The Need for Expedited Approval: Policy Recommendation for Oncology and Orphan Drugs in China

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Policy Systematic Review

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Executive Summary

The demand for cancer and orphan drugs is huge in China. The aging population accompanied with growth of chronic disease burden will overwhelm the healthcare system in the coming decades. Patients with cancer or rare diseases in China struggle with no effective drug therapy. Even though some oncology or orphan drugs are in the market for several years in the US, Chinese patients have no access to them due to the delays involved in having new drugs approved for use in the US, but not approved for use in China. Acknowledging the importance of providing patient with effective and safe drugs, the Chinese government has heavily invested in drug research and development. However, changing the advance in scientific research into drug therapy available requires more effort on policy reform in drug approval.

The Food and Drug Administration (FDA) in the United States has experience in dealing with this challenge - how to speed up approval of drugs for patients with serious and life-threatening diseases who have no time to wait. In other words, FDA recognizes how to balance the safety and efficacy in the approval process. Four FDA expedited programs are widely considered as effective mechanisms to speed up a drug approval: fast track designation, accelerated approval, priority review designation and breakthrough therapy designation.

This paper includes a policy systematic review to analyze how expedited approval apply on oncology and orphan drugs. It identifies twenty-one studies that satisfied the full review criteria. Most of the studies investigate approval mechanism and characteristic of approval of oncology and orphan drug, such as review time, safety issue, clinical trial design and efficacy of endpoint etc. In the included studies, three studies hold a positive attitude towards accelerated approval, two studies remain skeptical, while one vigorously opposes this regulation by stating expedited programs is driven by pharmaceutical sponsor interest.

In accordance with China's healthcare and pharmaceutical market environment, it is recommended that China introduces regulation of the expedited approval for cancer and orphan drugs to be in effect immediately: 1) China Food and Drug Administration (CFDA) should build a rationale to give guidance to drug sponsors; 2) develop a dialogue mechanism between sponsors and CFDA; 3) post-approval confirmatory studies need to be conducted carefully. Further study is needed to focus on reimbursement of oncology drugs and orphan drugs to realize its affordability to patients.

Background

The demand for oncology drugs in China is huge. While infectious diseases such as tuberculosis and other respiratory infections have declined in past 20 years, rates of chronic disease including cancer, are soaring.[1] There were 4.3 million new cancer cases in China in 2015, which contribute to 20% of worldwide total.[2] The cancer mortality in 1970 was 74.2 per 100,000, rising to 135.9 per 100,000 in 2004.[3] Cancer is the leading cause of death in China, which is responsible for 28% of all death.[4] According to a Pfizer report in 2008, there is 3.1 million people living with cancer in China.[5] Even though the US has a smaller population, it has 50% more cancer survivor, which is 4.7 million.[5] The report of Deutsche Bank also claims that "the overall 5-year survival rate for cancer in China is just over 30 percent, less than half the level in the United States."[6] Lung, liver, stomach, esophageal, and colorectal cancer are the most common cause of cancer death in the Chinese population.[7] Similarly, the most common cause of cancer death in the US is lung cancer, following by colorectal cancer, pancreatic and breast cancer.[8] Rare disease means any disease has a low prevalence in population. Most rare disease are genetically determined and life-threatening.[9] Rare disease in the US refers to disease affect patient population smaller than 200,000 people, while the definition for rare disease in China is not clarified in legislation.[10,11] Some experts suggest rare disease in China can be any disease with a prevalent less than 1/500,000.[11] It is a conservative estimation that patients with rare diseases in China is greater than 10 million.[12] In this paper, orphan drug indicates the drug treating rare disease.

China faces a serious problem of an aging population, which will make the challenge of cancer even worse for future. This is because that people over 65 years are at high risk for cancer.[13] The mortality rate for the people over 65 years is 16 times greater than the rate for

group aged less than 65 years. [13] In 2015, people over 65 represented 9.5% of the Chinese population.[14] The United Nations predicts this percentage will reach to 27.5% by 2050. [14] This data implies an upward trajectory of cancer incidence and increasing demand for effective treatment.

