OPINION

The changing landscape of clinical trial and approval processes in China

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Abstract | In the past decade, the standards of clinical trials in China have moved closer to international standards, thus encouraging the development of innovative drugs. However, a large backlog of pending applications for both drug approval and clinical trial registration has arisen owing to the complexity of the approval process, the volume of applications and a lack of staff available to process these applications, among other reasons. To improve the drug approval process, a 'four-colour-light' strategy was introduced. Different drugs are classified into redefined categories of innovative and generic drugs, with priority being given to approval decisions concerning innovative drugs. Other improvement strategies are now also being implemented, including the development of a new clinical trial approval system and several measures designed to encourage greater participation of Chinese researchers and research centres in international clinical trials. In this Perspective, the changing landscape of clinical approval in China is described, including the difficulties that drug approval authorities face in this rapidly developing nation and the novel strategies that are being used to find solutions.

In the past 10 years, following substantial increases in the number of patients available to be enrolled in trials and the opportunities created by the availability of many new anticancer drugs, the standards of clinical trials conducted in China are approaching those of international, multicentre trials. Nevertheless, the processes that regulate the testing and approval of novel anticancer drugs in China have not always replicated the performance of other regulatory and approval systems. Over the past 15 years, the development of anticancer drugs in China can be divided into three different periods with varying characteristics. Firstly, during 2003–2008, the number of clinical trial applications was low and the approval process was generally effective; furthermore, the availability of numerous patient resources for clinical trials expedited the drug-development and drug-approval processes, which were approximately equal in terms of performance to those of other nations. Between 2010–2013, increasingly large numbers of applications for both new drug approvals and clinical trials were submitted to the China Food and Drug Administration (CFDA), without any notable increase in resources or staffing levels, which resulted in a severe backlog of applications and delays in the drug-approval process. During this period, the development and approval of anticancer drugs remained not dissimilar to that of several other countries. After 2013, however, the backlog increased and the extent of delays in clinical trial and drug marketing approval decisions was extended. For example, during this period, immune-checkpoint inhibitors, including anti-CTLA-4 and anti-PD-1 antibodies, became the focus of international, multicentre clinical trials, and have demonstrated exciting efficacy and safety profiles in patients with advanced-stage melanoma or non-small-cell lung cancer (NSCLC), and a variety of other malignancies. By contrast, these paradigm-shifting agents, including nivolumab, pembrolizumab, and atezolizumab only entered clinical trials in China in as recently as July 2015 (NCT02825940), October 2015 (NCT02593786), or January 2016 (NCT02835690). According to the current pace of clinical research in China, clinical trial data on the safety and efficacy of these agents in Chinese patient cohorts will be published at least 3–5 years later than the equivalent data from cohorts of patients in other countries. If this situation continues, this gap in the time taken to obtain meaningful clinical data in China compared with the USA could increase further, possibly even to 10 years.

On the basis of data from clinical trials with large cohorts of patients, verification of the effectiveness of new agents was previously simple and enabled access to new drugs within an acceptable timeframe. However, owing to the large and increasing numbers of innovative anticancer agents that are currently available, the time delay involved in drug-approval decisions has increased substantially. This situation has resulted in considerable delays in the speed of both clinical trial enrolment and in the time taken to reach an approval decision, despite an abundance of eligible patients both for clinical trial participation, and that could benefit from new treatments. These delays in approval come during a period in which the Chinese biopharmaceutical industry is undergoing rapid development. Furthermore, the emphasis of this industry is moving away from generic drugs, towards the development of innovative drugs. Currently, a large number of new and generic drugs await registration or approval by the CFDA[1]. Thus, clinical trial registration and drug-approval processes in China are facing unavoidable challenges.

