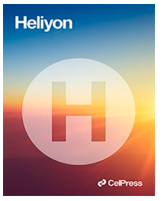
Heliyon 10 (2024) e35454

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Analysis of post-marketing requirements for oncology drug conditional approvals in the United States and China

Chenghao Ge [a,1], Jing An [a,b,1], Xiaoyuan Chen [a,c,*]

[a] Tsinghua Clinical Research Institute, Tsinghua Medicine, Tsinghua University, Beijing, China
[b] R&G PharmaStudies Co. Ltd, China
[c] Office of Clinical Trial Institute, Beijing Tsinghua Changgung Hospital, Beijing, China

A B S T R A C T

Background: Conditional approvals, also known as accelerated approvals, have been introduced by many pharmaceutical regulators around the world, allowing innovative drugs to enter the market earlier on the basis of limited evidence. This research aims to systematically analyze and compare the post-marketing requirements for conditional approvals of oncology drugs in China and the United States. By collecting and categorizing different types of post-marketing requirements, this study seeks to elucidate how these requirements are proposed and discern the underlying logic and patterns.
Methods: This study delved into oncology drug approvals, encompassing FDA accelerated approvals (up to December 31, 2022) and NMPA conditional approvals (from 2017 to December 31, 2022). Leveraging review documents from FDA and NMPA, comprehensive data on product characteristics, all post-marketing commitments and requirements, and especially those related to confirmatory requirements were extracted. The analysis incorporated descriptive statistics, visualizations such as Upset plots, and thorough examination of confirmatory requirement timeframes.
Findings: This study examined 168 FDA accelerated approvals and 41 NMPA conditional approvals for oncology indications. Post-marketing requirements displayed diversity: FDA emphasized confirmatory studies, clinical pharmacology studies, and more, while NMPA predominantly focused on confirmatory studies. Confirmatory requirement timeframes indicated higher FDA-required completion times for new confirmatory trials compared to continued completion of original pivotal trials. In contrast, NMPA's requirement patterns were comparatively singular, with relatively fixed timeframes. FDA's evolving trend showed decreasing timeframes over time, suggesting an increasing demand for timely confirmatory data.
Interpretation: Conditional approvals offer a unique approach to bring potentially life-saving drugs to the market faster, despite limited supporting evidence. Our analysis of oncology drug conditional approvals in the U.S. and China reveals diverse post-marketing requirement patterns. This study provides valuable insights for regulatory decision-making in a dynamic pharmaceutical landscape. Balancing the risks and rewards of conditional approvals is crucial in ensuring both patient safety and timely access to innovative treatments.

1. Research in context

1.1. Evidence before this study

Accelerated approval of oncology drugs is a hot topic at the moment. Prior studies have critiqued the FDA's accelerated approval policy or analyzed clinical data supporting accelerated approval, but there has been a lack of systematic analysis of the FDApost-marketing requirements, as well as a comprehensive study of Chinese conditional approval data.

* Corresponding author. Tsinghua Clinical Research Institute, Tsinghua Medicine, Tsinghua University, Beijing, China; Office of Clinical Trial Institute, Beijing Tsinghua Changgung Hospital, Beijing, China.
E-mail address: cxya02648@mail.tsinghua.edu.cn (X. Chen).
[1] Joint first authors.

https://doi.org/10.1016/j.heliyon.2024.e35454
Received 26 April 2024; Received in revised form 24 July 2024; Accepted 29 July 2024
Available online 30 July 2024

1.2. Added value of this study

This research provides the first systematic comparison of post-marketing requirements for oncology drugs under conditional approval in the U.S. and China, revealing regulatory nuances and trends. The findings inform policy development and decision-making, fostering a balance between timely access to innovative therapies and ensuring robust evidence of their safety and effectiveness.

1.3. Implications of all the available evidence

All available evidence indicates that conditional approval is a crucial mechanism for expediting the availability of novel treatments, necessitating a cautious approach to strike a balance between therapeutic benefits and potential risks. Appropriate and well-defined post-marketing requirements, coupled with realistic timelines, are essential in achieving this equilibrium.

2. Introduction

Conditional approval or accelerated approval policies have become instrumental on a global scale for expediting drug approval processes and fostering innovation. Innovation, in this context, is defined as offering substantial therapeutic gains compared to existing therapies, which includes significant improvements in efficacy, safety or addressing unmet medical needs. This regulatory framework facilitates early market access for drugs based on limited yet crucial clinical evidence, contingent upon meeting pre-defined conditions post-approval [1–3]. The adoption of conditional approval significantly shortens pre-market development and approval timelines, ensuring prompt access to efficacious drugs for the benefit of patients [4].

