Exploring The Impact Of Biologicals On The Pharmaceutical Landscape In South Africa

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ABSTRACT

This paper explores the growth of biological medicine in the South African pharmaceutical sector for the period 2019 to 2023. The study analysis revenue trends over time and investigates challenges experienced and suggests possible solutions. Results show that small-molecules and biologicals follow a similar pattern with a major peak in 2021 and a decline thereafter, with total revenue for small molecules much higher than for biologicals over these years. Biologicals generally had growth through 2021, then experienced a significant decline in sales and growth in the following years. To promote the growth of biological medicines in South Africa, it is vital to streamline regulatory frameworks for quicker approval of biologicals and biosimilars while ensuring safety and efficacy. Implementing affordable pricing strategies and fostering collaboration between public entities, pharmaceutical companies, and insurers will enhance reimbursement policies. Additionally, increasing educational initiatives for healthcare providers will improve awareness and prescribing practices. Investing in local manufacturing can reduce costs and create jobs, while raising awareness of biosimilars as cost-effective alternatives will further boost their adoption and accessibility.

KEYWORDS: Biologicals; Small-molecules; Pharmaceutical.

ABBREVIATIONS: SAHPRA: South Africa Health Products Registration Authority; DMARDs: Disease-Modifying Antirheumatic Drugs.

1. INTRODUCTION

South Africa currently has the biggest pharmaceutical market in the Sub-Saharan region [1]. The industry has made significant strides in the development of medicine over the decades, particularly in small molecules and biological medicines [2]. Whilst both add great value to patients in terms of health benefits, the two categories are vastly different in how they are delivered to the body, their mechanisms of action inside the body, costs, accessibility to patients and results in patient outcomes. In South Africa, small molecules are mainly procured by the government sector, predominantly for use in primary healthcare, while the private sector is a notable market for the more advanced small molecules [3].

Biologicals have increased steadily, particularly in the private market, for patients covered by medical insurance, and create added diversity in treatment options with new innovative medicines geared towards the global trend of better optimised and personalised therapy [4]. Whilst the availability of different and more effective medicines creates a more expansive market to both patients and physicians, the adoption of biologicals has been slow, with the biotherapeutic industry facing various challenges in the South African market.

Small molecules have been the standard of treatment for various diseases in South Africa and remain the mainstay of treatment available today. It is classified as a synthetic chemical developed to imitate, improve, or lessen the actions of innate substances or effects within the human body. Chemically, they're structures are relatively simple, which can be customised to meet a given therapeutic result [5]. Small molecules are available in various formulations, including tablets, syrups, inhalers, suppositories, patches and injectables, allowing for flexibility in administration and delivery of the product. The development and production of small molecules has improved, with companies able to reproduce large-scale batches accurately and at high speeds. Examples include paracetamol, salbutamol, vildagliptin and fentanyl [6].

Biologic medicines are derived from organic cells or through a biological process [7]. They are quite complex structures frequently involving proteins, celluloses, nucleic acids, cells or tissue matter for transplantation, or a composite compound of these materials [8]. Examples comprise hormones, vaccines such as smallpox and rubella, blood products, monoclonal antibodies such as rituximab, recombinant hormones and interferons, insulin and cell and gene therapies (used to treat HIV and different types of cancers) [8]. Biological medicines are more complex structurally, as they consist of larger molecules, making their development, manufacture and delivery more complicated. They are usually administered through infusions or injections and treat medical conditions ranging from auto-immune diseases, various cancers and neurological conditions to genetic disorders.

Taking the above into account, the cost related to the development and production of small molecules is much less than that of biological medicines [9]. Cutting-edge technology in the biopharmaceutical industry has resulted in the discovery of innovative, target-specific, highly effective drugs. The investment in technology, research, and development of these molecules, however, has not been to the benefit of the patient. Due to complexities in manufacturing biological medicine, the limited ability of local manufacturers to produce biologicals, the affordability of these medicines is a huge challenge in low- and middle-income countries like South Africa [10].

Table 1: Differences between biological medicine and traditional small molecules.