Patients with life-threatening diseases are eager to have early access to therapy. Even though some oncology drugs have been in the market for several years in the US, Europe and even other developing countries, Chinese patients have no access to it. Shao et al find that 291 new drugs were approved by the FDA in 2004-2014. Meanwhile, 183 new drugs were approved by CFDA.[15] The number of new drug approval in China is about 63% for new drugs approval in the US. Of the 291 drugs approved in the US, 79 were approved in China.[15] Although the drugs approved in the US are supposed to demonstrate clinical benefit in clinical trial, only 27% of them get approval in China. This huge gap between the US and China is due to "drug lag". A drug lag indicates the postponement in making a drug accessible to patients in a certain market.[16] In this paper, "drug lag" is defined as delays involved in FDA approved drugs in the US approving in China.

The approval time discrepancy of oncology drugs between FDA and CFDA clearly exemplifies the drug lag. As ***Appendix 3*** shows, the author makes a comparison of first approval time of ten most sold oncology drugs in world. The time of FDA first approval is used as a reference point. The author finds that it takes more than 4 years for most drugs in the list to gain approval in China compared to the first approval by FDA. Three drugs: Neulasta, Revlimid, Velcade have not been available for Chinese patients until the research date (January in 2017). Wu Zhen, the vice minister of CFDA claims that innovative oncology drugs were approved in the US more than 5 years before they became available on the Chinese market, including

Erlotinib (Tarceva) and Bevacizumab (Avastin). [17] The orphan drugs treating hepatitis C such as Daklinza and Sovaldi are widely used in other countries since 2014, but patients with this disease have no access to them in China. [18]

Wu Zhen points out that the number of drugs waiting for approval is in excess of 21,000.[19] CFDA requires clinical trial in China from the second phase to include local Chinese patients data, even if the process is already complete in another country.[19] This repetition of clinical trial is an apparent reason for drug lag. Wu also pronounces the approval backlog is a result of a lack of transparency. [19] In other words, there is an information asymmetry between the drug regulatory agency and drug developers. Uninformed of the requisites for approval, drug sponsors recognize the materials they submitted do not meet the criteria of getting approval after long time review due to their misinterpretation of the requirement. This process not only wastes time and effort, but also aggravates the backlog of registration and approval (R&A), which could be avoided at an early stage through an open channel of communication. Transparent communication would allow drug sponsor to request some scientific and professional advice from the regulator.

Some patients with serious diseases have no time to wait and turn to unofficial channels and purchase drugs in the grey market. For example, they buy unapproved drugs from distributors or manufacturers in India or other countries, which is unsafe and illegal. [6] This is particularly true of people with rare diseases. Based on the first national survey conducted by China-Dolls Center for Rare Disorders, respondents with 142 distinct rare diseases have limited access to drug therapy.[20] This social issue related to drug lag is of great concern to the whole society in China. Should CFDA adopt FDA expedited programs to speed up oncology and orphan drugs approval?

Current Registration and Approval (R&A) process in China

Before new drugs are available to patients in China, China Food and Drug Agency must review their application and data to assess the effectiveness and safety. CFDA approval for new drugs contains two stages: clinical trial application (CTA) and new drug application (NDA) for manufacturing and marketing. The materials required for clinical trial conduct includes summary, pharmaceutical research data, pharmacology and toxicology research data, and clinical trial information. Based on the results of its clinical trial study, the NDA review evaluates the drug's safety and efficacy, taking quality control during the marketing stage into consideration as well. After drug developer application, the CFDA Administrative Acceptance Service Center will execute the format examination to check if the application meets the requirement. If it meets the requirements, the status of application is shown as "acceptance." CDE should complete the technical review within 90 days. In format examination and technical review, supplementary material may be required. CFDA have the right to authorize the license to new drugs upon reviewing all provided data and then deliver its decision to applicants.

CFDA policy reform

In 2015, CFDA has proposed laws to change the drug approval process. The trend of CFDA policy reform is concentrated on eliminating the drug lag and ensuring timeliness.[17] CFDA has renewed the "new drug" definition and registration classification and given priority to innovative drugs with significant clinical value already. New drugs met with approval including: 1) innovative drugs with significant clinical effectiveness that have not been launched anywhere; 2) innovative drugs for HIV, cancer, and rare diseases with significant therapeutic benefit to

patients over existing treatments; 3) innovative drugs that may be used to potentially treat diseases for which no known effective therapy is yet available.

Although CFDA has proposed laws to enhance the drug approval process, implementation of those laws have not happened yet because of the lack of concrete guidance for how to reform the drug approval process. The recommendations in this following paper intend to fill this hole.

Using FDA expedited programs as a model for policy reform

With largest pharmaceutical market in the world, the influence of US FDA extends across Europe and Asia. The basic process of registration and approval of CFDA is adopted from FDA. The author plans to look through the FDA expedited programs to learn from them.

