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Original Article

Comprehensive bibliographic study of the framework of complex generic drugs

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الملخص

أهداف البحث: لوحظ مؤخرا نمو هائل في التحليل الببليوغرافي. ارتفع الطلب على الأدوية الجنيسة بشكل كبير على مدى العقود الثلاثة الماضية، ويبدو أن السوق مشبع. ونتيجة لذلك، تركز شركات الأدوية على الأدوية الجنيسة المعقدة لتحسين الطلب من المرضى والنمو الاقتصادي. تسلط هذه الورقة الضوء على الاتجاه البحثي الحالي للأدوية الجنيسة والمعقدة من خلال التحليل الببليوغرافي.

طريقة البحث: تم استرداد جميع المستندات المتعلقة بالأدوية الجنيسة والمعقدة من قاعدة بيانات "سكوبس" من ٢٠١٣-٢٠٢٣. بعد تطبيق معايير الإدراج، تم اختيار ١٤٤٠١٥ ورقة بحثية عن الأدوية الجنيسة و ٨٤ ورقة بحثية عن الأدوية الجنيسة المعقدة للدراسة. تم استخدام برنامج مايكروسوفت اكسل و "فوس فيوير" لتمثيل الدراسة التفصيلية والبيانات الخاصة بالأدوية الجنيسة المعقدة.

النتائج: تم تحديد المنشورات المتعلقة بالأدوية الجنيسة والمعقدة وفحصها ومقارنتها وتلخيصها لتوفير نظرة ثاقبة لاتجاهات البحث ونطاقات المستقبل. من عدد المقالات التي تم الحصول عليها، من الواضح أن المنشورات الجنيسة أصبحت مشبعة، وأن عدد الدراسات الجنيسة المعقدة يتزايد بشكل كبير. تركز الأسواق المنظمة وشبه المنظمة الآن بشكل كبير على الأدوية الجنيسة المعقدة. للتغلب على هذا الصراع، مولت الأسواق المنظمة مثل الولايات المتحدة أدوية جنيسة أكثر تعقيدا من الأدوية الجنيسة البسيطة. يشير مساهمة المؤلف إلى أن المؤلفين الرئيسيين الذين ركزوا على الأدوية الجنيسة بدأوا مؤخرا في العمل على الأدوية الجنيسة المعقدة في نفس الوقت. وفقا لتحليل المجموعة، تركز الأدوية الجنيسة البسيطة بشكل أكثر شيوعا على جودة الحياة. في المقابل، قدمت مجموعات الأدوية الجنيسة المعقدة تحديات في مراحل مختلفة، مما ألقى الضوء على نموها.

الاستنتاجات: تقدم هذه الدراسة نظرة عامة شاملة على تطور الأدوية الجنيسة المعقدة ونمو السوق. علاوة على ذلك، يركز الباحثون على الأدوية الجنيسة المعقدة أكثر من الأدوية الجنيسة. من ناحية أخرى، قد يكون نمو الأدوية الجنيسة المعقدة أسرع بسبب التحديات الملحوظة في البحث وتطوير التركيبات واللوائح. ويمكن توقع ثورة عالمية في مجال العلوم الصيدلانية إذا تعاون جميع خبراء أصحاب المصلحة وركزوا على هذا الدواء الجنيس القادم.

الكلمات المفتاحية: القياس الببليومتري؛ تحليل المجموعات؛ جودة الحياة؛ التحديات؛ اللوائح

Abstract

Background: Recently, extensive growth in bibliometric analysis has been observed. The demand for generic drugs has markedly increased in the past three decades, and the market appears to be saturated. Consequently, pharmaceutical companies are focusing on complex generics to improve patient demand and economic growth. This article highlights current research trends in generic and complex generic drugs through bibliometric analysis.

Method: All documents from 2013 to 2023 associated with generics and complex generics were retrieved from the Scopus database. After application of the inclusion criteria, 144,015 articles on generics and 84 articles on complex generics were chosen for inclusion. Microsoft Excel and VOSviewer software were used to represent detailed studies and data on complex generics.

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Results: Publications associated with generic and complex drug products were identified, examined, compared, and summarized, to provide insights into trends and the future research scope. The number of obtained articles clearly indicated that the number of publications on generics is becoming saturated, whereas the number of complex generic studies is markedly increasing. The top regulated and semi regulated markets are now highly focused on complex generics. Concordantly, regulated markets such as those in the United States have funded more complex generics than simple generics. According to cluster analysis, studies on simple generics frequently focused on quality of life. In contrast, the clusters of studies on complex generics indicated challenges at various stages, thus shedding light on the growth of this field.