For conditional approval, the most critical regulatory measure is the proposed post-approval requirements. The United States Food and Drug Administration (FDA) pioneered this approach through the introduction of the Accelerated Approval (AA) policy in 1992 [5], a regulatory strategy steadfastly upheld for over three decades. Products granted accelerated approval undergo post-marketing research requirements to address limitations identified during regulatory scrutiny. In 2011, the FDA provided a definitive definition of post-marketing research, categorizing it into post-marketing requirements (PMRs) and post-marketing commitments (PMCs) [6]. PMRs encompass mandated studies, while PMCs are voluntary commitments by applicants [7]. The incorporation of "confirmatory trials" to validate clinical benefits granted through accelerated approval has become integral. Successful confirmatory trials may lead to conversion to regular approval, while failures or safety concerns may prompt market withdrawal or label modifications [8]. Nevertheless, China, through the National Medical Products Administration (NMPA), embraced conditional approval relatively later, starting in 2017 [9]. The NMPA's Drug Evaluation Center issued guidelines in 2020, encouraging innovation and delineating procedures for conditional approval based on surrogate or intermediate endpoints [10]. In 2023, the NMPA sought public opinions on procedures for conditionally approved products and confirmatory trials [11]. These developments indicate a progressive refinement of conditional approval requirements in China.

The requirements that govern drugs after they have received conditional approval differ across countries due to factors such as regulatory history and national context. However, the ultimate aim is to satisfy unmet clinical needs by speeding up market access based on incomplete clinical data. These expedited routes allow drugs to reach patients more quickly, with a requirement for ongoing data collection post-approval to enhance the evidence for a drug's benefit-risk profile. The establishment of PMRs is based on approvals using incomplete clinical data. These requirements may include conducting confirmatory trials, ongoing evaluation of known serious risks and clinical pharmacology studies. Confirmatory trials are particularly important as a focus of regulatory agencies in PMRs.

Previous studies underscore the escalating trend in anti-tumor drugs receiving accelerated approval and highlights the delicate balance between risk and reward in drug regulation. Previous research showed that the FDA's approved 93 indications for 64 anti-tumor drugs under the accelerated approval policy from its initiation until 2017. Over time, there is a rising trend in the number of accelerated approvals, with 104 anti-tumor indications approved in the 5-year period from 2018 to 2022, surpassing the approvals in the previous 25 years [12]. Recent research primarily focuses on overall trends in post-approval status updates for conditionally approved drugs. A published study analyzed confirmatory trials for 278 drugs granted accelerated approval between December 1992 and December 2021. Approximately half of the accelerated approvals transitioned to regular approval within a median time of 3.2 years, while 38 % remained in the accelerated approval status [5]. Although many recent publishments have critically examined the FDA's accelerated approval policy and carefully analyzed its benefits and risks [13,14], there is still a lack of systematic analysis of the FDA's strategy for proposing PMRs, and there is an even greater dearth of studies that have comprehensively examined the conditional approval data in China. This study endeavors to fill this gap by providing an in-depth comparative analysis of the PMRs associated with conditional approval in China and the United States, further exploring the delicate balance between benefits and risks in the process of accelerated drug approval.

3. Methods

3.1. Data screening

Approval cases included in this study include all accelerated approval of oncology drugs by the FDA by December 31, 2022, and all conditional approval of oncology drugs up to December 31, 2022 after the NMPA formally implemented the conditional approval system in 2017.

3.2. Data collection

The information collected mainly included types of products, approval classification, indication classification, the content of PMRs, the study design of confirmatory trials, the timeframe for completion and the status of subsequent full approvals/withdrawals for that conditional approval. In this study, we included both PMRs and PMCs under the umbrella of post-marketing requirements to provide a comprehensive analysis of the regulatory considerations by both the FDA and NMPA. The sources of information involved are review documents or approval letters disclosed in the FDA's official drug database, as well as review documents disclosed officially by the NMPA. All information on accelerated approvals or conditional approvals included in the analysis is provided in Supplementary Table 1, and all PMRs are detailed in Supplementary Table 2.

