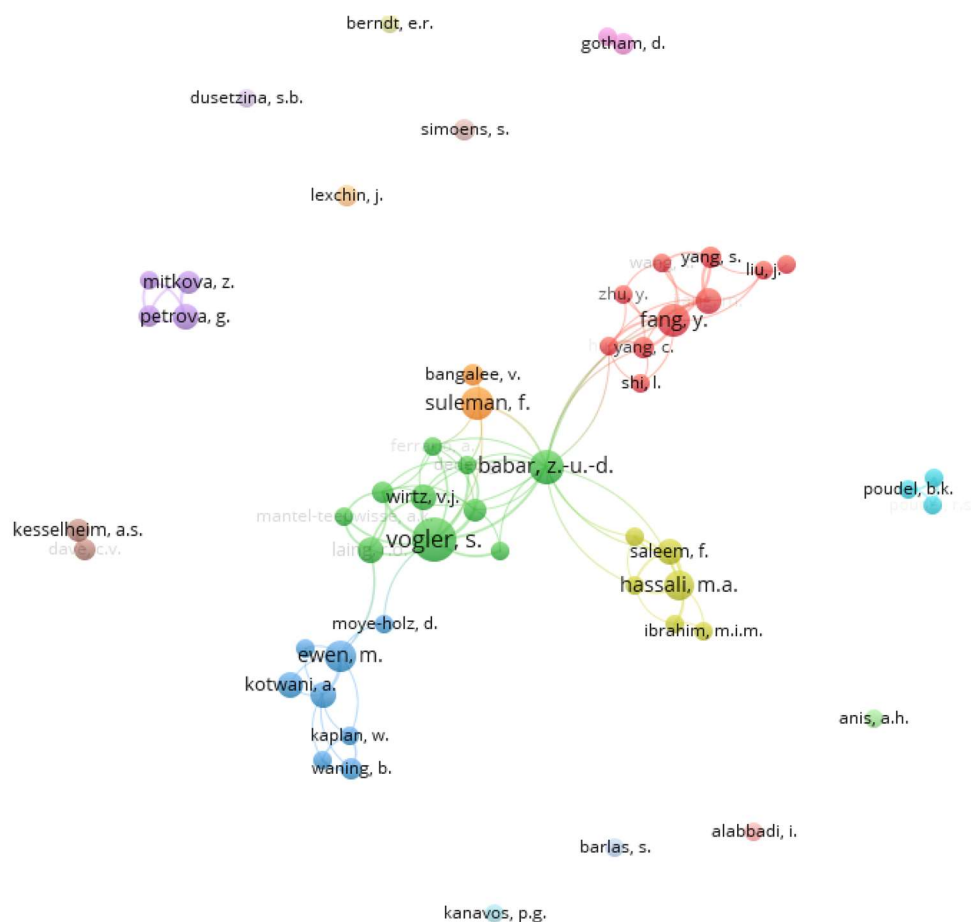


Figure 2.5: Co-authorship map representing relationships between the authors

The co-citation network (Figure 2.6) reflects three prominent groups with similar intellectual structures and a high association index. Further deep diving indicates the first group of (Cameron et al., 2009) with significant work on the “WHO-HAI methodology”. The study with a sample of 36 developing and middle-income countries has been cited 486 times. The second group, “Prices of generic medicine and branded prescription drugs”, highlights the effects of generic competition. A study by (Lexchin, 2004) has been cited 67 times, while a study describing price response to generic entry in the market for originator by (Frank & Salkever, 1997) has been cited 64 times. The third group indicates the “Pricing and Reimbursement policies” like external reference pricing, differential pricing, and comparison of international prices. The study by (Simoens, 2007) on generic price-regulation systems in nine European countries has been cited 47 times. Further, the study by (Danzon & Furukawa, 2008)

highlighting the pharmaceutical spending, usage, availability, and prices in twelve countries, including the United States, has received citations in about 100 papers.

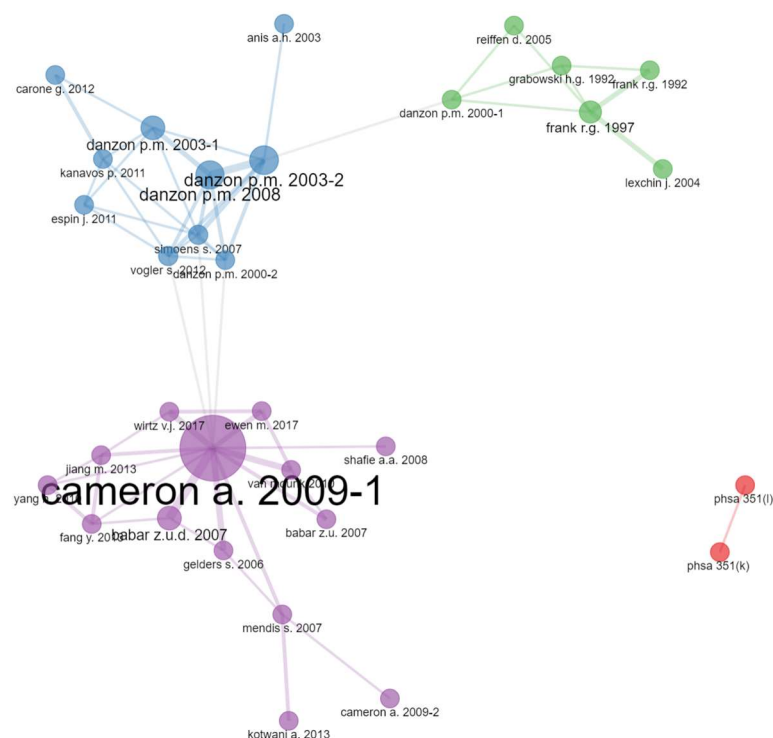


Figure 2.6: Co-citation map - relationships between the cited publications.

Note: It depicts the three major groups of researchers and themes described in the co-citation section. Developed through the Louvain clustering algorithm with 100 node strength and a minimum of two edges as the threshold limit.

2.4.4 Concluding observations from SLR

The findings highlight that the biosimilar price subject has gained momentum only after 2010, leading to significant research publications. Few themes, like “biosimilar prices and quality”, have evolved, but the basic foundational concepts like medicine prices, generic competition and essential medicines have remained unchanged in the evolutionary process. It is observed that most of the deliberations on the prices are restricted to essential medicines, while areas like neglected diseases and orphan drugs are left out of major consideration.

While the research on biosimilars prices is building up at a significant rate, the current share in terms of research publication is only 11% and remains minuscule in the full set of generic medicine and essential drugs domain. The results of various studies performed are summarised in Table 2.4.

Table 2.4: Summary of SLR observations

Study Vertical	Study Parameter	Key Findings
Trend Analysis		
Performance Breakdown	Time	Most of the articles relating to price determinants are published between 2011 to 2020
	Country	Articles from USA, Switzerland and Canada are cited a maximum number of times
	Journals	Value in Health, PLOS ONE and Journal of Pharmaceutical Policy and Practice are publishing significant number of research papers in this domain
	Authors	Sabine Vogler, Laing R and Babar Z.U.D have contributed significantly to the development of the area
Collaborative Trends	Co-occurrence trends	Drug cost control, generic drug industry, essential drug, health services accessibility and healthcare policy have high co-occurrence scores
	Co-authorship trends	Sabine Vogler, Yu Fang, and Babar Z.U.D share the high social interaction scores with link strengths of 27, 24, and 20 respectively
	Co-citation trends	WHO-HAI methodology, prices of generic medicine / branded prescription drugs and pricing cum reimbursement policies are three prominent groups

The review of grey literature uncovered substantial initiatives from WHO and its collaborating partners in this direction. At the 54th World Health Assembly, WHO member states passed a resolution that demanded a mechanism for voluntary monitoring of the prices of medicines and a global system for drug price reporting. In response to the resolution, the WHO/Health Action International (HAI) project on medicine prices and availability was launched in 2001. Under the project, HAI has conducted surveys in more than 50 countries. Extensive literature,

including technical reports, white papers, guideline documents, medicine price books, and data generated from the surveys, is available on the WHO website.

It is evident from the review that the biosimilar prices domain is a multifaceted web of innovators, manufacturers, suppliers, distributors, pharmacies, and in-hospital chains. Moreover, most end users are not aware of the difference between the originator and biosimilars, leading to high out-of-pocket expenses.

2.5 Identified research gaps

- The review of literature reveals that most of the studies are descriptive, and only a limited number of empirical studies are performed.
- It is clear from the findings that most research focuses on market dynamics. Therefore, medicine prices are primarily influenced by market forces. There is limited research on manufacturing costs and product parameters.
- The review raises an important question: in the absence of significant research on other factors and the availability of pharmacoeconomic data for many molecules, is it justified to continue with market-based costing policies? or the decision-makers should start exploring other efficient alternatives.
- Policies like external referencing, value-based and switching policies have been extensively researched. However, the supply side (reimbursement) and procurement (tendering) policies need further research to untangle the complexities of the biosimilar pricing mechanisms.
- Studies on incentives and profit margins associated with the last-mile delivery and accessibility of high-cost cancer biosimilars are essential for their improved adoption.
- It is worthwhile to note that there cannot be a “one size fits all” framework/ rule that can be applied to all countries. Hence, there is a need to develop country-specific

costing and pricing strategies that align with the politics, regulations, market dynamics, and economic ecosystem of that country.

- It is noteworthy that in the absence of a synchronised method to determine the payment rate, US federal agencies usually pay different prices for the same prescription drugs (Chalkidou et al., 2011). In the future, it is important to extend this research to cover other aspects of pricing, like costing models and pricing mechanisms used by nations, that may help reveal unidentified factors that drive pricing decisions.
- The efforts and policies developed for the uptake of high-cost biosimilars are not different from generic medicines. Biosimilars have different manufacturing processes (biological processes) as compared to generic drugs (chemical synthesis). Hence, the pricing mechanisms and regulation policies developed for generic medicines cannot be replicated for biosimilars.
- Emerging themes that invite future research are biosimilar costing mechanisms, healthcare insurance/expenditure, and associated pricing regulations. These areas are relatively less explored and demand greater efforts to develop the knowledge of the subject.

2.6 Conclusion

This chapter reviewed the available publications on the pricing mechanism of medicines. The review of the five dimensions of the pricing ecosystem helped in developing an overall understanding of the entire theme. The SLR section of the Chapter generated quantitative information and trends, which helped in identifying the research gaps for the study. These research gaps are further translated into the research questions in the next Chapter.

Research Methodology

3.1 Introduction

This Chapter describes the methodology employed to achieve the targeted objectives of this research. It builds on the knowledge acquired from the previous Chapter on literature review and translates it to focused research objectives. This Chapter also serves as the backbone of the thesis and provides an overview of the research questions, sample selection, data collection tools, databases used, and study design, along with the research objectives and methodology. For easy understanding, we tried to map the methods used in this research with their respective objectives in separate sections of this Chapter.

3.2 Research Questions

RQ 1: How are the prices of biotherapeutics defined at the firm and national levels?

RQ 2: Is it possible to develop an evidence-based tool for pricing biologics in India?

RQ 3: What are the determinants of the prices of biotherapeutics? Is there a need for a harmonised global mechanism for regulating or monitoring the prices of biotherapeutics?

RQ 4: How can we make biotherapeutics affordable and accessible in India?

3.3 Research Objectives

3.3.1 A reference for the research & development costs of biotherapeutics

RO 1: To develop a reference for the development costs of a few biosimilars at the industry level

3.3.2 Framework of the price indicators

RO 2: To identify the most significant factors that determine the prices of biotherapeutics in India

RO 3: To develop a set of indicators/antecedents for defining the prices and develop a hierarchical framework of the factors affecting the prices of the biotherapeutics in India

3.3.3 Modelling the fair price equation and multi-country comparison

RO 4: To develop a fair price equation for biosimilars and compare the pricing framework with 5 countries.

RO 4.1: To develop a mathematical equation and validate the tool to define the ideal characteristics of the fair pricing framework.

RO 4.2: Multi-country comparison of price framework adopted by pricing authorities of 5 countries and map the recommendations.

3.4 Research Objective 1: A multiple case study of biopharma companies in India

A case study is an empirical inquiry that investigates a contemporary phenomenon (the “case”) in depth and within its real-world context, leading to the investigation of important contextual conditions pertinent to the case (Rashid et al., 2019). A case study relies on multiple sources of evidence, with data needing to converge in a triangulating fashion, and benefits from the prior development of theoretical propositions to guide data collection and analysis (Robert K Yin, 2014).

Among many benefits of qualitative research, the case study approach helps to explain the presumed causal links in real-world interventions that are too complex for survey or experimental methods. A case study can illustrate certain topics within an evaluation in a descriptive mode. Further, case study research may be used to enlighten those situations in which the intervention being evaluated has no clear, single set of outcomes. Case studies can be useful when researchers want to understand how interventions are implemented in different contexts, and how context shapes the phenomenon of interest (Sibbald et al., 2021).

Despite being one of the most used qualitative research methods in academic research, researchers have not yet developed a consensus on the planning and implementation of a case

study, which impedes its complete evolution (Yazan & de Vasconcelos, 2016). Although the case study is not considered a reliable approach by many researchers, as it lacks scientific rigour, it is the best choice for generalising and describing the cost of the development of biosimilars. The validity and triangulation techniques as proposed by (Yin., 2014) would be used to restrict the limitations of the qualitative research using a case study.

The cost dynamics of biosimilars are a complex process; multiple situational variables exist that impact the bill of materials as well as the market price of the product. The multiple case study approach is adopted to describe the causal links and generate an outcome that can be generalised. The study would facilitate the acquisition of qualitative data on the developmental costs of a few biosimilars commonly prescribed in the oncology space. The case study will be conducted in four phases as described by (Rashid et al., 2019).

Table 3.1: Case study methodology

Foundation phase	Philosophical consideration, inquiry techniques, and research logic consideration
Pre-field phase	Decide on the various steps and develop a case study protocol
Field phase	Contact followed by Interaction
Reporting phase	Case study reporting

The "Eisenhardt Method" is primarily used in this study to construct concepts from multiple case studies(Eisenhardt, 2021). While replication logic acts as the foundation for the findings, the cross-case analysis also applied pattern recognition to generate recommendations (Robert K Yin, 2014). The cost dynamics of biosimilars is a complex process; multiple situational variables exist that impact the bill of materials as well as the market price of the product. The multiple case study approach is adopted to describe the causal links and generate an outcome that can be generalised. The case study relies on multiple sources of evidence, with data convergence in a triangulating fashion (Sibbald et al., 2021).

Research Question: “How”, “What,” and “Why”?

How is the reference cost for the development of a biosimilar determined, and why is it important to estimate the costs of development? What are the various factors that impact the process and may hamper the harmonisation of the prices at national and international scales?

3.4.1. Case design

The research design is an adaptive, inductive, and holistic multiple-case study approach. Due to the sensitive nature of cost and pricing information in biosimilar development, most manufacturers prefer not to publish this data in the public domain. Therefore, the identities of the case subjects have been kept confidential, and the data obtained from various cases are generalised to draw meaningful inferences. To prevent pinpointing the financials of a particular company or product, the aggregated data in the study presents average or range values instead of specific values of individual entities. Phase-wise data have been combined across multiple firms to provide a broad industry-wide view rather than focusing on any one company's processes.

3.4.2. Sample selection

The case selection process is crucial since the study must model the complete biopharmaceutical ecosystem to generalise the findings. To increase the generalisability of the findings across contexts, a standard process design approach was adopted for selecting cases about the same focal phenomenon but in different settings. Biopharmaceutical companies at various scales of operation, employee size, and number of products were selected as cases. The selection parameters are summarised in the case protocol annexed as 3A. The number of years a company has been in the biosimilars business, the number of biosimilars in the pipeline, manpower dedicated to biosimilars operations, product manufacturing capacity, and in-house marketing strengths are a few parameters considered for each selected company. Different types of businesses, including large corporations with multiple products on the market, start-

ups, Indian biopharmaceutical enterprises, and MNCs with a global presence, were contacted. A large number of biopharmaceutical companies with biosimilars on the market declined to disclose the pricing information. Companies providing incomplete, insufficient, or unverifiable data were excluded. In addition, a few companies with unique manufacturing processes, such as single use bioreactors, were excluded. Enrolling companies as cases for this costing study yielded a success rate of approximately 40%. We tried to include a sample of two biosimilars from each case point, preferably one from microbial and the other from mammalian systems.

3.4.3. Data collection tools

Data were collected through various research instruments, including literature reviews, questionnaires, checklists, and interviews of key officials. The first drafts of the case protocol and questionnaire were developed by the authors using their experience and available literature. The questionnaire was then vetted by three industry leaders before sending it to the six case companies for data collection. The interviews were conducted by the authors in multiple rounds between June 2022 to August 2023. The respondents are senior officials from the six biopharmaceutical companies in India. A template of the case protocol, questionnaire, and checklist used for data collection is available in Annexures 3A and 3B.

3.4.4. Data interpretation and case reporting

The collected data were interpreted by the authors with the help of an independent biopharmaceutical professional and respondents from the participant companies. For validating the data, a checklist with inclusion and exclusion criteria was developed for the respondents. Moderation was performed on the data, based on identified patterns, interviews, and the experience of the authors. Similar findings from multiple sources, like the questionnaire, checklist and interview transcripts were correlated to generalise the findings. The cooperative case study process was adopted (Rashid et al., 2019).

3.5 Research Objective 2: Mapping the determinants of biotherapeutic prices through an enhanced bibliometric approach

To identify the relevant determinants of biosimilar prices, both quantitative and qualitative methods are adopted. Instead of adopting the standard bibliometric approach, a modified study design was developed to suit the research objective. While bibliometric methodology quantitatively assesses the performance of academic literature, the qualitative synthesis is performed manually for a subjective review of shortlisted publications. The various approaches available for domain-based review, comprising structured, framework, bibliometric, hybrid, and theory-based methodologies, are considered before finalising the combination of bibliometric analysis and qualitative synthesis for this study (Paul & Criado, 2020). Various bibliographic tools are utilised to quantify the available information for generating the themes around prior research, understanding the progression of the themes and identifying the gaps; the results of the bibliometric analysis are used for developing the qualitative synthesis leading to the identification of factors influencing the prices of biotherapeutics (Linnenluecke et al., 2020). Further, the identified themes and price factors facilitated the generation of recommendations for future research.

The methodology, as illustrated in Table 3.2 and Figure 3.1, involves defining the search strategy, inclusion and exclusion criteria, data extraction, analysis, investigation, and result interpretation. The methodology section can be described in four different phases: i) Database and searching keywords selection, ii) Study design, iii) Data extraction and analysis, iv) Network visualisation mapping.

3.5.1. Database and selection strategy

Web of Science and Scopus databases are used to collect the published literature with keywords "Biologic" OR "Biosimilar" OR "Biotherapeutic" OR "Medicine" OR "Generic" AND "Price" OR "Affordable". The selection strategy is developed carefully and is kept broad; by using the combination of relevant scientific keywords used for biosimilars in different geographies and keywords related to price and affordability; primarily to capture all the published literature in the said group, secondly to study the impact or relation of biosimilars within this larger inter-related group of terminologies and thirdly it helped in assessing the evolution of various themes in the available literature. In addition, the medicine and generic words are included as search keywords as many research papers are common for generic drugs and biotherapeutics, including biosimilars.

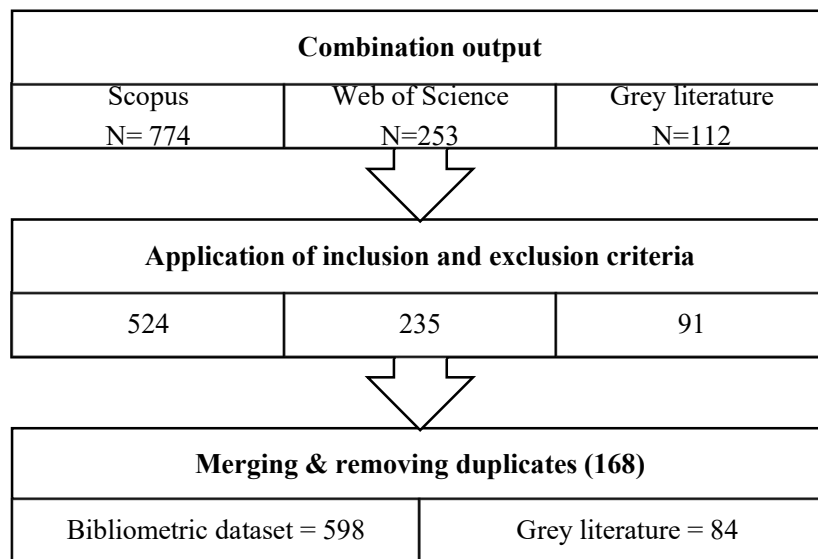
In addition, grey literature available on the websites of various organisations such as WHO, OECD, MSF, and UNICEF are retrieved. Wherever possible, research articles, book chapters, conference papers, review papers, commentaries, perspectives, and editorials are included. To efficiently organise a large number of documents, they are primarily reviewed for the title of the documents. Further, the inclusion and exclusion criteria as described in Appendix 1 are applied. The time regime for the trend analysis is selected as 01st January 1965 to 17th August 2021; over five decades, because it helped in collecting the maximum available information in the Web of Science and Scopus databases that are used for this study (the maximum period possible in the selected database).

Table 3.2: Keywords selection strategy

Web of Science and Scopus data search builder (Date of Extraction: 17 August 2021)

Combinations	Booleans	Field	Keywords
#1		Title	Biologic
	OR	Title	Biosimilar
	OR	Title	Biotherapeutics
	OR	Title	Medicine
	OR	Title	Generic
#2	AND	Title	Price
	OR	Title	Affordable

INCLUSIONS	EXCLUSIONS
Publication Year: 1965 – 2021	Author Name: Undefined
Language: English	Country/territory: Undefined

**Figure 3.1:** Selection plan & outcome

3.5.2. Study design

The study design is a distinctive approach developed by the authors for analysing the trends of the prior literature and identifying gaps for future studies. Further, the same can be adopted by research scholars in the early phase of their research, irrespective of the subject domain. The study design comprises three major sections with a series of sub-sections. The result of one section feeds into the other section, leading to the qualitative synthesis of the concept. The study design and interlinkages between its sections are depicted in Figure 3.2.

Section 1: Trend analysis provides the performance quality of the available literature. Performance breakdown of the various research components is analysed using various bibliometric tools. This section uses the bibliometrix package of R Studio to provide a pragmatic way of mapping the year-wise trends of authors, sources, affiliations, countries, and keywords. A graphical bibliometric review is generated for concerted and historical trends. The collaborative tool generates the co-occurrence of keywords, co-authorship, and co-citation. The co-occurrence methodology calculates the incidence frequency and helps in exploring the present and future relationships between the topics, while the co-citation trends are used to understand the research area and to provide similarity measures that help in the development of the basic themes. The results, while providing quantitative information, facilitate the qualitative synthesis.

Section 2: The thematic assessment helps in the identification of the themes and their evolution in the larger group of publications on the prices of generic medicine and biotherapeutics. The thematic assessment is the process of developing the themes around the given concept for enhanced interpretation of research in the experimental domain. Towards this end, the section creates thematic maps based on co-word analysis and clustering methodology. The section utilises the co-occurrence tool to generate basic, active and emerging themes around the

available literature. Further, the chronological tool is used to show the evolution of the themes across the three slices of time zone.

Section 3: The qualitative synthesis is a subjective analysis supplemented by results of bibliometric studies to reduce the author-associated bias. To observe the dual approach of this research paper, which involves bibliometric as well as qualitative analysis, the selected dataset succumbs to manual subjective analysis. A recent study by (Post et al., 2020) indicates that generating theoretical contributions to any field requires a combination of integrative and generative approaches. While the integrative approach synthesises the prior published research, the generative approach helps in creating novel ideas to provide a strategic platform for future researchers. To this end, a pragmatic, four-step block generation approach is adopted to generate subjective knowledge and recommendations for future research. a) *Concept development* that involves co-occurrence methodology and subjective knowledge of the authors to generate clusters along with their percent contribution to the topic b) *Advancing the concept* expands the understanding of the selected cluster by an extended study with refined dataset and inclusion period c) *Subjective review* on the refined dataset involves focussed analysis of existing literature by identifying, collating, and recognizing the patterns and relationships, intending to generate the information around the concept d) *Knowledge synthesis* entails the formation of logical arguments by critically analysing the key finding of the previous sections to summarise the various dimensions of the research. Through this analysis, the authors try to map important areas of agreement, disagreement, and new knowledge requirements (Torraco, 2016).

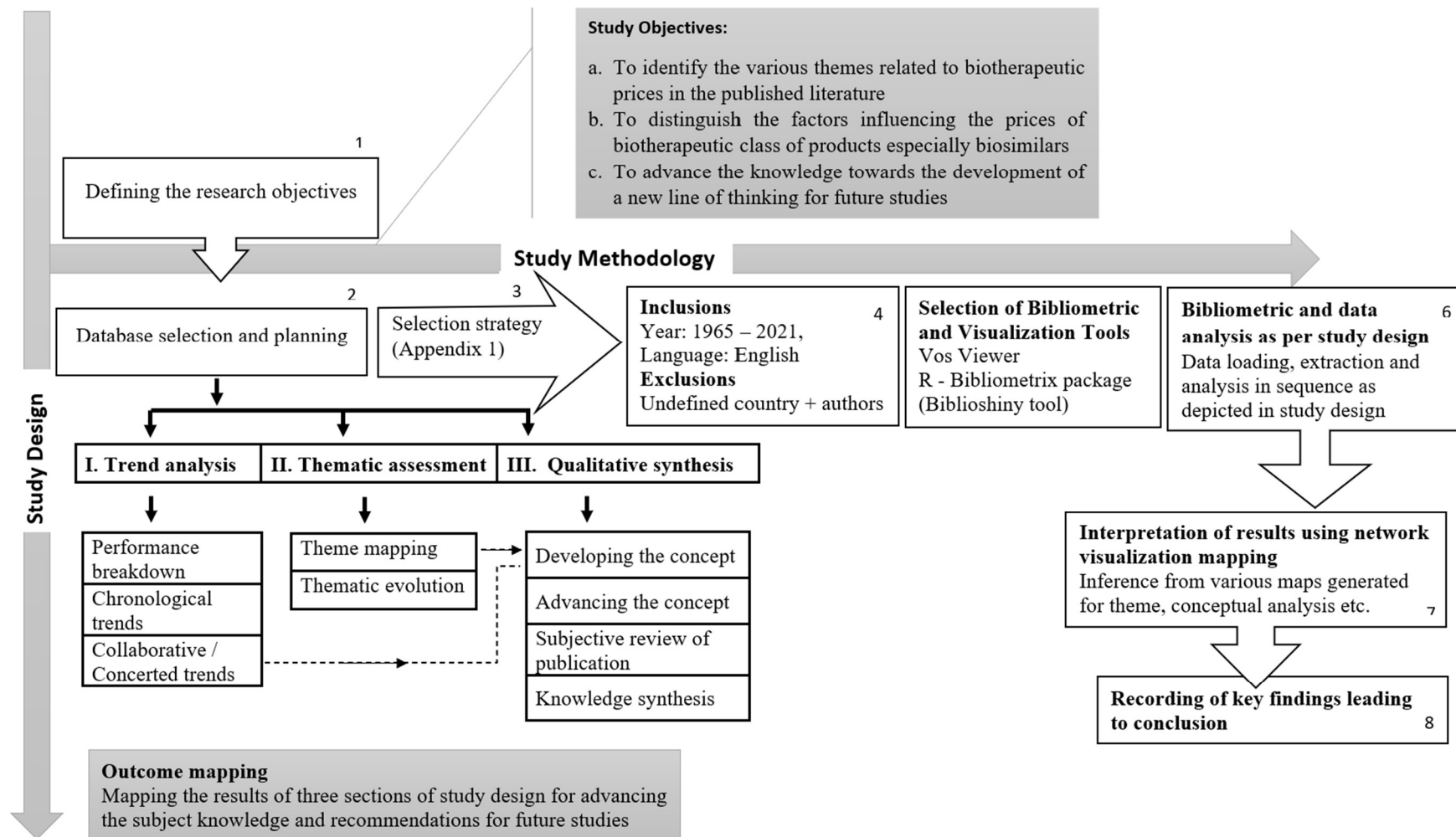


Figure 3.2: Methodology and study design - modified bibliometric approach

3.5.3. Data extraction and analysis

Data extraction is conducted as per the searching keywords and combination strategy described in Table 3.2 and Figure 3.1. The inclusion and exclusion criteria are defined to capture the maximum relevant publications from the Web of Science and Scopus databases. The data extraction leads to the shortlisting of 431 articles, 53 reviews, 81 letters, 20 books/chapters, 11 conference papers and 163 miscellaneous documents. After removing the duplicates, the final dataset for the bibliometric study comprises 598 documents. 84 documents selected from the grey literature are reviewed manually.

3.5.4. Network visualisation mapping

This study is conducted through the open-source bibliometrix package of R Studio (Aria & Cuccurullo, 2017) and VoSviewer (Visualization of Similarities) software.

