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EDITORIAL

Criteria and regulatory considerations for the conditional approval of innovative antitumor drugs in China: from the perspective of clinical reviewers

1 | BACKGROUND

Before the State Council of the People's Republic of China issued the "Opinions on the Reform of the Examination and Approval System of Pharmaceutical and Medical Devices" [1], several problems existed in China's drug evaluation and approval system. The long approval time and low efficiency of new drug marketing seriously affected the enthusiasm for drug innovation. To this end, the current "Drug Registration Regulation" (DRR) [2] was initiated by the National Medical Products Administration of China and officially implemented on July 1, 2020. To encourage clinical value-oriented drug innovation, four expedited drug programs were first proposed, including breakthrough therapy drugs, conditional approval, priority review, and special approval procedures. For drugs listed in the expedited programs, the drug regulatory authorities and professional technical institutions should provide policy and technical support, prioritize the allocation of communication and review resources, and thereafter shorten the review time as much as possible.

The breakthrough therapy drug procedure is mainly devoted to the drugs used to prevent and treat diseases that threaten lives or seriously affect the quality of life. More evaluation resources, such as priority communication and more flexible discussion forums of pivotal registration trial design, should be assigned to breakthrough therapy drugs that show obvious clinical advantages during early clinical trials [3, 4]. The purpose of the conditional approval procedure is to "shorten the research and development time of clinical drug trials, making these drugs accessible as soon as possible for patients with critical diseases who can no longer wait" [5, 6]. The priority review procedure is devoted to reducing the waiting time in the marketing authorization application process by implementing a shorter review deadline, giving priority to the arrangement of inspection and verification, and accepting rolling supplementary technical information. The special approval procedure is an accelerated procedure set up to meet the needs of the public for prevention and treatment drugs when there are potential public health emergencies or when public health emergencies occur.

Among the four expedited programs, conditional approval is directly aimed at shortening the time of drug clinical trials, and its supporting policies and approval standards attracted more attention from the industry than the other three programs. Conditional approval may be applied for medicines targeting serious life-threatening diseases for which no effective treatment is available, or medicines that are urgently needed in public health, if the following conditions are met, there are evidence supporting the efficacy and predicting the clinical values of the drugs, or for vaccines that are urgently needed in special circumstances and whose benefits are assessed to outweigh the risks. When comparing with the other applicable situations of conditional approval, "drugs for serious life-threatening diseases without effective treatment" has relatively wider potential applicable objects whose clinical design requirements and review standards are more likely to receive persistent focus with greater regulatory challenges. China's conditional approval has similarities with the United States accelerated approval pathway [7], European Union (EU) conditional marketing authorization [8] and Japanese conditional early approval [9], but differs in details [10]. The current DRR has only been implemented for 2 years, while some China innovative antitumor (including hematological malignancies) drugs have been approved for marketing based on the concept of conditional approval before its official implementation. Additionally, tumors are the most common

List of abbreviations: AML, acute myeloid leukemia; CDE, Center for Drug Evaluation; CR, complete remission; DRR, Drug Registration Regulation; FDA, U.S. Food and Drug Administration; LDAC, low-dose cytarabine; MAH, marketing authorization holder; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1.

indication type to be conditionally approved following the conditional approval procedure coming into force. As of October 1, 2022, 60 of the 77 conditionally approved drugs (calculated by indications) in China are tumor-related. Thus, tumor indications are the forerunners and active practitioners of conditional approval, as well as the relatively mature indications for regulatory consideration. To make the process and standard of technical review of conditionally approved drugs more open and transparent, this paper was developed to demonstrate the criteria of conditional approval in China from the perspective of clinical reviewers of the Center for Drug Evaluation (CDE) with antitumor innovative drugs as the entry points. Additionally, the key challenges faced by regulators in the implementation of conditional approval were also summarized with suggestions to provide directions and ideas for program optimization.

2 | KEY POINTS IN THE PROCESS OF CONDITIONAL APPROVAL COMMUNICATION AND TECHNICAL REVIEW

When reviewing whether a new drug can be studied in clinical research or when submitting a marketing application according to the conditional approval procedure, CDE reviewers will communicate with the applicant many times. In the communication process, the clinical reviewers need to evaluate the clinical data of the drug cautiously and decide whether the drug can be included in the conditional approval procedure. They must also specify the key research data used to support conditional approval application for the drug included in the conditional approval procedure, as well as the confirmatory research requirements for converting to routine approval after marketing. Therefore, conditional approvals differ from routine approvals in early communication, technical review and post-marketing requirements. The applicability and technical requirements of conditional approval may be influenced by the characteristics of the target indication and the degree of innovation of the drug. This may change substantially as clinical practice evolves, highlighting the importance of communication. In the communication of conditional approval of innovative antitumor drugs, the following issues should be addressed:

(1) Applicability of conditional approval corresponding to the target indication. Applicants should analyse the most urgent medical needs of target indications and confirm the target populations that could best benefit from the innovative drug based on the mechanism of action of drugs and the potential advantages according to the existing clinical data. The technical requirements for conditional approval are different between different populations, which is of importance in the formulation of clinical development plans.
(2) Design strategies of the pivotal registration trials supporting the conditional approval. Single-arm trials are usually carried out in heavily treated patients with tumors who showed poor response to the current treatment or experienced multiple recurrences and had no effective therapies available. A randomized controlled trial is more appropriate if the target population has standard treatment or recommended treatment.
(3) Whether surrogate endpoints or proposed intermediate clinical endpoints can predict the long-term clinical benefit? Applicants can prove this with prior data obtained from the same tumor type, but it should be noted that the drug action mechanism may also affect the correlation or degree of correlation between the surrogate/intermediate endpoint and the clinical endpoint. For example, it is generally believed that imaging evidence of tumor shrinkage (objective response rate, ORR) and response duration can reasonably predict the overall survival (OS) of patients. However, the results from confirmatory studies showed that the initial ORR to immune checkpoint inhibitor programmed cell death protein-1 (PD-1) monoclonal antibody is not always a good predictor of long-term survival in patients with cancers [11]. It would offer a strong foundation to present the good correlation between them if data from early clinical trials reflecting the extent of improvement in surrogate and clinical endpoints could be provided and analysed.
(4) To what extent an improvement in a surrogate or intermediate clinical endpoint is considered a "significant improvement"? Applicants should propose a reasonable surrogate endpoint improvement goal and prove that it could benefit patients. Demonstrating this may be very difficult, as there are many cases in which the surrogate endpoint was improved considerably but failed to translate into a long-term survival benefit or to a much lower degree than expected. In patients with acute myeloid leukemia (AML) who were not eligible for intensive therapy, venetoclax combined with low-dose cytarabine (LDAC) increased the complete remission (CR) rate to 47%, compared with 15% from LDAC monotherapy, but the OS was not significantly improved (hazard ratio = 0.75, $P = 0.11$) [12]. Therefore, to reasonably predict clinical benefit, it should not only focus on whether the surrogate endpoint is achieved in conditional approval but also the clinical endpoint data that have been obtained.
(5) Specific requirements for confirmatory trials. Conditional approval should not affect the normal progress

of clinical research and development plans, nor should it be a reason for interrupting or delaying confirmatory trials. Applicants should reach an agreement with CDE on the specific requirements for confirmatory trials at the time of communication of the technical requirements for the conditional approval of marketing. According to the general research and development law, the applicant should start confirmatory trials as soon as possible if the trial results supporting the conditional approval are positive. The drug registration certificate for conditional approval should contain specific confirmatory studies. In principle, the marketing authorization holder (MAH) should not make substantial changes to the target population, treatment regimen, control treatment, primary efficacy endpoint and other elements of the confirmatory study for reasons such as unsuccessful study conduct or inconsistent results.

3 | REVIEWERS' DECISION PROCESS FOR THE APPLICABILITY OF CONDITIONAL APPROVALS

After the applicant applied for the conditional approval procedure, the decision-making process and evaluation dimensions of the CDE review department attracted much attention. Reviewers' key considerations and general criteria in the decision process of the conditional approval applicability are shown in Figure 1. The applicability of conditional approval of an innovative drug should be supported with its own clinical data rather than the experiences of other drugs with similar action of mechanism. In the absence of reliable historical data, applicants should consider conducting small randomized controlled trials as a basis for decision-making on the applicability of conditional approval.

Noticeably, it is impractical and unfair if all conditional approvals apply a quantified and rigid decision criterion, as the innovativeness, the understanding of the product mechanism and disease, and the urgency of medical needs of the target indication population vary and affect the technical requirements of the conditional approval. Since clinical value orientation is the core of the conditional approval process, the review department's suggestions in each communication address the temporal clinical needs of the target treatment population at the time when communication occurs. Drug approval for marketing depends on the treatment available to the target indication population at the time of regulatory decision-making and the therapeutic advantage identified from the clinical data. This means that applicants should adjust their research and development strategies in time once important changes have arisen in clinical practice.