3.3. Statistical analysis

For the baseline information of the varieties included in this study descriptive statistics were used to present percentages. In terms of the classification and composition patterns of PMRs, visualization in the form of Upset plots was presented. For confirmatory requirement timeframes, differences in timeframes for different types of confirmatory requirements were compared in the form of bar scatter plots, and the Mann-Whitney test was used to test for between-group differences. The simple linear regression was used to present trends in the timeframes for completion of FDA and NMPA confirmatory requirements over time. Data analysis and graphing were performed using R Studio (version 2023.03.0) and GraphPad Prism 9.5.1.

3.4. Role of funding

This study was supported by the China Society for Drug Regulation under grant number 2023-Y-Y-002. All authors had access to the raw data and approved the manuscript for publication.

4. Results

4.1. Description of included data

From 1992, when the FDAinitiated its accelerated approval policy, to the end of 2022, a total of 290 indications based on surrogate endpoints were granted accelerated approval by the FDA. Notably, 198 of these indications were in oncology (Fig. 1). This study exclusively focused on initial approvals and new indications, encompassing 98 initial approvals and 70 expansion of indications (Table 1). For NMPA conditional approvals, only locally manufactured Chinese products were considered (Fig. 1). This study included 27 initial approvals and 14 new indication approvals for conditionally approved oncology drugs by NMPA. Table 1 provides a detailed breakdown of the types of products, with 59.5 % of FDA approvals being drugs and 40.5 % biologics. For NMPA approvals, 46.3 % were drugs and 53.7 % were biologics. The indications for both agencies are categorized into solid tumors (62.5 % for FDA and 63.4 % for NMPA) and hematologic tumors (37.5 % for FDA and 36.6 % for NMPA).

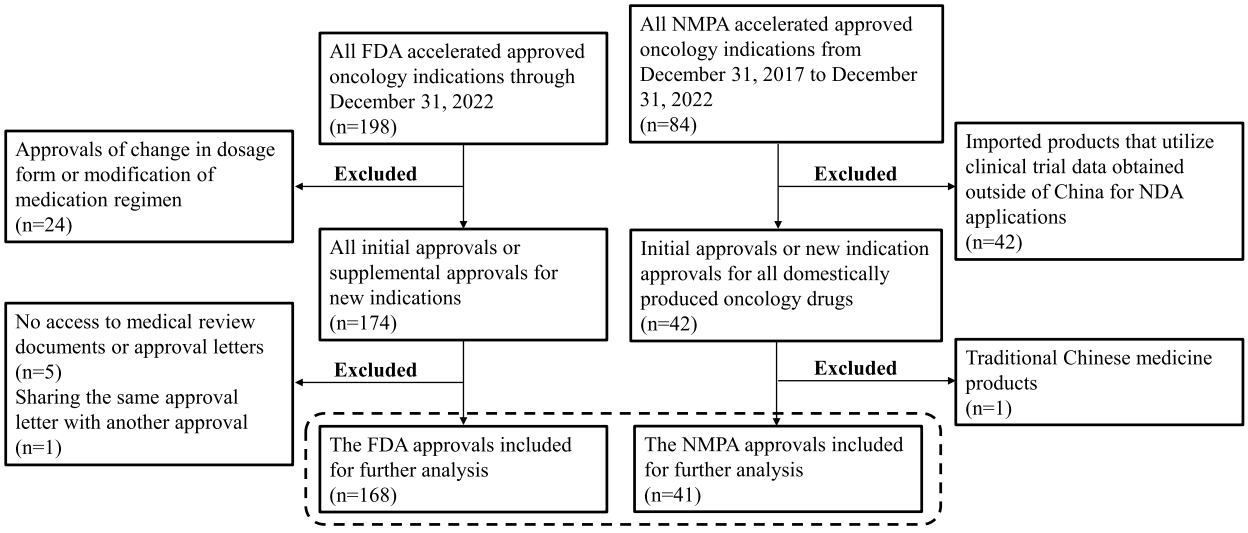


Fig. 1. Study flowchart.
The flowchart illustrates the inclusion and exclusion criteria applied to FDA accelerated approvals and NMPA conditional approvals analyzed in this study. FDA, Food and Drug Administration (the U.S.); NMPA, National Medical Products Administration (China); NDA, New Drug Application.