Existing problems

Data management. The management of clinical trial data in China requires further improvement. Before 2015, data from most clinical trials were recorded primarily in paper case-report forms, which complicated the review process, reduced approval efficiency, and delayed the processing of approval applications. However, in August 2016, the technical guidelines for electronic data capture (EDC) in clinical trials were released in an official announcement by the CFDA, and resulted in EDC becoming the standard approach to the management of clinical trial data in China[2].

Severe application backlogs. The approval procedures for innovative drugs and those for generic drugs in China are different; in general, although the time take for approval of innovative drugs has historically been shorter than that for generic drugs, a severe backlog of pending approval decisions has accumulated for novel agents. Furthermore, vast numbers of generic drugs remain on the waiting list for approval, owing to delays in examination and approval of each case by the CFDA. This backlog arose, in part, from a lack of trained staff.

With the approval queue growing excessively long, the CFDA currently faces considerable pressure. In 2014, the backlog of cases pending an approval decision from the National Center for Drug Evaluation (CDE) was as high as 18,597; in 2015, >21,000 applications awaited review by the CDE. The majority of these applications were for generic drugs. According to the previous CFDA 'administrative measures for drug registration (2007)' (REF. 3), the durations of clinical trial registration and drug product application review should be 90 working days and 150 working days (approximately 4 and 7 months), respectively. In reality, in the past few years, most of this time has been spent in a queue before a decision process even being started, and the actual duration of the review decision depended on both the number of applications and the efficiency of the CDE: between 2013–2015, the average time delay for an application to register a clinical trial of an innovative drug was 14 months. The duration of the approval process for icotinib, an EGFR tyrosine-kinase inhibitor (TKI) indicated for the treatment of advanced-stage NSCLC, was 10 months. For apatinib, a VEGFR TKI used in the treatment of patients with advanced-stage gastric cancer, the approval process was initiated after completion of the phase III trial in July 2013 and the drug was approved in September 2014 — an interval of 14 months[4]. Delays of such a length in turn result in delayed access of patients with life-threatening diseases to potentially curative, or life-preserving treatments.

With the rapid development of anticancer drugs, many researchers have shifted the focus of their work from chemotherapy to targeted therapies and/or immunotherapy, which have generally demonstrated improved efficacy and often lower risks of toxicity compared with chemotherapy. The toxicities associated with immunotherapies are, however, very different from those typically associated with chemotherapies. Therefore, attempting to make approval decisions regarding the use of these novel therapies using basically the same approaches as were used 20 years ago will probably further prolong the approval process. In particular, the approval of anticancer agents with entirely new mechanisms of action, such as oncolytic viruses, has led to the feasibility of the traditional evaluation system being called into question[5,6]. Furthermore, several immune-checkpoint inhibitors, such as anti-PD-1 antibodies, have been approved by both the FDA and EMA for clinical use in the USA and Europe, respectively, but clinical trials investigating the safety and efficacy of these agents in China, including anti-PD-1/PD-L1 antibodies in patients with advanced-stage or recurrent solid tumours (NCT02593786 and NCT02825940) or advanced-stage NSCLC (NCT02835690) commenced enrolment as late as January 2016. Importantly, responses to these agents should be defined using a different set of criteria to those used to define responses to chemotherapy or targeted therapy.

The 'closed-door enrolment' policy. The clinical trial registration and approval process used by the CFDA is different from that used by the FDA. The FDA uses an investigational new drug (IND) filing system. If the available data demonstrate that the safety and tolerability profile of a drug is acceptable, the clinical trial under application can be initiated 30 days after IND filing. By contrast, the CFDA uses a clinical trial approval (CTA) process whereby the CDE reviews each trial protocol individually, even if the trial is designed for a generic drug. The applicant must then obtain an approval letter from the CDE before a clinical trial can be initiated. After all approved clinical trials are completed, a new drug application (NDA) must also be submitted to the CDE. Several steps of this approval process are repetitive. Both the heavy workload involved in obtaining a CTA and the duplication of several aspects of this work in submission of the NDA are major reasons for the severe backlog of applications and the major delays in the processing of new drug approvals in China[7,8].