Conclusion: This study provides a comprehensive bibliographic overview of the development of complex generic drugs and market growth. Researchers are currently more focused on complex generics than generics. A global revolution in pharmaceutical science can be expected if all stakeholder experts collaborate and focus on generic version of complex drugs.

Keywords: Bibliometric; Challenges; Cluster analysis; Quality of life; Regulations

Introduction

A generic drug is a prescription medication made to be identical to an innovator product, produced without a license from the innovator company, and sold after the expiration of the innovator product's patent or other exclusivity rights. Generic medications are markedly less expensive than branded drugs, yet provide nearly identical quality, safety, and efficacy. Given their therapeutic results and affordability, generics have provided windfalls for the healthcare system in many countries.[1] Most people in developing countries require greater access to crucial pharmaceuticals. Generic drugs are important for increasing access to essential medical commodities, because they provide the same quality, efficacy, safety, and therapeutic results as branded drugs at lower cost.[2] Although generic medications are relatively inexpensive to create, competition among generic producers usually drives their prices far below those that purchasers would be willing to pay for branded products.[3] The Generic Drug User Fee Act (GDUFA) was enacted into law as part of the US Food and Drug Administration (FDA) Safety and Innovation Act on July 9, 2012. The GDUFA is intended to improve the predictability of the generic drug application review process, and ensure rapid delivery of safe and effective generic pharmaceuticals to Americans. According to the findings of Pardhe's survey, the GDUFA has aided in increasing the manufacturing and export volumes of generic medication abroad, and has had favorable effects on the Indian pharmaceutical industry and economy.[5,6] The coronavirus pandemic has also highlighted the importance of providing inexpensive health care to all people.[7] *Patient satisfaction* is an excellent approach that helps pharmaceutical organizations maintain a competitive atmosphere. During the COVID-19 pandemic, patients relied more on generic drugs than branded medicines.[8] In a study conducted in 17 countries aimed at determining the affordability, availability, and costs of critical diabetes treatments.It found that, despite the presence of lower-priced alternatives, consumers relied on branded drugs, because high-income countries were able to pay the prices. Consequently, generic forms of complex drugs are scarce.[4]

The generic versions of complex drugs are called complex generics, super generics, or hybrid drugs. Complex drugs combine two or more active components or technologies to treat complex diseases.[9] Although "complex" generics lack a specific definition, they can be informally referred to as generic medications for which therapeutic equivalence is highly challenging to demonstrate, according to the Orange Book.[10] The FDA uses the term "complex product" to describe products with one or more of the following five traits, according to the "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018−2022 letter" ("GDUFA II Commitment Letter")[11,12]: complex active ingredients, a complex drug delivery pathway, a complex formulation, a complex drug-device combination, and a combination of complex products. The FDA provides definitions and examples of complex products in the draft guidance ("Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA").[13,14] Two categories of complex drug products can be defined: (a) goods with complex active components or complex formulations for which both PE and BE are challenging to demonstrate, and (b) goods with complex dosage forms, complex drug-device combinations, or complex delivery routes that are difficult to establish. The development of instruments and methods for characterizing complex drugs is an ongoing process. The functionality, characterization, and techniques of these products may differ from those of other therapeutic products. The Indian pharmaceutical market has surpassed the rest of the world in terms of fixed-dose combinations (FDCs).[15] More than 6000 FDCs have been reported to exist in India.[16] Difficulties in analytical methods have limited the production of low-cost generic forms of FDCs.[17] The hurdles in demonstrating efficacy of product, process control, validation, and technique justification must crucially be overcome.[18] Two-chamber pacemakers are approximately twice as expensive as single-chamber pacemakers.[19] Thus, developing complicated medical devices such as heart stents and pacemakers provides significant benefits to the public. Complex generics are expected to achieve substantial growth in the next several years.

In this study, a comparative bibliometric analysis of the peer-reviewed literature was performed to evaluate and compare the growth paths for generics and complex generics. Numerous variables were included in the analysis to elucidate the growing prominence of complex generics over generics, and to focus on achieving better future growth of complex generics.

