Analysis of Class II Patent Claims Data

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Abstract

[Objective] To investigate the existing problems in China' s Marketed Drug Patent Information Registration Platform and propose strategies that generic drug enterprises need to adopt. [Methods] Using data mining, an overall analysis and case-by-case comparison were conducted on two types of patent declaration data in China' s Marketed Drug Patent Information Registration Platform. [Results] Ten candidate chemical generic drug varieties are recommended. [Limitations] Comparative research between China' s drug patent linkage data and that of overseas countries. [Conclusion] The absence of an ex officio error-correction mechanism in China's Marketed Drug Patent Information Registration Platform constitutes a major defect in China' s drug patent linkage system.

Full Text

Analysis of Type II Patent Declarations for Generic Drugs in China

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Abstract:
[**Objective**] This study investigates existing problems on China' s drug patent information registration platform and proposes strategies for generic pharmaceutical companies.
[**Methods**] Through data mining, we conducted a comprehensive analysis and case comparison of Type II patent declaration data on China' s drug patent registration platform.
[**Results**] We recommend ten chemical generic drug varieties for selection.
[**Limitations**] Comparative study of drug patent linkage data between China and overseas countries.
[**Conclusion**] The lack of an error correction mechanism for ex officio review on

the Chinese drug patent information registration platform represents a major flaw in China' s drug patent linkage system.

Keywords: Drug Patent Declaration; China' s Drug Patent Registration; Drug Patent Linking System

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Since 1985, China has implemented patent-related legal systems, and the drug patent linkage system was constructed based on lessons from foreign experiences. In 2007, the former State Food and Drug Administration revised the *Drug Registration Administration Measures*, gradually introducing the concept of a drug patent linkage system to the public. Since 2017, China has attempted to build a complete drug patent linkage system. To protect both drug innovation and generic drug development, the State Council clarified that applicants must make declarations regarding corresponding registered drug patents. The fourth revision of the *Patent Law* in 2020 introduced solutions for drug patent disputes into fundamental law for the first time, accelerating the establishment of patent declaration mechanisms. On July 4, 2021, the *Measures for the Implementation of the Early Resolution Mechanism for Drug Patent Disputes (Trial)* was adopted, with Articles 6 and 12 stipulating the patent declaration system for generic drug applicants, who must submit declarations for each relevant patent of the reference listed drug registered on the information platform when applying for generic drug marketing authorization.

The classification of patent declarations includes: **Type II Declaration**, where the relevant patent rights for the reference drug listed on China's drug patent information registration platform have expired or been declared invalid, or where the generic applicant has obtained a license from the patent holder; **Type III Declaration**, where relevant patents for the reference drug are listed on the platform and the generic applicant commits not to market the generic drug before the expiration of the corresponding patent term; and **Type IV Declaration**, where the relevant patent rights for the reference drug listed on the platform should be declared invalid, or the generic drug does not fall within the scope of the relevant patent protection. With these provisions, China' s drug patent linkage system has been fully established [**?**]. Currently, China' s early

resolution mechanism for drug disputes remains in its infancy, and research on the drug patent declaration system is not yet mature. Numerous scholars have focused on macro-level discussions of the drug patent linkage system [**?**] without specifically examining drug patent declarations or analyzing the issue from the perspective of China' s drug patent information registration platform to propose systematic recommendations based on data. This reflects a relatively singular research methodology [**?**][**?**]. Consequently, understanding of generic drug patent declarations may be biased. Integrating data analysis from China' s drug patent information registration platform can undoubtedly enhance the reliability of literature analysis conclusions and enrich research on drug patent protection in China [**?**]. This study examines Type II drug patent declaration data to explore trends in generic Type II patent declarations, supported by extensive actual data, and discusses the rationality and necessity of establishing a more systematic patent declaration system from perspectives including China' s pharmaceutical market and existing problems. Simultaneously, we analyze potential issues in China' s generic drug Type II patent declaration system to provide data support for continuous improvement of the generic drug patent declaration system under China' s drug patent linkage framework and decision-making references for generic companies facing challenges posed by this system.

1. Data Sources and Methods

We obtained legal and policy information on China' s drug patent declaration system from the official website of the National Medical Products Administration (NMPA). Drug marketing authorization information was sourced from the NMPA Data Query Portal (https://www.nmpa.gov.cn/datasearch/home-index.html?79QlcAyHig6m=1659567530287#category=yp) and the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm). Type II patent declaration registration data for Chinese listed drugs was obtained from the China Listed Drug Patent Information Registration Platform (https://zldj.cde.org.cn/home, hereafter referred to as "the Platform"). Relevant patent information was obtained from the China National Intellectual Property Administration (CNIPA) (https://www.cnipa.gov.cn/col/col1510/index.html). The retrieval cutoff date was March 31, 2023, with some information corrected until August 31, 2023.