4.2. Variety of post-marketing requirements and comparison of FDA and NMPA recurring patterns

To shed light on how PMRs are formulated, this study systematically analyzed all PMRs associated with conditionally approved oncology indications in FDA and NMPA. The analysis categorized PMRs into seven types: new confirmatory trials, continuing pivotal trials with confirmatory purpose, additional evidence of safety and effectiveness, clinical pharmacology studies, dose optimization studies, pharmacological studies, and others (including toxicology, immunization, etc.). This study illustrated the distribution of the different types of requirements imposed by the FDA and NMPA for different approval classification. A graphical analysis of the number and mix of each type of post-marketing requirement revealed recurring patterns.

The graphical representation in Fig. 2 vividly portrayed the distinct post-marketing requirement patterns between FDA and NMPA. The chart revealed that FDA requirements were characterized by a broader spectrum, encompassing various types such as new confirmatory trials, clinical pharmacology studies, and dose optimization studies. In contrast, NMPA's requirements predominantly centered around confirmatory studies. Furthermore, the figure highlighted a notable trend that initial approvals tended to be associated with a more extensive array of PMRs compared to approvals for expanding indications. In the 98 instances of FDA initial approvals, 85 approvals required the initiation of new confirmatory trials, while 17 approvals allowed the continuation of the original pivotal trials as the confirmatory requirements. Notably, 4 approvals necessitated both new confirmatory trials and the continuation of the original pivotal trials. In addition to confirmatory requirements, many approvals included PMRs for conducting clinical pharmacology studies (57/98) and providing evidence related to effectiveness or safety beyond other confirmatory requirements (57/98). Requirements for dose optimization, pharmacological, toxicological or immunization, were also frequently combined with confirmatory requirements. For FDA approvals expanding indications, aside from confirmatory requirements, the predominant requirements were for supplemental evidence related to effectiveness or safety (33/70). Other studies, such as clinical pharmacology, dose optimization, and pharmaceutical studies, were relatively less common.

In the case of NMPA initial approvals for 27 indications, 24 required new confirmatory trials, and 3 used the continuation of the original pivotal trials as confirmatory requirements. Beyond confirmatory requirements, NMPA initial approvals often included requirements for supplemental evidence related to effectiveness and safety (14/27) and clinical pharmacology studies (9/27). Moreover, other studies (such as pharmaceutical, toxicological, immunological) were less frequent compared to FDA requirements for initial approvals. NMPA's supplemental applications primarily focused on confirmatory requirements, with fewer other requirements compared to initial approvals.

4.3. Temporal analysis of regulatory timeframes and transition periods

To explore the temporal of regulatory timeframes, we conducted an analysis of the timeframes provided for all confirmatory requirements in both FDA and NMPA. As shown in Fig. 3, the median time required for the completion of confirmatory clinical trials, as stipulated by the FDA, varies depending on the type of confirmatory requirement. For those cases where a new confirmatory trial needs to be initiated, the median time for the completion timeframe was 23.7 months. However, for one-trial mode where the confirmatory requirement was for the continuation of the original pivotal trial to be completed, the median time for the completion timeframe was 45.1 months. Overall, the FDA-required completion timeframe for new confirmatory trials was higher than in the case of continued completion of the original study ($p = 0.0004$). For the timeframes provided by the NMPA for confirmatory requirements, they were relatively fixed, and due to the limited number of cases involving the one-trial mode, the comparison between the two modes did not reveal significant differences.

The FDA established specific timeframes for completion in PMRs, including periods for protocol submission, trial completion, and report submission. These timelines varied depending on the type of confirmatory requirement and different indications. The timeframe for the completion of NMPA PMRs was generally fixed and usually set at 3–5 years after approval for marketing. NMPA also had many approvals without explicitly stated timelines, resulting in a significant amount of missing data.

As time progresses, there is a discernible trend of decreasing time intervals for FDA accelerated approvals transitioning to regular approvals or withdrawals (see Fig. 4). In the past five years, the majority of accelerated approvals have experienced transition times ranging from 3 to 5 years. Due to the limited number of cases and challenges in obtaining transition time data for NMPA's conversions to regular approvals, and with no instances of conditional approvals being withdrawn by NMPA to date, a graphical analysis of transition time intervals for NMPA conditional approvals has not been undertaken at this time.

Table 1
Overview of oncology drug information conditionally approved by the FDA and NMPA.