The 'closed-door enrolment policy', imposed on approval decisions relating to a new drug, describes an overly strict approach to the approval of clinical trial applications, contrasted by an overly lax approach to the approval of marketing applications. This policy has resulted in a notable widening of the gap between domestic and international clinical research, resulting in China falling many years behind other countries in terms of the approval of new drugs. Thus, a robust approval strategy should involve a more-permissive attitude to clinical trial applications while, at the same time, introducing a more-stringent attitude to marketing approval: only in this way can the current delays in clinical trial and approval processes for anticancer drugs in China be improved. Indeed, the clinical implementation of several new drugs in China has been delayed for several years after their FDA approval (TABLE 1). Despite these widespread delays, some urgently needed anticancer drugs with notable anticancer effects were granted accelerated approval by the CDE, resulting in the more-rapid approval of these selected drugs (TABLE 1).

Improving clinical trial procedures

Changes in clinical approval processes also promote improvements in clinical trial standards within China, including improved data management. The clinical value-oriented approval principle will guide enterprises to pursue the development of innovative agents, as well as cost-efficiency. On 23 November 2015, the CFDA submitted a report to the State Council (the *CFDA Announcement of Policies on Review and Approval of Drug Registration*[9]), which made specific stipulations on the optimization of the clinical trial application process. The announcement pointed out that a 'one-off' approval should be applied to the registration of clinical trials of new drugs; the scientific merit and safety of the clinical trial protocol should be the key elements for review; communication between the reviewers of the application and the applicants should be optimized; and applicants should maintain and update their research data in a timely manner. Furthermore, the report emphasized that the process for approval of innovative versus generic drugs should be separated. Bioequivalence tests for generic drugs should be changed from an approval system to a system in which the information is recorded, thus promoting investment into clinical trials of innovative agents, and facilitating improvements in the standards of clinical trials. The use of an IND filing system for anticancer drugs, similar to that deployed by the FDA, is currently under discussion.

Similar to the approach used by the FDA, the testing and approval processes for new drugs in China requires further classification, for example, according to the standard phase I–III clinical trials schema, and after approval, phase IV studies. Furthermore, use of EDC, instead of applicants submitting data recorded in other ways to the CFDA

is now the recommended approach to data management. The required sample sizes for cohorts of Chinese patients are now calculated according to the relevant statistical principles, rather than the previous approach, which was based on limitations in minimum sample size. Furthermore, the CFDA has constructed a 'Platform for Registry and Publicity of Drug Clinical Trials', and all clinical trials (including bioequivalence studies, pharmacokinetics studies, phase I, II, III and IV clinical trials) approved by the CFDA and conducted in China should be registered on this platform, including public study information. Meanwhile, all trials should be carried out at sites with 'Good Clinical Practice' certification, in order to ensure strict adherence to serious adverse event reporting and auditing mechanisms. In addition, the CFDA drafted the '*Technical Guidelines of Data Management in Clinical Trials*' (REF. 10), the '*Technical Guidelines of EDC in Clinical Trials*' (REF. 2) and the '*Guidelines of Planning and Reporting Data Management and Statistical Analysis in Clinical Trials*' (REF. 11). These guidelines are intended to improve data management in clinical trials in China, and have facilitated in-depth discussions and education on these issues among clinical technicians[12,13]. All results reported to the CFDA are reviewed strictly; however, no explicit standard for publication of clinical trial data has been established thus far. Safety reporting regulations, including those for severe adverse events (SAEs), should also follow international standards. With this in mind, applicants are required to submit drug monitoring protocols and annual reports to the Adverse Drug Reactions Monitoring Center during each clinical trial stage, and after approval of the agent. As part of the process of drug registration, the CDE conducts on-site inspections, causal inspections, unannounced inspections, and institutional reviews of the relevant clinical trial locations, as well as production-site inspections before premarketing approval, in order to confirm the authenticity, precision, and integrity of the information contained in the submitted dossier.