2.1 Overall Analysis of Type II Patent Declaration Data

Between July 9, 2021, and March 31, 2023, Type II patent declarations involved 44 generic drug names from 102 different generic manufacturers. By registration classification, there were 320 chemical drug Category 4 applications, 12 chemical drug Category 5.2 applications, and 1 therapeutic biologic application, totaling 333 Type II patent declarations. During data collation, we discovered that four original drug patent information listings had been withdrawn, yet generic companies still submitted Type II patent declarations (Table 1). In

some cases, the patent information in Type II declarations did not match the original drug's patent listing. For instance, Jiangsu Wanhao Pharmaceutical Co., Ltd., Pingguang Pharmaceutical Co., Ltd., and Jiangxi Renqi Pharmaceutical Co., Ltd. submitted four Type II patent declarations for Pfizer' s levamlodipine besylate tablets (2.5mg, 5mg) regarding patent ZL01140027.7, while the original drug' s patent listing showed CN202110353060.1 for ShiHuiDa Pharmaceutical Group (Jilin) Co., Ltd. (2.5mg, 5mg), titled "Composition Containing Levamlodipine Besylate Hydrate and Preparation Method Thereof," expiring on November 7, 2039. These data discrepancies may lead to post-market litigation burdens for generic drugs. Some Type II declarations contained errors. For example, Orion Group listed patent CN00812645.3 for levosimendan injection on the Platform, yet four generic companies submitted Type II declarations for levosimendan injection regarding two patents: CN00812645.3 and CN90100645.9 (5ml:12.5mg). Notably, Nanjing Chia Tai Tianqing Pharmaceutical Co., Ltd.' s approach to patent declaration for sacubitril/valsartan sodium tablets warrants examination. Novartis listed three patents on the Platform: CN200680001733.0, CN201110029600.7, and CN201210191052.2, with CN200680001733.0 partially invalidated. For this patent, Nanjing Chia Tai Tianqing simultaneously submitted both Type II and Type III declarations, raising questions about the effectiveness of Type II declarations for partially invalidated patents and how generic companies should limit their patent declaration claims.

2.2 Type II Patent Declarations for Therapeutic Biologics

Shandong Boan Biological Technology Co., Ltd. submitted a Type II patent declaration on July 30, 2021, for Amgen' s therapeutic biologic denosumab injection 120mg (S20190025) regarding patent CN201310052370.5 (anti-OPGL antibody). This patent had already been announced as terminated before the Type II declaration was submitted.

2.3 Case Analysis of Type II Patent Declarations for Chemical Generic Drugs

We analyzed generic drugs with numerous Type II patent declarations to provide references for generic drug selection.

Table 1: Drug Varieties with Withdrawn Patent Information Listings That Received Type II Patent Declarations

Generic Manufacturer	Withdrawn Patent Listing
Guilin Nan Pharmaceutical Co., Ltd.	ZL200480037612.2
Jiangsu Huayang Pharmaceutical Co., Ltd.	ZL201010508824.1
Jiangxi Qingfeng Pharmaceutical Co., Ltd.	ZL201110304983.4

Generic Manufacturer	Withdrawn Patent Listing
Qilu Pharmaceutical (Hainan) Co., Ltd.	ZL201210155386.4
Shanghai Desano Biopharmaceutical Co., Ltd.	ZL201010113414.7
Shijiazhuang No. 4 Pharmaceutical Co., Ltd.	ZL02827814.3
Sichuan Pharmaceutical Preparation Co., Ltd.	(Phosphoric acid tedizolid tablets)
Yangtze River Pharmaceutical Group Jiangsu Zilong Pharmaceutical Co., Ltd.	(Phosphoric acid tedizolid for injection)
Jiangsu Haosen Pharmaceutical Group Co., Ltd.	(Febuxostat tablets)
Sichuan Pharmaceutical Preparation Co., Ltd.	(Aprepitant capsules)