	FDA approvals (n = 168)	NMPA approvals (n = 41)
Types of products		
Drugs	100 (59.5 %)	19 (46.3 %)
Biologics	68 (40.5 %)	22 (53.7 %)
Approval classification		
Initial approval	98 (58.3 %)	27 (65.9 %)
Expansion of Indication	70 (41.7 %)	14 (34.1 %)
Indications		
Solid tumors	105 (62.5 %)	26 (63.4 %)
Hematologic tumors	63 (37.5 %)	15 (36.6 %)

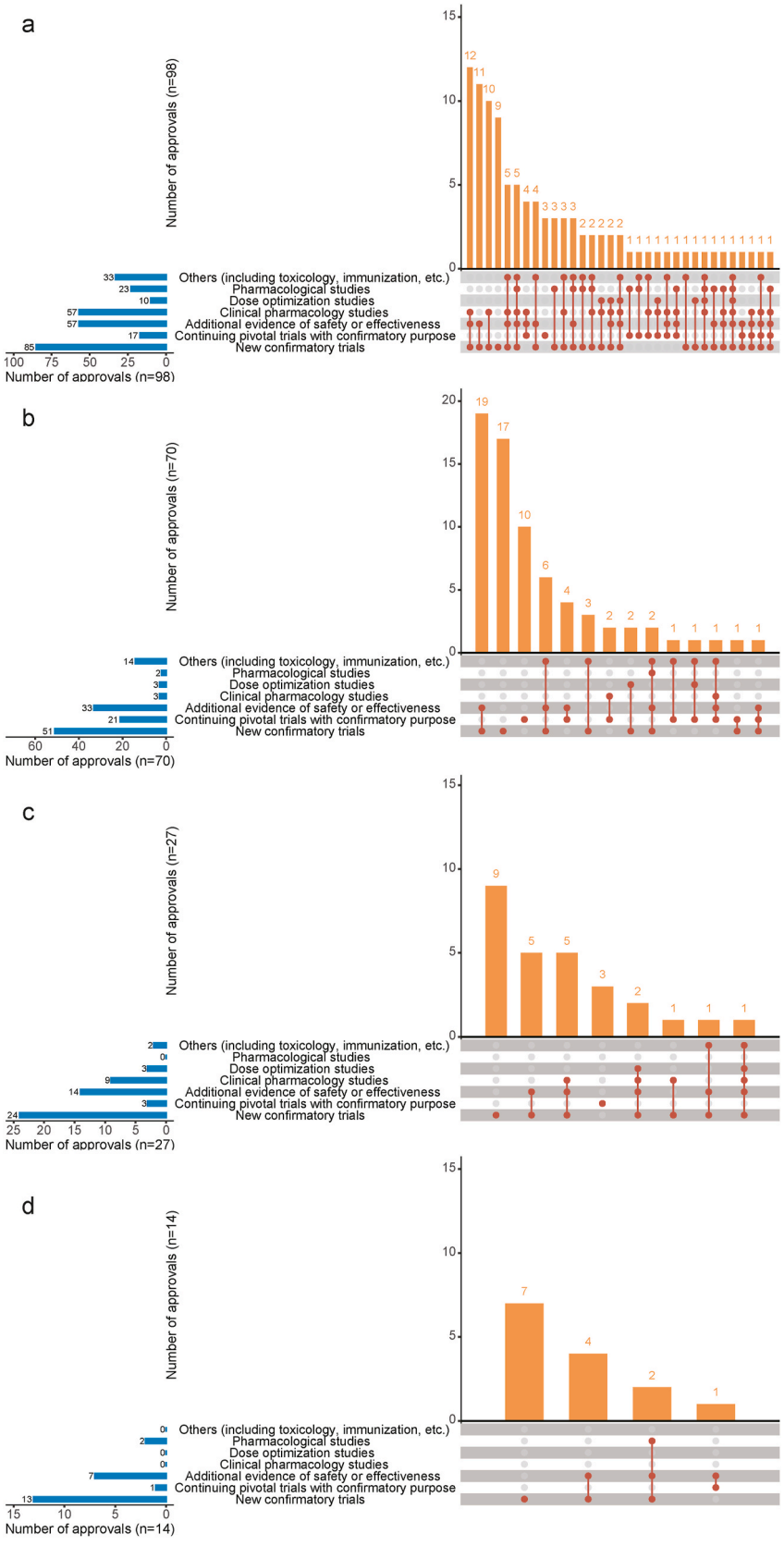


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Fig. 2. Illustration of post-marketing requirement patterns.
This set of Upset plots visually depicts the patterns of PMRs imposed by FDA and NMPA for conditional approvals. Each row in the plot represents a type of requirement, and the connections between solid points in different rows illustrate the combination patterns of different requirement types. Panels a-d correspond to FDA Initial Approval, FDA Expansion of Indication, NMPA Initial Approval, and NMPA Expansion of Indication, respectively.

