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Original Research Article

Clinical, regulatory, and economic landscape of improved new drugs in China: a retrospective study of products marketed between 2020 and 2025

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ABSTRACT

Introduction In China, improved new drugs with known active ingredients, optimized through a new dosage form, formulation process, or administration route, have attracted increasing attention due to relatively low research and development risks and accelerated regulatory pathways. However, their clinical evidence, regulatory performance, and economic characteristics remain unclear. **Methods** We retrospectively reviewed all improved new drugs (Class 2.2 improved new drugs) approved and marketed in China between January 2020 and September 2025 using data from the YAOZH and Center for Drug Evaluation databases. We evaluated the following characteristics of each product: therapeutic area, dosage-form transition, clinical evidence type (bioequivalence [BE] or non-BE), duration of regulatory review, expedited-pathway designation, and price. Additionally, we identified published clinical trials on products supported by non-BE evidence. Price premiums were calculated as defined daily dose cost differences relative to the earliest marketed formulation of the same active pharmaceutical ingredient and indication. **Results** Across 14 International Classification of Diseases 11th Revision categories, 71 products (70 chemicals and 1 traditional Chinese medicine) were approved. Overall, 53.5% were approved through BE evidence and 22.5% received priority review. The median review time was 551 days; priority reviews had significantly shorter timelines than standard reviews (374 *vs.* 582 days; $P = 0.00027$). Within the priority review cohort, non-BE approvals were non-significantly faster than BE approvals ($P = 0.100$). Among 30 products eligible for pricing analysis, the median price premium was 91.24% (interquartile range 46.35%–339.05%) relative to the earliest formulations. **Conclusions** Improved new drugs represent a pragmatic innovation route that balances development efficiency with regulatory accessibility. For standard reviews, non-BE evidence may facilitate faster approval; further, substantial price premiums were observed and may not consistently align with patient-centered values. Future studies should integrate usability, adherence, safety, real-world outcomes, and pharmacoeconomic evaluations in order to inform value-based reviews and reimbursements.

KEYWORDS

improved new drugs, regulatory review, traditional Chinese medicine, price premium

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1. Introduction

Although there have been major advances in biomedical science and technology, there remain challenges in translating these gains into approved therapeutics. There has been an increase in the capitalized pre-launch research and development (R&D) costs for novel therapeutics, which range from ≈ $161 million to $4.54 billion. Further, prolonged clinical development and regulatory review processes have resulted in substantial uncertainty and financial risk.[1] Contrastingly, improved new drugs have a relatively shorter development cycle (≈ 6.5 years) and smaller cost (≈ $300 million),[2] which highlights their growing strategic role in expanding treatment options.

In China, the 2020 "Requirements for Registration Classification and Application Dossiers of Chemical Drugs" refined the registration taxonomy for chemical drugs.[3] Under this framework, products that optimize known active pharmaceutical ingredients (API) through structural modifications, dosage forms, formulation processes, administration routes, or indications, with significant clinical advantages, are categorized as Class 2 new drugs. They can be further divided into four subcategories; among them, products based on novel dosage forms or administration routes (Class 2.2 [dosage-form/route] improved new chemical drugs) account for most of the recent approvals. Compared with first-in-class drugs, improved new drugs offer a pragmatic innovative approach with lower R&D risk and higher regulatory accessibility. Additionally, they provide technical feasibility, relatively controllable timelines and risks, and clear pathways for demonstrating clinical benefits and translational impacts.[4,5] Specifically, innovations in dosage form and administration route often yield advantages with respect to safety, adherence, and usability, which in turn enhance the overall clinical and market value.

In 2020, the Center for Drug Evaluation (CDE) issued the "Technical Guidance for Clinical Trials of Modified New Chemical Drugs" to clarify the evidentiary expectations for clinical advantage and incentivize R&D.[6] Further, the "Measures for the Administration of Drug Registration" facilitate the access of eligible Class 2 products to expedited programs, including breakthrough therapy designation and priority review, which accelerates the time to market.[7] Given the time-, cost-, and risk-related constraints inherent to first-in-class drugs, improved new (Class 2.2) drugs crucially contribute towards efficiently addressing unmet needs.[8]

Given this background, this study aimed to evaluate the characteristics of Class 2.2 drugs approved in China between January 2020 and September 2025. First, we aimed to describe approval-related trends, including volumes, therapeutic area distribution, and dosage form transitions, in order to identify current R&D priorities. Next, we aimed to assess key regulatory perfor-

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mance metrics, including the pivotal clinical evidence (bioequivalence [BE] *vs*. non-bioequivalence [non-BE]), review timelines, and use of expedited pathways. Additionally, we aimed to assess the available clinical evidence regarding the efficacy and safety of formulation changes. Finally, we aimed to analyze the price premiums of Class 2.2 drugs relative to the earliest marketed formulations of the same active ingredient and indication. Taken together, this study may provide empirical insights for future product development and value-oriented policy refinements for formulation-driven innovation in China.