Methods

Study design

Publications in the Scopus database (https://www.scopus.com, Elsevier, Amsterdam, the Netherlands) were searched on May 16, 2024. All possible articles were searched with suitable keywords for generics and complex generics separately. Keywords were separated with various Boolean search operators (ORs) to maximize the number of relevant publications. For generics, the search was based on the keywords "Generic drug" OR "Generics" OR "Generic*." Documents associated with complex generics were searched with the keywords "Complex generic," "super generics," OR "hybrid generics." The search returned comprehensive results associated with generics in various domains. Strict inclusion and exclusion criteria were implemented. The search results were refined by restriction of the search to the timeframe of 2013–2023, during which the growth of complex generics was particularly active. The search was also limited to certain document types (original articles, review articles, book chapters, and conference articles) and source types (journals, books, book series, and conference proceedings). Short survey reports, meeting abstracts, editorial content, letters, and notes were excluded from the study. Language restrictions were applied, wherein articles published in languages other than English were excluded (n = 4,562 for generics and n = 14 for complex generics). The following data were retrieved for analysis: authors with a relevant number of publications within the prior 3 years, keywords, countries/regions affiliations, and funding organizations. All information was exported from the Scopus database into CSV format as a reference record for further data analysis. Version 16.1.8 of VOSviewer software was used to generate bibliometric network maps (cluster or bursts analysis) of the most frequently used keywords.

Sample size

This study covered approximately 1,44,015 publications in the case of generic drug products (including 92,529 articles, 6,205 reviews, 6,430 book chapters, and 38,851 conference articles) and 84 publications in the case of complex generic drug products (including 44 articles, 17 reviews, 8 book chapters, and 15 conference articles).

Results

During our search, the Scopus database revealed many results (306,653 articles on generics; 179 articles on complex generics); of these, 144,015 documents associated with generics and 84 documents associated with complex generics met the inclusion criteria and were considered for analysis. A total of 162,638 (generic) and 95 (complex generics) articles were excluded from the analysis. The flowchart (Figure 1) indicates the selection parameters and publication trends. Figure 2 shows the top countries with the most research output. The United States (US) contributed the most articles associated with both generics (23 %) and complex generics (36 %). Countries such as Europe, India, China, and France also showed an increasing focus on upcoming specialty generic drugs.

We further profiled institutions substantially influencing the creation and expansion of generic medicinal products. Among the top funding institutions for generics and complex generics, the US and European institutions provided more funds, sponsor development, and research. The obtained data demonstrated substantial cooperation among organizations within the same country (Figure 3). Hence, the figures depict sponsorship by country rather than institute. For the author analysis, only the common authors whose work in 2021–2023 specialized in complex generics were selected. A comparison was conducted for the common authors in these years.

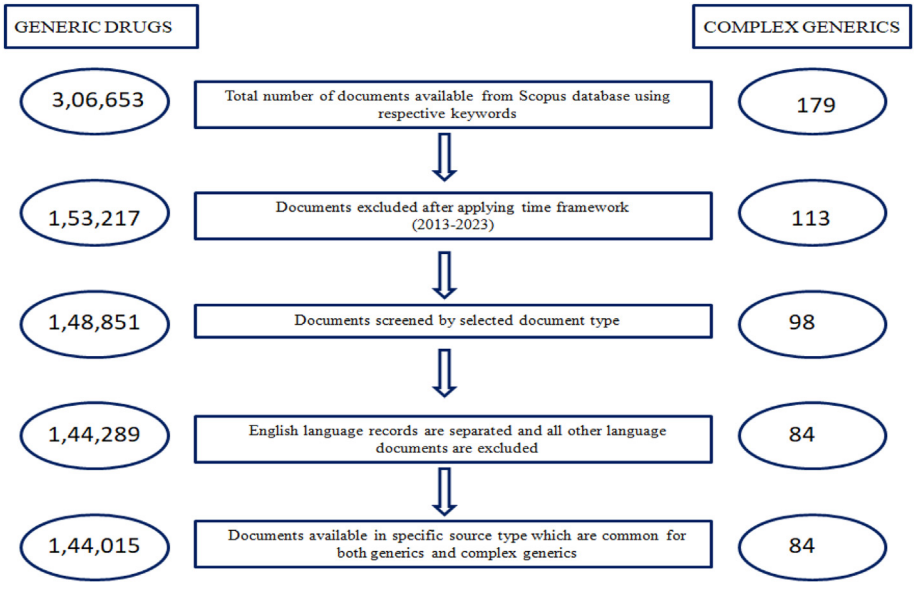

Figure 1: Systematic sorting of documents and trends in publications on generics and complex generics.