(1) Empagliflozin Tablets

Empagliflozin tablets are highly selective SGLT-2 inhibitors for improving glycemic control in type 2 diabetes patients. According to MENET data, combined sales across China' s three major terminals and six markets (statistical scope detailed in the appendix) have grown rapidly in recent years, exceeding 600 million RMB in 2022 with a growth rate near 40%. Public hospital terminals (urban public hospitals + county-level public hospitals) now account for over 68% of sales, representing the primary market, while retail pharmacy terminals (urban physical pharmacies + online pharmacies) comprise approximately 23%, and public primary healthcare terminals (urban community centers + township health centers) less than 9%. As of August 16, 2023, marketing authorization holder Boehringer Ingelheim obtained approval for empagliflozin tablets (10mg, 25mg; National Drug Approval Numbers HJ20170351, HJ20170352) in China. On June 29, 2021, Boehringer Ingelheim listed three patents on the Platform: CN201310368328.4, CN201310379906.4, and CN201310414119.9, all declared invalid before the Type II patent declarations were submitted. Twelve generic companies submitted 51 Type II generic patent declarations for empagliflozin tablets (10mg, 25mg) (as of March 31, 2023), with Hangzhou Huadong Medicine Group Zhejiang Huayi Pharmaceutical Co., Ltd. (25mg, National Drug Approval Number H20233704) and Lepu Pharmaceutical Co., Ltd. (10mg, 25mg, National Drug Approval Numbers H20233895, H20233894) receiving approval.

(2) Nintedanib Soft Capsules

Nintedanib soft capsules are selective immunosuppressants for treating idiopathic pulmonary fibrosis. MENET data shows global nintedanib sales exceeded $2 billion in 2020, with Chinese urban physical pharmacy terminal sales growing remarkably over 600% year-over-year, projected to exceed 40

million RMB in 2021 (193.73% growth). In 2022, Chinese sales reached 450 million RMB. As of August 17, 2023, marketing authorization holder Boehringer Ingelheim obtained approval for nintedanib soft capsules (100mg, 150mg; National Drug Approval Numbers HJ20170354, HJ20170355) in China. On June 28, 2021, Boehringer Ingelheim listed four patents: CN200980121067.8, CN201510660732.8, CN200580044703.3, and CN03817530.4, with the first three declared invalid before Type II declarations were submitted. Five generic companies submitted 26 Type II patent declarations for nintedanib soft capsules (100mg, 150mg) (as of March 31, 2023), with Qilu Pharmaceutical Co., Ltd. and Sichuan Kelun Pharmaceutical Co., Ltd. receiving approval (100mg, 150mg, National Drug Approval Numbers H20233841, H20233842, H20233582, H20233583).

(3) Rivaroxaban Tablets

Rivaroxaban tablets are anticoagulants for treating and preventing recurrence of venous thromboembolism (VTE) in children. According to Pharmcube data, global rivaroxaban sales grew from 42.06 billion RMB in 2017 to 53.76 billion RMB in 2021, with a compound annual growth rate of 6.3%. During 2017-2021, rivaroxaban sales maintained continuous growth of 5%-9% year-over-year, with Chinese sales also growing rapidly from 970 million RMB in 2017 to 3.7 billion RMB in 2021 (39.6% CAGR). MENET data shows Chinese public medical institution terminal sales exceeded 2.5 billion RMB in 2019, growing over 20% year-over-year in the first half of 2020. As of August 18, 2023, marketing authorization holder Bayer obtained approval for rivaroxaban tablets (2.5mg, 10mg, 15mg, 20mg; National Drug Approval Numbers HJ20200024, HJ20181081, HJ20181082, HJ20181083, H20181085, J20180076, H20181084, J20180077, H20181086, H20181087) in China. On June 28, 2021, Bayer listed one patent on the Platform: CN200480035106.X, declared invalid before Type II declarations were submitted. Twelve generic companies submitted 22 Type II generic patent declarations for rivaroxaban tablets (2.5mg, 10mg, 15mg, 20mg) (as of March 31, 2023), with approvals granted to Lepu Pharmaceutical Co., Ltd. (10mg, National Drug Approval Number H20223861), Shandong Yuxin Pharmaceutical Co., Ltd. (15mg, 20mg, National Drug Approval Numbers H20233929, H20233595), Suzhou Easton Biopharmaceuticals Co., Ltd. (20mg, National Drug Approval Number H20233402), Suzhou Second Leaf Pharmaceutical Co., Ltd. (10mg, 15mg, 20mg, National Drug Approval Numbers H20223642, H20223253, H20223254), and Tianjin Institute of Pharmaceutical Research Co., Ltd. (2.5mg, 10mg, National Drug Approval Numbers H20234023, H20233194).