2. Methods

2.1. Ethical approval

No ethical approval was required for this study because the research did not involve human or animal experimentation. The work solely involved the analysis of non-identifiable or publicly available data.

2.2. Data sources and extraction

We identified all improved new drugs, which were defined as pharmaceutical products containing known active ingredients that were developed using a new dosage form, formulation process, or administration route. We selected drugs that were approved and marketed in China between January 2020 and September 2025. For consistency, we excluded other types of drug improvements, including new indications, compound combinations, or manufacturing processes that do not alter the dosage form. To ensure accuracy and completeness, product information was primarily obtained from the YAOZH database (https://www.yaozh.com/),[9] cross-verified with data from the CDE,[10] and National Medical Products Administration (NMPA).[11] Two investigators (YNJ and HQS) independently extracted the data, with a third investigator (WXT) performing crosschecks for accuracy and completeness.

Extracted data were entered into a structured Microsoft Excel 2019 database (Microsoft, Seattle, WA). The extracted variables included drug name, active ingredient(s), strength or specification, dosage form, approval date, indication(s), regulatory pathway, type of randomized controlled trial (RCT) supporting approval (BE or non-BE), review duration, expedited review designation, National Reimbursement Drug List status, price, and original dosage form before modification when applicable. For products supported by non-BE evidence, we further identified related clinical trials and summarized their main efficacy and safety findings. Therapeutic areas were classified based on the International Classification of Diseases, 11th Revision (ICD-11);[12] additionally, the earliest marketed formulation for each API was defined based on the first approval date by the NMPA.

2.3. Statistical analysis

Cost was quantified using the defined daily dose (DDD) cost for each API, with comparison of the approved Class 2.2 formulation with the earliest marketed formulation of the same API and indication. Prices were standardized in Chinese yuan using the 2025 median winning procurement price (reference date: June 2025). We excluded products with missing price data from the cost analyses. In case there were multiple strengths or pack sizes, the unit prices were normalized to the smallest purchasable unit in order to derive the DDD cost. Treatment costs were calculated based on the labeled dosage and administration. For products with multiple indications, the costs were computed based on the indication with the largest market share. For weight-based dosing, we assumed adult and pediatric body weights of 60 kg and 20 kg, respectively. For dosing based on body surface area, we assumed a patient body surface area of 1.7 m^2. For each matched pair, the DDD cost for the Class 2.2 and original formulations were calculated, followed by derivation of the price premium as follows:

$$\text{Premium} = \frac{\text{cost_innovative} - \text{cost_original}}{\text{cost_original}}$$

3. Result

We identified 71 Class 2.2 drugs (70 chemicals and 1 traditional Chinese medicine [TCM]). Further details are provided Appendix 1.

3.1. Approval landscape and dosage forms

Taken together, these products covered 14 ICD-11 therapeutic categories. The annual approval volumes showed an initial low baseline, followed by a rapid increase and subsequent stabilization at a relatively high level with fluctuations (Figure 1). Specifically, only one product was approved for mental, behavioral, or neurodevelopmental disorders in 2020. In 2021, this number increased to 12 drugs covering eight ICD-11 categories, including neoplasms (n = 3) and mental, behavioral, or neurodevelopmental disorders (n = 3). In 2022, this number further increased to 16 drugs across eight categories,

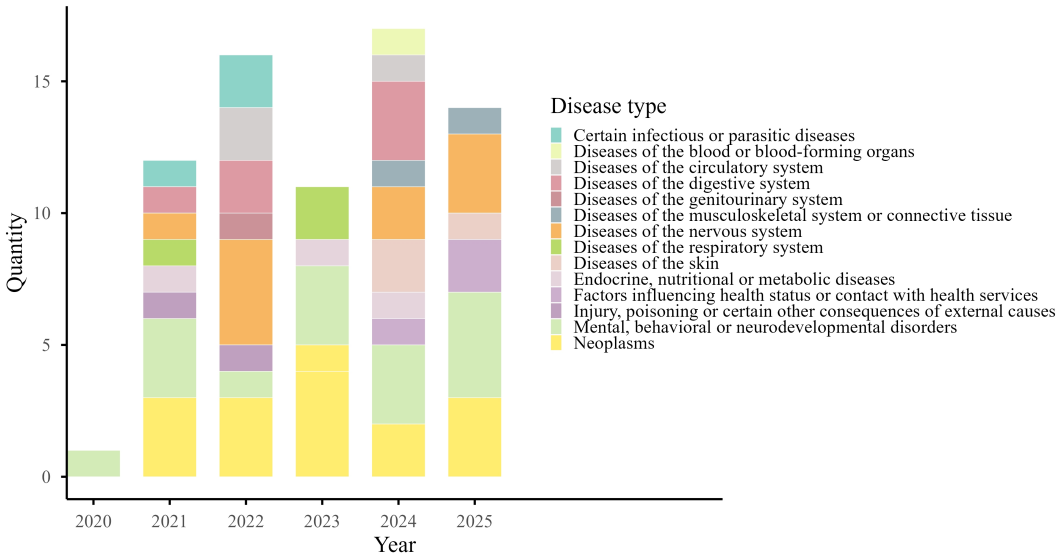

Figure 1 Annual approvals of Class 2.2 drugs in China (2020 to Sep 2025) according to ICD-11 therapeutic category

Notes: ICD-11: International Classification of Diseases, 11th Revision.