3.6 Research Objective 3: Hierarchical framework and its validation

3.6.1. Total Interpretive Structural Modeling

Total Interpretive Structural Modeling (TISM) is a model building technique to perform an exploratory study using a pairwise comparison method, leading to a framework of factors. The modified version of Total Interpretive Structural Modeling, mTISM (Sushil, 2017) has been used to interpret the mutual relationships between the various factors impacting the prices of biosimilars. mTISM is the advanced form of Interpretive Structural Modeling (ISM) and is used to interpret direct and transitive relationships between different factors. ISM is a methodology to map intricate relationships between multiple variables in a complex situation. This methodology allows for the generation of a systematic framework of various qualitative viewpoints collected in a study and helps in arranging these complex variables hierarchically. The constraints of the ISM approach, such as the interpretation of nodes in the structure while disregarding the links, can be resolved by TISM. All the transitive links are removed in ISM,

while in TISM, some transitive links are retained, thereby providing a better structure. TISM can decipher both the nodes and links and can answer the ‘what’, ‘how’ and ‘why’ questions of the proposed framework. Furthermore, the TISM aids in comprehending the underlying causes of relationships and can assist in merging several pair-wise comparisons through a hierarchical model utilising the fundamental method of ISM. The step-wise methodology adopted in research Objective 3 is explained in Figure 3.3 and findings are detailed in Chapter 6.

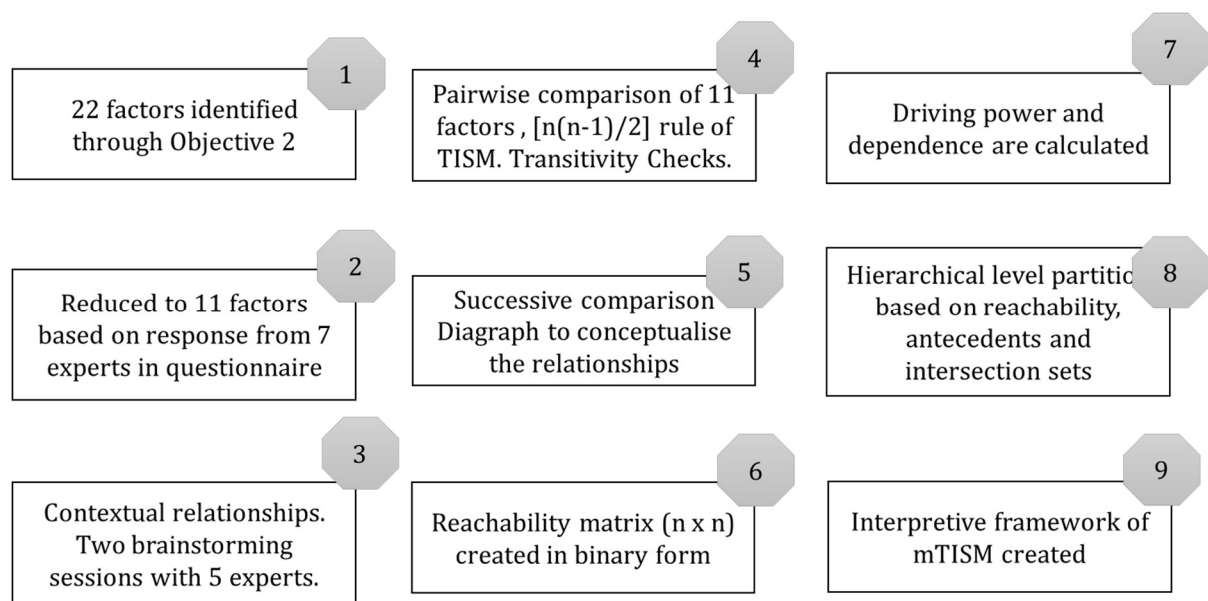


Figure 3.3: Methodology for mTISM

The response from the subject experts was gathered at three stages during the model development process through structured questionnaires and brainstorming sessions. The experts' profiles range from manufacturers to biopharma consultancy firms. We also included the expertise of a biosimilar price data management company. Most of the experts are in senior positions and are either departmental heads or CEOs of the selected companies. The minimum experience required in the biosimilar field was limited to 15 years. We tried to enrol experts from all the sub-themes of the biopharmaceutical sector and stages of product development cycle to get a complete overview of the biosimilar price ecosystem.

The total interpretive structural modeling approach has become popular in healthcare studies and can be used to identify the framework of the various healthcare systems. For example, to model the factors that have a significant effect on the quality of life (QOL) of diabetic patients (Ajmera & Jain, 2019).

3.6.2. Matrice d'Impacts Croisés Multiplication Appliquée à un Classement (MICMAC)

MICMAC analysis helps in identifying the autonomous, dependent, linkage, and independent variables. It classifies the variables into four quadrants based on the binary relationships developed in the reachability matrix so as to be able to examine the dependence and driving power of the variables.

Quadrant 1: Autonomous: The variables reflect less dependence and driving powers.

Quadrant 2: Dependent: The variables have a weak driving power and strong dependence on other variables.

Quadrant 3: Linkage: The variables have strong dependence and driving power.

Quadrant 4: Independent or Driver: The variables have strong driving power with less dependence on other variables.

It should be noted that the MICMAC analysis is an internal test used to verify the correct placement of variables across different layers of the model. External validation of the model's direct links, to assess its integrity, was conducted with the assistance of subject experts.

3.7 Research Objective 4: Modelling biotherapeutic price equation and multi-country comparison

Once the TISM model is validated through the MICMAC approach, the mathematical equation to determine the prices of biosimilars is developed through the method depicted in figure 3.4 and detailed in Chapter 7 of the thesis.

The price equation was validated on four market biosimilars, two from microbial origin and two from mammalian origin. This validation helped establish the proper functioning of the

variables and identify the constant. The multi-country comparison, i.e., BRICS comparison, is the final step of the thesis and helped in framing the ideal characteristics for the price equation and recommendations for easy adaptation within the current pricing ecosystem.

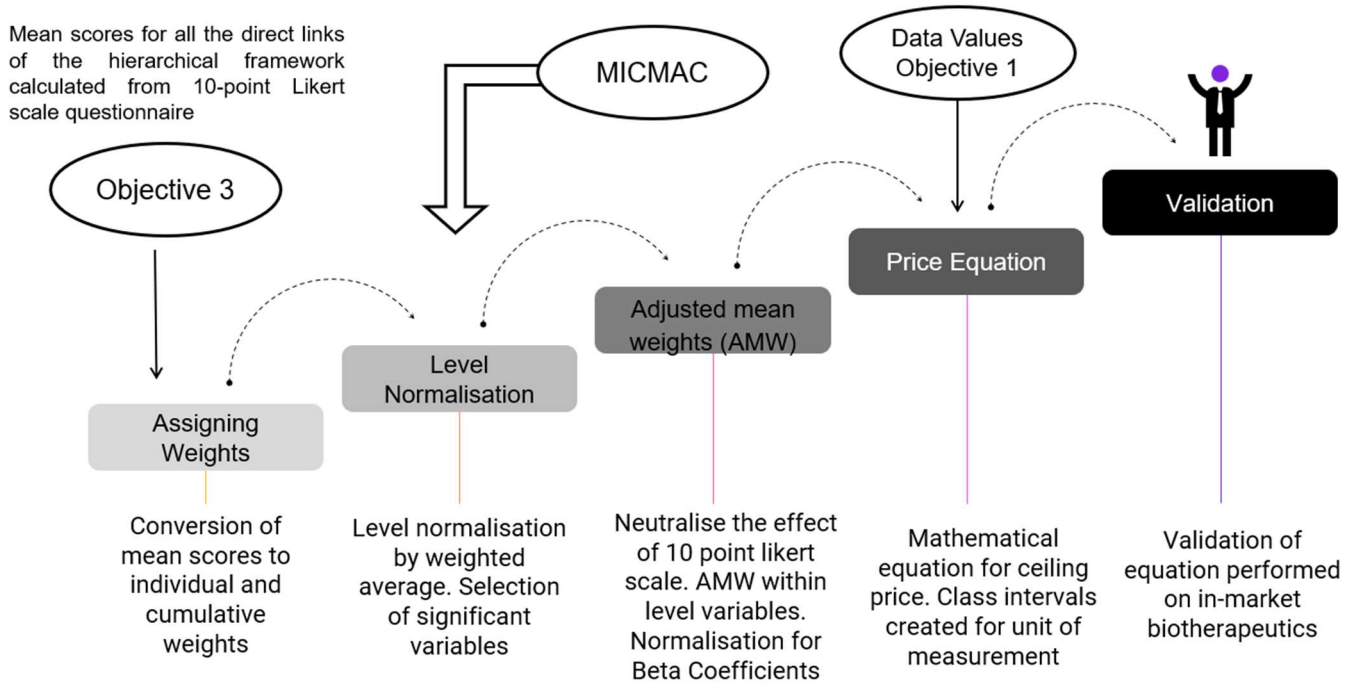


Figure 3.4: Methodology for price equation development

3.8 Conclusion

To conclude, the overview of the research methodology followed for the study is explained in Figure 3.4. This chapter defines the research questions, study design, and methodology adopted for this research work. The primary data analysis, followed by TISM, is considered the most suitable methodology for the study as the biosimilar pricing ecosystem is a complex web of multiple variables. The TISM allowed us to understand the interrelations between these variables. The unavailability of historical price data for the biosimilars ruled out the possibility of quantitative methods.

The multiple rounds of interviews and brainstorming sessions with the subject experts provide the rigour required for the research work.

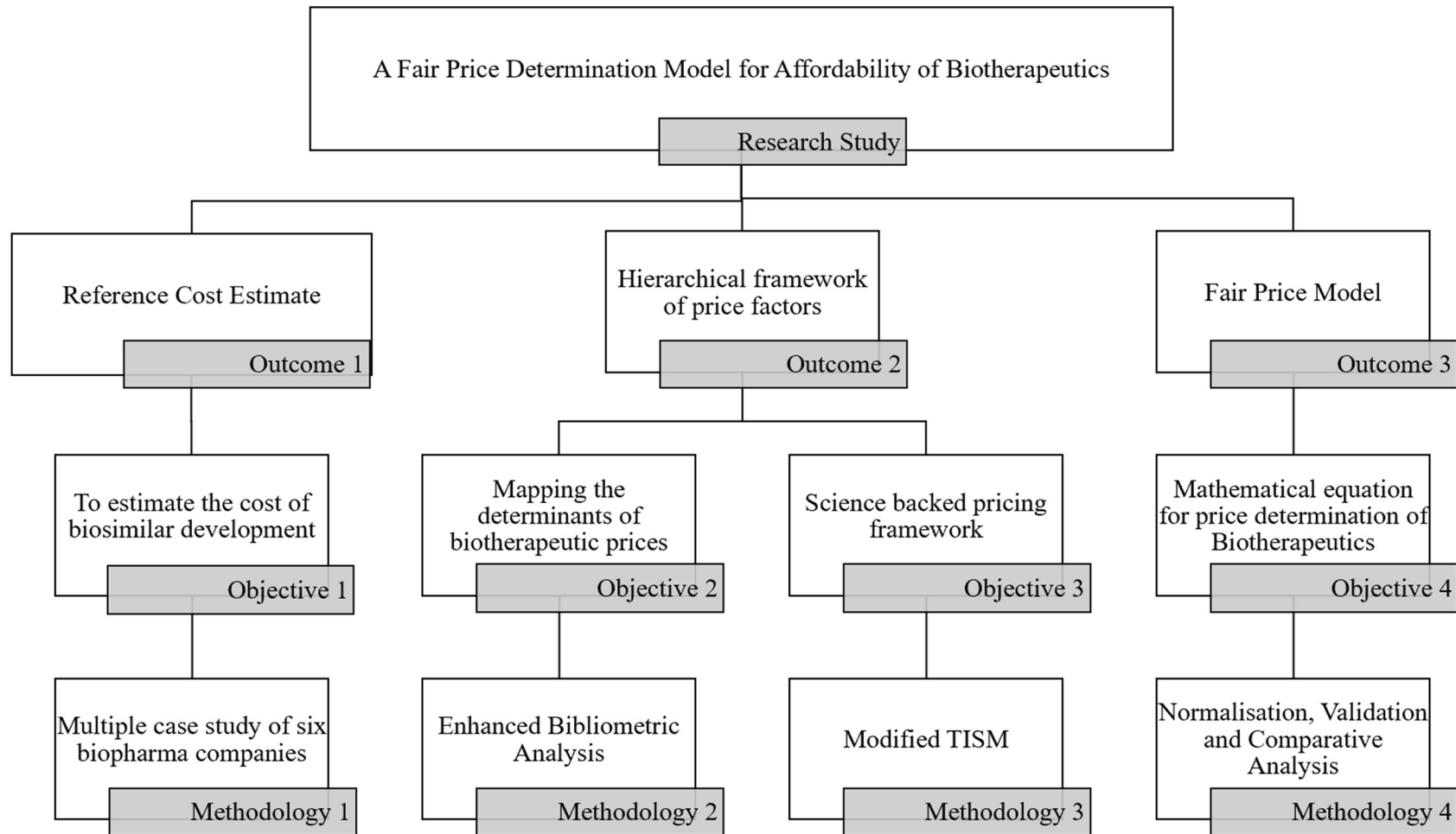


Figure 3.5: Research methodology adopted in this study

3A Annexure - Case Protocol including questionnaire and sample selection criteria

The economics of translating a biosimilar from lab to market – A multiple case study of biopharma companies in India

Introduction

In India, biosimilars are known as similar biologics. According to the Central Drugs Standard Control Organization (CDSCO) and Department of Biotechnology (DBT) guidelines released in 2016 (DBT, 2016), a similar biologic product is one that is similar in terms of quality, safety and efficacy to an approved reference biological product based on comparability.

The biosimilars are widely prescribed in the therapy regimen for cancers and autoimmune diseases. With the increase in demand for affordable and cost-effective treatment and the end of the term of patent portfolios for many originator biologics, the development of similar versions is enhanced. The availability of biosimilars with proven clinical safety and efficacy to the originator product has great potential for cost savings to healthcare systems (Rugo et al., 2019). Hence, the pricing of biosimilars has become an important agenda of the healthcare community (Blackstone & Fuhr, 2013). It is often said that manufacturers justify the high cost of biosimilars on account of high Research and Development (R&D) costs including but not limited to, capital-intensive lab infrastructure, manufacturing plants, the production cost of trial batches, clinical studies, high failure rate and regulatory requirements. In the absence of any reference for the development costs for biosimilars, it is difficult for biopharma companies to justify the high costs of development to the regulatory authorities. Also, it is considered a research gap by the regulatory and global health organisations for developing a standardized pricing mechanism or regulatory policy for the country.

This study aims to enhance knowledge about the economics of developing a biosimilar in Indian settings and to develop an R&D cost reference for the industry, regulatory and international health agencies, as an effort toward harmonising the prices of similar versions of originator biologics.

The R&D cost here refers to the cost involved in the development of any molecule from the very inception of the developmental process. In India, the biosimilar guidelines define the various regulatory requirements to obtain manufacturing authorization for a biosimilar or similar biotherapeutics. As per a report, 201 active biosimilars are in the pipeline of 52 Indian pharmaceutical companies (BIRAC, 2019). The various steps to develop a similar

biotherapeutic and key features of the regulatory guidelines are published and deliberated by many researchers (Ratih et al., 2021) (Rugo et al., 2019).

Many reports⁷ and studies provide an estimate of R&D expenditure by a biotech company (country-wise or across countries). A study by Evaluate Pharma calculated that global private-sector expenditure on biopharma R&D increased from US\$136 billion in 2012 to US\$186 billion in 2019. OECD⁸ has developed two indicators to monitor R&D expenditures – “Business enterprise expenditure on Pharmaceutical R&D” and “Government budget allocation for health-related R&D”. Currently, these indicators are used as investments or R&D input cost data by the biopharmaceutical industry. These indicators act as proxies for investments, but the available literature also identifies many other factors that can impact the investment and developmental cost of a biosimilar.

Most of the available literature discusses the costs of one or two phases of developing biosimilars; a study (Webster & Woollett, 2017) highlights the substantial costs required for performing the bridging studies between local and foreign versions of an originator biologic without providing any additional patient benefit or scientific data for the regulatory approval of the biosimilar. The cost of biosimilar development can be estimated at \$250 million, while the cost of generic drug development is around \$1–4 million (Mullard, 2017). (Adwal & Baghel, 2019) evaluates the variation of cost among different brands of anti-cancer drugs available in the Indian market. The literature review led to research papers on cost variations, but none of them maps the costs against the developmental stages as defined by the regulatory agencies.

The review revealed that the price difference of biosimilars from their reference product is not the same as the generic and its originator product in the pharma domain. This is because of the complex manufacturing process of biosimilars. (Ditani et al., 2021) calculated the estimated cost of biosimilar therapy in the oncology sector. As per the analysis, the current expenditure on therapy is approximately 35% of the cost of targeted biological drugs. The use of biosimilars in cancer treatment reduces the burden of the cost of biologics. Similarly, the studies reflect the various aspects of biosimilar development like affordability and accessibility (Trapani et al., 2021) but the gap is found in the literature for estimating the actual costs involved in the development of a biosimilar. This study is an effort towards bridging this gap.

⁷ EvaluatePharma ([https:// www.evaluate.com/](https://www.evaluate.com/))

⁸ (https://stats.oecd.org/Index.aspx?DataSetCode=MSTI_PUB#)

Methodology

A case study is an empirical inquiry that investigates a contemporary phenomenon (the “case”) in depth and within its real-world context, leading to the investigation of important contextual conditions pertinent to the case (Kaarbo & Beasley, 1999). A case study relies on multiple sources of evidence, with data needing to converge in a triangulating fashion, and benefits from the prior development of theoretical propositions to guide data collection and analysis (Yin & Davis, 2007).

Among many benefits of qualitative research, the case study approach helps to explain the presumed causal links in real-world interventions that are too complex for survey or experimental methods. A case study can illustrate certain topics within an evaluation, in a descriptive mode. Further, case study research may be used to enlighten those situations in which the intervention being evaluated has no clear, single set of outcomes. Case studies can be useful when researchers want to understand how interventions are implemented in different contexts, and how context shapes the phenomenon of interest (Sibbald et al., 2021)

Despite being one of the most used qualitative research methods in academic research, the researchers have not yet developed a consensus on the planning and implementation of a case study, which impedes its complete evolution (Yazan & de Vasconcelos, 2016). Although the case study is not considered a reliable approach by many researchers; as it lacks scientific rigour; it is the best choice for generalising and describing the cost of the development of biosimilars. The validity and triangulation techniques as proposed by (Yin., 2014) would be used to restrict the limitations of the qualitative research using a case study.

The cost dynamics of biosimilars is a complex process; multiple situational variables exist that impact the bill of material as well as the market price of the product. The multiple case study approach is adopted to describe the causal links and generate an outcome which can be generalised. The study would facilitate the acquisition of qualitative data on the developmental costs of a few biosimilars commonly prescribed in the oncology space. The case study will be conducted in four phases as described by (Rashid et al., 2019).

Table: Case study methodology

Foundation phase	Philosophical consideration, inquiry techniques, and research logic consideration
Pre-field phase	Decide the various steps and develop a case study protocol
Field phase	Contact followed by Interaction
Reporting phase	Case study reporting

Research Question: “How” “What” and “Why”?

How is the reference cost for the development of a biosimilar determined and why is it important to estimate the costs of development? What are the various factors which impact the process and may hamper the harmonisation of the prices at national and international scales?

Case design: The case design will be a multiple-case study approach. The names and identities of the case points will be kept confidential, and it will be a blinded study. The information with regard to the cost and prices of the various phases of biosimilar development is confidential data and the manufacturers sometimes do not wish to publish this data in the public domain. Hence, the data obtained from different cases would be generalised to develop inferences.

To avoid biasedness, and enhance validity and reliability, semi-structured interviews with key officials from each case would be conducted. Wherever possible multiple sources of information will be utilised to triangulate the research outcomes.

Sample selection criteria: It is proposed to include a sample of two biosimilars from each case point preferably one from microbial and the other from mammalian systems. It is also desirable to keep the indication the same for the selected biosimilars as the cost of clinical studies varies drastically with the change in indication. The effort is also towards keeping the sample biosimilars the same across all the case points for better comparisons and rationalisation.

Data instruments: The data will be collected through various case research instruments like literature review, questionnaires, checklists and interviews of key officials.

Questionnaire for the Company

Section A: Characteristics of the participating company

S. No.	Parameter	Case 1	Case 2	Case 3
1.	How old is the Company?			
2.	How many biosimilars are in the pipeline?			
3.	How many biosimilars are on the market?			
4.	What is the approx. employee size?			
5.	What is the biosimilar production scale?			
6.	Are the products developed and marketed in-house?	Developed: Yes/No Marketing: Yes/No	Developed: Yes/No Marketing: Yes/No	
7.	What is the approx. net biosimilar sales for FY 2021 – 2022?			

Section B: Questionnaire for determining the cost of biosimilar development

S. No.	Development phase	Biosimilar (approx. cost in INR) (Microbial)	Biosimilar (approx. cost in INR) (Mammalian)	Key factors impacting the cost	Approx. time taken	Challenges / Suggestions for harmonisation
I. RESEARCH & DEVELOPMENT – LAB SCALE						
	Process development and optimisation					
	Physicochemical and functional assays					
	Non-clinical – Pharmacodynamics, Toxicology / Animal Studies					
II. PRODUCTION AT GMP FACILITY						
	Batch production (Upstream and downstream)					
	Fill finish					
	Validation					
III. QUALITY CONTROL AND ASSURANCE						
	Analytical & Product Characterization					
	Stability and Shelf life studies					
IV. CLINICAL STUDIES						
	Comparative Clinical					
	Safety and Efficacy studies, Immunogenicity					
	Clinical Pharmacology (PK/PD studies)					

V. REGULATORY APPROVALS						
	Fees and approval costs					
	Sample retention					
VI. PACKAGING, MARKETING AND POST-MARKETING STUDIES						
	Packaging & Supply chain - Artworks, Cold Storage etc					
	Pharmacovigilance					
	Post Marketing Studies (Phase IV)					
VII. MISCELLANEOUS COSTS						
	Infrastructure					
	Manpower					
	Discounts, Incentives & promotional costs					
	Utilities					

Name of the Expert: _____

Designation & Affiliation: _____

Signature: _____

Data interpretation and case reporting: The collected data will be interpreted with the help of participants and experts. The cooperative process as proposed by (Gummesson, 2002) will be followed. The interview transcripts would be verified by the interpretation of the questionnaire response and the participants will be asked to check the accuracy of the data outcomes and generated ideas.

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3B Annexure: Follow on checklist used for generalisation

We thank you for your contribution in the case study on developing reference cost for translating a biosimilar from lab to market. The data provided by you is analysed for pattern recognition, repeatability checks and important recommendations are mapped. However, there are few data points which needs moderation for developing a reliable cost reference. For this moderation of the data points received from all the companies, we have developed a checklist to understand the perspective of each respondent. In particular, we would like to know the inclusions and exclusions, and the basis for estimates, so that data across different organizations can be compared fairly on a like-to-like basis.

Your 10 - 15 minutes in completing the below mentioned checklist would help in finishing the research objective:

S. No.	Development phase	Components included in the costing data provided by me are as mentioned below (Please highlight/add/delete)	Remarks
RESEARCH & DEVELOPMENT – LAB SCALE			(Please add any other comments that help to understand what you have included or excluded or otherwise covered in your cost estimate)
	Process development and optimisation	Which of the following costs have you included in your estimate? a) Manpower b) Raw materials and consumables c) Land, building and laboratory construction d) Laboratory equipment and instruments e) Laboratory operating costs and overheads Have you included the costs for the following components? a) Cell line development or acquisition b) Cell banking and characterization c) Viral clearance studies For infrastructure like land, laboratory space and equipment, how have you considered the cost	

		a) Full capex cost of land, building, labs and equipment (total or divided by number of products in pipeline) b) Depreciation cost of above items (total or divided by number of products in pipeline) c) Any other approach? Please explain	
	Physicochemical and functional assays		
	Non-clinical – Pharmacodynamics, Toxicology / Animal Studies	Are animal studies outsourced? (Y/N) If animal studies are in-house, which of the following costs have you included: a) Animals procurement or breeding b) Animal maintenance c) Operating costs of animal house d) Capex of animal house (Please indicate approach for considering capex of animal house, similar to the capex question in Process Development) Have you included Reference Product (innovator product) cost in the estimate? (Y/N)	
PRODUCTION AT GMP FACILITY			(Please add any other comments that help to understand what you have included or excluded or otherwise covered in your cost estimate)
	Batch production (Upstream and downstream)	How many batches at what scale have you considered for your estimate? Is manufacturing done in house or outsourced? If done in-house please answer the following: Have you considered the following costs? a) Manpower b) Facility utilities and other operational costs and overheads c) Raw material & consumables	

		For infrastructure like land, manufacturing facility, equipment and support infrastructure (utilities etc), how have you considered the capex cost a) Full capex cost of land, building, manufacturing facility and equipment, and support facilities shown as estimate b) Depreciation cost of above items (total or divided by number of products in pipeline) shown as estimate c) Any other approach? Please explain How have you allocated the cost to one individual product? a) Total capex or depreciation incurred by the company considered b) Total capex or total depreciation converted to per batch cost and applied to number of batches manufactured c) Any other approach (please elaborate)	
	Fill finish	How many batches at what scale have you considered for your estimate? Is manufacturing done in house or outsourced? If done in-house please answer the following: Have you considered the following costs? d) Manpower in Production, QC, QA, Support functions (Maintenance, Warehouse, Logistics) e) Facility utilities and other operations and overheads f) Raw material & consumables For infrastructure like land, laboratory space and equipment, how have you considered the cost d) Full capex cost of land, building, labs and equipment (total or divided by number of products in pipeline) e) Depreciation cost of above items (total or divided by number of products in pipeline) f) Any other approach? Please explain	

	Validation	Have you included following activities in the estimate for manufacturing? a) Process characterization b) Process validation (Drug Substance) c) Process Validation (Drug Product) d) Media fill studies (Drug Product) e) Analytical validation If yes, are the included components and the approach for estimating capex similar to above or different? If you have considered these items elsewhere, please mention where.	
QUALITY CONTROL AND ASSURANCE			(Please add any other comments that help to understand what you have included or excluded or otherwise covered in your cost estimate)
	Analytical & Product Characterization	Have you included biosimilarity assessment studies in your estimate? If yes, have you included cost of Reference Product procurement in your estimate?	
	Stability and Shelf life studies		
CLINICAL STUDIES			(Please add any other comments that help to understand what you have included or excluded or otherwise covered in your cost estimate)
	Comparative Clinical	Your clinical trials (for which you have provided cost estimate) are planned for which territory registration (highlight all that apply) -India -US -EU -Any other (please elaborate)	

		Are clinical trials conducted in India or outside? (If part here and part outside, please give broad distribution of amount of CT work done in India vs outside)	
		Please mention indication / therapy area of the product	
	Safety and Efficacy studies, Immunogenicity	Have you considered comparative efficacy study in your estimate? If so, have you considered Reference Product procurement cost? What is the total number of patients considered in your clinical cost estimate (total of all arms of patients)?	
	Clinical Pharmacology (PK/PD studies)	Have you considered comparative PK/PD in your estimate? If so, have you considered Reference Product procurement cost? What is the total number of patients considered in your clinical cost estimate (total of all arms of patients)?	
REGULATORY APPROVALS			(Please add any other comments that help to understand what you have included or excluded or otherwise covered in your cost estimate)
	Fees and approval costs	In your estimate, which official fees have you included? Have you included costs of hiring any external consultants for dossier or submission documents writing, review or liaison? Have you included internal manpower costs for regulatory document preparation?	
	Sample retention		
PACKAGING, MARKETING AND POST-MARKETING STUDIES			(Please add any other comments that help to
	Packaging & Supply chain -	Please mention what marketing and post-marketing cost components you have included in your estimate.	

	Artworks, Cold Storage etc		understand what you have included or excluded or otherwise covered in your cost estimate)
	Pharmacovigilance		
	Post Marketing Studies (Phase IV)		
ENABLING COST			
	Infrastructure	Please mention if any other costs are included in the estimates provided by you, which are not covered in the above individual breakups.	(Please add any other comments that help to understand what you have included or excluded or otherwise covered in your cost estimate)
	Manpower		
	Discounts, Incentives & promotional costs		
	Utilities		

Thank you for the valuable inputs. We would like to acknowledge your contribution in the publication(s) coming out of this research. Please answer the below mentioned:

My name and affiliation can be acknowledged in the publication(s): Yes / No

Name of the Expert: _____

Designation & Affiliation: _____

Signature: _____

Research & Development Cost of Biotherapeutics in India

4.1 Introduction

This Chapter of the thesis aims to establish a cost basis for biologics manufacturers and policymakers by quantifying the price and time required to bring a biosimilar from the lab to market. For the efficient implementation of a cost-based policy, especially for life-saving medicines like biosimilars, it is imperative to establish a benchmark for the cost involved in biosimilar development. In this holistic multiple-case study, stage-wise cost estimates of biosimilar development were obtained for microbial and mammalian systems. The investigation of six biopharmaceutical companies based in India concluded that biosimilar development through the microbial system costs ~ 18 million USD and the mammalian system ~ 21 million USD. Additionally, 45 – 50 million USD is required as a one-time capital investment. Further, US/EU authorisation can cost ~ 25 million USD per product. Clinical studies are the most expensive and account for 60 - 70 % of total development costs.