Despite the various issues with clinical trial registration and drug-approval processes, clinical trials of innovative anticancer agents with particular relevance to Chinese patients have gained international recognition. Data on drugs, such as icotinib[14], apatinib[4], and chidamide[15], from clinical trials conducted in China have been published in various high-profile oncology journals (TABLE 2). In addition, other anticancer drugs that are likely to be of particular relevance to Chinese patients, including volitinib[16] and icaritin[17,18], are currently in early phase clinical trials (NCT01985555, NCT01972672). The Chinese Thoracic Oncology Group (CTONG), which was founded in 2007, is a network involving specialists from the country's top 31 hospitals, which has initiated at least five multicentre clinical trials in patients with lung cancer. The CTONG has reported many original data, several of which have been published in high-profile oncology journals[19–22]. These results have led to substantial improvements in clinical practice. The CTONG is now carrying out novel clinical trials to develop new anticancer drugs, with designs similar to those of 'basket' or 'umbrella' trials performed in other countries[23–26]. Genomic-variant-driven trials are designed based on the presence of specific mutations, or other biomarkers[27,28]. In these trials, patients receive different treatment strategies based on the presence of a specific genetic variant rather than on the type of cancer, which is hoped will lead to better clinical outcomes. Such 'precision medicine' is currently being applied to cancer treatment. For example, the presence of *EGFR* mutations and the *EML4–ALK* fusion gene are routinely tested for before commencing treatment with EGFR or ALK TKIs in patients with advanced-stage NSCLC in major treatment centres in China. Other novel study designs, such as cluster trials[29] and *n*-of-1 trials[30] are also being adopted.

In addition, Chinese clinical research centres have participated in various international multicentre trials, which has enhanced clinical trials capacity and promoted the development of new drugs in China. Data from these international, multicentre clinical trials can also be used in decisions by the CFDA on the marketing approval of new anticancer drugs. Chinese investigators have contributed data to the clinical trials of gefitinib[31], erlotinib[19,21,32], pemetrexed[33], bevacizumab[34], sorafenib[35], crizotinib[36–38], ceritinib[27], and others. In clinical trials assessing the efficacy of afatinib in patients with NSCLC, Chinese investigators cooperated closely with those from other countries[39–42], providing a substantial amount of data. Furthermore, substantial differences exist in the incidence of *EGFR* mutations among patients with NSCLC, with a reported 27–62% of patients of East Asian ethnicity harbouring *EGFR* mutations[43–45], compared with 19% of African-American patients, and 10–15% of white patients[46–49]. This high level of genetic heterogeneity across patients of different ethnicities makes the use of international multicentre, collaborative trials very important, and provides opportunities for investigators in China to participate in international multicentre trials. A total of 317 trials involving patients with NSCLC were registered on the ClinicalTrials.gov website

Table 1 | **Selected anticancer drug approvals in China and in the USA**

Agent	Indication	FDA approval date	CFDA approval date
Delayed approval			
Dasatinib	Philadelphia-chromosome-positive leukaemia	June 2006	September 2011
Bevacizumab*	Advanced-stage NSCLC	October 2006	July 2015
Pemetrexed ‡	Non-squamous-cell carcinoma lung cancer	February 2004	December 2005
Everolimus	Advanced-stage renal cell carcinoma	March 2009	January 2013
Aprepitant	Chemotherapy-induced nausea and vomiting	March 2003	June 2013
Lenalidomide	Relapsed/refractory multiple myeloma	June 2006	December 2012
Axitinib	Renal cell carcinoma.	January 2012	April 2015
Accelerated approval			
Imatinib	Philadelphia-chromosome-positive CML	May 2001	April 2002
Gefitinib	Locally advanced or metastatic NSCLC	May 2003	December 2004
Erlotinib	Locally advanced or metastatic NSCLC	November 2004	April 2006
Nilotinib	Philadelphia-chromosome-positive CML	October 2007	July 2009
Crizotinib	Advanced-stage *ALK*- positive NSCLC	August 2011	January 2013
Sorafenib	Advanced-stage renal cell carcinoma	December 2005	September 2006
Sunitinib	Advanced-stage renal cell carcinoma	January 2006	November 2007