Figure 2: Top five countries with the most publications.

Seven authors worked on generics and complex generics (Figure 4). A comparison of their publications in these specific years revealed that some authors, such as Lionberger, Jiang, and Avora, stopped focusing on generics and have moved to complex generics. The studies indicated that work on complex generics has recently expanded to a greater extent than work on generics.

Cluster analysis was performed separately on the keywords extracted from Scopus to verify global research and development, and identify challenges to the growth of complex generics, which appeared to be slow and steady (Figure 5a and b). The cluster analysis for generics (Figure 5a) revealed how quality-of-life improvement factors are interlinked with socioeconomic growth, because of the cost-effectiveness of the medicine supply. The findings also highlighted the links among risk assessment factors to ensure the safety and efficacy of generic drugs. The four connected nodes highlight the growth of generics worldwide. The nodes and subnodes of complex generics are interconnected, thereby revealing the keywords crucial for the future growth of complex generics. The blue nodes indicate the stakeholders or related departments where the studies were conducted, and drug approval challenges such as lack of classification, need for nonhuman studies, and

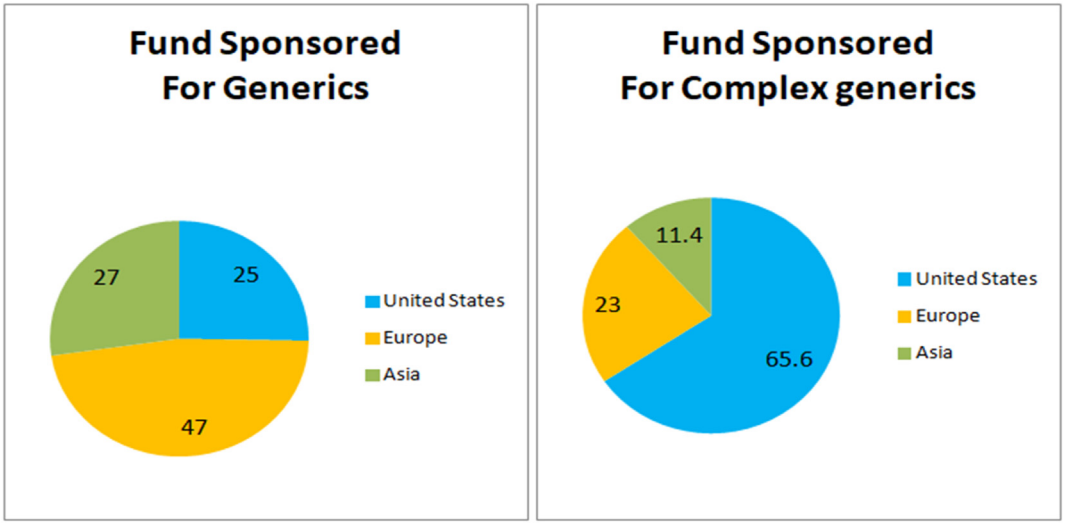

Figure 3: Percentage of funds provided by the top ten funding organizations.

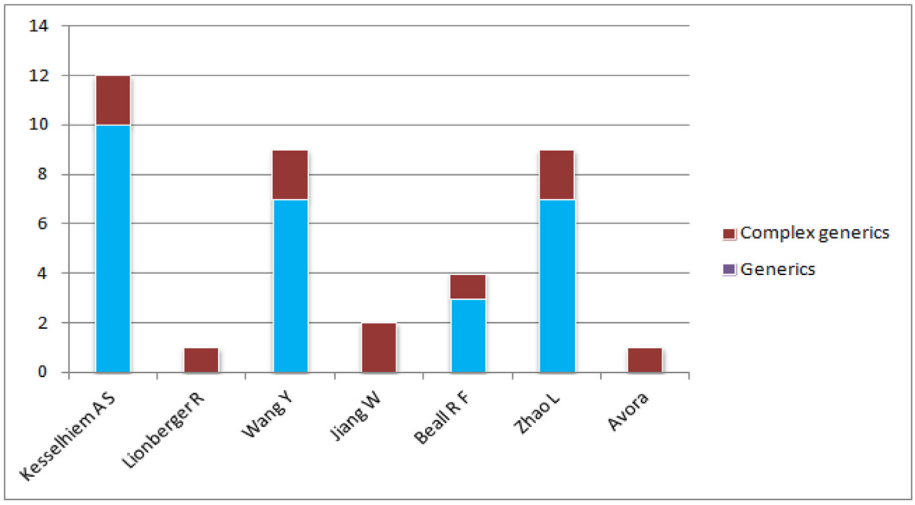

Figure 4: Authors with publications in the years 2021–2023.