	Small molecules	Biological medicine
Composition	Synthetic	Living cells
Manufacturing process	Chemical manufacturing processes	Manufactured using living cell tissues
Molecular structures	Small, low weight, well-defined	Large, high weight, complex
Stability	Stable	unstable
Precision on Reproduction	High even with large batch sizes	Low, smaller batch sizes
Immunogenic	No	Yes

Source: [11]

Small molecules are included in various medical curriculums, well documented in medical textbooks, publications and treatment protocols, while resources documenting biological medicine are not adequately covered [12]. Biologic treatment presents a probability of severe and opportunistic contagions, which is documented and a cause of concern to healthcare professionals due to the high tuberculosis infection rate in the country [13].

Research indicates that patients are willing to bear the risks associated with small molecules if they offer clinical effectiveness, help achieve or maintain remission, and prevent surgery based on their familiarity or experience with these treatments, despite biologicals offering greater efficacy and safety benefits, such as in the treatment of Inflammatory Bowel Disease [14].

Also, access to biologic medicines in South Africa is mostly reliant on patients having medical coverage, often through their employers [13]. Whilst some mitigation is possible, e.g., increase testing for infections, these factors, combined with the high cost of biological medicine, contribute to how biological medicine is adopted and included in treatment regimes.

Although biological medicines are safer, more targeted treatment for various chronic diseases, it is yet to have a significant impact on lowering the disease burden in South Africa due to their under-utilisation. Biologicals have been used extensively in global markets and have become an essential component in the treatment options of non-communicable diseases [15,16]. This has not been the case in South Africa, with high prices making it inaccessible to most of the population. The high cost, combined with the partial or absence of reimbursement by insurance companies or funders for biological medicines, has made it difficult for biological companies to cement their place in the market. This has resulted in small molecules, where not much innovation or development has occurred, remaining the treatment of choice for most conditions in South Africa.

Historically, limited resources resulted in a huge backlog of the review and approval of new medicine applications at SAHPRA, which increased the time to market for many products. Due to initiatives taken by the Health Authority in the past 5 years to clear the backlog of products for registration submitted prior to 2018, there has been a significant increase in the registration and availability of small molecules as well as biological and biosimilar medicines in the South Africa market [6]. This has resulted in a total of 5399 new medicine applications being registered between 2019 and 2023, with the highest registrations achieved in 2021 and 2022 (1654 and 1691 applications, respectively). The previously limited biological market grew immensely and created a new medical landscape in South Africa.

Biologics have altered treatment models for conditions like rheumatoid arthritis, psoriatic arthritis, and serious asthma [17]. The introduction of biological medicines in the treatment of rheumatoid arthritis has seen a dramatic improvement in the outcome of the disease over the past 20 years [18] and has resulted in the development of South African treatment guidelines. Patients who do not respond sufficiently to small-molecule DMARDs such as methotrexate have a more effective option in biological medicine targeting specific pathways [19]. This has led to a shift in the management of the condition from the use of small molecules as a first line to either a second-line or adjunct treatment in specific instances. There has also been an increase in the combined use of small molecules and biological medicine to achieve better control of certain diseases [19]. Using small-molecule DMARDs (e.g., methotrexate) in combination with biologics like tumour necrosis factor α inhibitors (TNF-i) improves outcomes in rheumatoid arthritis [18]. These approaches help optimize treatment efficacy through improved inflammatory control, prevent joint damage and reduce disability while minimizing the risk of adverse effects.

The entry of biosimilars into the South African market has increased patient access to biological medicine at a lower cost [17]. Biosimilars are replicas of authorized innovator biological products that have been shown to be similar to the corresponding originator product [20]. Both biological medicine and biosimilar medicine fall under the biological category

for registration in South Africa by the SAHPRA. Applicants are required to demonstrate the biosimilars' similarity to the reference biological medicine in terms of quality, safety, and efficacy using comprehensive analytical, animal, and clinical studies [6]. In addition, applicants must evaluate the biosimilar product in terms of chemical and physical qualities, manufacturing process, formulation, and its stability profile in comparison to the reference biological product. Biosimilars are characteristically not identical to the reference biological medicine, meaning the active components may have different attributes and the formulations may contain differences [7]. Due to these possible differences, reference biological medicines registered may not be switched with biosimilars, and the two products are not yet considered interchangeable in South Africa The availability of biosimilars, have however, led to a more balanced use of biologics and small molecules, as it allows for broader use of targeted treatment while maintaining small molecules as cost-effective alternatives. Approvals of biosimilars like filgrastim and trastuzumab [7] ensure access to critical treatment addressing previous gaps in treatment options for diseases such as breast cancer and haematological conditions. With increased awareness around the efficacy and safety of biosimilars, health care providers are more likely to prescribe biosimilars, especially as more data on patient outcomes, the impact on patient access and treatment adherence becomes available.