In order to speed up the patient access to the new drug to fill the unmet demand, FDA has four expedited programs: *fast track* designation, *accelerated approval, priority review* designation and *breakthrough therapy* designation. [21] Most orphan drug and oncology drug go through the expedited programs to gain approval. These four expedited programs might be applicable to use as a model for FDA in the future to introduce new guidance.

Fast track is a designation to reduce the review time of drugs to treat serious disease to fill the unmet demand. The drugs could treat the serious disease without any available therapy or have obvious advantage over the current therapy or drugs. Drugs that are eligible for *Accelerated Approval* or *Priority Review* might be eligible for *Fast Track*. [21]

Accelerated Approval is to provide early access to medicine for patients with life-threatening diseases. According to FDA "Subpart H", the grant of *Accelerated Approval* for oncology drug base on surrogate end points or intermediate clinical endpoints. [21] The surrogate is a factor to examine the association instead of a true outcome measure. The true outcome measure in

oncology requires a long period to find out, such as the overall survival. Therefore, the accelerated approval uses the surrogate endpoints to evaluate the efficacy of oncology drugs. A surrogate endpoint is a reasonable indicator of clinical benefit, but is itself not a reliable measure of clinical benefit. [22] The surrogate endpoint could be objective tumor response rate or time to progress. The relationship between the clinical benefit and surrogate endpoint largely depends on the current knowledge and understanding of biological plausibility. [23]

Compared with standard review, *Priority Review* is for a drug that treats a serious condition and shows a promising improvement in safety and effectiveness. The *priority review* always takes 6 months, while the standard review takes 10 months. The *priority review* is designed to allocate more attention to drug application would have significant improvement comparing with current therapy or prevention.

Kenneth Kern, an expert in Regulatory Affairs, believes the existence of *Breakthrough Therapy* designation resulted from the prior three attempts have been unsuccessful in increasing marketing approval rate. [24] In 2012, Breakthrough therapy designation was formed under FDA Innovation and Safety Act. [25] In *Breakthrough Therapy* designation, "clinically significant endpoint" is an intermediate clinical endpoint measuring of therapeutic effect that can be gained earlier than irreversible morbidity or mortality. [26]

Problem analysis

Methods

Review Protocol

The policy systematic review is conducted in four stages including 1) define eligibility criteria, containing inclusion criteria and exclusion criteria; 2) search relevant studies, articles in database; 3) evaluate the study quality and select qualified studies; 4) data analysis;

Study Eligibility Criteria

Studies identified in the search were included when they met all inclusion criteria listed. The inclusion criteria are:

1. They mainly discussed about mechanism or characteristics of expedited approval programs (including Fast Track, Accelerated Approval, Priority Review, Breakthrough Therapy).
2. They type of article could be primary studies, opinion, commentary, review, report or official documents etc.
3. The approved drug discussed in articles should be oncology drugs or orphan drugs, or drugs treating rare disease.
4. The approval process should be in Food and Drug Agency in United State.

The exclusion criteria are:

1. Studies mainly talked about approval process in EU, Japan, or any other countries even they mention US FDA or using US FDA as a comparison.
2. The approved drug is treating HIV or other diseases even they are under the expedited approval programs.
3. It is an official FDA drug approval summary for one specific drug. (Even it contains original and reliable data for the drug, which might be utilized in the future).
4. It is a short news or announcement to announce one specific drug gain approval or enter the market.

Search Strategy

Two parallel searching was conducted: one is FDA expedited programs in USA using database Medline; another is CFDA oncology approval using Google Scholar.

A comprehensive search strategy was developed using MeSH terms and keywords to generate sets for the following themes: 1) United States Food and Drug Administration, 2) Drug Approval, 3) Rare Diseases, and 4) neoplasms. Within each set, search terms were combined using "OR", and "AND" was used to find the intersection of these sets. There is no "English language" limiting. One professional research librarian, Heather Blunt from Dartmouth Dana Library provided assistance. Excluded conditions was not applied. The Medline search was conducted in February, identifying 109 results.

(United States Food and Drug Administration[mesh] OR FDA OR "United States Food and Drug Administration" OR "US Food and Drug Administration") AND (Drug Approval[mesh]) AND (Rare Diseases[mesh] OR "orphan disease" OR "orphan diseases" OR neoplasms[mesh] OR cancer) AND (drug therapy[subheading] OR "drug therapy") AND ("fast track" OR "priority" OR "accelerated" OR "breakthrough therapy")

The Google Scholar search identified 88 results excluded patent and citations.