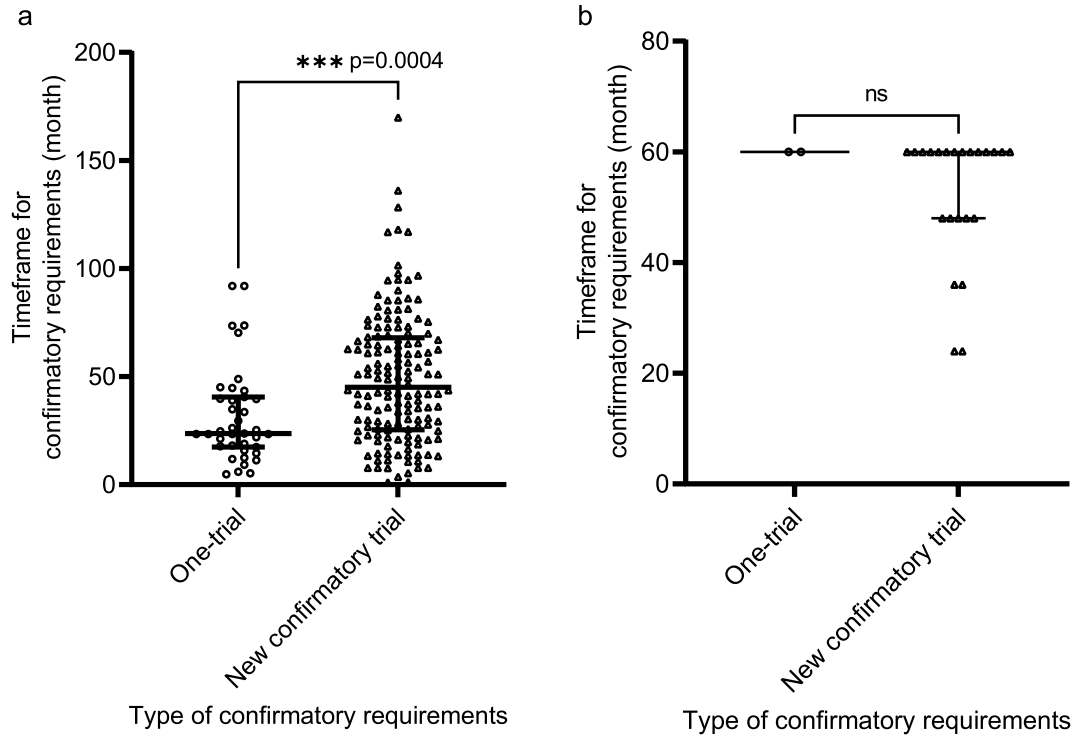

Fig. 3. Comparison of timeframes for different confirmatory requirements.
This figure depicts the specified timeframes for distinct types of confirmatory requirements by the FDA (a) and NMPA (b). The "One-trial" mode indicates the continuation of the original pivotal trial as a confirmatory requirement, while "New confirmatory trial" signifies the initiation of a new confirmatory trial. Each symbol in the figure represents an individual approval. The Mann-Whitney test was employed for intergroup difference analysis.

5. Discussion

This study conducted a comprehensive comparative analysis of the PMRs for conditional approvals of anti-tumor drugs in China and the United States, revealing significant differences in regulatory approaches. The FDA's requirements were broader in scope, including various types of studies. In contrast, NMPA's requirements were predominantly focused on confirmatory studies. The disparities observed can be attributed to a multifaceted array of factors, which this study will dissect in the following discussion. Additionally, the results revealed a trend that initial approvals were linked to a greater number of PMRs compared to approvals for expanded indications. This is likely because when companies apply for expanded indications, more is known about the drug's safety and efficacy, thereby necessitating fewer PMRs. In summary, this study contributed significantly to the understanding of the regulatory considerations of the FDA and NMPA when conditionally approving oncology innovator drugs.