Due to complexities in manufacturing biological medicine, the limited ability of local manufacturers to produce biologicals, the affordability of these medicines is a huge challenge in low- and middle-income countries like South Africa [10]. This is further accentuated in South Africa, where medical insurances either do not or only partially reimburse most biological medicines, resulting in a huge amount of out-of-pocket expenditure for patients [21]. It further limits the access of the wider population to these unique medicines, especially where competition in the market is limited. It is therefore important to study the effect of pricing on the usage of biologicals to further establish if a need for the review of the regulations of the pricing of innovative medicines is necessary in low- and middle-income countries with efforts working towards affordability and cost-effectiveness [21].

The objective of this study is therefore to review the under-utilisation of biologicals in South Africa, evaluate the impact of high prices and the lack of funding on the accessibility of biological medicines and the role of regulators in ensuring registration and pricing guidelines guarantees products entering the market is not only safe, effective and of good quality but accessible to the population it is meant to benefit.

2. METHOD(S)

This study employed a quantitative research design, utilizing secondary sales data for biological medicines marketed in South Africa from 2019 to 2023. Data on registered and marketed biologicals were obtained, with permission, from licensed databases accessible to the sponsoring company. The dataset, sourced from the IQVIA database, includes key variables such as the number of marketed biologicals and existing small molecules, pricing data, and usage trends per therapeutic area, allowing for comparisons within similar therapeutic classifications.

The research design is grounded in the analysis of secondary data available through clinical research software tools. These tools track medicine usage based on medical aid claims for biological therapies in South Africa. The dataset is accessible to any registered pharmaceutical company that holds a valid license for the software. Statistical analysis involves both descriptive and inferential techniques. Specifically, the study includes:

- An overall trend analysis of the pharmaceutical market for biologicals,
- Hypothesis testing to explore significant market factors, and
- ANOVA tests to evaluate differences in market behaviour between biological and small-molecule medicines across therapeutic areas.

This methodological approach enables a comprehensive assessment of the market dynamics and factors influencing the adoption of biological medicines in South Africa.

3. RESULTS

3.1 REVENUE OVER TIME

The revenue trends for small molecules and biologicals in South Africa from 2019 to 2023 exhibit distinct differences in their performance and market dynamics.

Both categories peaked in revenue in 2021; however, small molecules significantly outperformed biologicals, generating over six times the revenue of biologicals during this peak year. Small molecules increased sharply from around R247 million in 2020 to over 406 million in 2021, while biologicals peaked at about R66 million. This increase coincides with the increase in registration of new applications by SAHPRA between 2021 and 2022. New market entries, including the COVID-19 vaccine and blood glucose-lowering medicine (dulaglutide and semaglutide) in 2021, contributed to the increase in biological revenue.

Table 2: The revenue of small molecules and biological medicine between 2019 to 2023.

Type of Medicine	GenericFlag	2019	2020	2021	2022	2023
Small Molecules	G=Generic	154229651	157797037	249154620	184116624	187328564
	B=Branded (No Generic)	70393687	71859493	128357350	79695764	78056597
	O=Originator	53503376	49760561	61818782	48611411	46028003
	C=Clone	12071609	11800703	19565415	12441810	12776610
Biologicals	D=Biological “Branded”	5868936	6489021	8982186	6484554	6200301
	L=Biological “Originator”	1720083	1768749	3112803	1568550	1444779
	S=Biosimilar to Biological “Originato	1171260	1272747	1470489	1646220	1892802
	No Category	30	3	44130	543	84