(4) Sacubitril/Valsartan Sodium Tablets

Sacubitril/valsartan sodium tablets are angiotensin receptor-neprilysin inhibitors for treating chronic heart failure. According to Pharmcloud data, Novartis' s sacubitril/valsartan exceeded $3.5 billion in global sales in 2021 (42% growth), driving core performance for Novartis. In China, sacubitril/valsartan (brand name: Entresto) entered the market in 2017 for heart failure, was included in the 2020 National Reimbursement Drug List, and

in June 2021 became the first approved treatment for essential hypertension in China. In 2021, hospital sales exceeded 2 billion RMB (177% growth). As of August 18, 2023, marketing authorization holder Novartis obtained approval for sacubitril/valsartan sodium tablets (50mg [sacubitril 24mg/valsartan 26mg], 100mg [sacubitril 49mg/valsartan 51mg], 200mg [sacubitril 97mg/valsartan 103mg]; National Drug Approval Numbers HJ20170362, HJ20170363, HJ20170364) in China. On November 15, 2021, Novartis listed three patents: CN200680001733.0, CN201110029600.7, and CN201210191052.2, with CN200680001733.0 partially invalidated and CN201110029600.7 declared invalid. CN201210191052.2 remains valid. Four generic companies submitted 18 Type II patent declarations for sacubitril/valsartan sodium tablets (as of March 31, 2023), with no approvals granted yet.

(5) Lurasidone Hydrochloride Tablets

Lurasidone hydrochloride tablets are antipsychotics for schizophrenia and depressive episodes in bipolar I disorder. MENET data shows sales exceeded 60 million RMB in the first half of 2022 across Chinese urban public hospitals, county-level public hospitals, urban community centers, and township health centers (collectively "Chinese public medical institutions"), with growth reaching 221%. As of August 18, 2023, marketing authorization holder Sumitomo Dainippon Pharma obtained approval for lurasidone hydrochloride tablets 40mg (National Drug Approval Numbers J20190006, H20190021, H20191009) in China. On January 12, 2023, Sumitomo updated two patents on the Platform: CN201010564784.2 and CN201010564784.2, both declared invalid before Type II declarations were submitted. Four generic companies submitted 14 Type II generic patent declarations for lurasidone hydrochloride tablets 40mg (as of March 31, 2023), with no approvals granted yet.

(6) Ceftazidime/Avibactam Sodium for Injection

Ceftazidime/avibactam sodium for injection is a cephalosporin anti-infective for complicated intra-abdominal infections, hospital-acquired pneumonia, and ventilator-associated pneumonia. MENET data shows national urban public hospital sales reached 404 million RMB in 2021 and 265 million RMB in the first half of 2022. As of August 18, 2023, marketing authorization holder Pfizer obtained approval for ceftazidime/avibactam sodium for injection 2.5g (National Drug Approval Number H20190038) in China. On June 18, 2021, Pfizer updated two patents on the Platform: CN01816700.4 and CN200710001595.2, with CN01816700.4 announced as terminated before Type II declarations were submitted. Seven generic companies submitted nine Type II patent declarations for ceftazidime/avibactam sodium for injection 2.5g (as of March 31, 2023), with no approvals granted yet.

(7) Diquafosol Sodium Eye Drops

Diquafosol sodium eye drops are P2Y2 receptor agonists for dry eye disease symptoms. According to Pharmcloud statistics, this dry eye medication market grew rapidly, with national hospital sales increasing 64% year-over-year in 2022, exceeding 100 million RMB and ranking among the top nine ophthalmic solu-

tions by product name. As of August 18, 2023, marketing authorization holder Santen Pharmaceutical obtained approval for diquafosol sodium eye drops 3% (5ml:150mg) (National Drug Approval Numbers HJ20181012, HJ20170378) in China. On February 15, 2022, Santen updated one patent on the Platform: CN02132100.0, declared invalid before Type II declarations were submitted. Five generic companies submitted seven Type II generic patent declarations for diquafosol sodium eye drops 3% (5ml:150mg) (as of March 31, 2023), with no approvals granted yet.

(8) Lenvatinib Mesylate Capsules

Lenvatinib mesylate capsules are multi-target receptor tyrosine kinase inhibitors for thyroid cancer and renal cell carcinoma. According to Pharmcloud' s national hospital sales database, sales exceeded 800 million RMB in 2021 (734.54% growth), projected to exceed 1 billion RMB in 2022. As of August 18, 2023, marketing authorization holder Eisai obtained approval for lenvatinib mesylate capsules (4mg, 10mg; National Drug Approval Numbers H20180052, HJ20200044, HJ20200045) in China. On February 15, 2022, Eisai updated two patents on the Platform: CN01819710.8 and CN201080030508.6, both declared invalid before Type II declarations were submitted. Four generic companies submitted ten Type II generic patent declarations for lenvatinib mesylate capsules (4mg, 10mg) (as of March 31, 2023), with no approvals granted yet.