4 | ISSUES ENCOUNTERED DURING THE IMPLEMENTATION OF THE CONDITIONAL APPROVAL PROCEDURES AND REGULATORY CONSIDERATIONS

(1) Impact of conditionally approved drugs on the subsequent applications for conditional approval of the same indication. During the communication phase, several drugs may have obtained positive early research data in the same indication population during the same period, and all are permitted to conduct clinical studies in accordance with the conditional approval strategy. If drug A is the first to obtain conditional approval for marketing, other drugs can still submit conditional approval applications in accordance with the consensus reached with CDE after the completion of the pivotal registration study. However, once drug A completed the confirmatory study and successfully obtained routine approval, the existing treatment methods and clinical practice of the indication population changed, with the applicability or technical requirements for conditional approval changed as well. Thus, the subsequent conditional approval applications are likely to be rejected if the clinical trials are implemented according to the previous technical requirements, and other drugs with the same action mechanism as drug A will no longer be eligible for conditional approval for this indication.

(2) Conditionally approved drugs and priority review procedures. According to the current DRR [2], "drugs meeting conditional approval" can apply for priority review procedures. In principle, only drugs with outstanding clinical advantages indicated by clinical trials may be qualified for conditional approval and are usually included in the priority review and approval process. However, the clinical value of the application for conditional approval of the same indication will be greatly weakened if a drug with the same action mechanism has been conditionally approved, causing the loss of priority review and approval.

(3) Conditional approval of drugs and "available treatments". It is highlighted in the "Technical Guidelines for Conditional Approval of Drugs (Trial)" [6] that "drugs with conditional approval for marketing shall not be used as available treatment methods before clinical benefits have been confirmed". However, the guidelines also state that "available treatments refer to drugs accepted as standard treatments in China". It