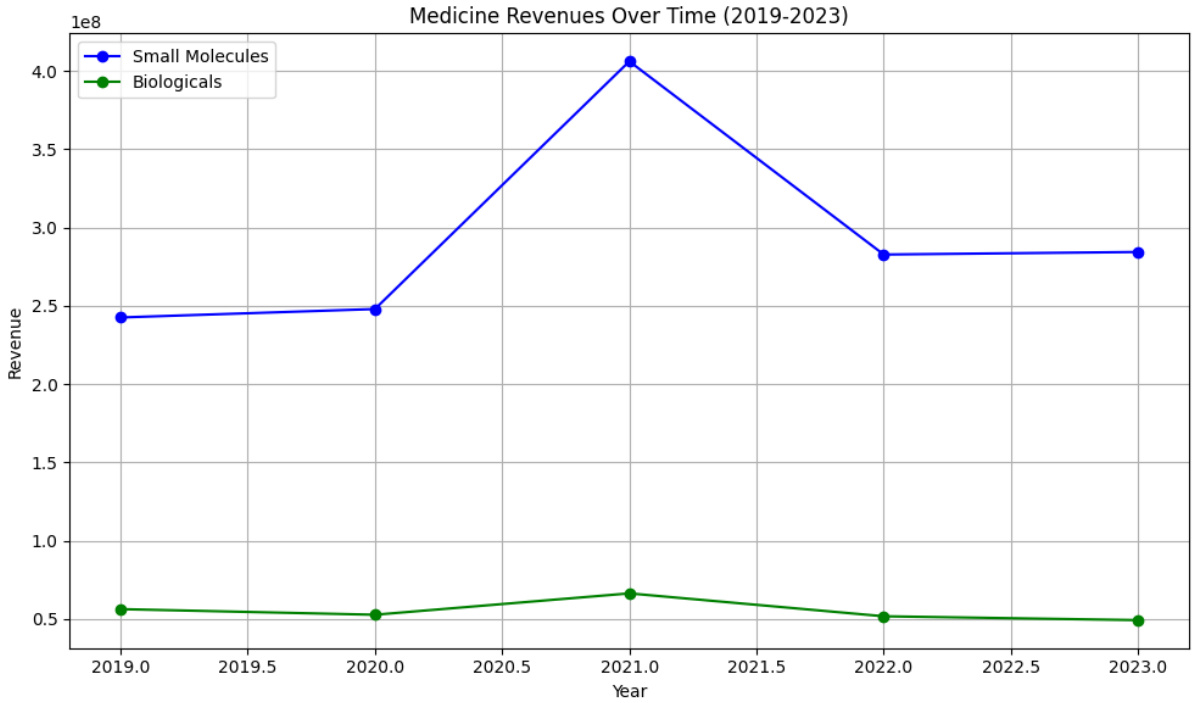

Figure 1: Revenue trend over time.

After the peak in 2021, both small molecules and biologicals experienced declines. However, the decline for biologicals was more pronounced, dropping from 66 million to 49 million by 2023.

3.2 GROWTH WITHIN BIOLOGICALS

Table 3: The growth rate of biologicals between 2019 and 2023.

Year	Revenue	Growth Rate
2019	8760309	
2020	9530520	9%
2021	13609608	43%
2022	9699867	-29%
2023	9537966	-2%

The revenue increase for biological medicines exhibits volatility over the five-year period. Following an upward trend during the COVID-19 pandemic from 2019 to 2021, the notable decrease in 2022 implies a reduction in the demand for biologicals (of note is the decline in the demand for the COVID-19 vaccine) and highlights the barriers that continue to impede broader adoption. Other possible challenges include client attrition or operational difficulties. Biologicals generally had growth through 2021, then experienced a significant decline in sales and growth in the following years.