CML, chronic myeloid leukaemia; CFDA, Chinese Food and Drug Administration; FDA, US Food and Drug Administration; NSCLC, non-small-cell lung cancer. *Plus carboplatin and paclitaxel. ‡Plus cisplatin.

between 1 January 2007 and 31 December 2015. Among these, 45 international multicentre trials were conducted with the participation of Chinese investigators.

Changes in registration

Improvement measures. In August 2015, the CFDA submitted to the State Council the '*Opinions on Reforming the Review and Approval System of Drugs and Medical Devices*' (REF. 50) (referred to as 'The Opinions'). The Opinions defined the targets, tasks, and measures for the reforms, and national conferences were convened to facilitate the dissemination and implementation of these reforms. A sectoral joint conference system has been established, and 10 supporting documents have been issued. Overall, the reforms have resulted in some initial progress.

The National Drug Approval System Reformation Conference was held on 24–25 August 2015, in Shanghai. On the basis of 'The Opinions', the head of the CFDA, Jing-Quan Bi, introduced a 'four-colour-light' strategy to be applied to the prioritization of approval decisions for drugs based upon the level of innovation and the intended indication[51]. The four-colour-light strategy classifies 'globally innovative drugs' into the 'no-light' category; innovative agents, which are urgently needed in the clinic and contribute to industrial restructuring, are classified into the 'green-light' category; generic drugs, for which alternative agents are also available, fall into the 'yellow-light' category; and agents for indications that are in the restricted approval catalogues are classified into the 'red-light' category. Classification in the 'red-light' category completely precludes clinical approval. The directory of restriction approval catalogues should be updated and published in a timely manner. Agents in the 'no-light' category include globally innovative drugs (those not listed in any country), such as chidamide, a novel benzamide-type histone deacetylase inhibitor, which is under investigation for the treatment of peripheral T-cell lymphoma[52]. Before these innovative drugs enter overseas markets, the government allows Chinese researchers to carry out clinical trials involving these agents. This approach encourages domestic clinical research centres within China to participate in international studies, and enables the high-quality clinical research data generated from such trials to be used for the approval of innovative drugs, thereby facilitating the synchronization of drug approval in China with that of the rest of the world. Drugs in this category, whether supplied by a domestic or foreign manufacturer, will receive the highest level of priority, resulting in the duration of the review process being dramatically reduced. All agents that are intended for urgently needed clinical indications or those deemed likely to substantially strengthen Chinese industrial output are generally classified into the 'green-light' category, which includes innovative drugs for the prevention and/or treatment of acquired immunodeficiency syndrome (AIDS), cancer, common infectious diseases, rare diseases that currently have no available treatment, and childhood diseases, as listed in the 'Chinese National Science and Technology Major Projects' list[50], provided by the CFDA jointly with the Development and Reform Commission, Ministry of Science and Technology, Ministry of Industry and Information Technology, Health and Family Planning Committee. Drugs within the 'no-light' and 'green light' areas are given priority, thus approval processes are accelerated and more patients are able to obtain benefits from these agents. The ultimate aim of this strategy is to prioritize the evaluation of innovative anticancer drugs with data that suggest considerable efficacy, so that such agents can be made available to patients as early as possible.