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including nervous system diseases (n = 4) and neoplasms (n = 3). In 2023, this number decreased to 11 drugs covering five ICD-11 categories, including neoplasms (n = 4) and mental, behavioral, or neurodevelopmental disorders (n = 3). In 2024, the number increased to 17 drugs across 10 categories, with the most common categories being mental, behavioral, or neurodevelopmental disorders as well as digestive system disorders (both n = 3). By September 2025, additional 14 drugs have been approved, with mental, behavioral, or neurodevelopmental disorders being the most common indication.

3.2. Dosage-form distribution and transitions

Ten dosage forms were identified across the 71 Class 2.2 drugs. The most common dosage form was injections (n = 38), followed by tablets (n = 18) and capsules (n = 5). For each API, we retrieved the earliest marketed dosage form in China and conducted a paired comparison with the approved Class 2.2 form. The earliest launch set comprised 12 dosage forms, which were predominantly injections (n = 36) and transdermal films (n = 8).

We constructed Sankey diagrams to visualize the transitions from the original to modified dosage forms across the ICD-11 categories. The greatest number of transitions occurred in mental, behavioral, or neurodevelopmental disorders, covering eight transition types. The most frequent transition type was transdermal film to tablet (n = 4), followed by nasal spray to injection (n = 3), syrup to tincture (n = 2), injection to tablet (n = 1), implantation to tablet (n = 1), and injection to solution (n = 1). Similarly, there were eight transition types for nervous system disorders. Here, the most frequent transition types were tablets to injection (n = 2) and transdermal film to tablet (n = 2), followed by oral solution to tablet (n = 1), granules to tablet (n = 1), tablet to capsule (n = 1), and injection to transdermal patch (n = 1) (Figure 2).

Among the included drugs, advanced reformulations were characterized by optimized routes/release; device-enabled delivery; and improved stability, palatability, and dosing flexibility in order to enhance usability, adherence, and safety. Table 1 summarizes these characteristics and provides representative product examples.

3.3. Clinical evidence from pivotal clinical trials

We identified 10 clinical trials that provided evidence for the included Class 2.2 drugs (Table 2). Most of the clinical trials adopted a non-inferiority or active-controlled design and applied conventional clinical endpoints, including overall survival, functional outcome after acute ischemic stroke, hormone or biomarker suppression, pain intensity, or composite clinical response rates. In oncology and stroke trials, improved formulations (e.g., goserelin acetate sustained-release microsphere injection *vs.* goserelin implant; tenecteplase *vs.* alteplase) consistently achieved non-inferior efficacy compared to the reference standard; contrastingly, some cases (e.g., sublingual edaravone dexborneol *vs.* placebo) showed modest but statistically significant superiority. For perioperative and symptomatic indications, improved products (e.g., intravenous injection of meloxicam, intranasal dexmedetomidine, and abobotulinumtoxinA) yielded clinically meaningful reductions in pain, sedation failure, or symptom severity versus placebo, with rapid onset and sustained effects where relevant.

The safety profiles were generally comparable between the improved and original formulations. In stroke and oncology trials, the improved formulation did not show increased rates of overall adverse events, serious adverse events, and key safety endpoints. Further, several studies demonstrated incremental advantages of formulation-related tolerability. For example, goserelin acetate sustained-release microsphere injection achieved similar castration and biomarker suppression to the goserelin implant but with fewer injection-site reactions. Additionally, the pediatric syrup formulation of Xiaoer Chiqiao Qingre was non-inferior to granules in terms of efficacy and had similarly low complication rates, while being more acceptable for children. However, few clinical trials included adherence, medication error rates, administration time, or broader patient- and system-level outcomes as primary endpoints. Taken together, current clinical evidence indicates that Class 2.2 drugs can reliably match and occasionally improve the efficacy and safety of reference regimens; however, the clinical trials do not comprehensively assess the added value with respect to usability and healthcare delivery.

3.4. Regulatory review timelines and expedited pathways

Among the 71 Class 2.2 drugs, 38 (53.5%) were approved based on BE evidence. The remaining 33 products were supported by non-BE evidence, including 21, 7, and 5 based on Phase 3, 2, and 1 RCTs, respectively. Further details are provided in Appendix 2.