The FDA's Accelerated Approval (AA) pathway, initiated in 1992, has been instrumental in expediting access to innovative oncology treatments. As of December 31, 2022, the FDAhas granted accelerated approval to 290 indications (including initial approvals, expanded indications, and changes in dosage/regimen) with anti-tumor indications constituting 67.9 % (197 indications). The analysis of 168 FDA accelerated approvals revealed a sophisticated and multifaceted framework for PMRs, with a strong emphasis on confirmatory trials, clinical pharmacology studies, and additional commitments. The prominence given to confirmatory trials underscores the FDA's dedication to substantiating the clinical benefits observed during the accelerated approval process. It is also important to explicitly acknowledge certain deficiencies in the FDA's use of confirmatory trials. A notable concern is the practice of allowing confirmatory trials that use surrogate endpoints to validate conditional approvals that were initially based on surrogate endpoints. This practice can perpetuate uncertainties regarding the actual clinical benefits of the drug. The reliance on surrogate endpoints may expedite drug approval processes but can also lead to approvals without definitive evidence of meaningful clinical outcomes [4]. A previous systematic review further highlighted these issues. Their study demonstrated substantial variability in the

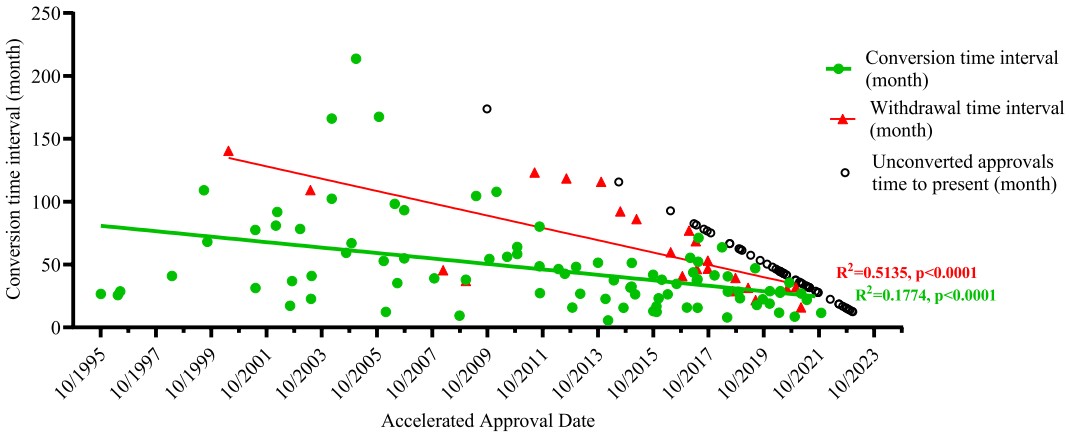

Fig. 4. Evolution of time periods for FDA accelerated approvals transitioning to regular approvals or withdrawals over time.
This figure presents the temporal evolution of the time periods associated with the transition of FDA accelerated approvals to either regular approvals or withdrawals. Each data point represents an individual accelerated approval, with the x-axis indicating the date of accelerated approval and the y-axis representing the duration of the transition period. For those approvals that have not yet undergone transition, the figure illustrates the duration they have been in the accelerated approval state as of the analysis date (December 31, 2023). The trendlines depict the results of simple linear regression analysis.

quantity and quality of post-approval clinical evidence for novel drugs first approved by the FDA based on limited evidence [15]. This reinforces the need for rigorous post-approval studies to substantiate initial findings. This underscores the importance of incorporating robust confirmatory requirements to ensure the clinical efficacy and safety of new drugs. In contrast, China's NMPA introduced conditional approval more recently, in 2017. The nascent nature of this policy was evident in the streamlined set of requirements, which predominantly centered on confirmatory studies and risk management plans. The examination of 41 NMPA conditional approvals suggested a trend toward a more targeted approach, with confirmatory studies being the primary focus. This streamlined approach may reflect the evolving nature of China's conditional approval policy and its emphasis on post-marketing risk control. The FDA's approach was marked by a greater diversity and complexity of post-marketing obligations, reflecting its extensive experience with expedited approval pathways. In contrast, the NMPA's requirements were more streamlined and focused, aligning with the early stages of development of its conditional approval framework.

In addition to the difference in the length of time that the two regulators have introduced the conditional approval policy, there are also differences in the innovativeness of the drugs approved by the two regulators. The drugs approved by the FDA often represent the first in the world to utilize new mechanisms of action or target novel sites, which inherently entails greater uncertainty. During the approval process, the review agencies focus not only on clinical efficacy but also on optimizing dosage, pharmaceutical formulation and clinical pharmacology aspects. Compared with the FDA, there are relatively few global first-in-class drugs approved by the NMPA [16]. At the time of NMPA approval, there are already some reference data, and the review logic of the two regulatory agencies is different [3]. Therefore, the main PMRs of NMPA are the requirements for confirmatory trials, and other exploratory requirements are less. As China's innovative pharmaceutical industry continues to develop [17], regulatory authorities are faced with the challenge of conducting thorough evaluations of entirely new drugs.