A further aim of the 'four-colour-light strategy' approval system is to accelerate the drug-approval process. A series of other reforms were also introduced with this aim, including new systems of compensable service, professional team review, project management, meetings between reviewers and applicants, expert advisory committees, and the publication of review information. In addition, a clinical efficacy-oriented review system was established in an attempt to speed up the approval process. To promote this process, the reform is mainly focused on "changing the approval system, solving the backlog, and increasing the quality" (REF. 53). In 2015, the number of cases processed by the CDE was 9,601, which exceeded the number of applications submitted for approval (8,211) by 1,390 (REF. 53).

One reason for the backlog of applications for processing by the CFDA is that submitting an application for approval of a new drug in China is inexpensive. The cost of a new drug-approval application made to the CFDA before 2015 was approximately 25,000 yuan (US$3,623), while the approximate cost of a similar FDA approval application was $569,000. This low cost of approval

Table 2 | **Published data from clinical trials of innovative anticancer drugs in China**

Innovative drug	Publication	Journal	Year
Icotinib	Icotinib in patients with pretreated advanced oesophageal squamous cell carcinoma with EGFR overexpression or *EGFR* gene amplification: a single-arm, multicentre phase II study.	*J. Thorac. Oncol.*	2016 (REF. 62)
	Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomized, double-blind, phase III non-inferiority trial.	*Lancet Oncol.*	2013 (REF. 14)
	Phase I study of icotinib hydrochloride, an oral EGFR–tyrosine-kinase inhibitor, in patients with advanced-stage NSCLC and other solid tumours.	*Ann. Oncol.*	2011 (REF. 63)
Apatinib	Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction.	*J. Clin. Oncol.*	2016 (REF. 4)
	Apatinib for chemotherapy-refractory advanced-stage metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial.	*J. Clin. Oncol.*	2013 (REF. 64)
	YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity *in vitro* and *in vivo*.	*Cancer Sci.*	2011 (REF. 65)
Chidamide	Results from a multicentre, open-label, pivotal phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma.	*Ann. Oncol.*	2015 (REF. 15)
	Phase I study of chidamide (CS055/HBI-8000), a new histone deacetylase inhibitor, in patients with advanced solid tumours and lymphomas.	*Cancer Chemother. Pharmacol.*	2012 (REF. 66)

EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; VEGFR, vascular endothelial growth factor receptor.

applications might stimulate the development of new drugs by pharmaceutical companies, although it also causes companies to submit speculative applications without a sufficient level of prior consideration, thus greatly increasing the burden placed upon on the drug-approval agency. In order to limit the total number of approval applications received, the CFDA implemented a compensable service policy, which involves charging applicants based on the application classification. Now, the cost of an approval for a novel drug from international pharmaceutical companies is 593,900 yuan ($86,072), 432,000 yuan ($62,608) for a novel drug from domestic pharmaceutical companies, 502,000 yuan ($72,754) for a generic drug from international pharmaceutical companies, and 318,000 yuan ($46,087) for a generic drug from domestic pharmaceutical companies[51].

In an attempt to eliminate the issue of clinical trial data falsification, the CFDA published the '*Announcement of the State Food and Drug Administration on Carrying out Self-checking and Checking of Drug Clinical Trial Data*' (REF. 54) in July 2015. Since the date of promulgation of this announcement, all applicants for drug registration that have been declared or are pending review must carry out self-checking and be able to guarantee the authenticity, reliability, and standardization of the submitted clinical trial data and any other relevant materials. If the data are found to be falsified, the sponsor is banned from submitting a NDA or biologic license application for 3 years.

The CDE is one of the main sectors of the CFDA, and has a very important role in the drug-approval process: the CDE is predominantly responsible for the review of all information provided by the applicant on the efficacy and safety of the drug, the approval of clinical studies, and assessments of clinical results. Before August 2015, the CDE had only 120 staff, meaning that the CDE was poorly equipped to handle the average annual workload of >9,000 applications — another reason for the backlog of applications. Thus, increasing the number of CDE employees will increase the speed of drug approval decisions, and the State Council of China is currently providing increased funding to enable the CDE to hire and train more staff.