knowledge gaps between complex versus simple generics. The red nodes indicate the primary regulatory agency, the US FDA, which has focused on increasing of the supply of complex generics. Moreover, our findings demonstrated how complex generics are affected by formulation, patent exclusivity, drug cost, and drug marketing differences. The green clusters shed light on analytical challenges such as drug development stages, formulations, drug delivery systems, variations in particle size, therapeutic equivalence, and the development of models. Biological models, such as physiologically based pharmacokinetic models, are expected to help decrease development and time costs, and rapidly increase supply. A characterization of the top ten cited publications on complex generics (Table 1) highlighted the rationale underlying their gradual development.

Discussion

The findings from our quantification and comparison analysis clearly highlighted the increasing demand for complex generics in the pharmaceutical landscape. Our analysis of selection parameters indicated that the number of generic drugs researched over several decades has increased approximately 47 % in the past 10 years. In contrast, complex generics, which have been researched for less than a decade, have also achieved the same growth rate of 47 % as generic drugs globally. According to the list of the global studies of generic drugs and complex generics, the countries contributing the most to related research, such as the US, are moving toward studying complex generics, thus hinting at future scope and development. A comparison of funding agencies worldwide indicated that investment in generics and complex generics tends to increase before a surge in sponsorship activity. Among these, the US has made the most contributions toward the development of complex generics. The FDA alone contributed nearly 40 % of the research funds for complex generics in the past several years. In 2020, the University of Maryland and the University of Michigan were awarded a 5-year grant by the FDA to establish a research center for complex generics.[30] The establishment of the Center for Research on Complex Generics highlights the subsequent growth of complex generics. Although researchers are aware of the potential and possible developments of complex generics, a study of authors and their works over the last three years indicates that their attention is not solely focused on generics; as per the bibliographic mapping of keywords, most generic drugs focus on quality along with economic status a high preference for formulation combinations, drug development, and marketing. Focuses included drug safety and efficacy, to demonstrate bioequivalence to reference or standard drugs. Few changes in other parameters, such as physiochemical properties, clinical efficacy, and follow-up studies, have been reported.

In contrast to generics, complex generics focus on different parameters, which are considered uniquely challenging factors. These factors include drug approval, bioequivalence, drug development, drug delivery systems, and physicochemical and therapeutic equivalency. The cluster analysis also revealed that biological models can be used to overcome these challenges. The outcomes of the top-cited complex generic articles emphasized challenges including development, manufacturing, characterization, evaluation, and regulatory challenges. According to the cited journals, only limited steps have been implemented to overcome these challenges Our findings indicate a need for further research in complex generics, given that developments in the economic impact of complex generics would deliver substantial social benefits by improving patient outcomes and satisfaction. In addition, a high-quality healthcare regulatory system, cooperation, and collaborative activities should achieve fruitful outcomes. Furthermore, our findings suggest that