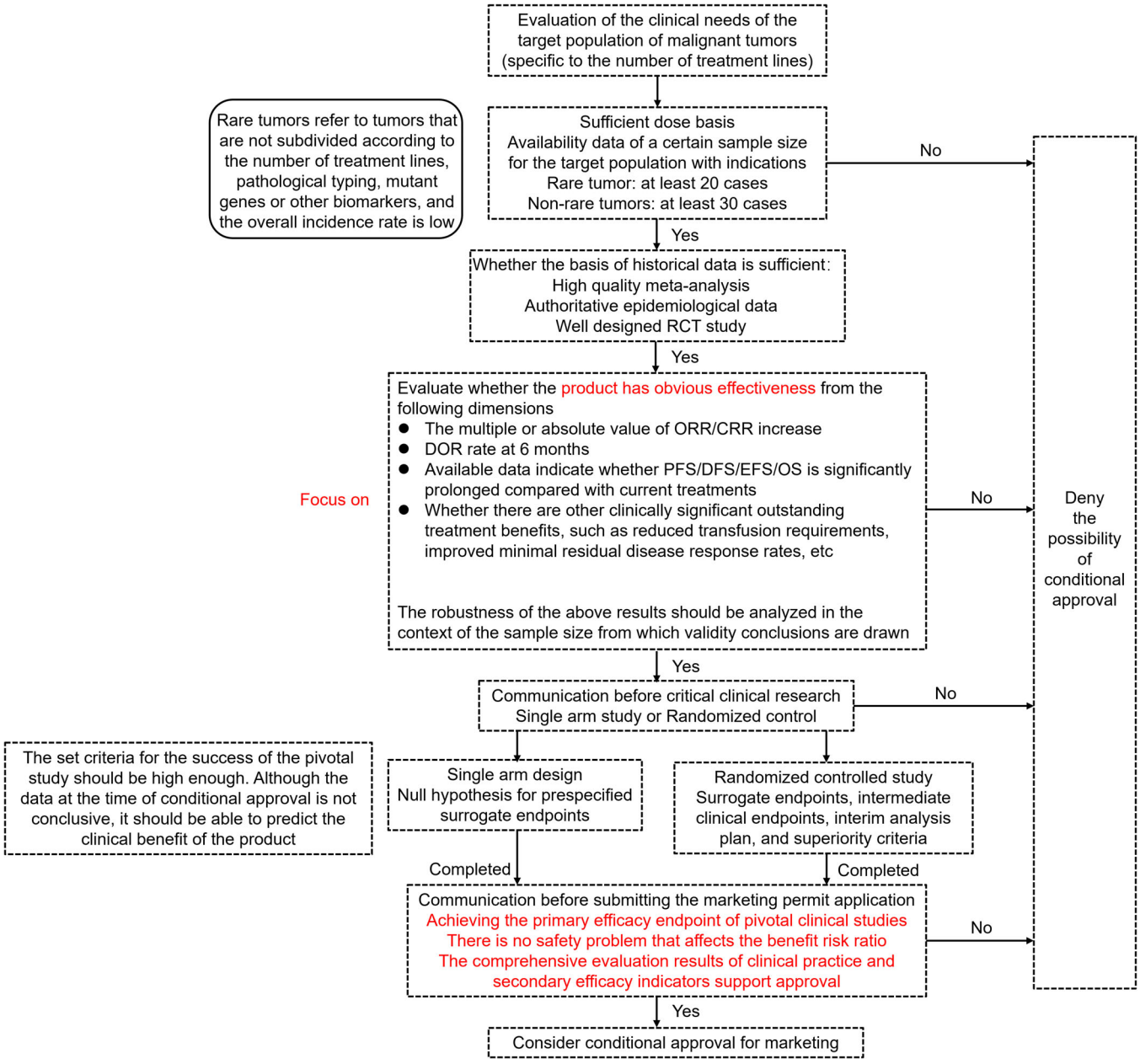

FIGURE 1 Applicability decision tree of the working procedures for conditional approval of innovative antitumor drugs.
Abbreviations: RCT, randomized controlled trial; ORR, objective remission rate; CRR, complete remission rate; DOR, duration of remission; PFS, progression-free survival; DFS, disease-free survival; EFS, event-free survival; OS, overall survival.

is not uncommon that clinical practice-defined standard treatment is not completely consistent with the drug's approved indications. For example, azacitidine has not been approved by regulatory agencies globally for the treatment of AML with ≥30% bone marrow blasts, but it has been accepted by hematologists worldwide as the standard treatment regimen for AML patients who cannot receive intensive chemotherapy. There is no reason to exclude these drugs from available treatments. Even if not used as an "available treatment", research results of conditionally approved drugs are part of the historical data and provide a good review reference for other drugs pursuing conditional approval targeting the same indication. In this case, the EU states that "While the specific obligations are not yet fully completed, it is not possible to confirm the full benefit of a conditionally authorized product, therefore another medicinal product could potentially address the same unmet medical needs, provided it is expected, based on appropriate scientific

data, that such a product addresses the unmet medical needs to a similar or greater extent than what is understood for the already conditionally authorized product. A second (or subsequent) medicinal product could in such case be recommended for a conditional marketing authorisation".

(4) The validity period of the registration certificate for conditionally approved drugs and the time limit for the completion of the confirmatory trial. The validity period of the certificate for routinely approved drugs is 5 years [2], so the validity period of the registration certificate for conditionally approved drugs cannot be longer than 5 years. The review time limit for the supplementary application of confirmatory trial data is 200 days [2]. Therefore, the application needs to be submitted within 4 years of the conditional approval in principle. In fact, it is a very legitimate problem for all relevant drug regulatory agencies to press the MAHs to complete confirmatory trials as soon as possible after conditional approval, and setting an expiration date should be a practical solution. The time from marketing approval to carrying out the confirmatory studies was more than 6 years in 21% and 27% of the drugs conditionally approved by the US Food and Drug Administration (FDA) and European Medicines Agency [13]. Thus, China's time limit places pressure on drugs that are under conditional approval. It has been shown by US FDA data that the time from approval to completion of confirmation is significantly shorter (3.1 years vs. 5.5 years) for drugs that have already initiated confirmatory studies when accelerated approval is granted, than those drugs which have not started a confirmatory study at the time of obtaining accelerated approval [13]. Apart from the time advantage directly brought by early start-up, the fact that the attitude of subjects with control treatment will be affected by the expected benefit of the test drug makes the enrolment of the confirmatory trial started after the accelerated approval more difficult.

5 | CONCLUSIONS

The specific process and decision-making criteria for accelerating the marketing registration process have attracted wide attention since the date of implementation. Tumor indications account for the highest proportion of the indications of conditionally approved drugs for marketing. The new antitumor drug research and development companies pay close attention to the perspectives and criteria that the CDE tumor indication team typically uses to evaluate the clinical advantages of antitumor drugs. The publication of the technical considerations formed in the review process can enable the industry and academia to better understand the review conclusions of the regulatory agencies and can also help research and development companies to more specifically summarize and analyze the clinical research results of new drugs to improve the clinical development efficiency of new drugs. At the same time, during the implementation of China's conditional approval procedure, there will inevitably be technical and management problems. Only by constantly summarizing and sorting these out can problems be solved or working procedures be continuously optimized. As a direct practitioner, CDE must be open and transparent in order to maximize the incentive effect of accelerating the marketing registration process to encourage innovation. This would serve to allow patients to benefit from drug innovation as soon as possible. We hope this article can help new drug developers and trigger more thinking and discussion on China's conditional approval procedure.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Research concept and design: Zhimin Yang, Limin Zou, and Yueli Qi. Collection and/or assembly of data and policy: Limin Zou, Yueli Qi, Yongling Jiang, Ling Tang, Yu Du, Boyuan Zhao, Yanzhe Sun, Jun Ma, and Meiyi Xiang. Analysis and interpretation of data and policy: Limin Zou, Yueli Qi, Yongling Jiang, Ling Tang, and Yu Du. Writing the article: Limin Zou and Yueli Qi. All authors approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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AVAILABILITY OF DATA AND MATERIALS

The datasets used during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

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