Influence of drug classification. The previous drug registration classification system could not efficiently facilitate the priority review of applications involving innovative drugs. Thus, the scope of 'special approval procedures' and priority approval has been expanded. According to this 'special approval procedure', in 2015, the CFDA approved three new vaccines: an inactivated polio vaccine, an inactivated foot-and-mouth disease-EV71 vaccine and a *Helicobacter pylori* vaccine[55–57]. In addition, the CFDA has also conducted an expedited review of a clinical trial application regarding a domestically produced, independently developed recombinant Ebola vaccine[58] that has enabled this agent to enter clinical testing in patients (NCT02326194).

On the 26th of February 2016, the CFDA published the '*CFDA Opinions on Priority Review and Approval of Registration Backlogs*' (REF. 59). This document states in detail that drugs in the 'no-light' or 'green-light' categories with significant clinical value — those that can be used to prevent and/or treat serious diseases, with obvious clinical advantages — should be included for priority approval. This policy is one of the implementations of the 'four-colour-light' principle.

The definition of 'new' drugs has been redefined. Globally innovative drugs were previously defined as 'new' drugs. Furthermore, agents in this category were divided into 'innovative' and 'modified' new drugs. Among these new drugs, most are classed as new chemical entities or new molecular entities, which refer to drugs with distinctly different chemical structures to those of widely used agents, and are clinically safe and effective. The '*Registration reform work program of chemical agent classification*' (REF. 60) published by the CFDA has updated the categories of chemical drug registration, and redefined the definition of 'innovative drug' from nationally innovative drugs (drugs not listed in China) to 'globally innovative drugs' (those not listed in China or in other countries). Drugs that are optimized versions of previously approved agents (with a known structure and active ingredient), which are, therefore, often similar in terms of structure, dosage, route of administration, indication and/or use as a combination therapy, and often also treatment outcome, are no longer eligible for classification as 'new' drugs. The CFDA emphasizes 'clinical value-oriented approval', therefore, drugs with designs that are based on those of previously approved agents must show superior efficacy compared with that of the previously approved agent[60].

The definition of a 'generic drug' was also updated from a generic version of an existing national standard drug to a generic version with quality and efficacy that is consistent with that of the original drug[60]. From 2007 to 2015, new drugs belonging to category 3.1 (drugs marketed abroad and not in China) have comprised the commonest of all approval applications, and have been classified as generic drugs. Since 2015, however, new drug-registration classifications have been introduced. For example, candidates for approval are no longer defined as 'domestic' or 'foreign', thus supporting an increasingly international approach (TABLE 3). The introduction of these new drug-registration classifications indicates the determination of the Chinese government to encourage innovative drug development. Nevertheless, the future version of the '*Registered Classification of Chemicals and Requirements of Application*' requires further development. In summary, the core objective of these various reforms is to encourage innovative drug development, especially of globally innovative drugs and to limit the number of applications for approval of drugs in the 'yellow-light' and 'red-light' categories.

The Chinese government, following the announcement of these new approval processes, also announced that, within 3 years, drug-approval rates would be adjusted, that an efficient scientific evaluation system would be established, and that the approval of drugs for which many alternative treatments are available would become more strictly controlled. The government set a timeline for dealing with the backlog of applications before the end of 2016, and routinely delivering approval decisions within a stipulated time limit by 2018 (REF. 61).