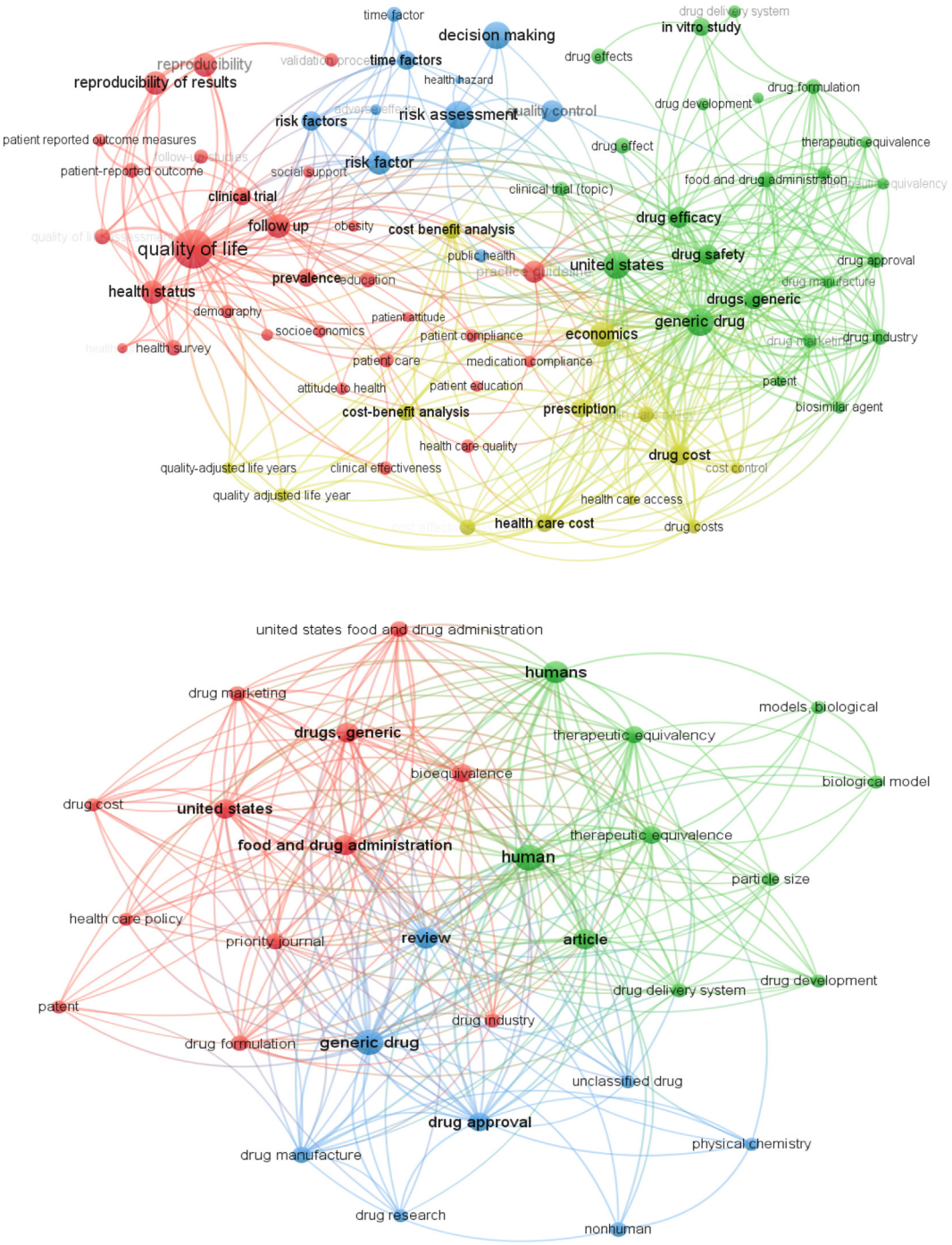

Figure 5: a: Cluster analysis of keywords associated with generic drugs. b: Cluster analysis of keywords associated with complex generics.

research and development on complex generics will greatly expand in the coming years and achieve outcomes surpassing those of generics, and that globally renowned research organizations show increasing focus on, and contribution toward, achieving better health care outcomes globally.

Limitations

Data availability led to several limitations in this study. Other databases, such as Web of Science, do not provide access to specific articles in the study. Only ten articles in Web of Science contained the term "complex generic," thus precluding bibliometric analysis. Because complex generics are a newly emerging topic, relatively few articles have been published in this field. Scopus is a comprehensive multidisciplinary database that provides numerous articles on this topic. The CSV file is user-friendly in VOSveiwer but not Web of Science. Further limitations were introduced by the free version of the bibliographic software. An additional limitation is that non-English literature was not included in

Table 1: Characterization of the top ten cited complex generic publications.