Comparison of timeframes for confirmatory requirements is also a key aspect of this study. The downward trend in the duration of timeframes in FDA's accelerated approvals suggested that regulatory stringency for accelerated approval of products is increasing, and that timely validation of a drug's efficacy is highly beneficial to patients and can reduce the uncertainty associated with accelerated approval of products. Recent studies have raised significant public concern by criticizing the FDA's delay in withdrawing accelerated approvals or questioning the clinical value of these approvals [14,18,19]. These criticisms highlight that some oncology products, even after failing confirmatory trials, were not necessarily withdrawn by the FDA, raising questions about the robustness of the accelerated approval process [8]. However, our study showed that the transition periods associated with the conversion of FDA accelerated approvals to regular approvals or withdrawals demonstrated a notable trend of diminishing intervals over the past five years. This trend underscored the FDA's commitment to promptly obtaining the requisite data to either validate the therapeutic benefits of the drugs or to initiate regulatory action in response to emerging concerns. However, the NMPA, in the early stages of conditional approval implementation, proposes more fixed timeframes, typically ranging from 2 to 5 years, but with the potential for variation based on regulatory communication.

The results of our analysis also suggested that the timeframes given by FDA for continuing to complete the original pivotal trial as a confirmatory requirement were generally shorter than the timeframes for starting a new confirmatory trial. This is because earlier initiation of a confirmatory study allows for earlier definitive clinical results and reduces the uncertainty associated with accelerated approval. However, it is important to note that definitive clinical trials do not always show benefits, which highlights the need for rigorous post-marketing surveillance and the readiness to withdraw approvals if trials fail to confirm the expected clinical outcomes. Recent studies have already shown a correlation between the timing of the initiation of confirmatory studies and the time experienced in withdrawing or converting an accelerated-approval product to routine approval [20,21]. FDA's premise for continuing to complete

a pivotal trial as a confirmatory requirement is that the pivotal trials are generally randomized controlled trials that utilize the results of an interim analysis or a surrogate endpoint to apply for accelerated approval. Furthermore, recent study has shown that the percent of randomized and blinded pivotal trials submitted to the FDA decreased between 1995-1997 and 2015–2017 [22]. This trend may impact the robustness of the evidence provided at the time of accelerated approval. Therefore, earlier initiation of confirmatory trials or the design of pivotal trials as randomized controlled trials that can satisfy confirmatory requirements should be encouraged.

The findings of this study have significant policy implications for both the FDA and NMPA. For the FDA, the diverse range of post-marketing requirements (PMRs) reflects a robust framework aimed at ensuring that conditionally approved drugs meet high safety and efficacy standards. However, our results also suggested that the FDA could enhance the monitoring mechanisms to ensure timely completion of confirmatory trials and other studies, thereby reducing the duration drugs remain in an accelerated approval status without full verification of their benefits. The FDA might also consider encouraging the initiation of confirmatory trials earlier in the drug approval process to ensure faster availability of robust clinical benefit data. For the NMPA, the primary focus on confirmatory trials underscored the importance of validating clinical benefits post-approval. Nevertheless, expanding the scope of PMRs to include additional studies related to safety and efficacy could strengthen the conditional approval process. Furthermore, by fostering international collaboration, the NMPA could enhance its framework and effectively manage the conditional approval pathway, drawing on the experiences of more established regulatory bodies.

In summary, this study offers valuable insights into the distinct strategies employed by the FDA and NMPA regarding conditional approvals for anti-tumor drugs. A comparison of PMRs for conditional approvals of oncology drugs between the FDA and NMPA revealed differences in regulatory considerations. The FDA's mature and multifaceted framework contrasts with the NMPA's more targeted and streamlined approach, reflecting the respective stages of development of their conditional approval policies. The variances in both the timeframes and patterns of confirmatory requirements underscore the dynamic nature of regulatory strategies in both jurisdictions. These findings are pivotal for informed regulatory decision-making, balancing the imperative for innovation with the necessity of safeguarding patient welfare in the rapidly evolving field of pharmaceuticals.

Funding statement

This study was supported by the China Society for Drug Regulation under grant number 2023-Y-Y-002.

Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Chenghao Ge: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jing An:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Xiaoyuan Chen:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35454.

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