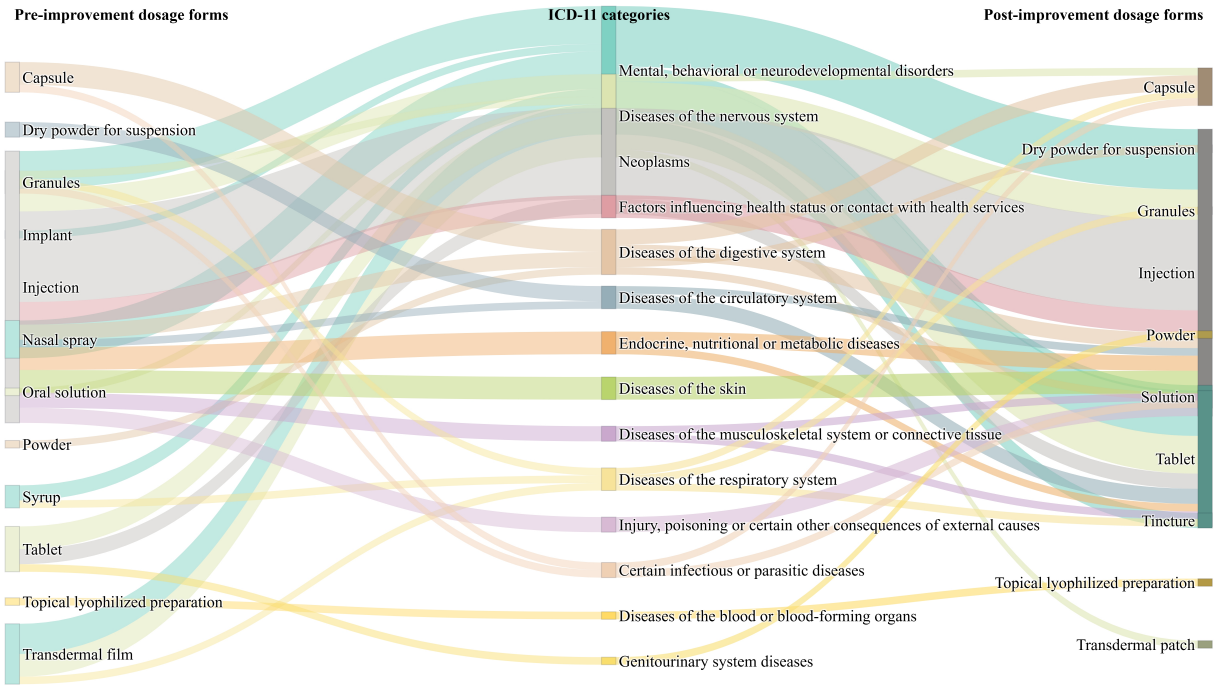

Figure 2 Transitions in dosage forms for Class 2.2 drugs in China

Notes: ICD-11: International Classification of Diseases, 11th Revision.

Table 1 Classification, characteristics, and advantages of advanced formulation innovations

Administration route	Dosage form	Characteristics	Advantages
Oral administration	Sustained-release granules	Gradually release the drug over time to maintain a stable plasma concentration.	Reduce dosing frequency and improve patient compliance.
	Syrup	Sweet, viscous liquid formulation with uniform drug dispersion.	Easy to swallow, palatable, and suitable for children.
	Dry suspension	Powder form that becomes a suspension after reconstitution with water.	Improved storage stability and convenient administration.
	Dispersible tablet	Rapidly disperses in water to form a fine suspension.	Enhances dissolution and absorption, which improves bioavailability.
	Oral solution	Drug completely dissolved in an aqueous vehicle.	Fast onset of action and suitable for patients with swallowing difficulties.
	Powder	Finely divided solid form with uniform particle size.	Simple formulation, stable, and allows flexible dosing.
	Oral dissolving film	Thin film that dissolves quickly upon contact with saliva.	Rapid absorption, discreet usage, and convenient administration.
	Orally disintegrating tablet	Disintegrates rapidly in the mouth without water.	Convenient for patients with swallowing difficulties and on-the-go use.
	Sublingual tablet	Dissolves and absorbs quickly through sublingual mucosa.	Provides rapid onset and avoids first-pass hepatic metabolism.
Parenteral administration	Microsphere	Microparticulate system for controlled drug release.	Enables sustained/targeted delivery and reduces side effects.
	Liposome	Spherical vesicle with lipid bilayer encapsulating drug molecules.	Prolongs circulation time as well as improves drug stability and targeting.
	Micelle	Colloidal carrier formed by amphiphilic molecules in aqueous media.	Enhances solubility and bioavailability of poorly soluble drugs.
	Implant	Solid sterile preparation for subcutaneous or intramuscular implantation.	Provides long-term controlled release and reduces dosing frequency.
Respiratory administration	Nasal spray	Liquid formulation delivered via nasal mucosa.	Rapid absorption, convenient use, and bypasses gastrointestinal metabolism.