The cost and time required to bring a biosimilar to market can vary depending on various factors. The development process typically involves extensive research and development, pre-clinical, clinical trials, manufacturing, regulatory approvals, and post-marketing studies (Thill et al., 2019). This can take several years and cost millions of dollars (Miriam Fontanillo et al., 2022). Additionally, multiple factors (Gandhi et al., 2023), especially differences in regulatory requirements across countries (Kang et al., 2021) can further impact the time, price, and cost of bringing a biosimilar to market (Ditani et al., 2021).

Biologics have emerged as the most popular category of pharmaceuticals in the United States (US)

and account for 46% of total spending. Over the past five years, the biologics market in the US has shown an average annual growth rate of 12.5%, surpassing that of non-biologics (IQVIA, 2023). However, their exorbitant cost has rendered them unaffordable and inaccessible to a significant number of patients in developed (Blackstone & Fuhr, 2013) as well as developing countries. The US Food and Drug Administration (FDA) states that a biosimilar is a biologic that is highly similar to and has no clinically meaningful differences in terms of safety, purity, and potency from an existing FDA-approved reference product (USFDA). Reimbursement policies for biosimilars vary among nations based on the adopted mechanism for reimbursement. Biosimilars in Europe are often available at a discounted price (by approximately 20% to 35%) compared to their corresponding reference products (Ortiz-Prado et al., 2023). In the US (Manning, 2017), the reimbursement for a biosimilar is calculated as the average sales price (ASP) of that biosimilar plus 6% of the ASP of its reference biologic product. India has only a few biosimilars in the health benefit packages of Ayushman Bharat - Pradhan Mantri Jan Arogya Yojana (AB - PMJAY) and is developing a mechanism to determine their reference cost (Prinja et al., 2020).

Although India is one of the top producers of biosimilars, it is still in the early stages with respect to the development of novel biologics. Along with multiple start-ups, it hosts a large biopharma industry with successful manufacturers such as Biocon Limited, Dr. Reddy's Laboratories, Intas Pharmaceuticals Limited, Reliance Life Sciences Pvt. Ltd., Cipla Limited, Zydus Lifesciences Limited, Glenmark Pharmaceuticals Limited, Hetero Healthcare Ltd, and Lupin Limited. Despite the fact that India boasts some of the lowest prices in the world, the prices are still too high for the vast majority of Indians and for that matter, most of the developed and underdeveloped economies (Rathore & Shareef, 2019).

Biosimilars are widely prescribed for the treatment of a variety of difficult to manage diseases,

including cancers (Ditani et al., 2021) and autoimmune diseases (Bachu et al., 2022). There has been an increasing demand for affordable and cost-effective treatments as well as a substantial increase in the number of originator biologics losing patent protection (BIRAC, 2019). The blockbuster biologics (based on global sales in 2022) that are losing patent protection in the US on/before 2033 are listed in Table 4.1. This is driving the phenomenal growth of biosimilars as both the public and government realise the significant potential they hold towards contributing to cost savings for healthcare systems (Rugo et al., 2019).

The price analysis of ranibizumab (Lucentis), the innovator for vision-threatening retinal diseases like wet age-related macular degeneration and diabetic macular edema, after the entry of its biosimilars in India, can further substantiate this claim (Narayanan & Sheng, 2024). The existing price of Lucentis per dose in India is approximately 250 USD per injection, a significant decrease from the 1750 USD per injection pricing in 2006, when it was first introduced in the country. The annual treatment cost, which consists of six injections, is approximately 1500 USD. This cost is further reduced by 50% through the "Buy one, get one free" patient assistance program of the originator. In contrast, the current pricing of Lucentis in the US market is on average 2000 USD per injection. In 2015, the world's first biosimilar of ranibizumab was introduced in India, resulting in a price reduction to approximately 70-80 USD per injection.

The discourse surrounding the regulation of the prices of medicines is not new. There has been considerable debate on the necessity of implementing price control policies (Babar, 2022; Blackstone & Fuhr, 2013; Rémuzat et al., 2017). It is often said that manufacturers justify the high cost of biosimilars on account of high Research and Development (R&D) costs, including but not limited to, capital-intensive lab infrastructure, manufacturing plant, production cost, clinical studies, and complex regulatory requirements. Sometimes, when compared to pivotal trials for the

approval of innovators, comparative efficacy trials for biosimilars can be as rigorous and even larger, longer, and more expensive (Moore et al., 2021). To date, no comprehensive reference for the development costs and associated profit margins is available for biosimilars, thereby creating a hurdle for regulatory and global health organisations (WHO, 2018) aiming to develop national pricing policy (Ratih et al., 2021).

This study aims to offer an insight into the economics of developing a biosimilar and to develop a cost reference that could be used by the industry, policymakers, regulators, and international health agencies and is an effort toward harmonising the prices of biosimilars while promoting innovation in R&D.

The R&D cost here refers to the expenses incurred in the development process of any molecule from inception to market. It is important to note that biosimilars provide the opportunity for affordable treatment, but their development involves a sizable financial investment in innovation, especially when compared to their small molecule counterparts, pharmaceuticals (Harvey, 2017). It costs between 2 million USD and 3 million USD to develop a generic drug, which takes two to three years and demands studies with 20 to 50 patients (Mullard, 2017). In comparison, it is reported that it costs between 100 million USD (Pfizer) to 200 million USD (GaBi) to develop a biosimilar, which takes eight to ten years and requires studies with about 500 patients (GaBi, 2022; Pfizer). Further, the Dutch Ministry of Health commissioned a study on the financial ecosystem for R&D of pharmaceuticals and reported the average cost for developing a drug as between 280 to 380 million USD (Consulting et al., 2022). The median cost of biosimilar phase-3 trial is 27.6 million USD and the median duration is reported to be around 13 months (S. Mehr, 2020). A study on the production cost of human insulin and analogues highlights the various cost components (Gotham et al., 2018). The existing literature addresses different aspects of

biosimilar development costs (Trapani et al., 2021), with some studies highlighting the substantial expenses involved in bridging studies (Webster & Woollett, 2017), partial cost estimates (Moore et al., 2021), and variations (Adwal & Baghel, 2019) but a comprehensive cost reference across all stages is lacking. This study is an effort towards bridging this gap.

Table 4.1: Blockbuster biologics going off patent between 2022 and 2033

Drug (Active Ingredient)*	Parent Company	Pharmacologic al Classification	Month & Year of Patent Expiry**	Global Sales in 2022*** (USD billion)
Humira (adalimumab)	AbbVie	Tumor necrosis factor (TNF) blockers	December 2016 April 2025 April 2027 September 2027 May 2032 March 2033 November 2033	21.20
Keytruda (pembrolizumab)	Merck & Co	Monoclonal antibody	June 2028 September 2031	21.00
Stelara (ustekinumab)	Janssen Biotech	Human immunoglobulin G (IgG)1 monoclonal antibody	January 2022 February 2022 May 2022 August 2022 September 2023	9.72
Opdivo (nivolumab)	Bristol Myers Squibb	Human monoclonal antibody	July 2023 February 2024 August 2024	9.50
Eylea (aflibercept)	Regeneron and Bayer	Vascular endothelial growth factor antagonists (VEGF-A)	November 2024	7.42
Trulicity (dulaglutide)	Eli-Lilly	Glucagon-like peptide-1 (GLP-1) agonists	October 2024 June 2025 May 2026 July 2026 December 2026 April 2027	7.40

Entyvio (vedolizumab)	Millenium Pharmaceuticals (Now Takeda Pharmaceutical)	Integrin receptor antagonists	June 2023	6.40
Cosentyx (secukinumab)	Novartis	Monoclonal antibodies	October 2030 November 2030	4.78
Enbrel (etanercept)	Immunex Corporation (Now Amgen)	Anti-TNFs or TNF blockers	July 2023 November 2028 April 2029	4.12
Prolia/Xgeva (denosumab)	Amgen	Monoclonal antibodies	June 2022 November 2023 February 2025	3.60
Avastin (bevacizumab)	Genentech	Monoclonal antibody and anti- angiogenesis drug	January 2022	2.30
Lantus (Insulin Glargine)	Sanofi	Long-acting insulin	July 2027 May 2031	2.30
Victoza (liraglutide)	Novo Nordisk	GLP-1 analog	February 2023 February 2026	1.81
Lucentis (ranibizumab)	Genentech	VEGF-A	November 2022	1.80

Source: Data collected by authors from multiple sources like Statista*, Drug Patent Watch** and Annual reports*** of the companies. <https://www.drugpatentwatch.com/>, www.statista.com.

Note: The blockbuster biologics going off patent between 2022 to 2033 are selected based on their global sales value in the year 2022. Many US patents are expiring before 2030 opening huge opportunities for biosimilars.

4.2 Results & Discussions

India currently boasts the maximum number of approved biosimilars, with more than 100 biopharmaceutical companies and 6000 plus biotech startups (BIRAC, 2023; Meher et al., 2019).

The number of biosimilars approved in some of the major global jurisdictions is mentioned in

Figure 4.1. The conducive regulatory ecosystem and relatively cost-efficient manufacturing capabilities of Indian manufacturers are the major factors behind India's emergence as a hub for biosimilar manufacturing (Rathore & Shareef, 2019). According to a global landscape of manufacturers on 304 follow on biologics for 18 active substances, the maximum number of biosimilars (78) is manufactured in India (Klein et al., 2023). Most of the biosimilars manufactured in India are for domestic use, with only a few companies like Biocon and Intas Pharmaceuticals targeting major markets like the US/EU. At present, producers can maintain and support production for the Indian market alone. However, the knowledge and experience gained from the vaccines, for which India is a leading worldwide supplier, can be successfully extended to the globalisation of biosimilars (Ortiz-Prado et al., 2021).

The terminologies and definitions for biosimilars can vary across regulatory jurisdictions (Rathore & Bhargava, 2021a, 2021b). Biosimilars are termed “Similar Biologics” by the Indian regulatory body, Central Drugs Standard Control Organisation (CDSCO). However, the first biosimilar was approved in 2000 for Hepatitis B, much before the official “Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorisation in India” were developed in 2012, with amendments in 2016. The European Medicines Agency (EMA) pioneered the development of the regulatory framework for biological products and approved its first biosimilar, Omnitrope, in 2006. Later in 2015, US FDA granted approval for their first biosimilar filgrastim-sndz. In an effort towards harmonisation with global regulations, CDSCO released a draft guidance document in February 2024 on “Post-approval changes in Biological Products: Quality Safety and Efficacy”.

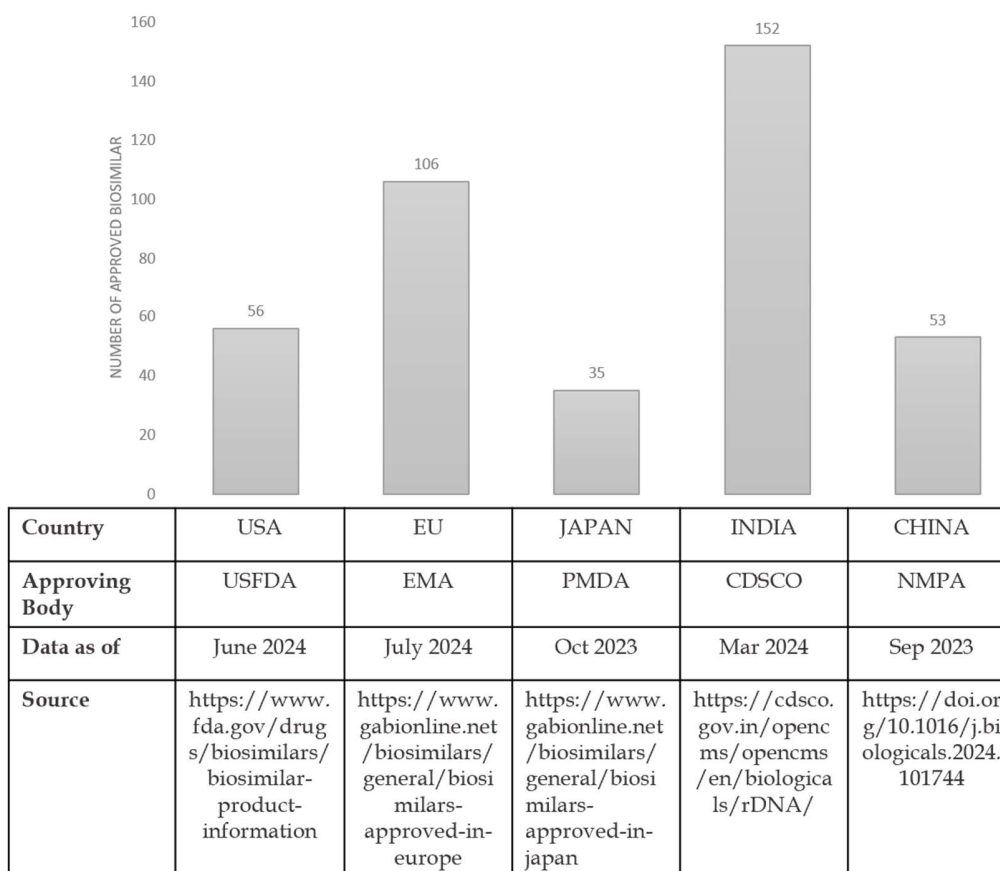


Figure 4.1: Number of authorised biosimilars in major jurisdictions.

Note: EMA has withdrawn 17 biosimilars after approval. Abbreviations: USFDA: U.S. Food and Drug Administration; EMA: European Medicines Agency; PMDA: Pharmaceuticals and Medical Devices Agency; CDSCO: Central Drugs Standard Control Organisation; NMPA: National Medical Products Administration

4.2.1 Key constituents of biosimilar development

Development of biosimilars necessitates a significant financial investment in the specialised infrastructure and technologies required to manufacture the product and to ensure that the biosimilar product is comparable to the innovator product. These significant capital expenditures are a major hurdle for the entry of small companies and offer an advantage to big pharma companies(Niazi, 2022a). Direct and indirect costs can be differentiated. While the direct costs are

unique to a product and can be estimated easily, the indirect costs are shared by several product lines and have a long-term impact on the organisation. Key constituents of biosimilar development cost (direct and indirect) are depicted in Table 4.2.

The major cost at the research and development stage corresponds to the procurement of clones, which requires significant licensing fees. The in-house development of clones is marginally cheaper, but the time and effort for characterisation are significant, thereby resulting in procurement by most of the case companies. The multipoint process analysis at several fronts of upstream and downstream process development and its optimisation is time-consuming and generates sunk costs. Further, various factors like the scale of operations, type of delivery and markets decide the type and number of studies required to develop a biosimilar. Animal studies are usually outsourced to independent Contract Research Organisations (CROs).

As the technology is transferred from the lab to the current Good Manufacturing Practices (cGMP) compliant manufacturing facility, issues related to process development or scale-up may emerge due to technology limitations. In addition, raw material availability can be a constraint for many developing nations where the dependence on certain vendors and countries makes the media cost high and often results in a supplier monopoly. Optimisation of the scale-up process, non-clinical batches, and additional batches to verify/demonstrate consistency are sunk costs (funds that cannot be recovered). The facility and equipment validation, including installation, operational and performance qualification (IQ/OQ/PQ), is expensive and demands skilled manpower to perform and document the process as per regulatory requirements.

The most expensive step in creating a biosimilar is the clinical evaluation, which includes pharmacology, safety and efficacy studies (Phases 1 and 3). The biosimilar guidelines in India recommend comparative pharmacokinetics (PK) and pharmacodynamics (PD) studies with their

reference product. Additionally, the biosimilar guidelines provide flexibility for combining PK and PD studies or combining the PD studies with phase 3, removing the requirement of a separate phase 2 study. The cost of the innovator product or the reference product is a heavy burden, and occasionally, these expenses increase due to the complexity of study design. For instance, a clinical trial on 200 subjects may need 500 vials of the innovator drug, costing 1000-3000 USD for each dose (for example, pembrolizumab is ~2500 USD per dose in India) for a total of 1.5 million USD. The manufacturer is further burdened by the replication of the efficacy and safety data of the reference product across all indications.

Table 4.2: Key constituents of biosimilar development cost

Key constituents of biosimilar development cost								
Direct Cost					Indirect Cost			
R&D	Manufacturing	Analytical & QC	Clinical	Regulatory	Marketing	Distribution	Infrastructure	Manpower
Expression clone, cell banking and characterisation	Media cost	Reference product	Innovator product	Regulatory fees	Labeling and packaging	Cold chain	Land, civil construction, validation (IQ/OQ/PQ)	Skilled Staff
Process development	Raw material	Method development and validation	Subject recruitment cost	WHO cGMP Certification	Adverse effect monitoring, drug utilisation & case-control studies	Temperature maintenance	Multiple production suites and fill finish	Principal Investigator
Formulation development	Process validation	Biosimilarity assays	Insurance coverage	Post Marketing Studies (PMS)/ Pharmacovigilance	Promotional cost	Incentives / Discounts	Equipment - Bioreactor/ Purification/ Analytical/Lab	Contract development manufacturing
Raw material	Cleaning cost	Stability and Shelf-Life studies	Data management	Administrative/ Compliance			Effluent treatment plant	Clinical research organisation
Trial, scaleup and consistency batches	Batch failure		PK/PD, bioanalytical testing	Procedural delays			Aseptic controls	
Animal trial/ pre-clinical			Clinical trial				HVAC/ Utilities	
							Facility overheads	

Abbreviations: R&D- Research and Development, QC-Quality Control, cGMP- current Good Manufacturing Practices, IQ/OQ/PQ- Installation, Operational, Performance Qualification, HVAC- Heating, Ventilation and Air Conditioning.

High-end machinery and technologically advanced infrastructure, including multiple production lines, make up most of the indirect costs. The cost of cleaning, contamination control, maintenance, and validation is a significant burden on the manufacturer and requires qualified engineers and microbiologists. Hiring a Contract Development and Manufacturing Organisation (CDMO) is a difficult decision that must be undertaken at least a year before commercial batch manufacturing. For biosimilars, which typically require storage between 2°C to 8°C, the necessity for logistics and a cold chain to ensure a consistent temperature cannot be ignored.

4.2.2 Cost of translating a biosimilar from lab to market

Biosimilar development is an expensive business. According to the opinion of selected cases of biosimilar manufacturers in India, the cost of land for setting up the manufacturing plant is over 12 million USD and varies with the location and level of government subsidy. Depending on the products that a manufacturer has in the pipeline, there may be a need for multiple single-product facilities, if not multiple production suites. Further, the solvent-proof and effluent treatment plant (ETP) requirement adds another 1-2 million USD to the infrastructure cost. An estimated 1.2 million USD is needed to purchase a clone. In-house development of clones, along with their characterisation, can cost about 0.7 million USD. One set of bioreactors (bioreactor train up to 2000 L) costs around 1.8 million USD, media cost per batch is nearly 0.25 million USD depending on the type of media and feed, small equipment costs approximately 0.6 million USD, and a purification set for three chromatography skids costs roughly 0.7 million USD (including chromatography columns and membrane separation skids). Analytical instruments cost in the range of 1-2 million USD, with the fill-finish equipment adding another 3.7 – 6.2 million USD, depending on the number of filling lines and technology used.

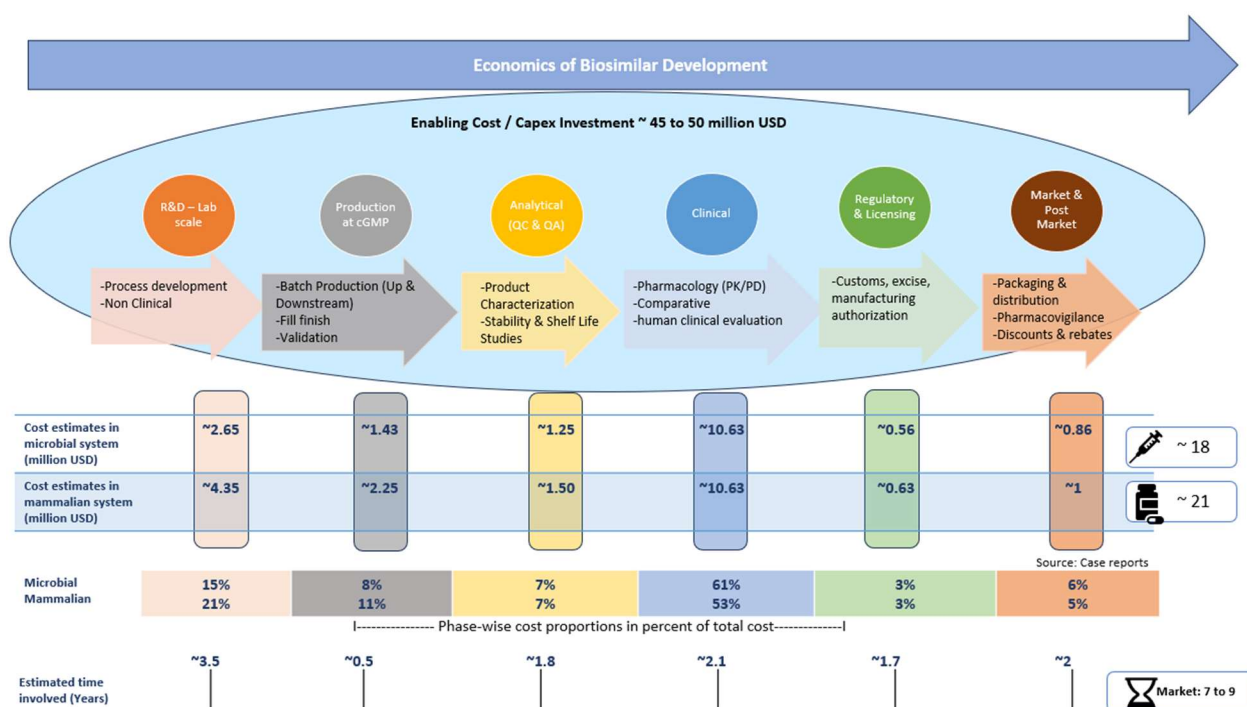


Figure 4.2: Estimated cost and time of biosimilar development in India

Note: The estimated costs are moderated and generalised from the case reports. These may change with situation, indication and geography. The currency conversion rate adopted in this chapter is 1 USD equals 80 INR.

Figure 4.2 represents the stage-wise cost of translating from lab to market for microbial and mammalian systems. The inclusions and exclusions are available in **Annexure 4A**. Although the cost varies with the scale of production, indication, yield, and marketed geographies, the cost of development for monoclonal antibodies is higher than microbial products like granulocyte colony stimulating factor, parathyroid hormone, human growth hormone and ranibizumab. Biosimilar development in India through the microbial route costs ~ 18 million USD and the mammalian route ~ 21 million USD. Additionally, 45 – 50 million USD are required as CapEx for land, building, lab construction, equipment and utility installation. Further, US or EU authorisation can cost an additional ~ 25 million USD/ product. The approximate authorisation fee for the US FDA is 3 to 4 million USD per product (USFDA). The additional data requirements for PK/ PD studies, and the cost of hiring external consultants

for dossier submission, document writing, review and liaison increase the expenses to 20 – 25 million USD per product. Clinical studies are the most expensive stage and account for ~ 60 – 70 % of the total development cost.

4.2.3 Biosimilar development – Time value of money

Cost control and a quick launch are essential for the success of biosimilars. Manufacturers, through multiple strategies, try to manage the cost of development for reasons like an increase in profitability, staying ahead in the competition and winning government procurements with subsidised costs. The Public Health Service (PHS) Act in the US grants product exclusivity to the originator. This means that a 351(k), abbreviated pathway application for the approval of a biosimilar, cannot be approved until 12 years after the date the originator was first licensed, and it cannot be submitted to the FDA for review until 4 years after the date the originator was first licensed (Food and Drug Administration, 2014; Niazi, 2022).

The Biosimilars Act in the US allows for a 12 to 42 month window of exclusivity for the first biosimilar or generic biologic. Future biosimilars must wait till that time before their approval. If the final decision or dismissal of all patent lawsuits brought against the first approved biosimilar is still pending, the approval of future biosimilars may be postponed. Thus, if the first approved biosimilar and the originator engage in patent infringement, the innovator may keep market exclusivity for the duration of the infringement lawsuit, and the first approved biosimilar will only be granted exclusivity after a final court decision or dismissal, leading to further delay in bringing the product to market.

As per the data received from the case companies (Figure 4.2), biosimilar development usually takes 7 - 9 years to reach the market, in contrast to 3 - 4 years for generic drugs (small-molecule pharmaceutical products). Research and development take 3–4 years before cGMP clinical manufacturing starts. The manufacturers try to complete R&D of the biosimilar before

the patent exclusivity period of the originator ends to accelerate development. Careful regulatory planning can further reduce the time to bring biosimilars to market.

4.2.4 Recommendations for cost reduction based on case interviews and reports

Indigenous manufacturing: Local manufacturing of media, resins, reagents, and high-end equipment has the potential to reduce the cost of biosimilar development. The bill of materials increases multiple times as these items are imported. Further, high-yielding host cell lines often have to be imported due to a lack of indigenously developed expression platforms in India. Amino acids, vitamins, glucose, trace elements, and growth factors are mostly imported for making chemically defined media for Chinese Hamster Ovary (CHO), *E. coli*, yeast, or any other platforms used in biopharmaceutical development. Resins add a significant cost as they are almost entirely imported. India is currently working to build its raw material capacity, with a few companies like HiMedia and Sisco Research Laboratories having made meaningful headway thus far. PharmNXT is another example to provide homegrown single use bioprocessing products at an affordable price. However, it will take perhaps another decade for users to replace the majority of the imported components with indigenous products.

Regulatory process harmonisation: By harmonising requirements across regulatory bodies like the US FDA, EMA, PMDA, and CDSCO, the costs associated with regulatory approval can be reduced. In India, the current guideline on Similar biologics (DBT CDSCO, 2016) supports accelerated development of biosimilars but biosimilars are still included under the New Molecules provisions of the current regulations. The New Molecular Entity (NME) and biosimilars are different classes of products and call for different regulatory pathways. Further, multiple approvals (Institutional Biosafety Committee, Review Committee on Genetic Manipulation, Institutional Animal Ethics Committee, Genetic Engineering Approval Committee, and CDSCO) are required to bring a biosimilar to market, leading to increased cost, time and effort as compared to regulated markets where only one submission is made at

the time of manufacturing and marketing approval. Besides, no regulatory framework exists to evaluate innovative technologies and manufacturing platforms. As an example, novel Micro Physiological Systems (MPS) to reduce dependency on animal tests have the potential to reduce the cost, but no clear guidelines are available for their market authorisation and subsequent adoption by the manufacturers.

Streamlining clinical studies requirements: The most expensive stage of developing a biosimilar is clinical trials. Several variables, including patient enrollment, availability and sourcing of reference products, and the patient's clinical history, impact the trial. As the trials are double-blinded and patients are not confident about receiving medication in the clinical study (control arm), they may be reluctant to participate in the trials. Furthermore, reference product sourcing is a challenge for most developing nations. According to the 2012 biosimilar guidelines, the reference product for comparative studies should be approved and marketed in India in an effort towards streamlining with international regulatory requirements. Further, CDSCO, through the 2016 amendment, has allowed the use of reference products marketed either in India or ICH countries (International Council for Harmonisation, i.e., European Union, Japan, United States, Canada, and Switzerland). Multiple suppliers supplying material as per regulatory standards should be considered to reduce supplier monopoly. A customised biosimilar development paradigm that ensures regulatory robustness without regularly requiring comparative efficacy and/or pharmacodynamic studies may be planned in discussion with CDSCO. As per the 2016 amendments, if PK and PD equivalence is shown in pre-clinical, in vitro characterisation with established PK methodologies and a PD marker that is a proxy of efficacy, residual risk is significantly reduced in Phase I. Phase III clinical trials in such a case may be waived. If required, an appropriate single-arm study in at least 100 subjects may be conducted in the most sensitive indication to address any residual uncertainty. EMA also has a policy on waivers for trials for certain products (EMA).

Enabling policies and conducive environment: The policies, including the tax regime of any nation, play a major role in transforming the economy. Favourable policies for R&D, innovation, manufacturing, and import/export can reduce the cost of development. The availability of ICH-GCP-trained Principal Investigators and CRO staff is a continuing challenge. Further, CROs need to upgrade with regard to the global regulatory requirements and data integration capacities for enhancing operational efficiency. Industry-academia collaborations, dedicated infrastructure, research-linked tax incentives, clear regulations and alignment of academic research with industry requirements are a few initiatives that can make the environment even more conducive for biosimilar development.

4.3 Conclusion

This Chapter concludes Objective 1 of the research and establishes a reference for the cost of translating a biosimilar from the laboratory to market in Indian settings. The cost reference was a critical research gap and no other research paper to the best of our knowledge details the stage-wise costing of various stages of biosimilar development. These findings are further utilised in Objective 4 of the thesis to develop the Biologics Price Determination Model (BPDM). The findings of this objective are published as

Gandhi, S., Patankar, D., Kashiramka, S., & Rathore, A. S. (2024). The economics of translating a biosimilar from lab to market in India. *Annals of the New York Academy of Sciences*, 1541(1), 219-229.