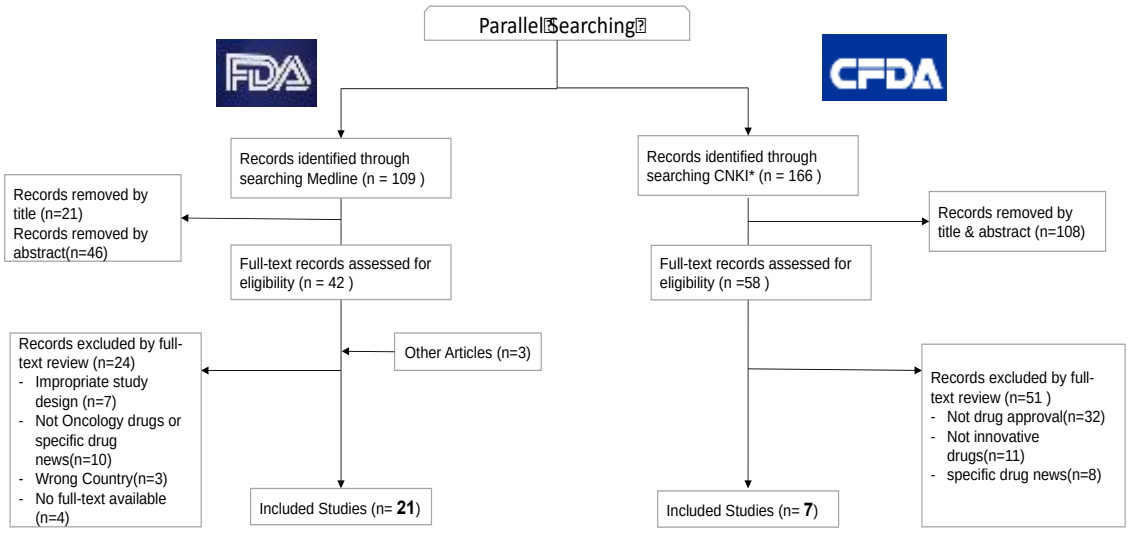
allintitle: drug approval "China Food and Drug Administration" OR SFDA OR "State Food and Drug Administration" OR oncology OR cancer

After looking through these 88 articles, no one is talking about China drug approval. So the author started search on China Knowledge Resource Integrated Database in Chinese. I used the "New Drug Approval" as topic, AND "innovative drugs" NOT "Traditional Chinese Medicine" in Chinese. The author uses the time limit from Jan. 1st. 2015 to the research date, which is February 25th 2017.

Results of Search

A study flow diagram is shown in ***Figure 1***. In the parallel search, there are 109 results identified in initial Medline searching. 67 of these are removed by screening by title and abstract, leaving 42 studies waiting for full-text assessment. An extra 3 studies discovered during the exploratory phase in background information searching were also included in the full-text assessment. Screening by full-text removed 24 studies, and 21 studies met the full eligibility requirements.