Table 2 Published clinical trials on Class 2.2 formulations

Clinical trial ID	Study design	Patient population	Intervention group	Control group	Efficacy outcome	Safety outcome
CTR2000033188[13]	Phase 3, multicenter, open-label, single-arm trial	Chinese men with locally advanced or metastatic prostate cancer	Triptorelin acetate (n = 125)	None	Day 28: 97.6% with testosterone <0.5 ng/mL; Day 84: castration maintained; 95.1% with <0.2 ng/mL; 71.3% with ≥ 90% prostate-specific antigen reduction.	Generally well tolerated; mild-moderate AEs; no unexpected signals.
NCT02008227[14]	Phase 3, multicenter, randomized, open-label, active-controlled trial	Patients with locally advanced or metastatic non-small-cell lung cancer previously treated with one or two lines of platinum-based chemotherapy	Atezolizumab (n = 425)	Docetaxel (n = 425)	Median overall survival 13.8 *vs*. 9.6 mos. (HR 0.73, 95% CI 0.62–0.87; P = 0.0003), with consistent benefit across subgroups.	Grade 3–4 treatment-related AEs: 15% *vs*. 43%.
CTR2300075629[15]	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial	Adults undergoing abdominal surgery under general anesthesia with expected moderate-to-severe postoperative pain	Intravenous injection meloxicam (n = 170)	Placebo (n = 85)	Lower pain AUC_{0-24} and morphine use with meloxicam formulation (both P < 0.0001).	Similar rates of overall AEs and ADRs; no dose-limiting toxicity or new signals.
NCT02450526[16]	Phase 3, multicenter, randomized, double-blind, active- and placebo-controlled trial	Chinese adults with moderate-to-severe vertical glabellar lines at maximum frown	Abobotulinumtoxin A (n = 325)	Matching aboBoNT-A placebo (n = 66); onabotulinumtoxin-A (n = 107); matching placebo (n = 22)	Day 29 responder rate 95.2% *vs*. 0.9% *vs*. placebo (P < 0.0001), non-inferior to onabotulinumtoxinA, with durable responses across cycles.	Mainly mild, local treatment-emergent AEs; no new safety concerns over 15 mos.

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Clinical trial ID	Study design	Patient population	Intervention group	Control group	Efficacy outcome	Safety outcome
NCT04563936[17]	Phase 3, multicenter, randomized, open-label, active-controlled, non-inferiority trial	Chinese men aged ≥50 yr with localized, locally advanced, or metastatic prostate adenocarcinoma eligible for endocrine therapy	Goserelin acetate sustained-release microsphere injection + bicalutamide (n = 144)	Goserelin + bicalutamide (n = 145)	Castration rates and maintenance to day 85 were non-inferior and comparable between goserelin acetate sustained-release microsphere injection and goserelin.	Overall treatment-emergent AEs similar, with fewer injection-site reactions on goserelin acetate sustained-release microsphere injection.
CTR20192084[18]	Multicenter, randomized, double-blind, double-dummy, parallel, active-controlled, non-inferiority trial	Children aged 1–13 yr with pedo-anemopyretic cold with stagnant syndrome according to TCM criteria	Xiaoer Chiqiao Qingre syrup + dummy granules (n = 147)	Xiaoer Chiqiao Qingre granules + dummy syrup (n = 142)	Total effective rates at day 3 were non-inferior in both analysis sets, with similar marked response and symptom resolution.	Low and comparable complication rates; no serious drug-related AEs.
NCT05295173[19]	Phase 3, multicenter, randomized, open-label, blinded-endpoint, active-controlled, non-inferiority trial	Adults aged 18–80 yr with acute ischemic stroke within 4.5 h of onset, eligible for intravenous thrombolysis	Reteplase (n = 706)	Alteplase (n = 706)	Primary endpoint is the 90-day mRS score (0–1); no efficacy results available.	Safety endpoints include symptomatic intracerebral hemorrhage, major bleeding, and 90-day mortality; no results available.
NCT05111431[20]	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial	Children aged 2–6 yr undergoing elective surgery under general anesthesia, American Society of Anesthesiologists Physical Status I, suitable for intranasal medication	Dexmedetomidine nasal spray (n = 107)	Placebo nasal spray (n = 50)	Higher rates of satisfactory separation and adequate sedation within 45 min with dexmedetomidine.	AEs were frequent but mainly mild bradycardia and blood pressure changes, with no serious events or deaths.
NCT04950920[21]	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial	Chinese adults aged 18–80 yr with acute ischemic stroke within 48 h, NIHSS score 6–20, pre-stroke mRS ≤1	Sublingual edaravone dexborneol (n = 450)	Matching sublingual placebo (n = 464)	Higher proportion with mRS 0-1 at 90 days and favorable ordinal shift; NIHSS endpoints were neutral.	Treatment-related and serious AE rates were similar to placebo.
NCT04915729[22]	Phase 3, multicenter, randomized, open-label, blinded-endpoint, active-controlled, non-inferiority trial	Chinese adults with acute ischemic stroke within 4.5 h of onset, NIHSS 1–25, eligible for intravenous thrombolysis	Tenecteplase (n = 732)	Alteplase (n = 733)	90-day mRS 0–1 met the non-inferiority margin, with other functional outcomes comparable.	Symptomatic intracerebral hemorrhage and 90-day mortality rates were low and similar between tenecteplase and alteplase.