Author	Year of publication	Citation	Outcome
O'Brien M. N. et al.[20]	2021	44	This article focuses on the most common technical and technology-specific challenges in long-acting injectables, and emphasizes the importance of collaboration among industry, academia, and regulatory bodies to advance opportunities.
Madabushi R. et al.[21]	2022	36	This article presents an effective approach for guiding the design of clinical trials, formulating new compounds, and planning in vivo research, known as "model-informed drug development." This approach may accelerate the approval process and enable cost savings, even for complex generic medicines.
Lim Y. W. et al.[22]	2022	26	This article explains development, manufacturing, characterization challenges, and complications of PLGA-based long-acting injectables/ implantables. Strategies for overcoming these obstacles in terms of drug release and encapsulation are emphasized.
Rouse R. et al.[23]	2018	26	This article focuses on the development and validation of biomarkers, novel humanized animal models, and translational predictive safety, by combining novel approaches to accelerate the development of complex generics.
Newman B. et al.[24]	2020	18	This article focuses on the FDA's weight-of-evidence strategy to address the scientific and regulatory challenges concerning generic oral inhalation drug products. The BE of these products is affected by numerous factors (formulation, site of action, device performance, and patient population).
Chockalingam A. et al.[25]	2019	13	This article describes the complex nature of certain topical ophthalmic products and how the challenges associated with establishing BE pose barriers to rapid regulatory approval for generic versions of the product. The sampling protocol for evaluation in rabbit models to replace clinical endpoint BE studies is described.
Lee C.-Y. et al.[26]	2016	12	This article describes the influences on generic manufacturers making product development decisions according to various factors, including those affecting the developmental stage.
Jadhav P. et al.[27]	2022	8	For complex generic inhalable regulatory approval, Q3 structural equivalency is essential. Thus, this article examines advanced and reliable analytical methods, as well as the benefits and drawbacks of products in a strengths, weaknesses, opportunities, and threats (SWOT) study.
Lunawat S. et al.[28]	2020	8	Although investment in complex generics is high, the market is enormous, given the few generic competitors. This study focuses on the present regulatory frameworks that the US, EU, and Canada have used to allow market entry of complex generics. Additionally, it discusses the regulatory differences among the three agencies in light of complex generics.
Zagalo D.M. et al.[29]	2022	7	The lack of specific and consistent regulatory guidelines (inconsistency across different regulatory markets or approaches within the same class of products) sheds light on the research and regulatory gaps in the establishment of BE, and indicates the need to develop a specific regulatory pathway.

this analysis. The currently available data might not accurately reflect industrial operations or patent-protected procedures, because they came primarily from top research universities/institutions.

Consequently, crucial research from non-traditional or gray literature sources might potentially have been ignored. Each class of complex generics may be included in the search strategy in future research. Despite these limitations, this study suggests areas for additional investigation and real-world applications, and highlights the need for standardized guidelines to overcome obstacles and improve research results.

Implications for the pharmaceutical industry

Numerous pharmaceutical industries are focusing on complex generics, given that the market for generic growth has become saturated. Increasing accessibility to complex generics has major consequences for healthcare professionals. For severe disease conditions in particular, complex generics can address patients' unmet needs and improve access to affordable pharmaceuticals in developing nations. Healthcare professionals' awareness of complex generics can provide better therapeutic equivalency and aid in appropriate treatment decisions during navigation of the regulatory and developmental landscape; aid in optimization of product portfolios; and take advantage of the increased demand for complex generics. Pharmaceutical organizations in complex generic studies encounter opportunities, challenges, and regulations.

Strengths and limitations

An overview of the published literature on generics and complex generics was presented, including details on the

publications per year, countries focusing on research on these products, funding institutions, authors, citation index values, top journals, and keywords. The results underscore the need for further research on complex generics and indicate a deficiency in data in this area. A slight chance exists that the findings might change if additional repositories were included in the data-gathering process.

Conclusion

This comparative bibliometric analysis highlights how the generic drug market is changing and how complex generics are becoming a key component of affordability and innovation. We highlighted market growth in various countries, dynamic institutions, authors, publications, and keywords, thus revealing the current status of simple and complex generics. This analysis sheds light on how policymakers, healthcare providers, and industry stakeholders navigate the changing generic market. Complex generics are becoming increasingly popular, and their future influence on healthcare cannot be ignored. Our findings may prompt researchers to plan research aimed at improving and increasing the manufacturing and marketing of complex generics.

Recommendations

On the basis of the results of this analysis, we recommend further investigation of complex generics to increase the availability of affordable medicines to the public. However, steps must be taken to overcome challenges in manufacturing, formulation, and the market approval approach. In addition, robust research collaboration, including governments, businesses, and academic institutions, should be conducted to produce a harmonized set of guidelines.

Source of funding

No funding was required.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The data were collected from subscription databases. Because no human or animal related work was conducted, ethical approval was not required for this study.

Author contributions

Virendra S Ligade: Conceptualization, Supervision, and Manuscript reviewing; Amatha Sreedevi: Original draft preparation, Data collection, Visualization, Comparison; Shailee Dewan: Validation of comparison results, Manuscript reviewing and editing. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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