4A Annexure: Estimated cost of biosimilar development in India

S. No.	Development Stage	Inclusions/Exclusions of Cost Estimates	Estimated Cost in Microbial System (million USD)	Estimated Cost in Mammalian System (million USD)
RESEARCH & DEVELOPMENT – LAB SCALE				
1.	Process development and optimisation (including physicochemical and functional assays)	Inclusions: f) Manpower g) Raw materials, media and consumables h) Laboratory equipment and instruments (depreciation cost divided by the number of products in pipeline are estimated) i) Laboratory operating costs and overheads j) Cell line development or acquisition k) Cell banking and characterization l) Viral clearance studies (Mammalian) Exclusions: CapEx of land, building, lab construction and equipment are not included.	1.9	3.1
2.	Non-clinical – Animal Studies	Inclusions: Animal studies are outsourced. Reference Product (innovator product) Exclusions: In case animal studies are performed in-house, below mentioned can be included: a) Animal procurement or breeding b) Animal maintenance c) Operating costs of animal house d) CapEx of animal house	0.75	1.25

PRODUCTION AT GMP FACILITY				
3.	Batch production (Upstream and downstream)	Inclusions: The estimated cost is for 10 batches at 10 - 100 L scale. Manufacturing is in-house and includes manpower, raw materials, consumables, operational costs and overheads. For infrastructure and equipment, depreciation costs divided by the number of products in the pipeline are estimated.	0.34	0.62
4.	Fill finish	Inclusions: The estimated cost is for 10 batches at clinical scale. For microbial, yield of 50 grams per 200L, and 300mcg dose, corresponds to over 1 lakh PFS. For mammalian, 200L with 2.5g/L purified yield will give 500g. If dose is 100mg, that corresponds to 5000 PFS. Manufacturing is done in-house and includes: a) Manpower in production, QC, QA, and support functions (Maintenance, warehouse, logistics, etc.) b) Facility, utilities, other operations and overheads c) Raw material and consumables For infrastructure and equipment, depreciation cost divided by the number of products in the pipeline are estimated. Exclusions: CapEx of land, building, labs and equipment.	0.34	0.5
5.	Validation	Inclusions: a) Process characterization	0.75	1.13

		b) Process validation (Drug Substance) c) Process Validation (Drug Product) d) Media fill studies (Drug Product) e) Analytical validation For infrastructure and equipment, depreciation cost divided by the number of products in the pipeline are estimated.		
QUALITY CONTROL AND ASSURANCE				
6.	Analytical & Product Characterization	Inclusions: a) Bio-similarity assessment studies b) Filter validation, extractable leachable and other product-specific studies viz., surface sterilization, etc. c) Reference product procurement Testing is performed In-house.	1.0	1.25
7.	Stability and Shelf-life studies	Cost estimates are for one product	0.25	0.25
CLINICAL STUDIES				
8.	Clinical Pharmacology (PK/PD studies)	Inclusions: Comparative PK/PD with Reference Product procurement cost. The number of patients enrolled is product specific but the clinical cost estimate (total of all arms of patients) is for 100 subjects. Estimates are for clinical trials conducted in India. (Indian registrations are usually accepted with WHO-GMP in the subcontinent, Asia and a few emerging markets) Oncology, Ophthalmic, Rheumatology, and Endocrinology indications are considered as per the availability of data. Exclusions: For US, PK/PD and BLA cost is approx. 20-25 million USD/ product.	5.0	5.0

		For EU, PK/PD and IMPD/MA cost is approx. 20-25 million USD/ product.		
9.	Comparative Clinical Studies (Safety and efficacy studies)	Inclusions: Comparative efficacy study with reference product procurement cost. The number of patients enrolled is product specific but clinical cost estimate (total of all arms of patients) is for 200 subjects.	5.63	5.63
REGULATORY APPROVALS				
10.	Fees and approval costs	Inclusions: Indian regulatory agency fees included for one product. (For US, approx. cost is 3-4 million USD/product) Internal manpower costs for regulatory document preparation Sample retention cost Exclusions: Cost of hiring external consultants for dossier submission, document writing, review or liaison.	0.56	0.63
PACKAGING, MARKETING AND POST-MARKETING STUDIES				
11.	Packaging & Supply chain Pharmacovigilance Discounts, Incentives & promotional costs Post Marketing Studies (PMS or Phase IV)	Inclusions: a) Artworks, Cold Storage, temperature monitoring, etc. b) Printing, distribution channel, etc. c) Digital marketing, branding, promotion, discounts, incentives, etc. d) Pharmacovigilance and PMS	0.86	1
ENABLING COST/CAPEX INVESTMENT				
13.	Infrastructure	Inclusions: Infrastructure cost includes CapEx of land, building, lab construction, equipment,	44.75	50

		effluent treatment plant and utilities installation.		
	Utilities	Annual operational expenditure for utilities (Annual expense/ product to be multiplied by the number of development years for calculating development cost)	0.5	0.63
Total Cost			~18 + 45	~21 + 50

Note: The estimated costs are moderated and generalised from the case reports. These may change with situation, indication and geography.

The currency conversion rate adopted is 1 USD equals 80 INR.

Abbreviations: PFS- Pre Filled Syringes, QC/QA – Quality Control & Assurance, PK/PD- Pharmacokinetics & Pharmacodynamics studies, PMS- Post Marketing Studies, BLA- Biologics License Applications, IMPD- Investigational Medicinal Product Dossier

Factors Influencing the Prices of Biotherapeutics

5.1 Introduction

The high prices of biotherapeutics remain an area of concern for various national and international agencies working towards developing strategies for monitoring, evaluating, and managing the prices of medicines to promote equitable access. This chapter determines the elements influencing the price of biotherapeutics, specifically biosimilars. The results are based on a bibliometric and qualitative synthesis approach detailed in Chapter 3 and generate a new line of thinking for future studies. The inferences from the qualitative synthesis led to the development of the key concept of the thesis and helped in knowledge synthesis. The findings enable knowledge assimilation for policy decisions. The results indicate that while factors like market share, market competition, and pricing policies are extensively explored by researchers, factors such as innovation capability, product development costs, and local factors like regulatory ecosystem can be further examined as potential influencers of prices. Further, pricing frameworks and regulations designed for generic drugs cannot be replicated to estimate the prices of biotherapeutics. As a result, policymakers must take the necessary actions to construct innovative pricing frameworks for this class of products that are in conformity with national policies, regulations, market dynamics, and economics. Moreover, studies on incentives and profit margins associated with the last-mile delivery and accessibility of high-cost biotherapeutics are essential for their efficient adoption.

The conceptual framework developed in this chapter determines the various antecedents, moderators and dependent variables of the pricing framework and acts as a precursor to the development of the TISM framework, as described in the next chapter.

5.2 Results and Discussions

5.2.1 Inferences from the thematic assessment for identification of major themes

The thematic assessment section divides the selected topic into four regions: basic, motor, emerging and niche themes. Figure 5.1 indicates the eighteen clusters based on “Development Degree” on Y-axis and “Relevance Degree” on X-axis. They are further arranged into four regions based on centrality (Relevance) and density (Development) scores provided in Table 5.1. The map reflects that themes like generic drugs, affordability, medicine prices, generic competition, and community pharmacy are basic themes with high relevance. On the other hand, themes like biosimilars, managed entry agreements, cancer medicine, quality, and cost-effectiveness are active themes with high development potential. These are the themes that have gained high traction from researchers. Further, the emerging themes which invite future research are drug price regulations and price determinants. These themes are relatively less explored, and further investigations are warranted.

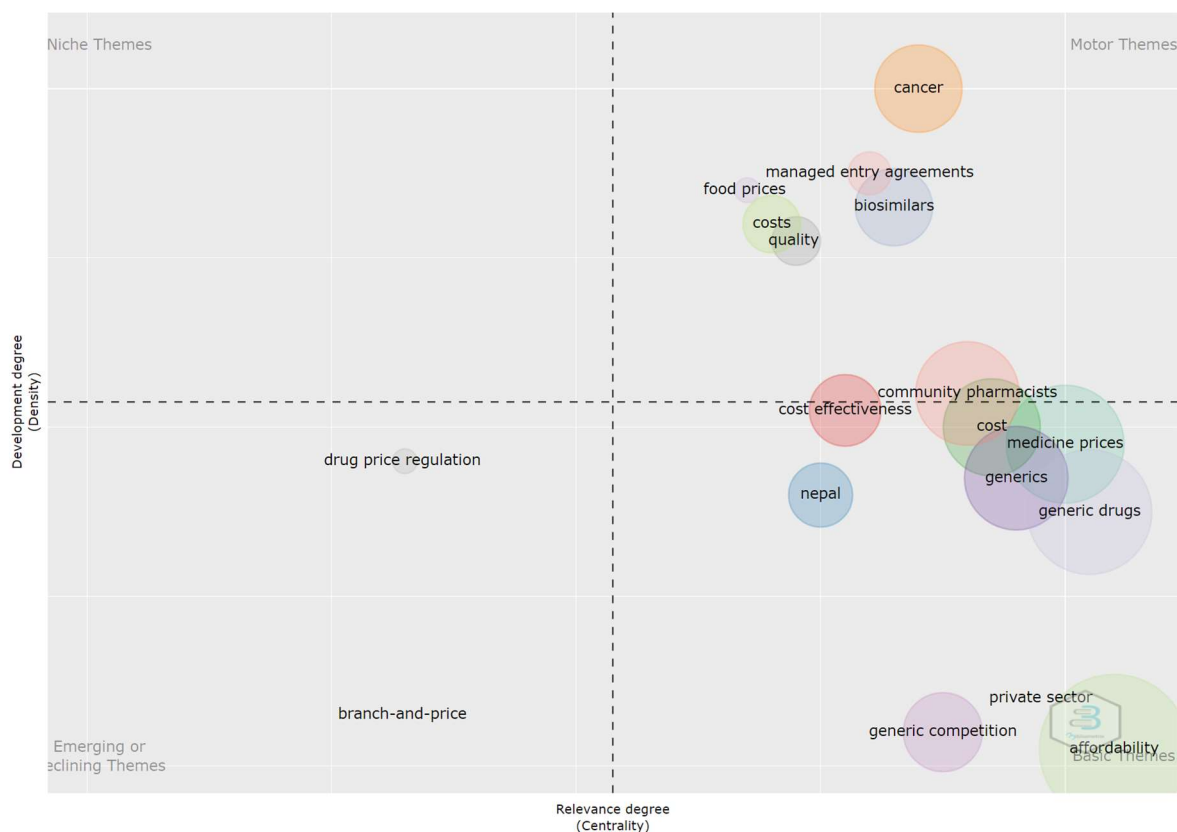


Figure 5.1: Thematic clusters

Note: developed through 500 authors' keywords with a minimum of 5 documents per thousand frequency.

Table 5.1: Centrality and density measurements of thematic clusters

Theme category	Cluster	Centrality	Density
Basic	Affordability	17.34	169.37
	Generic competition	3.47	169.74
	Private sector	6.83	193.20
	Generic drugs	10.35	200.09
	Medicine prices	9.48	235.68
	Community pharmacists	5.26	262.50
	Cost effectiveness	1.59	250.00
Emerging	Drug price regulation	0	216.67
	Branch-and-price	0	183.33
Motor	Quality	1.44	313.33
	Costs	1.18	313.64
	Biosimilars	2.04	374.72
	Food prices	0.75	375.00
	Managed entry agreements	1.62	393.75
	Cancer	2.77	442.16

To explore the evolution of themes, the full study period is sliced into three zones based on the chronological trends discussed in the earlier section and the subjective knowledge of the authors. To recall, the study on chronological trends revealed that most of the research papers were published in the time interval 2011 to 2020. Accordingly, time breaks are introduced in 2010, 2015 and 2020. The thematic progression map (Figure 5.2) indicates that the research themes, like essential medicines, generic drugs, prices, affordability, and price competition, are being researched from the period before 1965. The prices cluster has not witnessed significant changes between 2011-2015, and areas like generic medicines, affordability, and prices remained the top researched themes. However, the research related to cardiovascular medicine and hospital-based studies gained significant attention in this era. It is worthwhile to note that the period between 2016 and 2020 has witnessed the initiation of discussions on oncology, including the quality of cancer medicines. Events like the BPCI Act and Interchangeability have triggered the attention of researchers and policymakers toward high-cost biosimilars, specifically for cancer medicines. However, as concluded for the previous era, the research is dominated by generic themes of affordability and medicine prices. The 2021 time slice is introduced to analyse the latest developments in the domain. As expected, it reflects that the research interests are shifting towards themes like biosimilars and medicine prices.

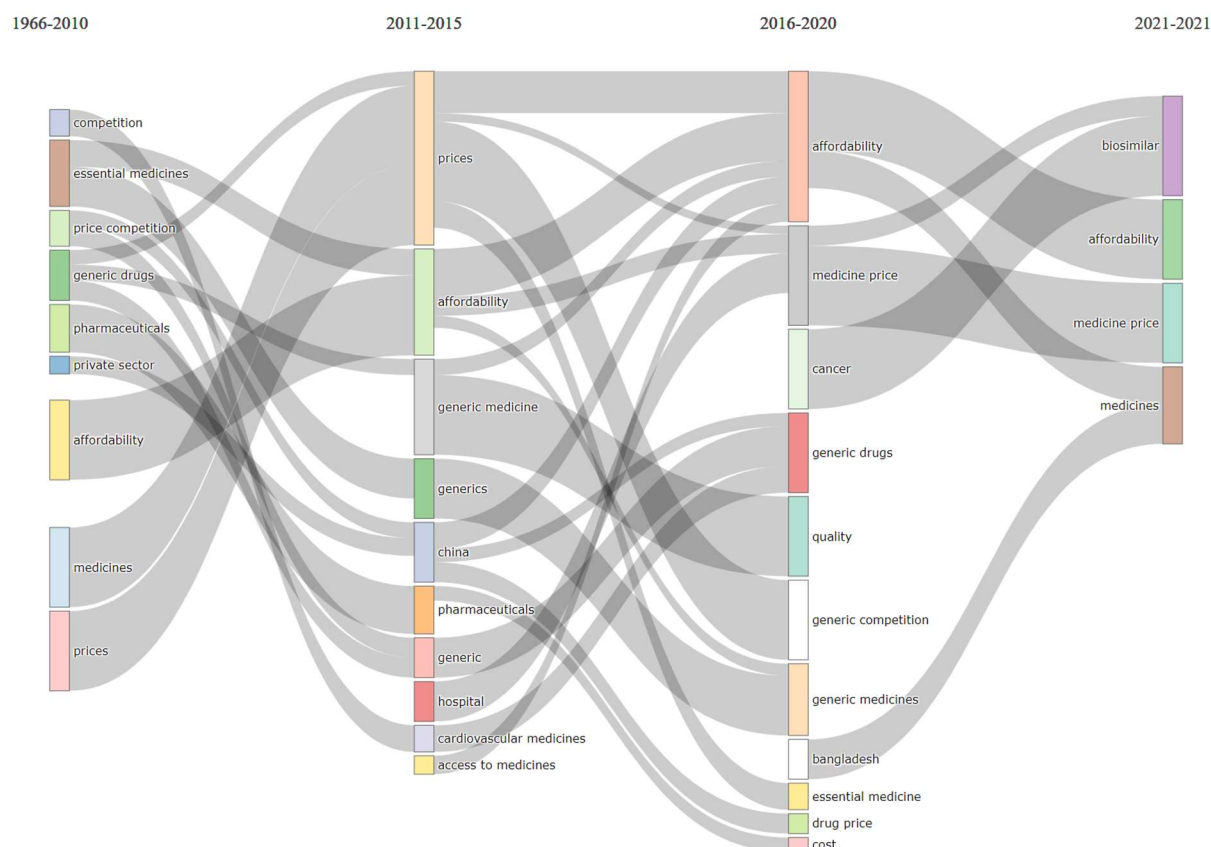


Figure 5.2: Thematic progression map

Note: Evolutionary information was generated through 1000 authors' keywords with a minimum cluster frequency of 5 and three time slices. The map describes the progression of the themes.

The results from Figure 5.1 and Table 5.1, based on the centrality and density measurements, highlighted that cancer, biosimilar, associated cost, quality and accessibility through managed entry agreements are the motor or active areas of research. In addition, the results of theme evolution studies, as presented in Figure 5.2, highlight that the research between 2016 and 2020 has witnessed the initiation of discussions on oncology, including the quality of cancer medicines. Further, the 2021 time slice reflected the shift of research towards themes like biosimilars and medicine prices. Based on all these inferences, more research is expected on biosimilar prices in the near future; hence, this cluster is selected for further examination. The

findings also suggest that healthcare economics with healthcare spending as a theme has high development potential in future.

5.2.2 Inferences from the qualitative synthesis

The qualitative synthesis section comprises four sequential steps: i) Concept development, ii) Advancing the concept, iii) Subjective review, and iv) Knowledge synthesis. Although the inferences from one step feed into the other for developing key recommendations, the inferences from individual steps are equally meaningful and worthwhile for consideration. The intent is to map significant areas of agreement, disagreement, and knowledge gaps through this systematic approach.

Concept development is based on the co-occurrence methodology and subjective knowledge. The degree of relevance of the articles to the cluster and the overall contribution to the topic is generated as on the understanding of the subject. While developing the concepts around each cluster, weightage is also given to the themes formulated through co-occurrence and co-citation analysis observed in Chapter 2.

The manual review assisted with themes identified through co-occurrence analysis and divided the complete dataset into 5 major clusters. As anticipated, most of the research is concentrated around the foundation themes like generic medicines and essential drugs. The WHO-HAI project and pricing mechanisms/policies raised significant interest among the researchers. Both clusters I and II on “Generic Essential Medicine” and “Pricing Mechanisms/Policies” collectively account for more than half of the research, i.e. 54%. The accessibility of medicines and healthcare economics, including out-of-pocket expenditure from cluster III, with a 19% contribution. Closely following with a 16% contribution is the research on high-burden diseases like Malaria, HIV and cardiovascular disorders as cluster IV. The lowest percentage of around 11% is towards cluster V on biosimilar prices, highlighting the research areas like the affordability of cancer medicines and comparative studies with the originator.

Subsequently, major themes are identified within each cluster, which are described in Table 5.2.

Table 5.2: Major themes within clusters (Percent contribution)

S. No	Cluster	Percent contribution	Major themes within the cluster
I	Generic drugs, essential medicine, and pharmacy	28%	Essential drugs for common diseases, Role of the private sector, Price impact on pharmacy type, Price patterns of generic medicine, Exclusivity restriction benefits
II	Pricing mechanisms and policies	26%	WHO-HAI project, Reference pricing, Price cap regulation, Impact of patient protection and affordable care act, Pricing strategies
III	Healthcare economics, accessibility and Market dynamics	19%	Healthcare expenditure, Medicaid drug spending, Health insurance, Cost benefits to healthcare, Out-of-pocket spending, Price elasticity, Market concentration
IV	Medicine for high-burden diseases	16%	Malaria, Cardiovascular medicines, Universal access to HIV treatment with antiretroviral drugs, Disease burden impact on costs and benefits
V	Biosimilar prices	11%	Affordable cancer medicine and healthcare delivery, Price comparison with originator, Biosimilar selection strategies, Managed entry agreement

Abbreviations:

HIV- Human Immunodeficiency Virus

WHO-HAI – World Health Organisation - Health Action International

Advancing the concept section attempts to expand the understanding of the “Biosimilar prices” cluster. As the results of the previous section suggested the need for an extended study in this domain, the dataset was refined by omitting the words "Medicine" OR "Generic" and restricted to the period 2010 – 2021 (The period with maximum publications). Figure 5.3 reflects research trends for biosimilar prices by mapping the various topics with the year of publication. As per the trends, 2012 marked a significant development of biosimilars. India made a significant contribution by approving a few biosimilars even before they were approved in Europe.

Moving forward, the US Medicaid system and the adoption of biosimilars generated significant publications in 2014. The trends further indicate that the amendments in the BPCI Act ignited the debate on the high prices and accessibility of biosimilars. Not to mention, the debate started with Insulin prices because of high demand and the high burden of diabetes, but the patent expiry of originator molecules and accessibility remained at the centre stage. 2017 and 2018 emerged as the years with significant expansion of the research into themes like interchangeability, cost-effectiveness, and health economics. 2019 witnessed the shift toward the oncology and inflammatory segments like cancer, trastuzumab, adalimumab, infliximab, and rheumatoid arthritis, which are high-cost biologics. Further, the trend highlights that topics like regulatory frameworks, cost-effective analysis, insurance, competition, and health economics are emerging within the biosimilar price cluster and have a high potential for future development.

The earlier sections, specifically Figure 5.1, also highlighted price regulation and related pricing mechanisms as emerging areas which need efforts for further development. The cost-effective studies in the form of health technology assessment and health insurance as universal health coverage (UHC) are ranked high among the most contested topics in health policy. The effective and efficient pricing structure supported by the right regulatory framework is particularly critical for LMICs, where medicine prices form a significant portion of health spending and can impact the implementation of UHC (Chalkidou et al., 2020). Hence, regulators should make the price regulations and mechanisms easier and more efficient to ensure the affordability and accessibility of high-cost medicines, particularly cancer biotherapeutics.

Table 5.3: Key factors influencing the prices of biotherapeutics

S. No.	Factor(s)	Key findings/ Impact on price	Reference
I. Market dynamics			
1.	Market share	The price varies as per the market share of generic medicines. Competition from generic medicines leads to price reductions. Generic market share is directly proportional to a decrease in prices.	Dylst & Simoens, 2011
2.	Market competition and demand	The chances of generic suppliers responding to factors influencing demand size and market competition are high. Originator suppliers set prices strategically to reduce compulsory licensing and generic competition threats.	Meiners et al., 2011
3.	Entry of new biosimilar	The introduction of the new biosimilar Pegfilgrastim over GCSF resulted in substantial cost savings for French healthcare.	Yang et al. 2021
II. Product-specific factors			
4.	Efficacy and safety	A biosimilar's price is only one aspect of its full value. In addition to taking into account development and manufacturing expenses, the outcomes of efficacy and safety in comparison to the reference biologic medicine are also taken into account.	Henry, D., & Taylor, C., 2014
5.	Package inserts	Price is a reflection of the quantity of information provided in inserts. Information provided with generic drugs is less than for brand drugs. The difference in the quantity of information is based on differences in manufacturer policy on the information.	Shiragami, 2015
III. Economic drivers			
6.	Per capita income	Per capita GDP is positively correlated with the unit price of insulin. The price of insulin drugs originating from OECD countries is higher than that imported from developing countries.	Helble & Aizawa, 2017
7.	Domestic manufacturing capabilities and paying capacity of the economy	Developing domestic manufacturing capacity is important but due to complexities, it is not a recommended option for emerging economies. It is recommended to expand the market and facilitate the import of biologics.	Rathore & Shareef, 2019
IV. Price discounts and incentives			

8.	List prices, net prices, discounts	The price drop is observed for originators after the entry of biosimilars or other substitutes in the market. The entry of biosimilars stopped the increase in list prices but net prices commence to decrease due to discounts offered by companies.	San-Juan-Rodriguez et al., 2019
9.	Reimbursement criteria	No specific difference was observed between the reimbursement criteria for biosimilars and other generic products in the selected CEE countries. The price of biosimilars is usually reduced in comparison to original drugs and huge price discounts are offered.	Kawalec et al., 2017
V. Process innovation and M&A			
10.	Innovation and M&A	Price does not correlate with market power based on industry concentration (HHI Index). M&A induced market concentration may weaken competition. The potential danger of market concentration is at the stage of regulatory approval.	Richman et al., 2017
11.	API, formulation (Raw material availability)	Competitive large-scale generic manufacturers can supply 5-10 times more MDR-TB treatment within current procurement budgets without major impact on profit margins.	Gotham et al., 2017
VI. Psychological factors			
12.	Consumer behaviour	Generic price terms like cheap and not expensive. The cheap word is associated with lower prices than the not-expensive word. It is not related to higher preferences for cheap drugs as it may evoke negative quality perceptions.	Weijters et al., 2018
13.	Trust and confidence of the physician	To increase the market acceptance of biosimilars, clinicians' and users' trust and confidence are essential. This may increase the demand and impact the price.	Camacho, L. H., 2017
VII. Selection strategy			
14.	Originator vs Generics	Switching originator drugs to generics results in savings of 65% for patients.	Zeng, 2013
15.	Selection strategy	The price of the originator varies with the selection strategy between branded and generic drugs in out-of-hospital pharmacies, but not in in-house pharmacies of medical facilities.	Takizawa et al., 2015
VIII. Pricing policy			

16.	Differential pricing policies	Differential pricing policies are feasible mostly for ‘global’ diseases, where drugs through worldwide sales recoup their R&D costs. The differential prices vary with the pharmaceutical industry and do not encourage sustainability or autonomy in developing countries.	Babar & Atif, 2014
17.	New public medicine procurement policy	The introduction of the NPMPP led to an increase in the prices of emergency medicines and gynaecological medicines, but a decrease in the prices of paediatric medicines.	Hu et al., 2019
18.	Pricing policies	Despite many efforts toward the implementation of policies like internal reference, tendering and generic substitution to increase biosimilar adoption, a large difference remains in the price and uptake of medicines between countries.	Ferrario et al., 2020
IX. Regulations			
19.	Price cap regulations	A continuous decline in the ceiling prices is associated with a high incidence of exit of generic firms from markets.	Zhang, Wei, et al. 2016

Abbreviations:

API - Active Pharmaceutical Ingredient

ARV - Antiretrovirals

CEE - Central and Eastern European countries

GCSF - Granulocyte Colony Stimulating Factor

GDP - Gross Domestic Product

HHI - Herfindahl-Hirschman Index

M&A - Mergers and Acquisitions

MDR-TB – Multi Drug Resistant Tuberculosis

NPMPP - New Public Medicine Procurement Policy

OECD - Organisation for Economic Co-operation and Development

WHO – World Health Organisation

Factors like market share, market competition, and pricing policies are extensively explored by researchers and can be considered major influencers of prices. Market-based costing strategies, as explained in the introduction, are currently in practice in many nations, including India and Pakistan. In this scenario, the price changes according to the market share of biosimilars; an

increase in competition by the addition of a new biosimilar in the market usually causes a decrease in prices. A decline in pricing is directly correlated with the market share of generic products (Dylst & Simoens, 2011; Meiners et al., 2011). The fact that originator suppliers strategically set prices to lessen the prospect of compulsory licensing and generic competition is also well recognised. Therefore, it is essential to stop such malpractices to increase the affordability of medications from a few manufacturers.

The potential influencers of biotherapeutic pricing include determinants like innovation capability (R&D), product development cost and local regulatory framework. Domestic manufacturing capability is considered one of the major factors of affordability (Rathore & Shareef, 2019). As mentioned before, the manufacturing of biosimilars is significantly different from generic drugs and is a complex process (Ratih et al., 2021). Information on costs associated with product development can aid in cost-effectiveness analysis and strengthen government price negotiations through appropriate regulations (Hill et al., 2018). Hence, variables such as technological innovation, R&D costs, production yield, regulatory ecosystem, and patent protection could be further explored as potential factors impacting the prices of biotherapeutics. We recommend evidence-based studies to understand the important primary and secondary factors affecting the prices of biosimilars.

The acceptance of biosimilars is significantly influenced by incentive policies and profit margins (Rémuzat et al., 2017). Prescription targets, primary substitution, reference price systems, clinical guidelines, fixed payments, and public tendering are some potential incentives and barriers to their effective adoption (Swartenbroekx et al., 2014). Depending on the adoption rate of biosimilars, the discounts vary greatly from product to product and nation to nation (Mullard, 2017). Even though different countries have different incentives for biosimilars, prescription quotas or budgets are frequent. Financial incentives or penalties were also noted in a few countries (Belgium and Germany), but the enforcement of such measures calls for

creative monitoring techniques (Rémuzat et al., 2017). Therefore, interlinkages between the factors leading to the complexities of the pricing mechanism are an interesting research area for further consideration.

Apart from these, it is also important to point out the studies on consumer behaviour, pharmacy type, and package inserts, which are often overlooked (Innovation & Shiragami, 2015; Weijters et al., 2018). These can be considered micro-influencers that impact biotherapeutic prices. One example could be market concentration brought on by M&A, creating a monopoly. At the time of regulatory approval, market concentration could be dangerous, demanding detailed analysis (Richman et al., 2017)

Knowledge synthesis section combines the findings from various sections of this chapter. The results from the bibliometric as well as qualitative synthesis sections are summarised, and interlinkages are developed to generate a new line of thinking for future studies. Table 5.4 provides a summary of the findings of the thematic assessment and Qualitative synthesis section and helps in advancing the knowledge towards the development of a new line of thinking for future studies.

Table 5.4: Summary of findings

Study vertical	Study parameter	Key findings
Thematic assessment		
Theme maps	Emerging themes	Drug price regulations and price determinants
	Active themes	Biosimilars, managed entry agreements, cancer medicine, quality and cost-effectiveness
	Basic themes	Generic drugs, affordability, medicine prices, generic competition, and community pharmacy
Qualitative synthesis		
Conceptualisation	Clusters (% contribution)	Generic drugs including essential medicines (28 %), pricing mechanism (26 %), healthcare market dynamics (19%), high-burden medicine (16%) and biosimilars price (11%)

Biosimilar price study	Significant expansion of research from 2017 onwards. Managed entry agreements, interchangeability, and affordability of cancer medicines for targeted therapies are active interest areas.
Factors impacting prices	<i>Major influencers:</i> Market dynamics, economic drivers, pricing policies and mechanisms <i>Potential influencers:</i> Product-specific factors, process innovation and regulations <i>Essential for adoption:</i> Incentive policies and profit margins <i>Micro influencers:</i> Selection strategy, psychological factors and M&A
Knowledge synthesis	• Need for evidence-based studies to understand the important primary and secondary factors affecting the prices of biosimilars. • Inter-linkages between the factors leading to the complexities of the pricing mechanism are an interesting research area for further consideration. • Studies on incentives and profit margins are essential for the efficient adoption of biosimilars. • Country-specific costing and pricing strategies are required to align with the local policies, regulations, and economic factors of the country. • The pricing mechanisms, regulations and policies developed for the generic drugs, synthesised by chemical route, cannot be replicated for biosimilars.