Notes: ADR: adverse drug reaction; AE: adverse event; AUC: area under the curve; CI: confidence interval; h: hour; HR: hazard ratio; min: minute; mos.: months; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; TCM: traditional Chinese medicine; yr: year.

The regulatory review time was defined as the interval from marketing application submission to approval. For all assessed products, the median review time was 551 days. Additionally, products undergoing priority review (n = 16) had significantly shorter median review times (374 days [Q1–Q3: 301.5–501.0]) than those undergoing standard reviews (n = 55; 582 days [Q1–Q3: 469.0–788.0]; P = 0.00027).

Within the priority review cohort, BE-based approvals had a longer median review time than non-BE approvals in both the priority and standard review cohorts, with median differences of 253 days (P = 0.100) and 100.5 days (P = 0.007). respectively. Among BE-based approvals, review times were non-significantly shorter under priority review than under standard review (median difference: 18 days; P = 0.437). Among non-BE approvals, review times were significantly shorter under priority review than under standard review (median difference: 170.5 days; P = 0.009; Figure 3).

Among the 16 (22.5%) products that received priority reviews, five were pediatric-use products, five received breakthrough therapy designations, three addressed urgent clinical shortages or targeted major infectious diseases or rare diseases, one met the criteria for conditional approval, one involved an innovative product or alignment with foreign-approved manufacturing lines or national key R&D programs, and one met other priority review circumstances.

3.5. Price premiums and market correlation

Among the 71 included drugs, we excluded products without publicly available prices upon at the time of analysis and cases in which the therapeutic population differed between the original and improved products for the same API (e.g., shifts from all-age populations to pediatric-only populations, including rivaroxaban dry suspension). Additionally, we excluded improvements that involved a change in indication (e.g., mitoxantrone hydrochloride and semaglutide). As a result, 30 drugs were included in the price analysis (Appendix 3). The median price premium was 91.24% ([Q1-Q3: 46.35%–339.05%]). Figure 4 shows the detailed premiums for the individual products.

4. Discussion

4.1. Main findings

In this study, most of the approved Class 2.2 drugs had neuropsychiatric

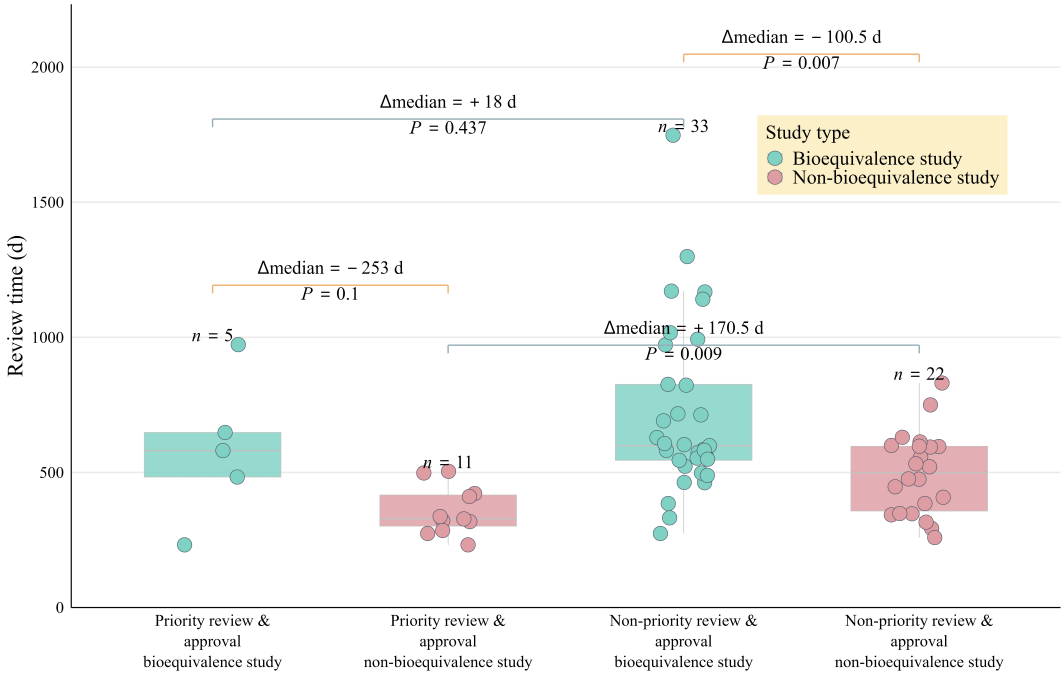

Figure 3 Regulatory review times for Class 2.2 drugs in China

Notes: d: day.