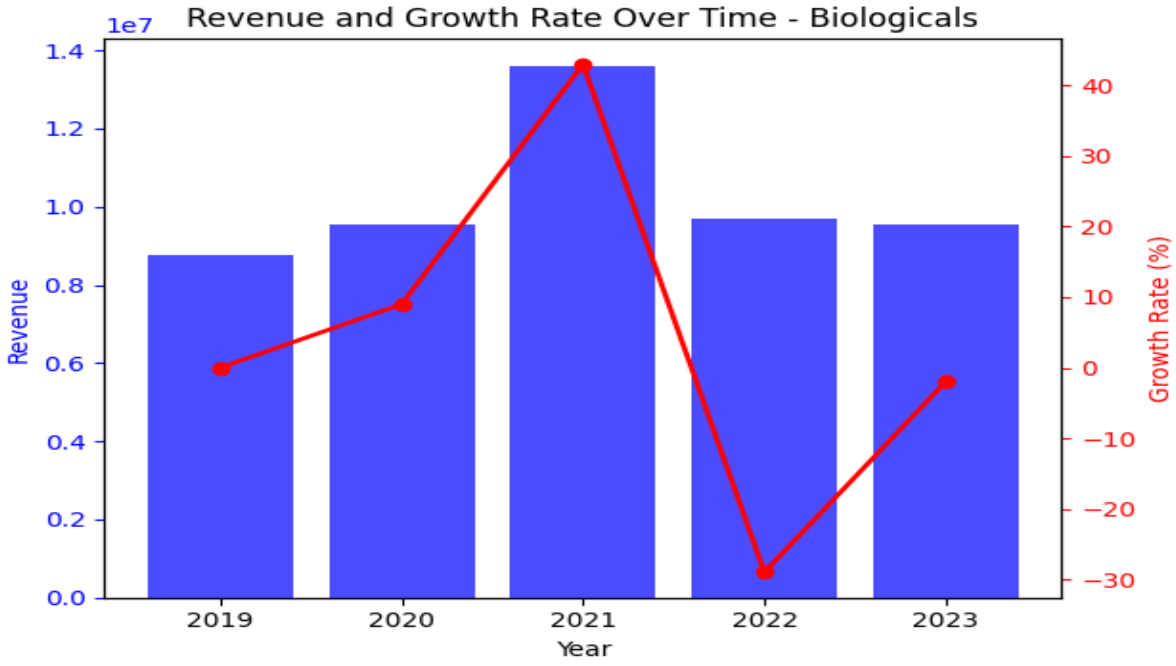

Figure 2: Biological revenue and growth rate over time.

3.3 PROPORTIONS OF SMALL MOLECULES VERSUS BIOLOGICALS

Table 4 displays the proportions of the Small Molecules and Biologicals category from 2019 to 2023 and the total revenue for each year.

Table 4: The growth rate of biologicals between 2019 and 2023.

	2019	2020	2021	2022	2023
Total - Small Molecules	97,07%	96,83%	97,12%	97,10%	97,14%
Total - Biologicals	2,93%	3,17%	2,88%	2,90%	2,86%
Grand Total -Rands	298 958 632	300 748 314	472 505 775	334 565 476	333 727 740

The proportion of small molecules remains consistently high, almost 97% each year, showing slight variation over time. This shows that small molecules dominate the market each year, with their share slightly increasing from 96.83% in 2020 to 97.14% in 2023. On the other hand, the proportion of biologicals is tiny, almost 3 % each year, with some minor fluctuations. The proportion for Biologicals increased slightly in 2020 (3.17%) but decreased marginally after that, indicating a stable but smaller presence than small molecules. Small molecules dominate the market, with a market share of around 97%, compared to biologicals, with a market share of about 2.9%. Both categories' total revenue stays reasonably consistent over the other years, except for a significant peak in 2021.

3.4 COMPARISON BETWEEN SMALL MOLECULES AND BIOLOGICALS

To assess whether there are statistically significant differences between small molecules and biologicals, the Shapiro-Wilk normality test was first conducted to evaluate the distribution of the datasets. The null hypothesis of the Shapiro-Wilk test states that the data is normally distributed. A p-value less than the conventional significance threshold of 0.05 leads to the rejection of the null hypothesis.

As shown in Table 5, the p-values for both small molecules ($p = 0.02576$) and biologicals ($p = 0.01474$) were below the 0.05 threshold. Consequently, the null hypothesis was rejected for both datasets, indicating that the distributions of small molecules and biologicals deviate significantly from normality.

Table 5: Shapiro-Wilk normality test.

Group	W	P-value
Small molecules	0,74328	0,02576
Biologicals	0,7183	0,01474

Given the lack of normality in both groups, a non-parametric statistical test, specifically the Wilcoxon Rank-Sum test, was deemed appropriate for comparing the two independent samples. The results, presented in Table 6**,** reveal a statistically significant difference between small molecules and biologicals (W = 25, p = 0.007937), supporting the conclusion that the two groups differ meaningfully in terms of their values.