Abbreviations:

HER 2 - Human epidermal growth factor receptor 2

TNF - Tumor Necrosis Factor

VEGF - Vascular Endothelial Growth Factor

WHO-HAI – World Health Organization - Health Action International

The results reflect that the concept of generic competition with originator medicine and related price impact is not a recent one; it appeared in publications even before the 1960s. Only after 2010 did the topic gain traction, resulting in considerable research papers. The key fundamental themes, like drug costs, generic competition, and critical medicines, have stayed constant throughout the evolutionary process, but a few themes, such as "biosimilar prices and quality,"

have emerged over time. It has been found that most price debates are limited to essential medicines, with sectors such as neglected diseases and orphan treatments being overlooked. Although research on biosimilar costs is growing rapidly, it still accounts for a very small portion of research publications (11 percent) in the entire field of generic medications and critical pharmaceuticals. Numerous researchers have focused on the cost and accessibility of cancer biosimilars, and this focus has accelerated since 2016. It should be highlighted that although specific pricing approaches are adopted by various nations, there is still significant disagreement in finding the best pricing mechanism for expensive therapeutics. Additionally, the majority of pricing strategies for essential medications include biosimilars in the same category as generic medications without considering many scientific elements associated with biosimilars. It is important to develop regulations/policies for biosimilars to justify the associated high innovation component as compared to a generic drug (Erwin, 2013; Food and Drug Administration, 2018). Further, scant literature on the pricing mechanisms of biotherapeutics makes the study challenging (Rao, 2011).

The bibliometric analysis reveals that a significant number of articles are published through sponsored research. “National Institute of Health” and “The U.S. Department of Health and Human Services” funded considerable research in this domain. Another key point deciphered from this review is that most of the studies are descriptive, and only a limited number of empirical studies are performed. As can be seen from Table 5.2, pricing mechanisms and policies like internal, differential referencing, tendering and switching policies have been extensively researched to untangle the complexities of biosimilar pricing. Moreover, studies on incentives and profit margins associated with the last mile delivery and accessibility of high-cost cancer biosimilars are essential for the efficient adoption of biosimilars. It is worthwhile to note that there cannot be a “one size fits all” rule that can be applied to all countries (Ferrario et al., 2020). Hence, there is a need to develop country-specific costing and pricing strategies

that align with the policies, regulations, market dynamics, and economic ecosystem of that country. Further, most of the efforts in this direction are concerted towards the generic drugs for high-burden diseases like HIV, Malaria and TB, while biotherapeutics have received scant attention on account of the different value chains including R&D, production, procurement, distribution, and usage network. Creating an optimal solution would demand a deep understanding of the pricing mechanisms and costing models for this class of products.

It is evident from the findings that most of the research is concentrated on market dynamics, leading to the impression that the prices of medicines are mainly driven by market forces, with manufacturing cost and product parameters playing a limited role. Accordingly, it is noteworthy that many countries prefer a market-based pricing mechanism for determining the ceiling prices of biotherapeutics over a cost-based one. However, the review also raises an important question: in the absence of significant research on other factors and the availability of pharmacoeconomic data for many molecules, is it justified to continue with market-based costing policies? or the decision-makers should start exploring other efficient alternatives.

5.2.3 Validation of the identified factors

The factors impacting the price of biotherapeutics identified in previous sections were subjected to validation by experts in the biopharmaceutical domain. The subject experts are senior individuals from various domains of the biopharmaceutical sector with an average of 15 years of active experience. The initial list of nineteen elements, as mentioned in Table 5.3, has been extrapolated and modified through expert inputs, resulting in the identification of a total of 22 factors. Further, the inputs from seven biotherapeutics experts, obtained through a structured questionnaire (Annexure 5B), facilitated the identification of the eleven most significant factors out of a total of twenty-two. Responses that met or exceeded an acceptance criterion of 50 percent were taken into consideration when selecting factors for modified TISM. The final set of factors selected for further analysis is mentioned in **Annexure 5C**.

5.2.4 Preliminary conceptual framework as a precursor to TISM

The conceptual framework of possible antecedents and moderating variables impacting the price of biotherapeutics is shown in Figure 5.4. The role of BPCIA in moderating pricing was underlined in an empirical study on the effect of market competition on biosimilar prices (Frank et al., 2021). A study by (Morton et al., 2018) assesses the influence of variables like market features and public policies on the entry, price, and penetration of biosimilars.

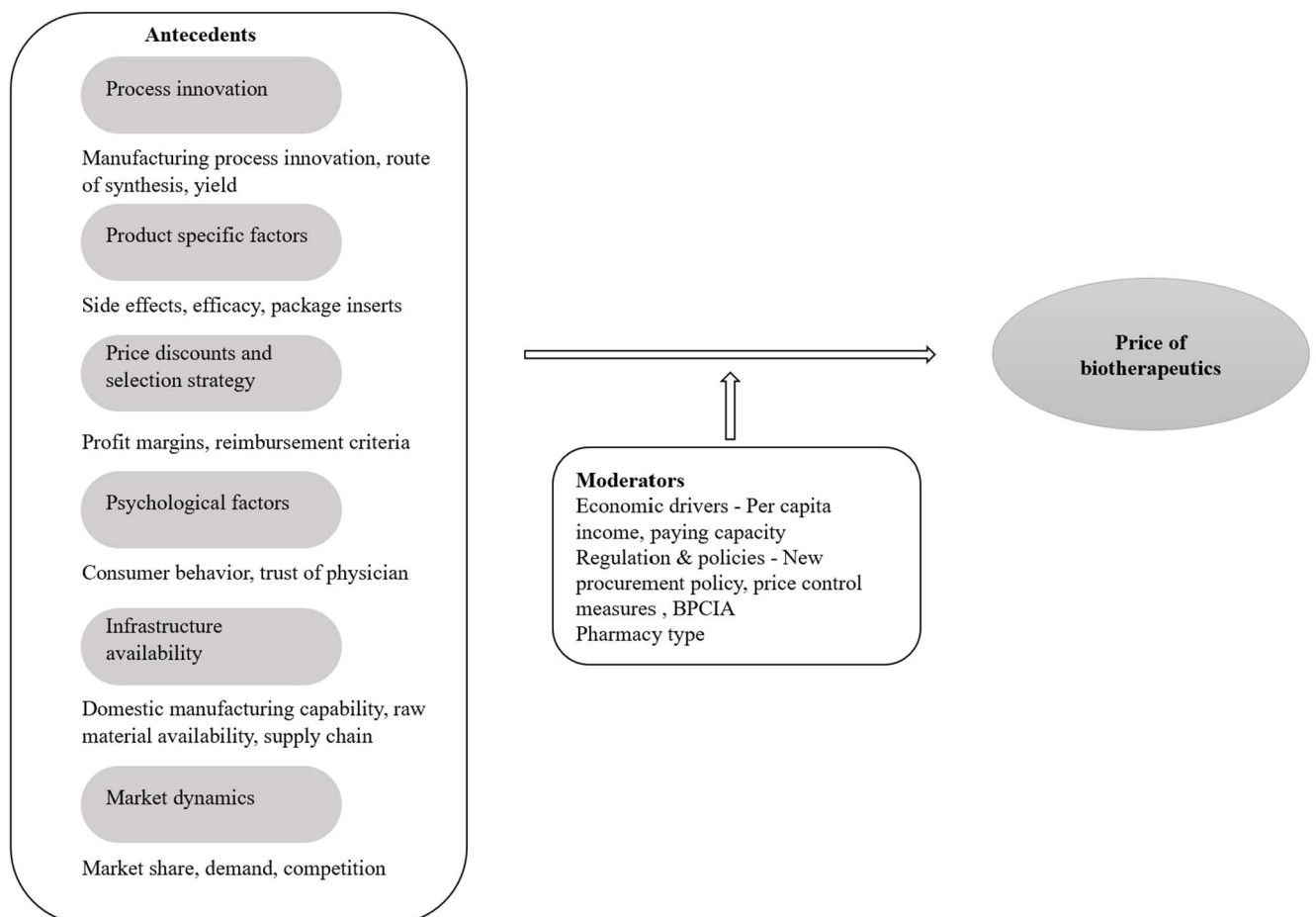


Figure 5.4: Conceptual framework of factors influencing the prices of biotherapeutics

5.3 Conclusion

This Chapter presents the findings of Objective 2 by describing the various factors influencing the prices of biotherapeutics. These are identified through a distinctive systematic bibliometric-based study design. These factors are utilised as building blocks for the development of a hierarchical model of biotherapeutic prices in the next Chapter on Objective 3. The conceptual framework developed in this Chapter provides a basic understanding of the price variables. This framework is further refined through a systematic method of mTISM into a graded structure of variables.

The findings from Objective 2 are published as

Gandhi, S., Kashiramka, S., & Rathore, A. S. (2023). Emerging themes and factors influencing the prices of biotherapeutics. *World Medical & Health Policy*, 15(4), 613-637.

Annexure 5A: Expert validation of identified factors

Code	Factor(s)	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Expert 6	Expert 7	% Acceptance
F1. Market dynamics									
F 1.1	Market share	Yes	Yes	Yes	No	Yes	Yes	Yes	85.71
F 1.2	Market competition and demand	Yes	Yes	Yes	Yes	Yes	No	Yes	85.71
F 1.3	Entry of new biosimilar	Yes	Yes	Yes	No	Yes	Yes	NA	83.33
F2. Product-specific factors									
F 2.1	Efficacy and safety	No	Yes	No	No	Yes	Yes	Yes	57.14
F 2.2	Package inserts	No	No	No	Yes	Yes	No	Yes	42.86
F3. Economic drivers (Economics)									
F 3.1	Per capita income	Yes	Yes	Yes	Yes	Yes	Yes	NA	100
F 3.2	Domestic manufacturing capabilities	No	No	No	No	No	No	Yes	14.28
F4. Price discounts and incentives									
F 4.1	List prices, net prices, discounts	Yes	Yes	Yes	No	Yes	Yes	Yes	85.71
F 4.2	Reimbursement criteria	Yes	Yes	No	No	Yes	Yes	Yes	71.43
F5. Process innovation and partnerships									
F 5.1	Innovation and M&A	Yes	No	Yes	No	No	Yes	Yes	57.14
F 5.2	API, formulation	No	No	Yes	Yes	No	Yes	Yes	57.14

F 5.3	Reference product cost	No	Yes	Yes	Yes	No	No	Yes	57.14
F 5.4	Public-private partnership	Yes	No	No	No	Yes	Yes	Yes	57.14
F6. Psychological factors									
F6.1	Consumer behaviour	Yes	Yes	Yes	No	Yes	Yes	Yes	85.71
F6.2	Trust and confidence of the physician	Yes	Yes	Yes	No	Yes	Yes	Yes	85.71
F7. Selection strategy									
F7.1	Originator vs generics	Yes	Yes	No	Yes	Yes	Yes	Yes	85.71
F7.2	Selection strategy	No	Yes	Yes	No	No	No	Yes	42.86
F8. Pricing policy									
F8.1	Differential pricing policies	No	Yes	Yes	No	No	Yes	Yes	57.14
F8.2	New public medicine procurement policy	No	No	NA	Yes	No	Yes	NA	40
F8.3	Pricing policies	Yes	Yes	Yes	No	Yes	Yes	Yes	85.71
F9. Regulations									
F9.1	Price cap regulations	Yes	No	No	No	Yes	No	Yes	42.86
F9.2	Insurance coverage	No	No	No	No	Yes	Yes	Yes	42.86
Acceptance: 50 % or more									

Annexure 5B: Questionnaire for validation

The following elements were identified through a comprehensive literature review and have the ability to affect biosimilar affordability. Please select the significant factors impacting the biosimilar prices in India from the list. Your responses would be used to develop a hierarchical model of biosimilar prices using Total Interpretive Structural Modelling (TISM) and a fuzzy MICMAC approach.

Code	Factor(s)	Key findings/ Impact on price	Reference	Is this factor significant?
F1. Market dynamics				
F1.1	Market share	The price varies as per the market share of generic medicines. Competition from generic medicines leads to price reductions. Generic market share is directly proportional to a decrease in prices.	Dylst & Simoens, 2011	Yes/No
F1.2	Market competition and demand	The chances of generic suppliers responding to factors influencing demand size and market competition are high. Originator suppliers set prices strategically to reduce compulsory licensing and generic competition threats.	Meiners et al., 2011	Yes/No
F1.3	Entry of new biosimilars	The introduction of the new biosimilar Pegfilgrastim over GCSF resulted in substantial cost savings for French healthcare.	Yang et al. 2021	Yes/No
F2. Product-specific factors				
F2.1	Efficacy and safety	A biosimilar's price is only one aspect of its full value. In addition to taking into account development and manufacturing expenses, the outcomes of efficacy and safety in comparison to the reference biologic medicine are also taken into account.	Henry, D., & Taylor, C., 2014	Yes/No
F2.2	Package inserts	Prices are a reflection of the quantity of information provided in inserts.	Shiragami, 2015	Yes/No

		Information provided with generic drugs is lesser than for brand drugs. The difference in the quantity of information is based on differences in manufacturer policy on the information.		
F3. Economic drivers				
F3.1	Per capita income	Per capita GDP is positively correlated with the unit price of insulin. The price of insulin drugs originating from OECD countries is higher than that imported from developing countries.	Helble & Aizawa, 2017	Yes/No
F3.2	Domestic manufacturing capabilities	Developing domestic manufacturing capacity is important but due to complexities, it is not a recommended option for emerging economies. It is recommended to expand the market and facilitate the import of biologics.	Rathore & Shareef, 2019	Yes/No
F4. Price discounts and incentives				
F4.1	List prices, net prices, discounts	The price drop is observed for originators after the entry of biosimilars or other substitutes in the market. The entry of biosimilars stopped the increase in list prices but net prices commence to decrease due to discounts offered by companies.	San-Juan-Rodriguez et al., 2019	Yes/No
F4.2	Reimbursement criteria	No specific difference was observed between the reimbursement criteria for biosimilars and other generic products in the selected CEE countries. The price of biosimilars is usually reduced in comparison to original drugs and huge price discounts are offered.	Kawalec et al., 2017	Yes/No
F5. Process innovation and partnerships				

F5.1	Innovation and M&A	Price does not correlate with market power based on industry concentration (HHI Index). M&A induced market concentration may weaken competition. The potential danger of market concentration is at the stage of regulatory approval.	Richman et al., 2017	Yes/No
F5.2	API, formulation (Raw material cost)	Competitive large-scale generic manufacturers can supply 5-10 times more MDR-TB treatment within current procurement budgets without a major impact on profit margins.	Gotham et al., 2017	Yes/No
F5.3	Reference product cost	The originator companies practise limit pricing or setting prices just high enough to prevent the entry of biosimilars. The reference products may have cost advantages due to economies of scale.	Blackstone & Fuhr, 2013	Yes/No
F5.4	Public-private partnership	The production of biosimilars to meet local public health requirements can be achieved through effective public-private partnerships between public health organisations, regional biosimilar producers, and international pharmaceutical companies.	Liang & Mackey, 2014	Yes/No
F6. Psychological factors				
F6.1	Consumer behaviour	Generic price terms like cheap and not expensive. The cheap word is associated with lower prices than the not-expensive word. It is not related to higher preferences for cheap drugs as it may evoke negative quality perceptions.	Weijters et al., 2018	Yes/No
F6.2	Trust and confidence of the physician	To increase the market acceptance of biosimilars, clinicians' and users' trust and	Camacho, L. H., 2017	Yes/No

		confidence are essential. This may increase the demand and impact the price.		
F7. Selection strategy				
F7.1	Originator vs generics	Switching originator drugs to generics results in savings of 65% for patients.	Zeng, 2013	Yes/No
F7.2	Selection strategy	The price of the originator varies with the selection strategy between branded and generic drugs in out-of-hospital pharmacies, but not in in-house pharmacies of medical facilities.	Takizawa et al., 2015	Yes/No
F8. Pricing policy				
F8.1	Differential pricing policies	Differential pricing policies are feasible mostly for ‘global’ diseases, where drugs through worldwide sales recoup their R&D costs. The differential prices vary with the pharmaceutical industry and do not encourage sustainability or autonomy in developing countries.	Babar & Atif, 2014	Yes/No
F8.2	New public medicine procurement policy	The introduction of the NPMPP led to an increase in the prices of emergency medicines and gynaecological medicines but a decrease in the prices of paediatric medicines.	Hu et al., 2019	Yes/No
F8.3	Pricing policies	Despite many efforts toward the implementation of policies like internal reference, tendering and generic substitution to increase biosimilar adoption, a large difference remains in the price and uptake of medicines between countries.	Ferrario et al., 2020	Yes/No
F9. Regulations				

F9.1	Price cap regulations	A continuous decline in the ceiling prices is associated with a high incidence of exit of generic firms from markets.	Zhang, Wei, et al. 2016	Yes/No
F9.2	Insurance coverage	ASPs for biosimilars have decreased as a result of Medicare insurance coverage for medicines, though data varies depending on the product. Additionally, due to rebate programmes and preferred placement on formularies, reference biologics are frequently the least expensive choice.	Nahleh et al., 2022	Yes/No

Please suggest any other factor which you think can influence the price of biosimilars.

We thank you for your valuable time and suggestions.

Name: _____

Affiliation: _____

Annexure 5C: Price factors selected for further analysis

Code	Factor	Description
F1	Market dynamics	Market share, market competition, demand and entry of new biosimilars constitute the market dynamics. The price varies as per the market share of medicines. The introduction of new alternative medicine can lead to substantial cost savings and a reduction in prices through competition.
F2	Product features	The efficacy, safety, raw material, active pharmaceutical ingredient, and finished product specifications are key parameters that determine the quality of the product. The prices may vary due to variations in the ingredients and final product parameters.
F3	Country's economy	Gross Domestic Product (GDP) is an indicator of a nation's economic well-being. Variables such as purchasing parity, per capita income, and paying capacity are interconnected with pricing and serve as reliable indicators of the whole health system.
F4	Government incentives	Product Linked Incentivisation (PLI) scheme, compulsory license, and Pradhan Mantri Jan Arogya Yojana (PMJAY) insurance coverage by the government promote indigenous development of medicines, and through subsidised rates, can impact the prices.
F5	Process innovations	Efficient, high yielding innovative technologies in research, manufacturing processes or supply chain can impact the cost of goods. Adoption of the latest upstream and downstream processing methods or the use of artificial intelligence (AI), machine learning

		(ML) and process analytical technology (PAT) are a few cost-effective technologies.
F6	Psychological factors	Patients' behaviour, perception, trust and confidence in the biosimilar version of the innovator product can impact the adoption. To increase the market acceptance of biosimilars, trust and confidence among clinicians or healthcare professionals are essential. Biosimilars are mostly administered in hospital settings unlike pharmaceutical generics, hence, the trust of clinicians affects the decision-making more than the patient.
F7	Originator vs. Biosimilar	Biosimilars are not the same as originator/innovator biologics or generics (small molecule drugs). The manufacturers prefer developed markets over emerging markets due to high profit margins, but a long-term strategy in emerging countries aligned with therapeutic areas specific to the target population can make biosimilars affordable and profitable through volumes.
F8	Price control policies including regulations	The pricing policies play an important role in determining the prices of essential medicines and biosimilars in the country. The NPPA in India through DPCO order implements the price control policies. The cost based, market-based mechanisms, differential pricing, reference pricing, and value-based pricing through Health Technology Assessment (HTA) can be instrumental in developing the prices in a country. The regulatory framework including the approval process and regulatory requirements for the manufacturing authorisation can influence prices.

F9	Patent expiry	The patent cliff and expiry of multiple originator patents in 2030 can change the dynamics of the biosimilar business. There has been an increasing demand for affordable and cost-effective treatments, with a substantial increase in the number of originator biologics losing patent protection. This is driving the phenomenal growth of biosimilars as both the public and government realise the significant potential they hold towards contributing to cost savings for healthcare.
F10	Manufacturer discounts/awards to clinicians	Promotional gimmicks are quite common in the biosimilar industry. Various nations offer incentives to encourage the adoption of biosimilars. Prescription quotas, budgets, financial incentives, and fines are prevalent practices in certain nations such as India, Belgium, and Germany. Those actions are linked to the last phase delivery and the availability of biotherapeutics.
F11	Partnerships (Including PPP and M&A)	Public Private Partnerships (PPP) and Mergers & Acquisitions (M&A) are increasing in the biosimilar arena. The biosimilar landscape can change due to mergers and acquisitions, leading to the introduction or withdrawal of biosimilars in the market. This M&A induced market concentration may weaken competition and can impact prices.

Note: The regulatory framework is added with policies as per the suggestion of experts. The factors mentioned here have significant potential to impact the prices of biosimilars.

Pricing Framework for Affordability of Biosimilars

6.1 Introduction

The National Pharmaceutical Pricing Authority (NPPA), the medicines price regulating body in India, has adopted a market-based pricing policy for determining the prices of medicines. However, various factors like production cost, product features, the country's economy, partnerships, and government incentives, which are likely to impact drug prices, were not considered. As criticised, this mechanism is not an ideal approach to control or cap the prices of medicines, especially for the biosimilars, wherein the market is dominated by the oligopoly of manufacturers. This Chapter describes the step-by-step approach towards developing the price framework for biosimilars. The conceptual framework developed in the previous chapter is further advanced through a structured approach of TISM. The reachability matrix, followed by level partitioning, resulted in the categorisation of price determinants into six levels. Section 6.3 of the Chapter conducts an in-house test on the framework by using the MICMAC approach. The external validation is performed with the help of biopharmaceutical professionals through a structured questionnaire. The validation facilitated the separation of independent variables from dependent and linkage variables, which are further analysed in the next chapter.

The direct links and interrelationships between the various factors are described in section 6.4. The research on interlinkages explained the connected relationships between various factors and helped in understanding the complex web of the biosimilar pricing ecosystem.

6.2 Demystifying the biosimilar price framework: “Step-by-Step” approach

6.2.1: The factors impacting the prices of biotherapeutics, as identified in Objective 2 and explained in Chapter 5-Annexure 5C, are further employed for developing the TISM

framework. After the validation from the subject experts, the pairwise comparison of eleven factors as per the $[n(n-1)/2]$ rule of TISM was performed through two brainstorming sessions. Five experts from various fields of biotherapeutics participated in the sessions. The reachability matrix ($n \times n$) in binary form has been created with simultaneous transitivity checks. The binary relationship, with 1 and 0 scores, respectively, indicates the presence or absence of a relation between the variables. Further, the transitive links are indirect relations and are expressed by 1*. The pairwise comparisons with direct and transitive links are depicted in the reachability matrix in Table 6.1. The driving power and dependence are calculated by the summation of scores in rows and columns, respectively.

Table 6.1: Reachability matrix representing direct and transitive links

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	Driving Power
F1	1	0	1	1*	1*	1*	1	1	0	1	1	9
F2	0	1	0	0	0	1*	1	0	0	0	0	3
F3	1	0	1	1	1*	0	0	1*	0	1*	1*	7
F4	0	0	0	1	1	1*	1*	1	0	1	0	6
F5	0	1	0	0	1	0	0	0	0	0	0	2
F6	0	1*	0	0	0	1	1	0	0	0	0	3
F7	0	0	0	1*	0	1	1	0	0	0	0	3
F8	0	1	1*	1	1	1*	1	1	0	1	0	8
F9	1*	1*	1	0	1	1*	1*	1	1	1	1*	10
F10	0	1*	0	1*	1*	1*	1*	1	0	1	0	7
F11	1	0	1*	0	1*	1*	0	0	0	1	1	6
Dependence	4	6	5	6	8	9	8	6	1	7	4	

6.2.2: Hierarchical level partition on the reachability matrix helped in creating levels based on reachability, antecedents, and intersection sets. This resulted in the structuring of price factors into six levels. The factors, for whom the intersection and reachability sets are similar, occupy the highest level in the hierarchy of TISM. The factor with a perfect match gets eliminated from

the table, and the process is repeated until all the levels are established. The detailed level partition for biosimilar price determinants is provided in Table 6.2.

Table 6.2: Level partitioning

Iteration 1				
Factor	Reachability Set	Antecedent Set	Intersection Set	Level
1	1,3,4,5,6,7,8,10,11	1,3,9,11	1,3,11	
2	2,6,7	2,5,6,8,9,10	2,6	
3	1,3,4,5,8,10,11	1,3,8,9,11	1,3,8,11	
4	4,5,6,7,8,10	1,3,4,7,8,10	4,7,8,10	
5	2,5	1,3,4,5,8,9,10,11	5	
6	2,6,7	1,2,4,6,7,8,9,10,11	2,6,7	I
7	4,6,7	1,2,4,6,7,8,9,10	4,6,7	I
8	2,3,4,5,6,7,8,10	1,3,4,8,9,10	3,4,8,10	
9	1,2,3,5,6,7,8,9,10,11	9	9	
10	2,4,5,6,7,8,10	1,3,4,8,9,10,11	4,8,10	
11	1,3,5,6,10,11	1,3,9,11	1,3,11	
Iteration 2				
Factor	Reachability Set	Antecedent Set	Intersection Set	Level
1	1,3,4,5,8,10,11	1,3,9,11	1,3,11	
2	2	2,5,8,9,10	2	II
3	1,3,4,5,8,10,11	1,3,8,9,11	1,3,8,11	
4	4,5,8,10	1,3,4,8,10	4,8,10	
5	2,5	1,3,4,5,8,9,10,11	5	
8	2,3,4,5,8,10	1,3,4,8,9,10	3,4,8,10	
9	1,2,3,5,8,9,10,11	9	9	
10	2,4,5,8,10	1,3,4,8,9,10,11	4,8,10	
11	1,3,5,10,11	1,3,9,11	1,3,11	
Iteration 3				
Factor	Reachability Set	Antecedent Set	Intersection Set	Level
1	1,3,4,5,8,10,11	1,3,9,11	1,3,11	
3	1,3,4,5,8,10,11	1,3,8,9,11	1,3,8,11	
4	4,5,8,10	1,3,4,8,10	4,8,10	
5	5	1,3,4,5,8,9,10,11	5	III
8	3,4,5,8,10	1,3,4,8,9,10	3,4,8,10	
9	1,3,5,8,9,10,11	9	9	
10	4,5,8,10	1,3,4,8,9,10,11	4,8,10	
11	1,3,5,10,11	1,3,9,11	1,3,11	

Iteration 4				
Factor	Reachability Set	Antecedent Set	Intersection Set	Level
1	1,3,4,8,10,11	1,3,9,11	1,3,11	
3	1,3,4,8,10,11	1,3,8,9,11	1,3,8,11	
4	4,8,10	1,3,4,8,10	4,8,10	IV
8	3,4,8,10	1,3,4,8,9,10	3,4,8,10	IV
9	1,3,8,9,10,11	9	9	
10	4,8,10	1,3,4,8,9,10,11	4,8,10	IV
11	1,3,10,11	1,3, 9,11	1,3,11	

Iteration 5				
Factor	Reachability Set	Antecedent Set	Intersection Set	Level
1	1,3,11	1,3,9,11	1,3,11	V
3	1,3,11	1,3,9,11	1,3,11	V
9	1,3,9,11	9	9	
11	1,3,11	1,3, 9,11	1,3,11	V

Iteration 6				
Factor	Reachability Set	Antecedent Set	Intersection Set	Level
9	9	9	9	VI

6.2.3: Diagram development, based on the level partition, for mutual relationships between the eleven factors was performed while retaining significant transitive links. The transitive links were assigned depending on their justifications. The diagram hence created was translated into an interpretive model. The mTISM model is a representation of an interaction matrix and diagram. The nodes and links as identified in the diagram were supported by interpretation in the model. The framework, hence developed, is depicted in Figure 6.1.