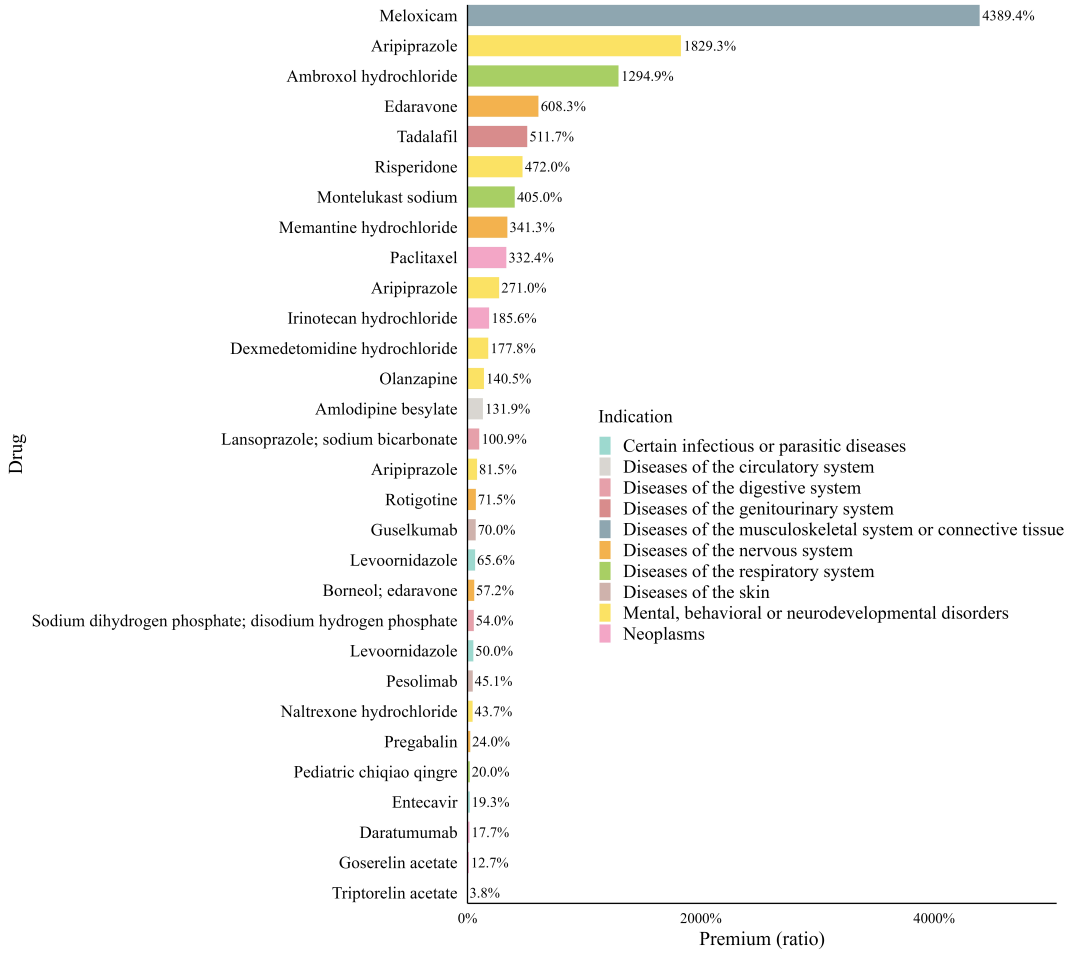

Figure 4 Price premiums of Class 2.2 drugs in China

and oncologic indications and were administered as injections and oral solid dosage forms. Additionally, more than half of the products were primarily approved based on BE evidence; however, those supported by non-BE evidence benefited more from expedited review pathways and shorter regulatory timelines. Notably, the median DDD cost premium was >90% relative to the earliest marketed formulation. However, only some products were supported by RCTs, which did not comprehensively capture real-world outcomes and patient-centered benefits as primary endpoints, especially for formulation-driven innovations and TCM reformulations.

Formulation patterns reflect both technological feasibility and real-world requirements. Most approved products were injections and oral solids; further, common formulation transitions were from transdermal films and oral liquids to tablets or injections. Generally, these formulation transitions are intended to achieve practical improvements for clinical use, including simplified dosing regimens, enhanced palatability, and favorable pharmacokinetic profiles.[23] This may in turn improve patient adherence and streamline clinical workflow. Modifications to the administration route or release profile should be supported by evidence of patient-relevant benefits to meet the goal of Class 2.2 drugs. In China, formulation innovations in Class 2.2 drugs are expected to improve clinical usability, medication adherence, treatment safety, and operational efficiency of drug administration.[24] Assessment of these attributes requires reliance on quantifiable administration-related endpoints, including rates of medication error, duration of infusion or chair time, and frequency of treatment discontinuation. Moreover, the clinical utility of these innovations should be established through patient-centered outcomes, including disease-specific patient-reported outcomes and long-term treatment persistence. Designing post-marketing observational studies or registries that explicitly capture these endpoints would allow substantiation of the real-world value of the selected Class 2.2 drugs.