Table 6: Wilcoxon Rank-Sum test.

Comparison	W	P-value
Small molecules vs. biologicals	25	0,007937

Furthermore, an examination of the mean values demonstrates a substantial numerical difference: small molecules recorded a mean value of 337,873,533, while biologicals had a significantly lower mean of 10,227,654. These findings reinforce the statistical conclusion that biologicals and small molecules differ significantly in their market characteristics, justifying separate consideration in pharmaceutical policy, pricing, and usage strategies.

4. DISCUSSION

Both small molecules and biologicals saw a major peak in revenue in 2021, followed by a decline in the subsequent years. However, the total revenue generated by small molecules has consistently been higher than that of biologicals over the study period. The higher revenue for small molecules suggests they remain the preferred treatment option in South Africa, primarily due to their lower costs and broader accessibility. In contrast, biologicals are often limited by high costs and reliance on medical insurance coverage, which restricts their adoption amongst patients.

Despite the potential benefits and initial growth, several challenges hinder the broader adoption of biological medicines in South Africa. The development and production costs of biologicals are significantly higher than those for small molecules. This high cost translates to increased prices for patients, making these treatments less accessible. Access to biological medicines is often contingent on having medical insurance, which is frequently inadequate or unavailable for many patients in South Africa. This reliance on insurance limits the population that can benefit from these advanced therapies. The complexities involved in producing biological medicines constrain local manufacturing capabilities. Limited production capacity leads to supply issues and further exacerbates accessibility problems.

The biotherapeutic industry faces challenges related to client retention and operational efficiency, which can impact market stability and growth. There is a lack of comprehensive education among healthcare providers regarding the benefits and safety of biologicals compared to traditional small molecules. This knowledge gap can influence prescribing practices and patient access.

The under-utilization of biologicals has significant implications for patient care in South Africa. While biological medicines offer targeted therapies for various chronic diseases, such as rheumatoid arthritis and certain cancers, their high costs and limited availability prevent many patients from accessing these potentially life-saving treatments.

Moreover, the slow adoption of biologicals contrasts with global trends where these therapies have become integral components of treatment regimens for non-communicable diseases. In South Africa, the reliance on small molecules persists, despite evidence suggesting that biologicals could provide enhanced therapeutic outcomes.

To address these challenges and enhance the growth of biological medicines in South Africa, a review and improvement of regulatory frameworks to facilitate quicker approval processes for new biologicals and biosimilars is necessary. Ensuring that these products meet safety and efficacy standards while also being accessible is crucial. The implementation of pricing strategies that promote affordability for patients, while the collaboration of public entities with pharmaceutical companies and insurance providers, could help develop better reimbursement policies for biological treatments. An increase in educational initiatives aimed at healthcare providers to increase awareness about the efficacy and safety of biologicals could improve prescribing practices and encourage more healthcare professionals to consider biological therapies as viable treatment options. Furthermore, more investment in local manufacturing capabilities for biological medicines to reduce costs and improve supply chains would make a significant impact on the affordability of biologicals. This could also enhance job creation within the pharmaceutical sector. Lastly, increasing the awareness of biosimilars among healthcare providers and patients to encourage their use as cost-effective alternatives to originator biologicals will increase the adoption of these medicines.

5. CONCLUSION

The growth of biological medicines in South Africa presents both opportunities and challenges. While there has been some progress in expanding treatment options through biologicals, significant barriers remain that limit their adoption and accessibility. Addressing these challenges through regulatory reforms, improved pricing strategies, enhanced education, investment in local manufacturing, and promoting biosimilars will be crucial for realizing the full potential of biological therapies in improving patient outcomes. By fostering an environment conducive to the growth of biological medicines, South Africa can enhance its ability to make innovative medicines more accessible to the general population and grow the pharmaceutical landscape.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this study.

CONFLICT OF INTEREST

None.

DISCLAIMER

The research was conducted independently and is not affiliated with, sponsored by, or representative of any company. All views expressed are those of the authors.

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