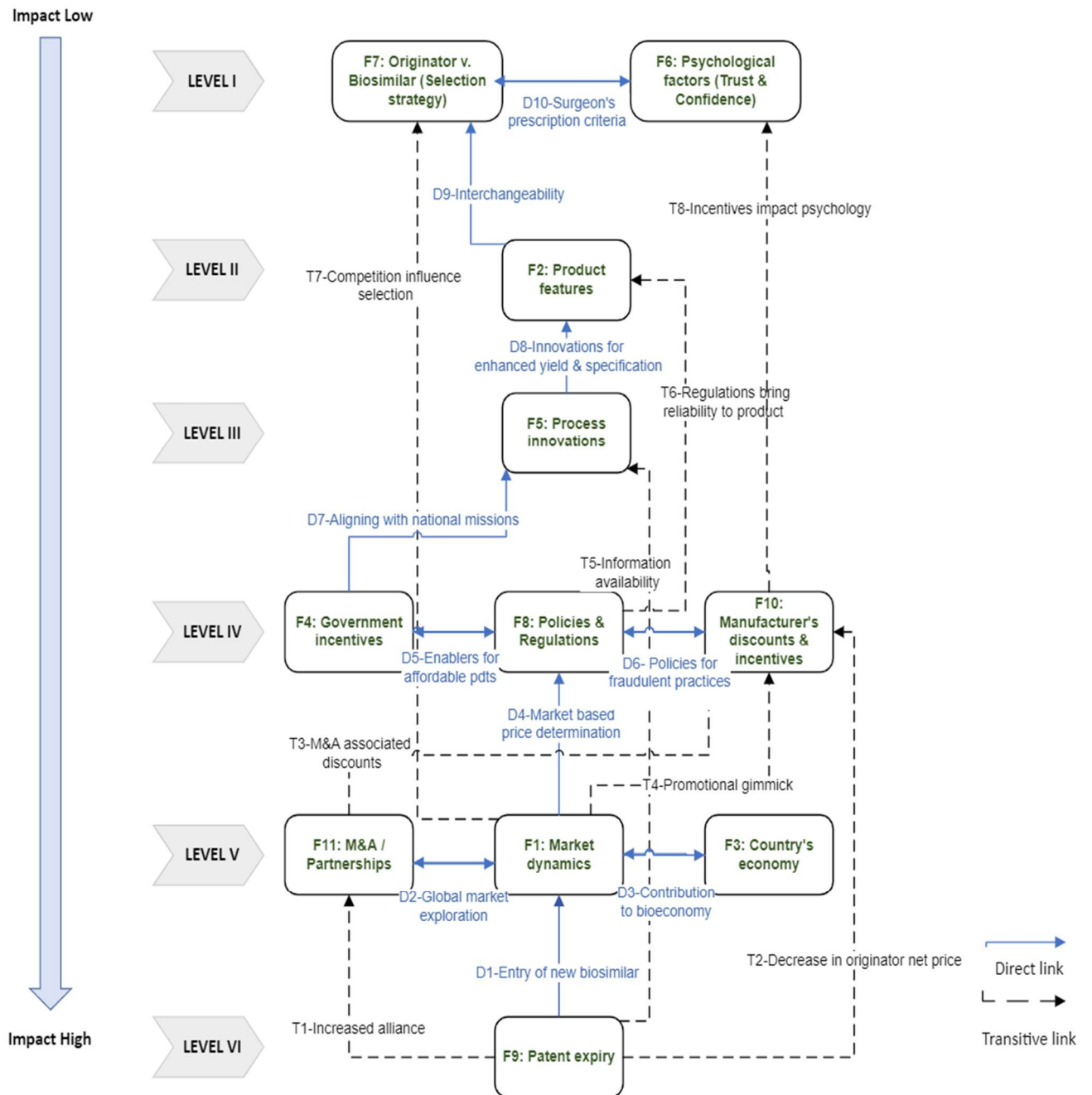


Figure 6.1: Hierarchical model of factors influencing biosimilar prices.

Note: Direct links are numbered from D1 to D10, and Transitive links are numbered from T1 to T8.

6.3 In-house testing and external validation of the biosimilar price framework

6.3.1. MICMAC

MICMAC has been used to test the developed framework by generating a correlation between the factors. The driving power and dependence, as calculated from the reachability matrix, were used for the classification of the variables into four quadrants. The graph with autonomous, dependent, independent and linkage zones is depicted in the in-house testing of the model through MICMAC analysis.

The factors in quadrant four, namely patent expiry period (Rémuzat et al., 2017), the country's economy (Trujillo et al., 2020), partnerships (Gagnon & Volesky, 2017), and market dynamics (Ferrario et al., 2020), are the independent variables with maximum driving potential. These factors are of maximum interest to policymakers as they can impact the prices of biosimilars in a significant way. These are considered drivers and are vital for determining the prices of biosimilars in India. These factors are located at the base of the model, and MICMAC also validated them as independent variables.

Linkage factors were identified by their high driving power as well as high dependence. Factors such as price control policies and the regulatory framework of the country, partnerships including mergers and acquisitions, and government incentives are located in the middle of the hierarchical model, depicting that they are linkage factors. MICMAC also rightly placed them in quadrant three of the graph.

Quadrant two comprises factors like process innovation, product features, physicians' psychology, and selection strategy between the originator and biosimilar. These factors are the dependent variables with high dependence and the least driving power. These are placed on top of the model and have a low impact on the prices of the biosimilars.

The autonomous factors in quadrant one reflect low dependence and driving power. This means that these factors are influenced by a few drivers and can influence only a few dependent variables. No autonomous variables were found in this study.

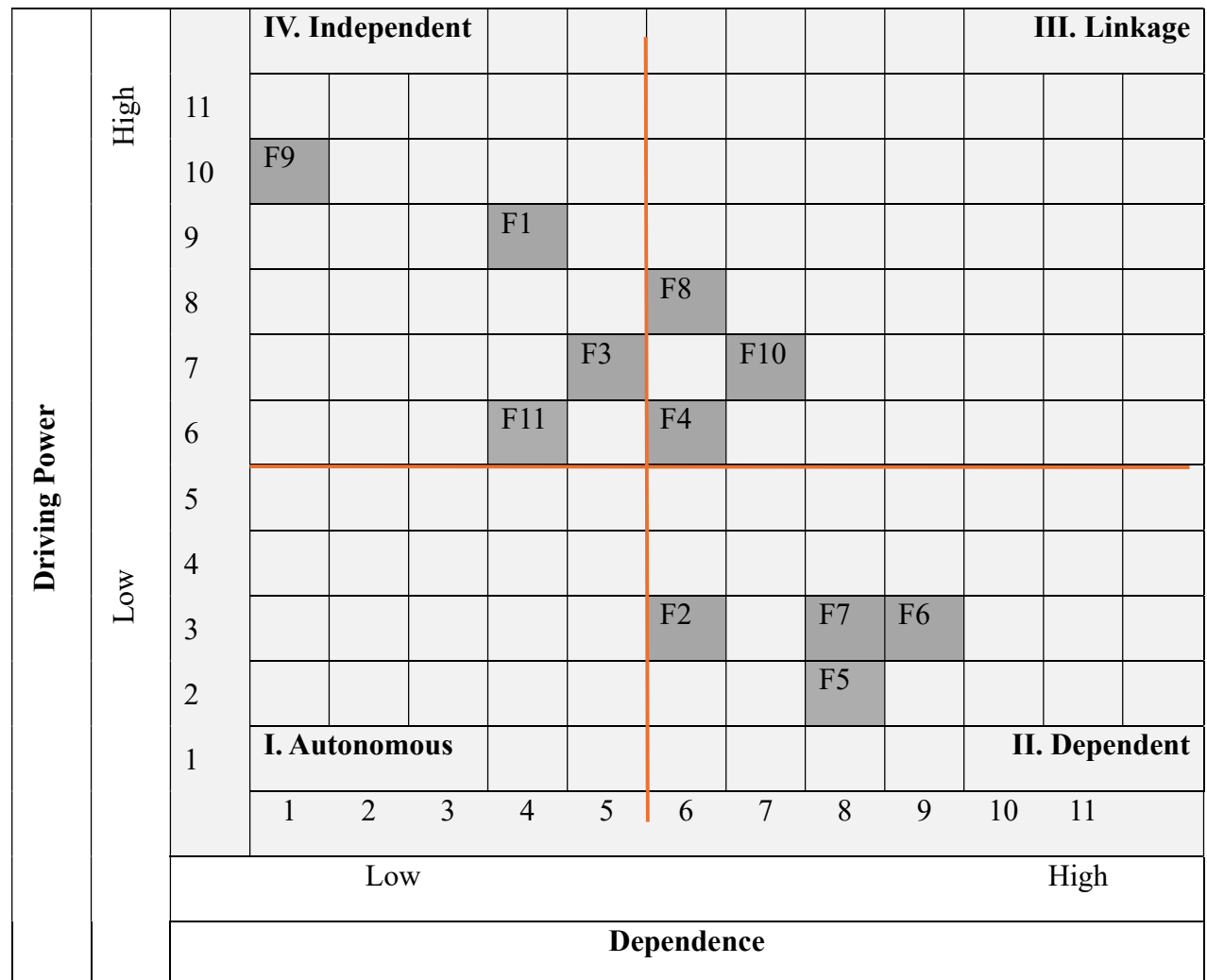


Figure 6.2: In-house testing of the model through MICMAC analysis

6.3.2. Expert validation

The validation of the hierarchical model was achieved through expert consultation. A structured questionnaire was used to assign weights to the direct links. The scores were collected on a 10-point Likert scale, with 1 indicating the lowest weight and 10 the highest. The average of scores assigned by experts to each link was calculated. Table 6.3 describes the scores, mean, standard deviation and variance.

Table 6.3: Validation scores based on expert consultation

Direct Links	1	2	3	4	5	6	7	Mean	Standard Deviation	Variance
F9-F1: Patent expiry will influence or enhance market dynamics	10	9	8	10	8	7	9	8.71	1.11	1.23
F1-F11: Market dynamics will influence or enhance partnerships	10	6	10	9	7	8	8	8.28	1.49	2.24
F11-F1: Partnerships will influence or enhance market dynamics	10	10	10	9	5	7	7	8.28	1.97	3.90
F1-F3: Market dynamics will influence or enhance country's economy	7	8	10	9	8	8	6	8	1.29	1.66
F3-F1: Country's economy will influence or enhance market dynamics	10	10	5	9	5	8	7	7.71	2.14	4.57
F1-F8: Market dynamics will influence or enhance pricing policies & regulations	10	9	10	9	9	7	8	8.85	1.06	1.14
F4-F8: Government Incentives will influence/enhance price control policies & regulations	6	6	6	10	8	9	7	7.43	1.61	2.62
F8-F4: Price control policies will influence/enhance government Incentives	6	9	10	10	6	7	7	7.86	1.77	3.14
F8-F10: Price control policies & regulations will influence/enhance manufacturer discounts	10	10	9	6	7	8	8	8.28	1.49	2.24
F10-F8: Manufacturer discounts will influence/enhance Price control policies & discounts	10	3	8	6	7	8	7	7.00	2.16	4.66
F4-F5: Government Incentives will influence/enhance process Innovations	10	10	10	8	8	9	7	8.86	1.21	1.47
F5-F2: Process Innovation will influence or enhance product features	10	10	10	9	9	7	8	9.00	1.15	1.33

F2-F7: Product features will influence or enhance selection strategy	10	10	8	5	5	7	5	7.14	2.27	5.14
F6-F7: Psychological factors will influence/enhance selection strategy	6	10	9	6	8	5	4	6.85	2.19	4.80
F7-F6: Selection strategy will influence or enhance psychological factors	1	3	2	5	6	5	3	3.57	1.81	3.28

6.4 Interpreting direct links to explore inter-relationships between factors

D1- Entry of new biosimilars: The entry of biosimilars in the market is restricted by the originator patents. The patent cliff (end of patent protection period and entry of biosimilars) leads to a drastic reduction in prices due to the competition of originator with biosimilars. As competition intensifies, profits decrease. In general, as more biosimilars successfully enter the market, it leads to decreased revenues, reduced market share for each brand, and lower profit margins (Rathore & Shaheef, 2019). After 2010, the next patent cliff is expected by 2030; it is projected that the biologics manufacturers can lose more than \$200 billion in annual revenue (Gardner, 2023).

D2- Global market exploration: The strategic partnerships between the developer and biopharma stakeholders are indispensable in the biosimilar business. The basic idea is that companies acquire or merge with other firms that own proven branded medications in the market or are on the verge of obtaining regulatory approval for their pipeline molecules. This strategy aims to reduce research and development costs and enhance the effective utilisation of capital expenditure. Competing in the market requires economies of scale, making small firms vulnerable to takeover. Sometimes, an M&A transaction can offer organisations the necessary financial resources to advance their products and global market presence. One example is the acquisition of Viatris global biosimilars business by Biocon Biologics in November 2022.

Biocon gained direct commercial capabilities in advanced and emerging markets (Biocon, 2022).

D3- Contribution to bioeconomy: With an annual value of \$16.8 billion, biotherapeutics have a significant presence in the biopharmaceutical sector. In the bioeconomy, the biotherapeutics industry generates about \$46.03 million each day and makes a monthly contribution of around \$1.4 billion, indicating its substantial impact on the industry and the country's economy (BIRAC, 2023). The GDP and economy, in turn, impact the purchasing power parity, leading to an increase in demand and market share of this high-cost medicine class.

D4- Market-based price determination: The National Pharmaceutical Pricing Policy (NPPP) in India employs a pricing methodology depending on market conditions. The pricing of essential medicines is determined by calculating the average price of all generic variants of a formulation that have a market share of at least 1 percent. In addition, a national retailer's margin of 16 percent is included in the pricing.

D5- Enablers for affordable products: The national policies and regulatory framework of any country provide the enabling environment for the growth of industry. The Department of Biotechnology (DBT), Government of India, has been providing an enabling ecosystem to promote biotechnology research and improve capacity building across the country. These incentives lead to the development of affordable biosimilars. One example is the National Biopharma Mission- Biotechnology Industry Research Assistance Council (BIRAC), which has led to the development of 21 biosimilar products for diseases like diabetes and cancer.

D6- Policies for fraudulent practices: The policies to control the fraudulent practices and incentives provided by manufacturers or medical representatives to clinicians are important for the affordability and accessibility of the medicines. The Government of India notified a Uniform Code for Pharmaceutical Marketing Practices (UCPMP) in March 2024 that bans gifts

and incentives to healthcare professionals. The increase in such unethical practices resulted in the implementation of a mandatory code of conduct instead of a voluntary one by the Department of Pharmaceuticals, Government of India (GoI, 2024).

D7- Aligning with national missions: The development of high-cost biosimilars is a costly affair with complexities in biosimilar manufacturing, which restricts the market growth. To promote the growth of the sector, the government provides incentives to boost R&D, innovation and infrastructure development. The Government of India, through the Department of Biotechnology, Ministry of Science and Technology, promotes the development of biotech-based products under the “Make in India” initiative. BIRAC, a public sector undertaking of DBT, supports biotech innovations from ideation to commercialisation.

D8 - Innovations for enhanced yield & specification: The Process innovations, like a change in technology or equipment, can enhance the yield and change the purity of the product. There is a chance to utilise innovations in clinical pharmacology and associated sectors to enhance the effectiveness of biosimilar development. In addition, improvements in quality attributes (structural and functional characterisation) can be linked to the development of efficient biosimilars (Wang & Strauss, 2023).

D9- Interchangeability: The switching or interchangeability between the originator, the reference product and alternative treatment options, the biosimilars is an important discussion around the globe. Product attributes like efficiency, quality parameters, and safety of biosimilars are major criteria for switching between the available treatment modalities (Ratih et al., 2021). The bridging studies are conducted by biosimilar developers with the reference product to prove the comparability with the originator.

D10- Surgeon’s prescription criteria: In a country like India, where the prescription of brand-name medicines is common rather than generic names, the trust and confidence of healthcare

professionals in biosimilars are crucial. As physicians are key influencers, companies attempt to manipulate their mindset by engaging in legal action against biosimilar developers (Wu et al., 2023). Adverse publicity or corporate scandals have the potential to harm the reputation, leading to a significant decline in sales. Sometimes, following the expiration of patent protection, originator companies may attempt to introduce their own “Authorised biosimilar” that will directly rival the other biosimilar products (Hagen, 2021).

6.5 Policy insights from the study

This study examined various variables that influence the price of biosimilars and emphasized the need for India to revise its market-based strategy. The results suggest that the addition of relevant factors to the ceiling price formula could enhance the effectiveness of the pricing mechanism. The patent expiry period, partnerships or acquisitions and the country’s economy, particularly its paying capacity, can be included with market dynamics to develop an effective pricing mechanism for biosimilars. Currently, the price equation takes into account only the commercial variable of market share for determining prices. Scientific, economic, and collaborative factors, such as patent expiry period, country's economy, and partnerships or acquisitions, have a direct influence on prices and should be included in the price calculation equation.

The TISM model classified government incentives as a linkage factor and regarded them as crucial elements in ensuring the affordability of medicines. The Pradhan Mantri Jan Arogya Yojana (PM-JAY), implemented by the government of India, is an extensive health insurance initiative. This research emphasized the need for an increase in the government's incentives in India for promoting inventions in the biosimilar area, current measures are minimal and insignificant. At present, Production Linked Incentive (PLI) schemes are limited to a few areas such as medical devices and electronics. It is recommended to extend these programs to biopharmaceuticals, which requires significant capital expenditure.

The manufacturer's discounts or promotional elements have come out as linkage variable with high driving power and dependence. Obligatory industry disclosure policies, or UCPMPs, were enacted in India in an attempt to stop fraudulent practices related to the prescription and sale of expensive medication. However, this study raised questions about how well the UCPMP is being implemented. Enforcing the program and developing an effective mechanism is necessary to ensure that biosimilars are affordable and easily available throughout the nation. Specific recommended steps involve imposing limitations on specific transactions involving cash and institutionalising transparency through self-monitoring for medical professionals and companies.

The policy framework including price control policies are specific to each nation and are necessary to develop a conducive ecosystem for affordable and accessible cancer medicines. The implementation of the Drug Price Control Order (DPCO) by the Government of India is ineffective in executing the recommendations of the task force. Only a limited number of biologics can have their prices monitored by the DPCO. More biologics should be included in the DPCO to enhance accessibility for patients. The order can be amended to include the recommendations and meet the demands of NGOs and industry.

Mergers and acquisitions significantly impact the development, marketing, and distribution of biosimilars. Due to the limited number of biosimilar manufacturers, it is essential to establish a monitoring system to assess the demand, break the monopoly and facilitate global market expansion. In order to attain economies of scale, it is necessary to enhance the demand for biosimilars through Public Private Partnerships (PPP) or exporting to other countries. This could contribute to establishing India as a prominent hub for biosimilar manufacturing.

Besides macroeconomic drivers like growth in Gross Domestic Product (GDP), rising purchasing power parity, and rising healthcare spending, a strong regulatory commitment is

required for cost reduction and improving treatment accessibility. A broader political and regulatory debate on the biologicals and biosimilars market in the country is needed to ensure access to inexpensive technologies, create a more competitive market, and support health systems' financial sustainability (Pontes et al., 2023). One possible step is to revise the DBT's guideline for biosimilars to converge the regulatory approval requirement with global standards.

In India, patients face out-of-pocket expenses for medications and are unable to purchase expensive branded biologics. The paying capacity of patients serves as an important driver in the increased adoption of biosimilars. Despite the existence of PM-JAY, the world's largest healthcare insurance program, studies indicate that the high cost of biologics is a significant barrier to their use, as most biologics aren't covered by insurance coverage. The PM-JAY packages should be revised to include more biosimilars.

6.6 Application of framework

The primary application of the biosimilar price model is to develop a new policy for determining the prices of biosimilars in India. Significant factors with a direct impact on the prices can be utilised to develop an efficient mechanism for controlling the prices of biosimilars in India. This fair price model will be data-driven and establish a scientific method of price determination instead of relying on market share only.

6.7 Conclusion

In this Chapter, modified Total Interpretive Structural Modelling (mTISM) is used to develop a hierarchical model of factors that impact the prices of biosimilars. The in-house testing is performed through MICMAC analysis, which also helped in identifying the dependent and independent variables. The findings from this Chapter reveal that the patent expiry period, partnerships/ acquisitions and the country's economy should be considered along with market dynamics for an effective pricing policy for biosimilars. Additionally, government policies, incentives, and regulatory frameworks are country-specific factors that are necessary to develop a conducive ecosystem for regulating the exorbitant cost of biosimilars used to treat cancer. The framework describes the relationships between the various factors and paves the way towards developing an improved pricing regime for biosimilars in the next Chapter.

Model for Price Determination of Biosimilars

7.1 Introduction

The objective of this chapter is to develop an efficient evidence-based mathematical equation to determine the ceiling price of biosimilars. The price framework developed in the previous Chapter helped in establishing the relationships between the various factors that impact the prices. The dependent and independent variables identified through TISM lead to the identification of significant factors for price determination model. The model developed in this Chapter can overcome the limitations of cost-based and market-based pricing mechanisms and has the potential to initiate the political dialogue with NPPA.

In India, the National Pharmaceutical Pricing Authority (NPPA) amended the Drugs Price Control Order (DPCO) and introduced a Market-Based Price (MBP) mechanism for determining the prices of medicines (The Drugs (Prices Control) Order, 2013, 2016). The Cost-Based Price (CBP) approach was adopted in 1979 and reinstated in 2013 based on the recommendation of a task force (Recommendations of Task Force Chaired by Pronab Sen, 2005). The enactment of MBP sparked multiple debates and criticisms (Motkuri & Mishra, 2020; Narula, 2015; Renganathan et al., 2016; Shinde et al., 2023), resulting in the urgent need for modifications to the enacted policy of drug pricing.

As per the recommendation of the task force, the ceiling price of all drugs in the National List of Essential Medicines (NLEM) shall be determined by calculating the weighted average price of the three most marketed brands by the value of a single Active Pharmaceutical Ingredient (API) formulation. However, DPCO calculates a simple average of the Maximum Retailer Price (MRP) of all formulations with a minimum of one percent market share and then adds a

sixteen percent national retailer margin. This approach neutralised the social impact created by affordable brands in the market. Further, a few recommendations of the task force do not apply to the high-cost biosimilars with a limited number of manufacturers, typically only two or three, in contrast to generic medications (pharmaceutical equivalents). For example, the task force recommended that price negotiation should be applied to all patented drugs and formulations. The reference price in these cases shall be the price of the closest therapeutic equivalent in the domestic market or the lowest price in the international market. According to this, the MBP for biosimilars can be easily impacted by the exorbitant prices of the originator drug in the international market. Additionally, regulating the Maximum Retail Price (MRP) fosters elevated trade margins and provides incentives to distributors. Significant variations are observed in the cost of biosimilars of different brands in India (Shinde et al., 2023). Moreover, manufacturers might entice clinicians and the hospital procurement system with additional savings, though these savings never reach the needy patients.

Biosimilars are high-cost therapeutic medications derived from biological sources and are used in the treatment of diseases like cancer, autoimmune disorders, hormonal irregularities, rheumatoid arthritis, anaemia, etc. They closely resemble their originator-licensed biological drug, the reference product (Miriam Fontanillo et al., 2022). The success of biosimilars as blockbuster biologics has demonstrated that they offer significant potential to decrease healthcare expenses (Moore et al., 2021). India is well recognised as a global manufacturer of safe and efficacious generic pharmaceuticals and offers the potential to repeat the success with respect to biosimilars (Narayanan & Sheng, 2024). The Indian government, through various initiatives like “Make in India”, “National Biopharma Mission” and “BioE3 – Biomanufacturing Policy”, is promoting the development of biosimilars, but the affordability and accessibility need a strong pricing policy and regulatory framework for biosimilars (BIRAC, 2023).

The previously implemented CBP method utilises the cost of manufacturing and other expenses of the medication development and incorporates an additional 100 percent margin over it. Both the CBP and MBP approaches have further limitations. Currently, there have been legal challenges to the MBP policy implemented by the government of India, and it is under evaluation (Mahajan, 2018) (AIDAN Petition Proceedings, 2023). In this context, establishing an effective pricing mechanism for biologics is likely to have a significant impact on the affordability of these products.

7.2 Converting the TISM framework to a mathematical equation for price determination

- 1) The validation scores, as detailed in Table 6.3, are considered the stepping stone for the mathematical equation development. The mean scores for all the direct links of the hierarchical framework developed in Chapter 6 and depicted in Figure 6.1 were calculated based on a 10-point Likert scale questionnaire from seven experts.
- 2) The mean scores are converted to independent and cumulative weights as per the calculations mentioned in Figure 7.1. The scores of the variables at the same level of the framework are added to generate the level-wise independent and cumulative weights. Not to mention, as we go down the level, the cumulative weights of the variables in a level increase. Hence, Level 6 has the maximum weightage and Level 1 the minimum.
- 3) Figure 7.2 represents the level normalisation by weighted average. Levels V and VI, comprising 4 variables, are selected for the mathematical equation based on high weights and maximum significance. The weights of Levels I to IV are less than 0.1 and therefore not selected for model creation because of the least impact on the prices.
- 4) The MICMAC analysis, Figure 6.2, also supports the argument. Four independent drivers, patent expiry period, market dynamics, the country's economy, and partnerships, are the most significant factors and are responsible for the maximum impact on the prices. Therefore, these are selected for incorporation in the mathematical equation.

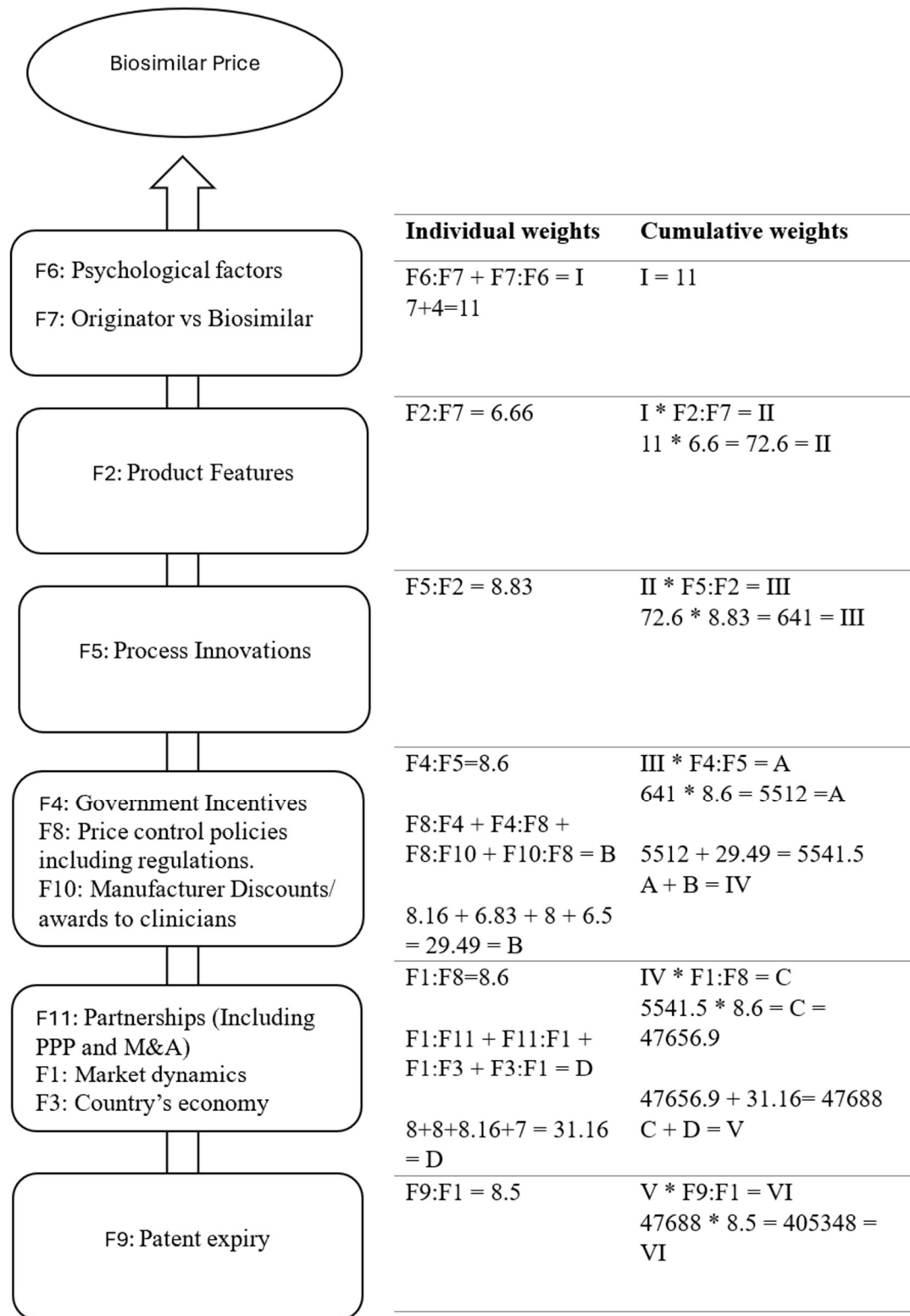


Figure 7.1: Assigning weights to direct links

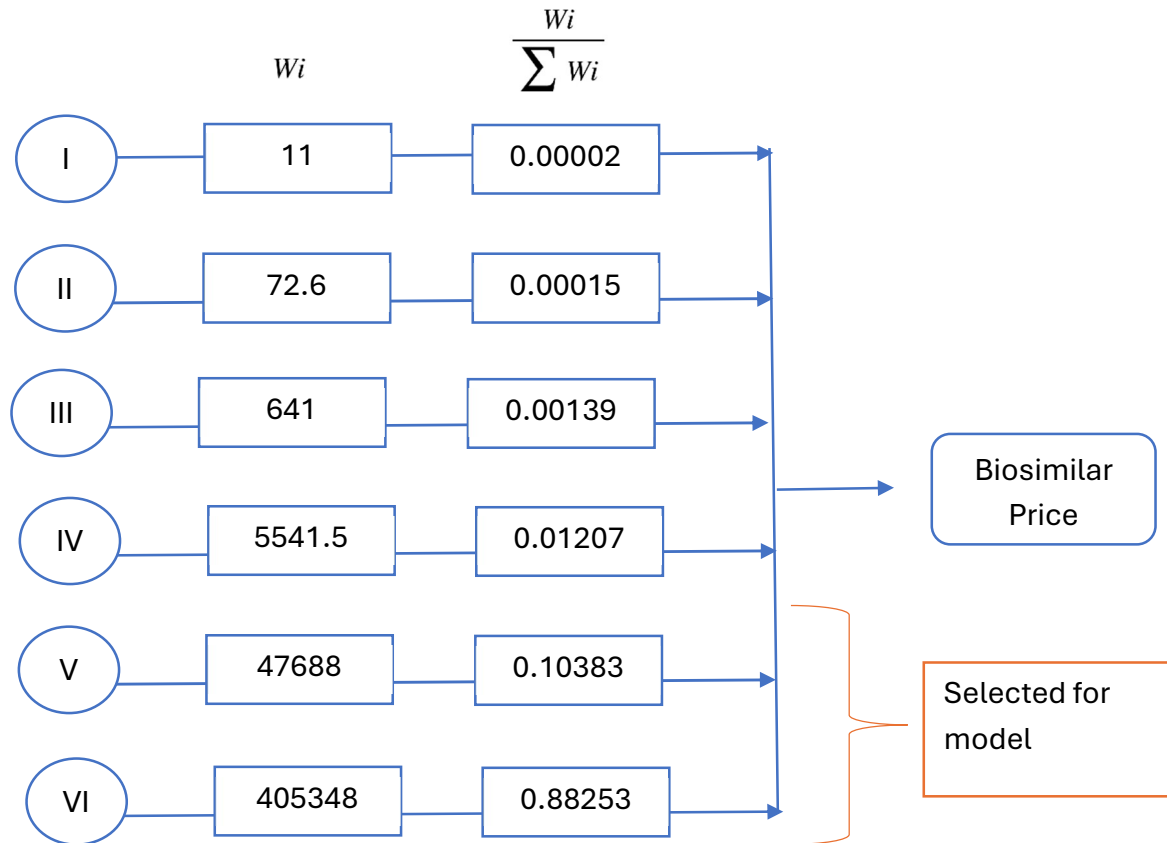


Figure 7.2: Level normalisation by weighted average

Note: Levels V and VI, comprising 4 variables, are selected for the mathematical equation based on high weights. Weightage of Level I to IV is less than 0.1 and therefore not selected for model creation.