These regulatory outcomes highlight the importance of obtaining clinically meaningful evidence to support product approval. More than half of the approved products were primarily supported by BE evidence. This indicates that the predominant development pathway is characterized by shorter clinical programs and lower upfront R&D costs but limited direct evidence of incremental clinical benefits. Among products granted priority reviews, those supported by non-BE evidence demonstrated notably shorter review timelines. This was especially evident in cases in which supporting evidence was derived from Phase 2 or 3 RCTs. The median reduction in the review time exceeded 170 days, suggesting a regulatory preference for more comprehensive clinical data. Although BE evidence allows shorter developmental cycles, it does not directly reflect clinical superiority or patient-centered benefits. Therefore, greater scrutiny on BE evidence is warranted given the increasing regulatory emphasis on demonstrable improvements in therapeutic effectiveness, safety, and usability.[25] Accordingly, a balanced development strategy should incorporate targeted RCTs and scientifically justified bridge approaches. Leveraging existing data from originator products can streamline development without compromising ethical standards,[26] as long as key clinical endpoints are prospectively defined and rigorously assessed.

As demonstrated in our cohort, TCM reformulations remain markedly underrepresented among Class 2.2 drugs. Although some modern drugs may trace their origins to natural products, our review of the 70 Class 2.2 drugs found no explicit acknowledgment of a TCM origin or "TCM-inspired" nature in any official labeling or regulatory documents. Nonetheless, a series of recent national policies[27-31] have created a favorable regulatory and industrial environment for TCM reformulations by explicitly encouraging dosage-form innovation, secondary development of marketed TCMs, and establishment of evaluation frameworks tailored to the characteristics and clinical value of TCMs. As summarized in Appendix 4, these frameworks describe a clinical-value-oriented principle, call for TCM-adapted efficacy and safety evaluation standards, legally define and refine the registration categories for innovative and improved TCMs, and embed such products into expedited review and approval pathways. Further, they operationalize the main registration scenarios for TCM reformulations as well as clarify the structure and level of pharmaceutical, non-clinical, and clinical evidence required, including comparisons relative to the original preparations. In addition, they encourage the use of real-world evidence as well as the strengthening of post-marketing safety and effectiveness evaluation systems suited to the TCM features. The policies also emphasize quality upgrading, digitalization, and whole-chain traceability in TCM manufacturing, as well clinical value assessment to inform reimbursement, procurement, and use. Taken together, this evolving policy framework describes specific technical and evidentiary requirements for TCM reformulations in order to support the development and evaluation of TCM reformulations, including Class 2.2 drugs.

4.2. Limitations

This study has several limitations. First, we included 70 chemical drugs and 1 TCM product, which highlights sample heterogeneity. Although these were analyzed together for a broad descriptive overview, they have distinct regulatory and scientific standards, which may confound the aggregate results regarding review times and evidentiary bases. Additionally, the inclusion of the TCM product in the pricing analysis may represent a methodological inconsistency. Future studies should strictly separate these products. Second, there may have been selection bias in our pricing analysis. Only 30 (42%) products were included in the pricing analysis, which may not fully represent Class 2.2 drugs. Further, the excluded products (e.g., recent launches or those with complex indication changes) may have different pricing dynamics, which may have biased the median premium finding. Third, the DDD-based premium analysis excludes indirect costs and savings, which may underestimate the value of innovations that reduce the administrative burden.

4.3. Policy and development implications

For formulation-driven Class 2.2 drugs, policies and development should move beyond BE evidence to a clearer demonstration of patient-centered and system-level values, especially when seeking higher prices or expedited pathways. In addition to traditional clinical endpoints, future studies should incorporate other key endpoints capturing usability; adherence; administration burden; safety in routine practice; and resource use, including treatment persistence, medication error rates, nursing and chair time, and downstream healthcare utilization. These dimensions are especially relevant for populations such as children, older adults, and patients with chronic or oncologic conditions who are sensitive to dosing complexity and administration route. Real-world evidence should be combined and systematically integrated with RCT evidence to enhance generalizability and support decision-making.[32,33] For improved TCM products, the existing policy framework has defined more favorable registration categories and technical pathways. Despite these conducive policy signals, sponsors still face substantial methodological and regulatory challenges in establishing multi-component, pattern-based TCM products as clinically meaningful therapies.

5. Conclusions

Improved new drugs represent a pragmatic innovation route that balances development efficiency with regulatory accessibility. For standard reviews, non-BE evidence facilitates faster approval; further, there are substantial price premiums that are variably related to patient-centered values. Future studies are warranted to integrate usability, adherence, safety, real-world outcomes, and pharmacoeconomic evaluations in order to inform value-based reviews and reimbursements.

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Author Contribution Statement

Yu-nong Jiang: Data curation, investigation, methodology, formal analysis, writing – original draft, and writing – review & editing. **Han-qiao Shao:** Data curation, methodology, investigation, formal analysis, visualization,

funding acquisition, writing – original draft, and writing – review & editing. **Wen-xi Tang:** Conceptualization, supervision, project administration, and writing – review & editing.

Declaration of Competing Interest

The authors have no competing interests to declare.

Electronic Supplementary Material

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