Future prospects

China has undergone 30 years of reform, including opening up to collaborations outside of China, and rapid economic development. As part of the 13th 5-year plan, the Chinese government aims to create a more innovation-oriented economy. As one of the more important components of the economy, the pharmaceutical industry is undergoing a period of reform with the aim of encouraging greater innovation. In 2015, the economic output of the Chinese pharmaceutical industry reached 2,884 billion yuan (about $443 billion). In the past 10 years, several thousand billion yuan have been invested in new drug research and development in China, including in state-owned and local scientific research institutes, private research institutions, Chinese pharmaceutical R&D teams that have returned from working outside of China and, especially, R&D centres of various foreign pharmaceutical companies in China. Great progress has also been made in basic life-sciences research. Many innovative

Table 3 | **Comparisons of the registration of drugs in China**

Drug category	New classification (after March 2016)	Old classification (October 2007–March 2016)
Global innovative drugs	'Global innovation drugs' now include those not listed in China or abroad. Among these new drugs, most are new chemical entities (NCEs) and new molecular entities (NMEs), which refer to drugs with new material bases that are clinically safe and effective	Drugs that are not marketed both domestically and abroad, including six subclassifications
	Drugs that are optimized versions of previously approved agents (with a known structure and active ingredient), and are therefore often similar in terms of structure, dosage, route of administration, indication and/or use as a combination therapy, and also treatment outcome are no longer considered 'global innovation drugs'	Modified new preparations (including different routes of administration) that were not previously marketed both in China and/or abroad
Generic drugs	A generic version must have quality and efficacy that is consistent with that of the original drug (either listed or not listed in China)	A generic version of a drug approved in China (also approved abroad), including: changes in the acid radical, base (or metallic element) of marketed formulations, without changing the pharmacological effects; changes in the formulation of preparations that have been marketed domestically, without changing the route of administration; or generic drugs containing active pharmaceutical ingredients or preparations that the national specification has been established on the basis of

drugs, prodrugs or other medicinal products are currently being investigated in early stage clinical trials. At the same time, at a national strategic level, policy, investment of capital and scientific research and multiple other means are being used to promote the transformation of the pharmaceutical industry from imitation to innovation. The main purpose of the strict controls applied to the registration of clinical trials, drug registration and reclassification, and generic conformance assessment is to enable innovative, effective and safe drugs to enter clinical use as soon as possible. Approval decisions for drugs that are not classified as innovative are subject to more-stringent assessment criteria, and are applied in order to avoid excessive numbers of imitation drugs being approved. Reform of the clinical trial and approval system is an important part of the overall approach to industrial restructuring and upgrading within China. With the implementation of these reforms, some details will likely be adjusted in the future; however, innovation will remain the basic principle and objective. The government of China will continue to adjust and optimize policies in order to create an environment that accommodates and stimulates innovative drug R&D. Thus, the reformed drug-approval process provides great opportunity for the development of clinical trials in China. Owing to expedited decision-making and greater standardization of data management, an increasing number of clinical centres in China will likely become involved in international, multicentre studies. These changes are expected to improve the overall standards of clinical trials in China, while also providing reliable and high-quality trial data that can be used worldwide. The availability of new drugs in China at the same time as these agents are approved by other regulatory agencies will enable more Chinese patients to benefit from novel treatments. Finally, we hope that China will become a major international centre for anticancer drug research and development.

Conclusions

Economic advancement and innovation have become the main themes of new drug research and development, and are the underlying principles for the future development of the Chinese pharmaceutical industry, including the development of clinical trial and drug marketing and approval processes. Over the past few decades, clinical trial, and new drug research and development capabilities within China have improved considerably. These improvements have enabled participation in, or even hosting of, international multicentre clinical trials, thus further enhancing the capacity of Chinese clinical research centres and promoting the development of new agents in China. Nevertheless, registration and approval backlogs have continued to have a negative influence on the initiation and implementation of innovative drug development programmes. In response to these challenges, the CFDA has modified approval policies in order to improve the efficiency and speed of the drug-approval process, particularly for innovative drugs. A series of clinical value-oriented approval policies, such as the four-colour-light strategy, are intended to encourage the development, registration, and approval of innovative drugs. In future, we hope that these reforms will enable the standards of clinical research and innovative drug research and development in China to reach the highest possible level.

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Author contributions

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Competing interests statement

The authors declare no competing interests.

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The Chinese Center for Drug Evaluation: http://www.cde.org.cn

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