(9) Levosimendan Injection

Levosimendan injection is a novel Ca^{2+} sensitizer for short-term heart failure treatment. MENET data shows sales approached 600 million RMB in Chinese public medical institutions in 2020 (13.58% growth). The product is in a rapid growth phase, with nearly 700 million RMB in the first three quarters of 2021. As of August 20, 2023, marketing authorization holder Orion Group obtained approval for levosimendan injection (5ml:12.5mg, National Drug Approval Number HJ20200028) in China. On July 28, 2021, Orion listed one patent on the Platform: CN00812645.3, announced as terminated before Type II declarations were submitted. Four generic companies submitted nine Type II patent declarations for levosimendan injection (5ml:12.5mg) (as of March 31, 2023), with no approvals granted yet.

(10) Rasagiline Mesylate Tablets

Rasagiline mesylate tablets are second-generation MAO-B inhibitors for Parkinson' s disease. Pharmcloud statistics show hospital sales reached 56.21 million RMB in 2021 (163.36% growth), approaching domestic selegiline sales (65.76 million RMB in 2021). In 2022, sales exceeded 100 million RMB (88% growth), surpassing selegiline (63.9 million RMB in 2022), demonstrating strong momentum. As of August 20, 2023, marketing authorization holder Teva obtained approval for rasagiline mesylate tablets (1mg, National Drug Approval Numbers HJ20170336, HJ20170337) in China. On July 5, 2021, Teva listed two patents on the Platform: CN200680005518.8 and CN96195710.7, with CN96195710.7 announced as terminated before Type II declarations were submitted. Seven generic companies submitted eight Type II patent declarations for rasagiline

mesylate tablets 1mg (as of March 31, 2023), with no approvals granted yet.

Based on all Type II patent declaration data for chemical drugs, traditional Chinese medicine equivalents, and biosimilars registered on the Platform, Type II declarations submitted between July 9, 2021, and March 31, 2023, involved Category 4, Category 5.2, and Category 3.3 therapeutic biologics, regardless of whether the original drug was approved domestically. Generic companies submitting Type II declarations are gradually obtaining approvals, marking China's drug patent linkage system has entered substantive implementation and achieved practical results. However, data collation revealed that four original drug patent information listings had been withdrawn but still received Type II declarations (Table 1). For levamlodipine besylate tablets (2.5mg, 5mg), the patent information in Type II declarations did not match the original drug' s patent listing. Both scenarios may lead to future conflicts between originators and generics, increasing litigation burdens. Additionally, some products like levosimendan injection had erroneous Type II declarations. These issues stem from the lack of an error correction mechanism for ex officio review on the Platform, representing a major defect in China' s drug patent linkage system. Therefore, we propose the following recommendations:

3.1 Improve Platform Functionality

Establish a dedicated notification registration and objection section on the Platform. After generic applications are accepted, applicants must not only notify the original drug marketing authorization holder of their latest patent declarations and supporting evidence within the prescribed working days but also register relevant proof materials demonstrating effective notification on the Platform [**?**].

3.2 Establish a Right-to-Know Relief Mechanism

If the original drug marketing authorization holder or patent holder objects after receiving notification, they should file objections with drug regulatory authorities within the specified timeframe through the Platform's corresponding section. If the marketing authorization holder' s actions prevent the patent holder from learning about patent declarations, generic applicants'liability should be reduced or exempted based on actual circumstances, with corresponding administrative penalties imposed on the marketing authorization holder.

3.3 Strengthen Data Tracking by Generic Companies

Generic companies should search the Platform before and after submitting Type II declarations to verify the accuracy of original drug companies' public information, including marketing authorization holders (not patent holders) and whether listings have been withdrawn. They should also monitor whether original drug companies subsequently correct relevant patent information to ensure smooth generic drug development and market entry. For partially invalidated

patents, generic companies should learn from Nanjing Chia Tai Tianqing' s experience by submitting both Type II and Type III declarations simultaneously —Type II for invalidated claims and Type III for valid claims.

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Author Contributions:
GU Donglei: Conceptualized the research, designed the study, and drafted the manuscript.
XIE Bingxin: Collected, cleaned, and analyzed data, and revised the final manuscript.

Note: Figure translations are in progress. See original paper for figures.