- 5) The adjusted mean weights are determined for each of the four shortlisted variables to neutralise the effect of the 10-point Likert scale. The individual mean adjusted weights are combined in case the variable impacts more than one factor.
- 6) Further, normalisation within variables is performed to adjust the unit of measurement.

The final beta coefficient values for the four variables are depicted in Figure 7.3.

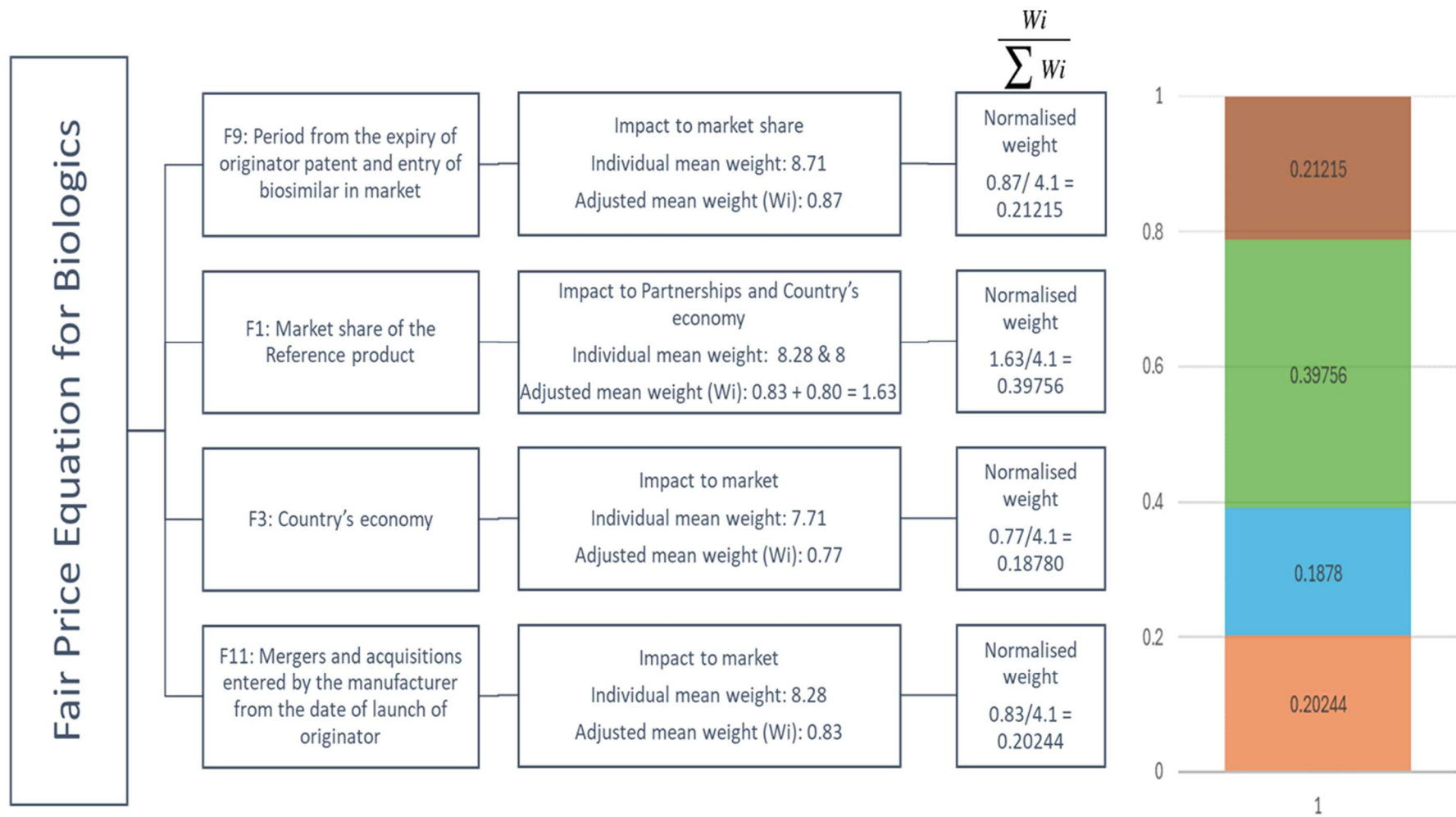


Figure 7.3: Determining the adjusted mean weights and normalisation within the variables

7.3 Mathematical model for pricing biologics

Based on the calculations, a mathematical equation (7.1) is developed to determine the ceiling price of biologics.

$$\text{Ceiling Price of Biologics (Pc)} = \overbrace{[\text{COBD}] + \mu}^{\alpha} + 0.39756 \{\text{Market share}\} + 0.21215 \{\text{Patent expiry period}\} + 0.20244 \{\text{Mergers \& acquisitions}\} + 0.18780 \{\text{Country's economy}\} \text{-----}(7.1)$$

Where,

Ceiling Price of Biologics (Pc): The maximum allowed price for one unit of the pack form.

$$\text{COBD}(\$/\text{g}) = \frac{\text{Total capital investment per year of operation} + \text{Annual operating cost} (\$/\text{year})}{\text{Annual production rate (g per year)}} \text{-----}(7.2)$$

Source: Gupta et al., 2021; Mahal et al., 2021; O. Yang et al., 2019

Cost of Biosimilar Development (COBD) is calculated as per equation 7.2. COBD includes fixed as well as variable components of cost. Objective 1 of this research work calculates the variable cost as 18 to 21 million USD for microbial and mammalian systems, respectively. Using these values, the COBD per gram is calculated in equation 7.2.1 for microbial and 7.2.2 for mammalian systems.

Assumptions: The assumptions of yearly manufacturing of around 500 kg were considered for the mAb therapeutic. Whereas, for microbial, a yearly throughput of 50 kg was taken. The average years of operation of a manufacturing facility is considered as 15 years (Gupta et al., 2021; Mahal et al., 2021; O. Yang et al., 2019).

$$\text{COBD (Microbial)} (\$/\text{g}) = \frac{45 \text{ M } \$/15 + 18 \text{ M } \$}{50,000} = 420 \text{ } \$/\text{g} = 33,600 \text{ INR/g} \text{-----}(7.2.1)$$

$$\text{COBD (Mammalian)} (\$/\text{g}) = \frac{50 \text{ M } \$/15 + 21 \text{ M } \$}{500,000} = 48.66 \text{ } \$/\text{g} = 3893 \text{ INR/g} \text{-----}(7.2.2)$$

It is to be noted that the estimated cost may change with scale, indication and geography. Also, the currency conversion rate adopted in this research work is 1 USD equals 80 INR.

The constant α in equation 7.1 accounts for two components. The first component is the COBD, as calculated above in equations 7.2.1 and 7.2.2. The COBD is included as the lower limit in the class intervals developed in Table 7.1. The second component is the Price Correction Constant (μ), which provides an adjustment to align the model with prevailing biosimilar prices. This constant is derived through validation of the model against existing market data. It is important to note that the adjustment is applied only once, to calibrate the model with current price trends of biosimilars, thereby minimising potential distortions or abrupt fluctuations in pricing outcomes introduced by the new model. The value of Price Correction Constant μ is fixed after trial on four biomolecules as 0.5 for Mammalian and 0.9 for Microbial systems.

The significant factors, as calculated from the TISM framework and MICMAC, are as mentioned below:

Significant Factors = $[0.39756 \{\text{Market share}\} + 0.21215 \{\text{Patent expiry period}\} + 0.20244 \{\text{Mergers \& acquisitions}\} + 0.18780 \{\text{Country's economy}\}]$

Where,

Market Share: Market share of reference product at the time of launch of the first biosimilar or expected market share to be captured by the biosimilar. In the case of an already existing biosimilar, the market share of the first biosimilar will be taken. **(Source: Statista)**

Patent Expiry Period: The period between the patent expiry of RP and the launch of a biosimilar. If the originator does not have a patent in India, the date of expiry of the US patent will be considered. **(Source: Drug Patent Watch)**

Mergers & Acquisitions: The number of deals entered by the biosimilar manufacturer, as acquirer, acquiring parent company or Investor, from the date of launch of the originator till the launch of the biosimilar. **(Source: Refinitiv)**

Country's Economy: The GDP of the country at the time of the launch of Biosimilar. **(Source: World Development Indicators)**

In the hypothetical situation where all independent variables are zero, the ceiling price of any biosimilar will be determined by the value of α , i.e. COBD and Price Correction Constant μ .

In real scenarios for determining the prices of a new biologic, the model will provide a fair price zone for both manufacturers and the NPPA. The upper and lower limits of the fair price zone will be determined using the class intervals specified in Table 7.1. Manufacturers can then fix the price and develop marketing strategies within this fair price zone, encouraging healthy competition. It is important to note that the model is currently validated on biosimilars only. The originator pricing mechanism demands a separate alignment study.

The Maximum Retail Price (M.R.P.) will be calculated by adding the applicable taxes specific to the country.

Hence, $M.R.P = P_c + \text{Taxes}$.

7.3.1 Normalisation with variables (Units of measurement)

As the units of measurement for variables included in the price equation are different, normalisation with variables is performed by developing class intervals for each one of them. The class intervals described in Table 7.1 provide a fair price zone for the ceiling price (P_c) of microbial as well as mammalian systems. The fair price zone provides flexibility for manufacturers to experiment with pricing strategies, thereby promoting competition. The

minimum value of Pc varies with the type of product and the strength of the pack form. It is to be noted that there is a hypothetical cost of development for biosimilars even if they fail to reach the market. The calculations, translating to per unit cost, reflect that the cost of biosimilar development is negligible in the total price of a biosimilar.

Table 7.1: Class intervals for variables of the price equation

Class Interval	Market Share of RP (%)	Patent Period (Months)	M&A (No. of deals)	Country's Economy (%)	Pc of Mammalian System (INR)	Pc of Microbial System (INR)
1	0 – 20	19 – 24	0 – 4	Negative	2000 – 15,000	10 – 500
2	21 – 40	13 – 18	5 – 8	0 – 5	15,001 – 30,000	501 - 1000
3	41 – 60	7 – 12	9 – 12	6 – 10	30,001 – 45,000	1001 – 1500
4	61 – 80	0 – 6	13 – 16	11 – 15	45,001 – 60,000	1501 – 2000
5	81 – 100	Before expiry	More than 16	Above 15	60,001 – 75,000	2001 – 2500

7.4 Validation of the model

The mathematical price equation developed in the previous section of this chapter is validated using four biosimilars, two from each of the microbial and mammalian systems. Prices of biosimilars for model validation are extracted from the CIMS database in December 2024 and do not represent the prices at the time of biosimilars' launch. Price, being a dynamic variable, may not reflect the right price at launch.

7.4.1 Biosimilar case 1: bevacizumab

Bevacizumab belongs to the class of monoclonal antibodies and is an effective, first-line treatment in combination with other conventional cancer medicines for a few cancers, such as kidney, lung, colorectal, and cervical. The reference product Avastin by Roche / Genentech was approved by the US FDA in 2004. The first biosimilar of bevacizumab in India was launched by Reliance on 10 June 2016, marketed by Lupin under the name Bevacirel at a discount of around 25% compared to Avastin.

Table 7.2: Prices of different brands of bevacizumab

S No	Brand name	Manufacturer	Pack Size	Price
1	Abevmy	Mylan	400 mg * 16ml	35,120 INR
2	Avastimab	RPG LS	400 mg * 16ml	37, 500 INR
3	Avastin	Roche	400 mg* 16ml	1,16,000 INR
4	Bevacirel	Reliance (2016)	400 mg * 16ml	38,856.34 INR
5	Bevatas	Intas	400 mg * 16ml	29,600 INR
6	Bryxta	Zydus Cadila	400 mg * 16ml	43,369.4 INR
7	Cizumab	Hetero Drugs	400 mg * 16ml	43,859 INR
8	Krabeva	Biocon	400 mg * 16ml	39,990 INR
9	Syndyma	Cipla	400 mg * 16ml	1,17,625 INR
10	Vastan	Taj Pharma	400 mg * 16ml	35,120 INR
11	Varsavo	Dr. Reddy's	400 mg * 16ml	34,000 INR

The patent for Avastin expired in January 2022 in Europe and in July 2019 in the US. The data for the significant variables, as captured from various sources, are as mentioned below:

Average Price: 37500 INR
Reference Product: Avastin by Roche / Genentech approved by FDA in 2004
Market Share: <10% in 2016
Patent Expiry Period: before expiry in 2023
Mergers & Acquisitions: 1
Country's economy: 8.25% in 2016

Adding these values in the price equation for identifying the value of μ leads to;

$$3 = 0.39756 \{1\} + 0.21215 \{5\} + 0.20244 \{1\} + 0.18780 \{3\} + \mu$$

$$\mu = 0.8$$

The values in brackets represent the class intervals developed in Table 7.1. For example, 3 as Pc is the class interval, not the actual average price of the biosimilar. Similarly, 1, 5, 1, and 3 are the class intervals for market share, patent expiry period, mergers & acquisitions, and the country's economy, respectively. It is also important to note that the COBD is already included as the lower limit of the class intervals of Pc of mammalian and microbial systems (Table 7.1).

The μ is the Price Correction Constant (PCC), which is established to validate the model against current biosimilar pricing trends.

7.4.2 Biosimilar case 2: trastuzumab

Trastuzumab is taken as a second sample for validation. It is a recombinant IgG1 monoclonal antibody. It acts on the HER2 (human epidermal growth factor receptor protein) receptors, responsible for the over-proliferation of cancer cells in breast and stomach cancer. The reference product of trastuzumab is Herceptin by Roche / Genentech, approved by the US FDA in September 1998. The first biosimilar in India was launched in 2014 by Biocon with Mylan Pharmaceuticals Pvt Ltd as Hertraz. Biocon markets it under the name of Canmab.

Table 7.3: Prices of different brands of trastuzumab

S No	Brand name	Manufacturer	Pack Size	Price (INR)
1	Biceltis	Emcure	440mg * 1	75,000
2	Brumidex-VT	Taj Pharma	440mg * 1	69,350
3	Canmab-Inj	Biocon (2014)	440mg * 1	59,981.6
4	Eleftha	Intas	440mg * 1	20,481.11
5	Herceptin	Roche	440mg * 50ml * 50ml	1,10,700
6	Herclon	Roche	440mg * 1	66,156.25
7	Hermab	RPG LS	440mg * 1	57,500
8	Hersima	Alkem	440mg * 1	54,662.74
9	Hertraz	Mylan	440mg * 1	58,820
10	Herveb	Taj Pharma	440mg * 1	59,400

11	Hervycta	Dr. Reddy's	440mg * 1	63,233
12	Neuzumab	Lupin	440mg * 20ml	57,800
13	Trasturel	Reliance	440mg * 1	61,132.12
14	Trumab	Glenmark	440mg * 1	54,662.74
15	Vivitra	Zydus Cadila	450mg * 1	58,633.92

The patent for Herceptin (trastuzumab) expired in Europe in July 2014 and the US in June 2019. The data for the significant variables, as captured from various sources, are as mentioned below:

Average Price: 58,343 INR

Reference Product: Herceptin by Roche / Genentech approved by FDA in 1998

Market Share: 68% in 2014

Patent Expiry Period: before 2019 in US

Mergers & Acquisitions: 5

Country's economy: 7.41% in 2014

Adding these values in the price equation for identifying the value of μ leads to;

$$4 = 0.39756 \{4\} + 0.21215 \{5\} + 0.20244 \{2\} + 0.18780 \{3\} + \mu$$

$$\mu = 0.4$$

7.4.3 Biosimilar case 3: filgrastim

Filgrastim belongs to a class of granulocyte colony-stimulating factors (GCSF), which stimulates the formation of neutrophils in bone marrow and has the ability to prevent infections in cancer patients after chemotherapy. It is mostly produced by recombinant DNA technology in *Escherichia coli* (E. coli).

Table 7.4: Prices of different brands of filgrastim

S No	Brand name	Manufacturer	Pack Size	Price
1	Colstim	Zydus Cadila	300mcg * 1ml	1,219.88 INR
2	Cytograf	Zyphar's	300mcg * 1	2,528.57 INR
3	Emgrast	Emcure (Gennova)	300mcg * 1mL * 1ml; 480mcg * 0.8mL * 0.8ml; 480mcg * 1.6mL * 1.6ml	2,800 INR
4	Endokine	Intas (2015)	300mcg * 1	1,442.59 INR
5	ES-Grastim	Esperer Bioreserach	300mcg * 1	1,442 INR
6	Fastograf	Alkem	300mcg * 1ml	1,442.33 INR
7	Fegrast	Claris	300mcg * 0.9ml	1,781.25 INR
8	Filcad	Cadila	300mcg * 1	2,740.38 INR
9	Filgen	Chandra Bhagat Pharma	300mcg * 1ml	2,499 INR
10	Fillif	Torrent	300mcg * 1mL * 1ml	1,162.5 INR
11	Frastim	RPG LS	300mcg * 0.5mL * 0.5ml	2,812.5 INR
12	Grafeel	Dr. Reddy's	300mcg * 1ml	1,504.03 INR
13	Grafeel PFS	Dr. Reddy's	300mcg * 1mL * 1ml	1,504.03 INR
14	Grastim	Dr. Reddy's	300mcg * 1ml	1,504.03 INR
15	Imumax	Abbott	300mcg * 1	2,443.68 INR
16	Innograst	BDR	300mcg * 1ml	2,249.92 INR
17	Itact	Zuventus	300mg * 0.5ml	2,644.22 INR
18	Lupifil	Lupin	300mcg * 0.5ml	1,474.32 INR
19	Mgrastim	Micron	300mcg * 1ml	--
20	Neugrow	BPRL	300mcg * 1ml	1,363 INR
21	Neukine	Intas	300mcg * 1mL * 1ml/	1,540.71 INR
22	Neumax	Dabur	300mcg * 1	2,031.25 INR
23	Neupogen	Roche	300mcg * 0.5mL * 0.5ml/	2600 INR/ 2600 INR
24	Neupokine	Panacea	300mcg * 1ml	2,523.81 INR
25	Nfil	Miracalus	300mcg * 0.9mL * 0.9ml	2700 INR
26	Neufil-Safe	Biocon	300mcg * 0.5mL * 0.5ml	2,249.9 INR
27	Xphil	Sun	300mcg * 1	2,142.8 INR
28	Xphil-Nu	Ranbaxy	300mcg * 0.5mL * 0.5ml	2,288 INR

The reference product of filgrastim is Amgen's Neupogen, approved by the US FDA in 1991. The first biosimilar in India was launched by Intas Pharmaceuticals Limited, called Accofil, in 2015. The patents for Neupogen expired in the US in December 2013 and in Europe in 2006. The data for the significant variables, as captured from various sources, are as mentioned below:

Average Price: 1950 INR

Reference Product: Amgen's Neupogen approved in 1991

Market Share: 84% in 2015

Patent Expiry: 2 years after expiry 2013 in US

Mergers & Acquisitions: 2

Country's economy: 7.99% in 2015

Adding these values in the price equation for identifying the value of μ leads to;

$$4 = 0.39756 \{5\} + 0.21215 \{1\} + 0.20244 \{1\} + 0.18780 \{3\} + \mu$$

$$\mu = 1.03$$

7.4.4 Biosimilar case 4: recombinant erythropoietin

Recombinant erythropoietin (EPO) is a haemopoietic growth factor and is used in the treatment of patients with anaemia or chronic renal disease. The recombinant EPO can be synthesised in *Escherichia coli* cells.

The reference product of EPO is Amgen's Epogen, approved by the FDA in 1989. The first biosimilar in India, Relipoetin, was launched by Reliance Life Sciences in December 2008. The US patent for Epogen expired in 2013, but the biosimilar in India was launched before the expiry of the patent.

Table 7.5: Prices of different brands of Recombinant Erythropoietin

S No	Brand name	Manufacturer	Pack Size	Price
1	Alpha Red	Samarth	4000IU/0.4 mL	1600 INR
2	Epocept		4000IU	2034
3	EpoFit	Intas	4000IU/0.4 mL	1613
4	Relipoiectin	Reliance (2008)	4000IU/0.4 mL	960
5	Renocel	Intas	4000IU/0.4 mL	1760
6	Zyrop	Zydus	6000IU/0.4 mL	1900
7	Repoitin	Serum	4000IU/0.4 mL	900
8	Epotin	Claris	4000IU/0.4 mL	1613
9	Hemax	Haledew	4000IU/0.4 mL	1750
10	Erypro	Biocon	4000IU/0.4 mL	845

The data for the significant variables, as captured from various sources, are as mentioned below:

Average Price: 1600 INR

Reference Product: Amgen's Epogen approved in 1989

Market Share: 62 % in 2008

Patent Expiry Period: before expiry in 2013

Mergers & Acquisitions: 1

Country's economy: 3.08% in 2008

Adding these values in the price equation for identifying the value of μ leads to;

$$4 = 0.39756 \{4\} + 0.21215 \{5\} + 0.20244 \{1\} + 0.18780 \{2\} + \mu$$

$$\mu = 0.77$$

7.5 Price regulation mechanisms of BRICS countries

7.5.1 Medicine pricing framework in Brazil

The Pharmaceutical Market Regulation Council (Câmara de Regulação do Mercado de Medicamentos; CMED), established on Oct 6 2003, regulates drug prices in Brazil. It supersedes the Câmara de Medicamentos (CAMED; Medicines Council), which was established in 2000. The CMED represents the National Health Surveillance Agency (ANVISA; Agência Nacional de Vigilância Sanitária) and the Ministries of Health, Finance, Justice, Industry, and Trade.

Pricing is regulated in Brazil by a government council based on the category to which the drug is assigned. The following medicinal product categories are established:

Category I: new product formulated with a new chemical entity which is under patent protection and that has a significant benefit when compared to other medicinal products marketed for the same indication in Brazil

Category II: new medicinal products that do not fall into Category I

Category III: new marketing presentation of a product already marketed by the company in the same pharmaceutical form

Category IV: new product of a specific company and a new pharmaceutical form of a product already marketed by the company

Category V: new pharmaceutical form not yet in the Brazilian market, and a new medicinal product combination formulated with active ingredients already marketed in the country

Category VI: generic medicinal products

The following are general rules for the price application to the new medicinal products:

Category I: The manufacturing price must be lower than the lowest price practised by the company in other countries. The product must be in at least three of these markets. If this condition is not fulfilled, the *Comitê Técnico-Executivo* (Technical and Executive Committee

of the CMED) may establish a temporary price by applying a *Coeficiente de Adequação de Preço* – CAP (Adaptive Reduction Coefficient) defined as the coefficient of the Brazilian Gross Domestic Product – GDP (PIB) per capita and the GDP per capita of the country that has the lowest price.

Category II: Manufacturing price is defined based on the cost of the treatment with or using other medicinal products for the same indication. It may not be higher than the price of the same product practised in other countries.

Category III: The manufacturing price has to be lower than the mean price of the other marketing presentations of the same strength and in the same pharmaceutical form already marketed by the laboratory.

Category IV: The manufacturing price may not be higher than the mean price of the marketing presentations of products with the same active ingredient and in the same strength and pharmaceutical form.

Category V: For new combinations formulated with monodrugs already marketed in the country, the price of the combination may not exceed the sum of that of the monodrugs. For new combinations formulated with monodrugs already marketed in the country that prove benefits compared to the monodrugs used separately. The applicant has to present the pricing rationale.

Category VI: Manufacturing price has to be 65% lower than the respective reference medicinal product price. New marketing presentations will have a manufacturing price lower than the mean price of the other product's marketing presentations with the same formulation.

For drugs at launch, therapies are classified into six categories, further divided into two groups: new molecules (Categories I and II) and new presentations (Categories III, IV, V and VI).

Category I: new patent-protected drugs that offer an advance in efficacy and/or safety relative to established treatments of the same therapeutic indication

Category II: new products that do not have a patent or do not offer a therapeutic improvement relative to established treatments (i.e., me-too drugs)

Category III: new presentations, in the same dosage form, of a drug already marketed by the same company

Category IV: new presentations of a drug for a company or new presentation in a new dosage form for a company

Category V: new presentations of a drug that is a new dosage form in Brazil or a new combination of active ingredients already available in Brazil

Category VI: new generic drugs

Drug prices are subject to analysis by the CMED, and a pharmaceutical company intending to commercialise a product in Brazil must submit documents demonstrating the category of the product (from I to VI). The CMED establishes initial launch prices, which are highly dependent on the level of innovation, clinical evidence, and economic analysis. The CMED reviews and publishes the Factory Price (*Prego Fabrica ou Prego Fabricante*; PF) and the Maximum Consumer Price (*Prego Maximo ao Consumidor*; PMC). The drug manufacturer submits an informative document to the CMED, applying for one of the categories mentioned above and the proposed Factory price (PF). The analysis is carried out within 90 days for pharmaceuticals classified in Categories I, II and omitted cases; and up to 60 days for products classified in Categories IV, V, and Category III, when applicable.

Biosimilars: According to the CMED, a biosimilar is considered to offer therapeutic gain if it offers:

- Higher efficacy than current medicines for the same therapeutic indication
- Same efficacy with a significant reduction of adverse reactions

- Same efficacy with a significant reduction in the overall cost of the treatment

Price setting will be determined as follows:

Biosimilars with therapeutic gain – the manufacturer price cannot be higher than the lowest price in any country of reference: Australia, Canada, Spain, USA, France, Greece, Italy, New Zealand, Portugal, and the country of origin.

Biosimilars with no therapeutic gain and that are new in the list of medicines produced by the manufacturer – the factory price (PF) will be determined by the average cost of the treatments with similar molecules, weighted by the sales, and cannot be higher than the lowest price in any of the countries of reference: Australia, Canada, Spain, USA, France, Greece, Italy, New Zealand, Portugal, and the country of origin.

Biosimilars with no therapeutic gain are manufactured by companies that already commercialise a similar biological molecule – the PF price will be defined as the average cost of the medicines commercialised by the company.

7.5.2 Medicine pricing framework in Russia

The Russian Ministry of Health (Rosminzdrav) controls pricing for drugs on the ZHNVLP (list of vital and essential medicines). All drugs on the ZHNVLP are subject to wholesale and retail markups that depend on the drug price. Non-essential drugs (drugs not on the list of ZHNVLP) enjoy free pricing at launch. Medicinal products for ONLP, federal target programs, regional benefit programs, and federal programs for rare diseases (highly expensive) are purchased via the procedure of state tenders.

The State regulation on prices for medicinal products is well established. The state regulation on prices for medicinal products is regulated by approval of the List of Vital and Essential Medicinal Products (LVEMP), which includes medicinal products under the international non-proprietary, chemical or grouping name and meets the following criteria:

- a) application of a specific medicinal product for the diagnosis, prevention and treatment of diseases, including those prevailing in the structure of morbidity in the Russian Federation
- b) advantage of a specific medicinal product compared with other medicinal products in certain diseases, syndromes or clinical situations
- c) therapeutic equivalence of a specific medicinal product over those with a similar mechanism of pharmacological action

The state registration of maximum selling prices for vital and essential medicinal products (included in the LVEMP) is performed by the Ministry of Health in cooperation with the Federal Antimonopoly Service (FAS). FAS performs economic analysis. The detailed methodology exists for calculating the maximum Manufacturer Selling Prices for VEMP for their state registration and re-registration.

Federal Service on Surveillance in Healthcare

This service (a state body of executive power reporting to the Ministry of Health of the Russian Federation) is responsible for the control of pricing for medicinal products included in the

LVEMP. The task of monitoring defectiveness or risk of defectiveness in connection with the pricing is also conducted by the Federal Service on Surveillance in Healthcare. Since September 2020, the RF Government has the right to set maximum selling prices for medicinal products not included in the LVEMP, as well as to limit their wholesale and retail markups in case of emergency or threat of the spread of any dangerous disease, in case of a price increase of 30% or more.

The markups for VEMP are limited in all regions. The percent of limitation varies in different regions. Mandatory price cuts are a regular feature. Price cuts imposed exclusively on ZHNVLP drugs might be offset by price increases on drugs that are not subject to such controls. To reduce the price of medicines, Russia follows economic analysis based on indicators in two ways. The first is the most common, in which the government selects the lowest price possible in its reference countries and registers it in Russia. The second way to regulate prices for original medicines is based on the assessment of the cost of a new therapeutic effect. This approach is called 'value-based'.

7.5.3 Medicine pricing framework in China

The National Healthcare Security Administration (NHSA) oversees the regulation of medical product pricing in China. The pricing of other drugs is formulated by manufacturers according to China's pricing laws. The NRDC, jointly with other ministries, has also traditionally been involved in drug pricing.

There is no direct price control as retail price ceilings were eliminated in 2015. Manufacturers are free to set prices. The government continues to seek discounts prior to reimbursement listing of drugs on the National Reimbursement Drug List (NRDL; a list of all drugs fully or partially reimbursed by the government) and the National Essential Medicines List, and through centralised volume-based procurement (VBP).

Patented/brand-name drugs

For patented drugs, inclusion on the NRDL is the only way for patients to be reimbursed by basic medical insurance.

Manufacturers must submit an application for price determination with supporting data that includes a drug overview, clinical evidence, and data regarding the potential economic impact. The NHSA then conducts technical and economic evaluations and negotiates pricing. They announce the final decision on their website (www.sdpc.gov.cn) and in their price journal.

Drugs on the NRDL lists A and B should be clinically necessary, safe and effective, reasonable in price, convenient to use, and have a guaranteed supply.

Generic/off-patent/biosimilar drugs

In China, a centralised VBP system is used for the distribution of generic, off-patent, and biosimilar drugs. In this system, the joint procurement office (JPO), consisting of representatives from the provinces, awards a contract to the lowest bidder who can guarantee at least 50% of the procurement volume for a given generic that has passed the Generics

Consistency Evaluation. This lowest price also applies to the same drugs manufactured by companies that did not win the bid.

Drugs should meet the clinical needs, manufacturer competition, and lower/lowest price.

Other pricing mechanisms faced by drugs in China are:

Pharmacy margins: Pharmacy margins are controlled; the maximum is 15%. Retail pharmacies have enjoyed increased attention due to the government's "dual channel" policy, allowing for drugs not carried by local healthcare institutions to be sold by these pharmacies.

Value-added tax (VAT): VAT was applied to all drugs at the standard rate of 17%, but in 2021, this was changed to 13%.

7.5.4 Medicine pricing framework in South Africa

According to Section 22G of South Africa, the pricing committee is appointed by the Minister of Health. The key function of the pricing committee is to make recommendations to the Minister of Health on concerns related to the transparent pricing system for all medicines and scheduled substances sold in the republic, including the introduction of a single exit price for all prescription medicines, restrictions on the logistics fees, and developing strategies for promoting transparency in the system.

The prices of pharmaceuticals in both the public and private sectors are regulated by the National Department of Health through separate mechanisms. The following agencies are involved in determining and establishing drug prices in the public and private health sectors:

The Access to Affordable Medicines directorate in the Department of Health coordinates drug tenders in partnership with the National Treasury.

A Central Pharmaceutical Procurement Agency (CPPA) is being established to control the procurement and financial management of certain drugs on behalf of the provincial health departments.

The National Essential Medicines List Committee (NEMLC) appoints four expert review committees, which are responsible for compiling the Essential Medicines Lists (EMLs) and standard treatment guidelines (STGs) for the primary, secondary, and tertiary/quaternary care levels.

The Office of the Chief Procurement Officer (OCPO) is a division of the National Treasury that oversees government procurement practices and compliance with the regulations, supply chain policy, norms and standards, and contract management.

The Pharmaceutical Economic Evaluation (PEE) Directorate within the National Department of Health (NDoH) evaluates and approves single exit prices. The information concerning annual single exit price adjustments (SEPAs) is sent to the PEE.

Table 7.6: Comparative analysis of BRICS countries

Brazil	Russia	China	South Africa
• The Pharmaceutical Market Regulation Council (Câmara de Regulação do Mercado de Medicamentos; CMED) was established under Law No. 10742 of Oct. 6, 2003. • The CMED represents the National Health Surveillance Agency (ANVISA; Agência Nacional de Vigilância Sanitária) and the Ministries of Health, Finance, Justice, Industry, and Trade. • Pricing is regulated in Brazil by a government council setting the price of a drug based on the six categories to which the drug is assigned.	• Russian Ministry of Health (Rosminzdrav) controls pricing for drugs on the LVEMP (list of vital and essential medicines). All drugs on the LVEMP are subject to wholesale and retail markups that depend on drug price. • Non-essential drugs enjoy free pricing at launch. • The State regulation on prices for medicinal products is established by the Federal Law. • State regulates the prices of medicinal products on the List of Vital and Essential Medicinal Products (LVEMP) • The State Registration of MSP for LVEMP is performed by the	• The National Healthcare Security Administration (NHSA) oversees the regulation of medical product pricing in China. • There is no direct price control as retail price ceilings were eliminated in 2015. • Manufacturers are free to set prices. • The government continues to seek discounts prior to reimbursement listing of drugs on the National Reimbursement Drug List and the National Essential Medicines List, and through centralized volume-based procurement (VBP).	• The prices of pharmaceuticals in both the public and private sectors are regulated by the National Department of Health through separate mechanisms and multiple agencies comprising of pricing committee. • The Access to Affordable Medicines directorate in the Department of Health coordinates drug tenders in partnership with the National Treasury. • A Central Pharmaceutical Procurement Agency (CPPA) controls the procurement and financial management.

• The CMED establishes initial launch prices, which are highly dependent on the level of innovation, clinical evidence, and economic analysis. • The CMED reviews and publishes Factory Price (Prego Fabrica ou Prego Fabricante; PF) and the Maximum Consumer Price (Prego Maximo ao Consumidor; PMC). • Separate pricing mechanism for Biosimilars	Ministry of Health in cooperation with the Federal Antimonopoly Service (FAS). • FAS performs economic analysis. • Separate price calculation methodology exists • Mandatory price cuts are a regular feature	• For patented drugs, inclusion on the NRDL is the only way for patients to be reimbursed by basic medical insurance. The NHTA conducts technical and economic evaluations and negotiates pricing. • A centralized VBP system is used for biosimilars. The joint procurement office (JPO) awards a contract to the lowest bidder who can guarantee at least 50% of the procurement volume. This lowest price applies to companies that did not win the bid.	• The National Essential Medicines List Committee (NEMLC) are responsible for compiling the Essential Medicines Lists (EMLs) and standard treatment guidelines (STGs). • The Office of the Chief Procurement Officer (OCPO) is a division of the National Treasury that oversees government procurement practices and compliance with the regulations, supply chain policy, norms and standards, and contract management.
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(Source: Clarivate)

7.6 Conclusion

This chapter finalises the research by presenting a Biologics Price Determination Model. All four objectives contribute to Objective 4, resulting in a model that can help make biosimilars more affordable. Objective 1 identified the development costs of biosimilars, which form the baseline for the pricing model. Objective 2 used a systematic bibliometric approach to pinpoint key factors, while Objective 3 incorporated these factors into a hierarchical pricing framework, highlighting the most crucial variables for building the model.

The cost estimates developed in this research are India specific and need a separate alignment study for adoption in LMICs. However, once the cost estimates are developed using the method proposed in this study, the same can be applied in the pricing model with minor modifications. The significant factors used in the mathematical equation are generic in nature and can be implemented by the LMICs. Hence, the deployment of the proposed pricing model in LMICs needs a minor validation study with regard to the cost estimates and the value of μ . The factors analysed through TISM and MICMAC are universal for the biosimilar ecosystem and research findings from the same can be applied directly to the LMICs.

The multi country comparison was essential to understand the global integration of the model. The recommendations and learnings from the four objectives are detailed in the next Chapter of thesis.

Conclusions and Recommendations

8.1 Introduction

This Chapter compiles the recommendations made from the four objectives of this research work. Although Chapters 4, 5, 6, and 7 provide significant insights into the policy and application aspects of the research, the recommendations are categorised according to the objectives and target groups in this Chapter. The important outcomes from the research work include 1) a cost reference for translating a biosimilar from lab to market, 2) unravelling the complex web of biosimilar prices through a hierarchical framework and understanding the linkages between the various variables impacting the prices, and 3) a price equation to determine the price of a biosimilar.

Objective 1 on developing a reference for the cost of biosimilar development has not only standardised the costs for pricing authorities but has also laid down important recommendations for biologics manufacturers to reduce the cost and time needed to bring the product to market. These are detailed in section 8.2 of this Chapter. Objectives 2 and 3 identify significant price factors and organise them into a hierarchical model. During this process, TISM has helped in understanding the interrelationships between variables, resulting in specific recommendations for India's pricing ecosystem. These are detailed in sections 8.3 and 8.4 of this Chapter. The recommendations collated in this Chapter outline the application of the work conducted in this research and propose a new approach to a biosimilar pricing framework for Indian settings. The Chapter concludes with documenting the limitations of the research work and outlining the future scope of work.

8.2 Cost optimisation and early market entry - recommendations from cost reference

8.2.1 Recommendations for manufacturers

Development Strategy: For biosimilar manufacturers, early market entry is essential. Multinational corporations try to block biosimilar versions of the originator through patents. The development and market entry strategy for manufacturers should be to complete the R&D of the biosimilar before the originator's patent expires and to accelerate the development process through proper planning.

Regulatory Approvals: The regulatory approvals in India for a biosimilar take around a year, and in some cases, it can be up to 2 years. Careful regulatory planning at RCGM, along with the clinical testing phase and manufacturing authorisation, can further reduce the time needed to bring biosimilars to market.

Indigenous manufacturing: Manufacturers should aim to validate and refine their processes using locally produced or available raw materials whenever possible. Changes in reagents or processes could result in the need to repeat assays during regulatory approval or commercialisation. Hence, the local production of media, resins, reagents, and high-end equipment has the potential to significantly reduce the cost of biosimilar development. The bill of materials increases multiple times as these items are imported.

Skilled Manpower: The availability of ICH-GCP-trained Principal Investigators and CRO staff is a continuing challenge for the biopharma Industry. Manufacturers should aim to start collaborations with Clinical Research Organisations or hospitals well ahead of time.

Infrastructure upgradation: The manufacturers should insist on adopting good clinical practices and automated data management software for clinical studies. CROs should upgrade with regard to the global regulatory requirements and data integration capacities for enhancing operational efficiency and alignment with global standards.

8.2.2 Recommendations for policymakers

- **Indigenous manufacturing:** Promote programs like Make in India, Vote for Local and PLI in the biotech sector.
- **Regulatory process harmonisation:** By harmonising requirements across regulatory bodies like the USFDA, EMA, PMDA, and CDSCO, the costs associated with regulatory approvals can be reduced. The regulators should collaborate with international authorities through various forums and aim to improve country-specific regulations while safeguarding the interests of Indian manufacturers.
- **Separate regulatory framework:** The New Molecular Entity (NME) and biosimilars are different classes of products and call for different regulatory pathways. No regulatory framework exists to evaluate innovative technologies and manufacturing platforms. The regulators should separate the new biologics from the biosimilar guidelines.
- **Single window clearance:** Multiple approvals (Institutional Biosafety Committee, Review Committee on Genetic Manipulation, Institutional Animal Ethics Committee, Genetic Engineering Approval Committee, and CDSCO) are required to bring a biosimilar to market, leading to increased cost, time and effort as compared to regulated markets where only one submission is made at the time of manufacturing and marketing approval. Single window clearance to reduce regulatory timelines has been a long pending demand from manufacturers.
- **Streamlining clinical studies requirements:** The most expensive stage of developing a biosimilar is clinical trials. Several variables, including patient enrolment, availability and sourcing of reference products, and the patient's clinical history, impact the trial. Regulators should ensure the NDCT 2019 Act aligns with requirements in other jurisdictions. The clinical trial waiver should be provided whenever necessary.

- **Enabling policies and conducive environment:** The policies, including the tax regime of any nation, play a major role in transforming the economy. Favourable policies for R&D, innovation, manufacturing, and import/export can reduce the cost of development.

8.3 Price indicators - Recommendations for policymakers

- The pricing mechanism of any country should be aligned with national priorities. Country-specific costing and pricing strategies are required to align with the local policies, regulations, and economic factors of the country.
- Domestic manufacturing capability is considered one of the major factors of affordability. Government incentives and schemes for local manufacturing of raw materials can reduce import dependency.
- The acceptance of biosimilars by clinicians is significantly influenced by rebates, discounts and profit margins. A monitoring mechanism for the control of such unethical practices is required. Financial incentives or penalties were also noted in a few countries (Belgium and Germany), but the enforcement of such measures calls for creative monitoring techniques.
- The pricing mechanisms, regulations and policies developed for the generic drugs, synthesised by chemical route, cannot be replicated for biosimilars. A separate pricing mechanism is required for this therapeutic class of medicines.

8.4 Recommendations from the hierarchical pricing framework

8.4.1 Recommendations for Niti Aayog, Department of Biotechnology and Invest India

- **Mergers and acquisitions** significantly impact the development, marketing, and distribution of biosimilars. A monitoring system and connection with the price equation should be established to ensure the affordability of biosimilars. Because there are few biosimilar manufacturers, it is crucial to create a monitoring mechanism to evaluate demand, break the monopoly, and support global market growth.

- In order to attain **economies of scale**, it is necessary to enhance the demand for biosimilars through **Public Private Partnerships (PPP)** or exporting to other countries. The promotion of export policies and bilateral trade agreements with other countries for the adoption of made-in-India biosimilars should be encouraged.
- **Obligatory industry disclosure policies, or UCPMPs**, were enacted in India in an attempt to stop fraudulent practices related to the prescription and sale of expensive medication. However, this study raised questions about how well the UCPMP is being implemented. Specific recommended steps involve imposing limitations on specific transactions involving cash and institutionalising transparency through self-monitoring for medical professionals and companies.
- Besides macroeconomic drivers like growth in Gross Domestic Product (GDP), rising purchasing power parity, and rising healthcare spending, a strong regulatory commitment is required for cost reduction and improving treatment accessibility.
- In India, patients face out-of-pocket expenses for medications and are unable to purchase expensive branded biologics. The PM-JAY packages should be revised to include more biosimilars.

8.4.2 Recommendations for NPPA

- This study examined various variables that influence the price of biosimilars and emphasised the need for India to **revise its market-based strategy**.
- **Scientific, economic, and collaborative factors**, such as patent expiry period, the country's economy, and partnerships or acquisitions, have a direct influence on prices and should be included in the pricing mechanism.
- The **manufacturer's discounts or promotional elements** have come out as linkage variables with high driving power and dependence.

- The policy framework, including **price control policies, is specific to each nation** and is necessary to develop a conducive ecosystem for affordable and accessible medicines.
- Biopharmaceutical companies should be encouraged to take **advantage of new financial models** and avoid pricing decisions that lead to reactionary price cuts, punitive regulatory actions or public scorn.
- **More biologics should be included in the DPCO** to enhance accessibility for patients. The order can be amended to include the recommendations and meet the demands of NGOs and industry.

8.5 Defining the ideal characteristics of the price model

- The price equation should be simple and easy to implement.
- It should be capable of conveying the complete value of the product, rather than relying on biased market values to determine prices.
- Should be able to demonstrate the extent to which the individual product components and other significant variables influence the price of the biologic.
- It shall be indicative of the expectations and evaluations of each consumer segment which is involved in making choices that affect its purchase, accessibility, and usage.
- The pricing model should reflect the connections between the key elements of its pricing ecosystem and complex network, which can influence the price.
- It should take into account the essential components of the cost structure that are required to facilitate its development, launch, and life-cycle management, including profits and rebates.
- The price equation should be adaptable to global pricing, taking into account moderating factors like reference pricing and parallel trade to provide a realistic and transparent price.

8.6 Recommendations from BRICS comparative analysis

- The pricing mechanism of Brazil is the most advanced among the BRICS nations.

- India can establish a mechanism to evaluate the level of innovation, clinical evidence, and economic analysis. Currently, no such mechanism exists for cost-benefit analysis.
- NPPA has a common price strategy for all the medicines in NLEM. A separate pricing mechanism is required for high-cost biosimilar therapies, as in Brazil and Russia.
- Price is a central government prerogative under NPPA. Additional state-level price mechanisms, like Russia, can complement and remove limitations of the current system. In Russia, the state registration of maximum selling prices for vital and essential medicinal products is performed by the Ministry of Health in cooperation with the Federal Antimonopoly Service (FAS). FAS performs comprehensive economic analysis. A detailed methodology exists for the calculation of maximum Manufacturer Selling Prices for essential medicines for their state registration and re-registration, unlike in India. NPPA can establish a FAS like body in India to perform a detailed analysis of the economic analysis of the medicine, not only at the national level but at the state level as the requirements of each state are different in India.
- The NHSA in China conducts technical and economic evaluations and negotiates prices. NPPA shall enhance the scope to take up such activities.
- Volume Based Procurement, like China, is a good option for certain classes of medicines but risky for the growth of companies, as it removes competition from the market.

8.7 Research contributions

- The reference or “Gold Standard” for the cost of translating a biosimilar from lab to market is a contribution for manufacturers, researchers and policymakers.
- Information on costs associated with product development can aid manufacturers in cost-effectiveness analysis and strengthen government price negotiations through appropriate regulations.

- This research proved that both the CBP and MBP approaches have further limitations. A separate pricing framework is required for biosimilars.
- The four significant variables identified through this research can act as price indicators of biotherapeutics for monitoring the prices and developing pricing policies.
- The TISM study helped in understanding the interrelationships between the various variables impacting the prices of biosimilars. A better understanding of the complex web of the biosimilar pricing ecosystem.
- The alpha prototype of the Biologics Price Determination Model (BPDM) is proposed in this research to make biosimilars affordable.
- This fair price model is data-driven and establishes a scientific method of price determination instead of relying on market share only.
- Due to ongoing legal challenges to the MBP policy implemented by the government of India, establishing an effective pricing mechanism for biosimilars is likely to have a significant impact.

8.8 Limitations

Despite being one of the most used qualitative research methods, researchers have not yet developed a consensus on the planning and implementation of an inductive case study (Yazan & De Vasconcelos, 2016). Data confidentiality requirements of case companies to hide profit margins have made the study less transparent and reliable. Although we tried to include a heterogeneous sample of companies as cases, the perspective of clinicians, policymakers, and regulators is lacking in the study. Further, it was proposed to include a sample of two biosimilars from each company, but we were unable to elicit responses from all six companies. In addition, we could not keep the indication the same across companies as originally intended, and as the cost of clinical studies varies significantly with the change in indication, to generalise the finding, it was decided to select a heterogeneous group of indications. A major caveat is

that the cost estimates are India-specific and so would need to be extrapolated for other geographies. However, efforts were made to mention the US/EU specific costs separately. The estimates of the depreciation costs of the CapEx are purely based on the experience of the company representatives and authors.

As previously mentioned, the systematic study design, which consists of a series of bibliometric and qualitative steps to identify the gaps in the subject area is novel. Researchers can utilise this tool to advance their research or improve their understanding of the topic. It is important to emphasise that the review study has several shortcomings. Firstly, while we made every effort to adhere to the PRISMA guidelines, some of the items on the checklist may have remained unchecked. Even though there are numerous measures employed to prevent author-specific bias, the qualitative synthesis and conceptual framework section may still be subject to individual prejudice. Some findings are based solely on title reviews because complete readings of all the articles in the chosen dataset were not possible. Additionally, while the review is concentrated on the elements that affect prices, other elements like costing models and pricing mechanisms have not been examined. Further, we may have missed some crucial material because we did not extend our search via the reference lists of the papers and instead conducted a very concentrated manual search for the grey literature publications from international agencies. Additionally, inconsistent reporting and a lack of published studies on this subject might hamper the generalisation of the findings.

Also, it is to be noted that although bibliometric analysis like co-citation is a good approach for developing the themes, it does suffer from certain limitations. The threshold limit excludes the recent publications which have not received the minimum number of citations. This could be a reason for the exclusion of the biosimilar prices theme which is an active area as per the results of other sections of this paper. One of the probable solutions to avoid this bias for old

papers is the manual examination of recent papers. The same is performed by the authors in the qualitative synthesis section.

The challenge of implementing the proposed price framework would be to identify the correct proxies for the variables and validate them with the existing biosimilar prices. Once validated, implementation and adoption would not be easy and would require the efforts and cooperation of all the stakeholders. One limitation of the model is that bias in the opinion-gathering process may exist since the proposed model is based on input from a small number of experts and was constructed through the study of selected factors. It should be noted that the model is developed for Indian settings and requires modification before adoption by other countries. The country specific dynamics would differ, but the overall methodology can be generalised.

It should be noted that the research work is qualitative research due to the lack of historical quantitative information on the prices of biosimilars. Validation of the price equation on four molecules is a study constraint due to the lack of retrospective information on variables. Therefore, the prices used for validation are not the launch prices of the biosimilars. The study assumptions, like production rate and years of operation, are well established and used by researchers globally, but they make the model vulnerable. Also, the study considers the conventional manufacturing process and does not include the next generation manufacturing practices and AI/ML, which have the potential to further reduce the cost. Finally, the applicability of the price equation is restricted to Indian settings; significant modifications are required for global adoption of the proposed framework.

8.9 Future scope of work

Global integration of the price equation or modifying the price equation as per the country specific requirements needs further research and is an interesting area to explore. The variety of pricing mechanisms as mentioned in previous chapters presents a huge challenge for integrating country specific local requirements with the global price ecosystem. The lack of

this integration leads to higher prices in some countries. The developed nations have significantly different price mechanisms as compared to the developing countries, this leads to a disbalance in the demand and supply chain of biosimilars.

The price indicators as identified in this research work can be further explored for performing state and country level quantitative studies. One interesting example of quantitative analysis could be to explore countrywide variations in biosimilar prices based on mergers and acquisitions data of biopharmaceutical companies. The impact of paying capacity or out-of-pocket expenses on price can shed interesting recommendations on the various state specific measures required for the affordability and accessibility of these high-cost medicines.

The use of cost reference as developed through this research can be used as a gold standard by the manufacturers and price control authorities, especially in LMICs. The cost reference can help manufacturers in justifying the high cost of developing a biosimilar to policymakers while regulatory bodies like NPPA and WHO can use it for implementing the national level policies for this class of medications. A few recommendations for researchers are as mentioned below:

- Inter-linkages between the factors leading to the complexities of the pricing mechanism remain an unmet research area to be further explored.
- There is a significant gap in the literature regarding evidence-based studies that identify the key primary and secondary factors influencing biosimilar prices.
- Research on incentives and profit margins is vital for the effective adoption of biosimilars.
- Variables such as technological innovation, R&D costs, payers' perspective and hospital procurement dynamics, production yield, regulatory ecosystem, and patent protection could be further explored as potential factors impacting the prices of biotherapeutics.
- The empirical studies on the proposed model can help in validation and deployment.

8.10 Concluding observations

This study provides a quantified cost basis for the development of biosimilars in India. The findings reflect that an investment of 65 - 70 million USD is needed for biosimilar development in India. Although various factors impact the development cost such as marketing strategies, the scale of production, indication, and geography; as a rule, the cost of development for monoclonal antibodies is higher than for microbial products. The cost of the Reference Product for clinical comparative studies is considered to be the most expensive part of biosimilar development. Its accessibility and import from other countries increase the challenge and time required to complete the clinical studies.

While significant capital expenditures are identified as a major hurdle for the entry of small companies, it is also noted that the advanced single use technologies with government subsidy are the possible solution with the potential to boost manufacturing of biosimilars in India and at the global level. Indigenous manufacturing is a much-needed futuristic demand which might take decades despite government efforts.

Careful regulatory planning towards developing the clinical study design in discussion with regulators can further reduce the cost and time to bring biosimilars to market. Although convergence of regulatory guidelines with global regulatory requirements is necessary, it is also important to safeguard the interests of small manufacturers. The adoption of alternative animal testing approaches in the regulatory regime is much needed and is also in line with the international shift towards complex *in vitro* systems.

Furthermore, the study emphasises the long timeline for biosimilar development, spanning nearly a decade from inception to post-market studies. In such a scenario, the success of a manufacturer will depend on being early to market while keeping development costs as low as feasible without compromising on product quality.

One of the applications of the findings of this study can be in the development of cost-based pricing policy for biosimilars in developing countries. After relevant modifications, the findings of this study can be extrapolated to determine the weighted average cost and average sales price of biosimilars in the US.

Having said that, it is to be noted that India's adoption of a market-based pricing mechanism is not an optimal strategy for controlling or capping the prices of medicines, particularly for oncology biosimilars. This is partly because the market is dominated by a few producers who have a monopoly. The National Pharmaceutical Pricing Policy, implemented in 2012 through the Drugs (Prices Control) Order of 2013, shifted from a cost-based approach to a market-based approach. However, this transition has negative consequences and requires the implementation of new and efficient measures to address its limitations.

The price framework, proposed in this study, explains the relationships between each element and establishes a pathway towards a new pricing regimen for biosimilars. The various facets of biotherapeutics pricing conclude that there are multiple factors which influence the prices of high-cost biotherapeutics, especially the biosimilar class of products. The biosimilar costing is a complex web that includes various stakeholders like innovators, manufacturers, suppliers, distributors, pharmacies, and in-hospital pharmacies. The intensity of the problem magnifies as the majority of end users do not understand the distinction between originator products and biosimilars, which results in high out-of-pocket costs. Many regulations and laws for the effective adoption of pricey biosimilars are analogous to those for generic medicines. In contrast to generic drugs, biosimilars are produced utilising a unique biological process. Therefore, the regulatory and price frameworks developed for generic pharmaceuticals cannot be applied directly to biosimilars. As a result, academics and decision-makers from all around the world have been interested in the discussions surrounding the price comparison of the originator with its biosimilar and associated strategies.

Although the review of grey literature describes the efforts by various international health agencies towards monitoring and control of medicines pricing as a whole; the uncertainties surrounding the affordability and effective uptake of high-priced health therapies like biosimilars require more collaborative efforts at every level of the healthcare system to untangle the complex web of pricing for this class of products. In future, it is important to extend this research to cover other aspects of pricing, like costing models and pricing mechanisms used by firms, that may help reveal unidentified facts that drive pricing decisions.

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BIODATA

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Sonia Gandhi is the Deputy General Manager and Head of Regulatory Affairs and Policy Advocacy at BIRAC, a PSU of the Department of Biotechnology, Ministry of Science and Technology, Government of India. At BIRAC, she has played a key role in almost all major funding and mentoring programmes, making a significant contribution to the Indian biotech start-up ecosystem. With extensive experience in techno-commercial evaluation and due diligence, she has audited more than 100 Indian life sciences companies. She has also been instrumental in developing and implementing multiple national and international projects in collaboration with renowned organisations such as WHO, the World Bank, the Bill & Melinda Gates Foundation, USAID and others. Before joining BIRAC, she managed quality assurance of biopharmaceutical products at Reliance Life Sciences in Navi Mumbai. She has participated as a delegate and speaker at various national and international workshops.

She is a certified quality management professional, an accredited lead auditor for ISO 13485:2016, with dual master's degrees in Biotechnology and Total Quality Management, and holds a doctoral degree from IIT Delhi. Her research interests include pricing mechanisms for biologics, health economics, price regulation, and the affordability of biosimilars in developing countries.

COURSE WORK

Course Code	Course Title	Credits	Grade Obtained
MSL 708	Financial Management	3	B
MSL 721	Econometrics	3	A-
MSL 806	Mergers & Acquisition	3	B
MSL719	Statistics for Management	3	B
MSL707	Management Accounting	3	A
HUL800	Research Writing	-	NP

CGPA Obtained: 8.67

PUBLICATIONS

Gandhi, Sonia, Dhananjay Patankar, Smita Kashiramka, and Anurag S. Rathore. "The economics of translating a biosimilar from lab to market in India." *Annals of the New York Academy of Sciences* (2024).

Gandhi, Sonia, Smita Kashiramka, and Anurag S. Rathore. "Emerging themes and factors influencing the prices of biotherapeutics." *World Medical & Health Policy* 15, no. 4 (2023): 613-637.

Gandhi, Sonia, Sushil, Smita Kashiramka, and Anurag S. Rathore. An interpretive price framework for the affordability of biosimilars (Communicated).