Figure 1. Study Flow Diagram



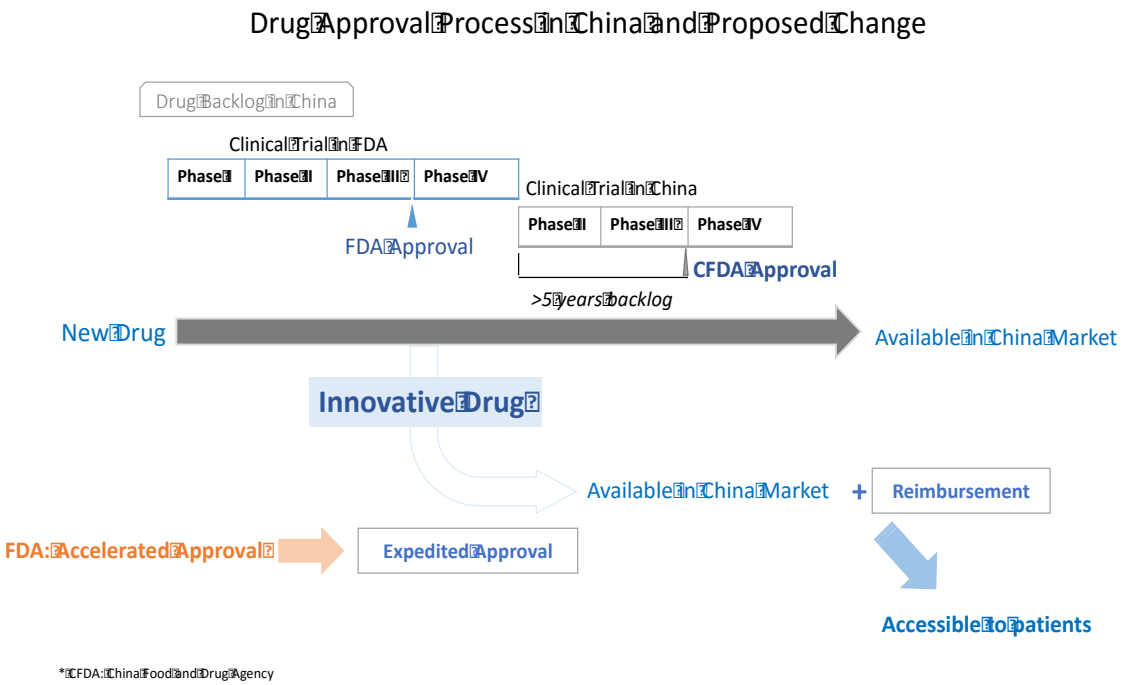
* CNKI= China Knowledge Resource Integrated Database. http://gb.oversea.cnki.net/kns55/

The search conducted in CNKI identifies 166 studies initially, and then108 records are removed by looking through title and abstract. Of these 58 studies, 51 studies are removed by full-text screening, leaving seven included studies that meet the eligibility requirements.

Methodological Quality Assessment

Studies are looking through and evaluating based on a list adopted from STROBE Statement. There are fourteen items considering title, abstract, introduction, method, results and discussion included in the list as ***Appendix 3*** shown. Each item equal to one point and the overall score is used to provide an overall quality of included studies. The overall score larger than 10 is considered as "good quality", which is highlighted in green. The overall score less than 6 is considered as "poor quality", which is highlighted in red.

Conceptual Model



In the gray box, it shows the problem of "drug backlog" that CFDA repeats Phase II and Phase III to get approval, even though these clinical trials already complet by FDA. New drugs need a long time get market access in China. To solve the "drug backlog", the proposed change is that new drugs could be approved by an "expedited approval" program once they meet the criteria of "innovative drug", which includes most oncology and orphan drug. This "expedited approval" program will adopt FDA expedited programs, such as Accelerated Approval.

For oncology drugs approved by FDA through expedited programs, the clinical trial period for orphan drug is around 4.5 to 7 years, while non-orphan drugs take about 6.5 - 8 years.[27] If the assumption that drug lag is more than 5 years is accurate, the approval by CFDA take more than 9.6 to 12 years for orphan drugs vs 11.5 to 13 years for non-orphan cancer drugs. Beside speeding up the approval, related reimbursement need to be done to make the drug more affordable to patients.

Evidence Results

The author identifies twenty-one studies satisfied the full review criteria. Detailed evidence results are shown in the ***Appendix 1***. Included studies are diverse in the study design, including primary study, commentary, opinion, commentary, review, report etc. Most studies investigate expedited approval mechanism and characteristic of approval such as review time, safety issue, clinical trial design and efficacy of endpoint. In the 21 included studies, 4 studies focus on drugs treating rare disease, and 17 studies are discussing oncology drugs. Few included studies talk about orphan drug with indication of treating cancer.

Synthesis and Discussion

Three studies hold positive attitude towards accelerated approval, two studies remain skeptical. One study vigorously opposes this regulation considering that expedited programs is driven by pharmaceutical sponsor interest.[28]

DiMasi et al imply that the R&D cost for oncology drug is higher than other drugs, and surviving from the transition from Phase II to Phase III is the key to manage the cost.[29] Compared to other drugs, the risk of failure in Phase III is higher in oncology drugs.[29] Yao et al also emphasize the Phase II/Phase III transition through their statistical analysis, recommending using positive predictive value as parameter to interpret data from Phase II. [30] Their study mainly investigates the inherent limitations of small, single arm studies. Based on incorrect assumption that surrogate endpoints indicate real clinical effect, the frequency of type I and type II error is increasing by conducting small, single arm studies. [30]

Several included studies mention Iressa (gefitinib), a lung cancer drug. Jeffrey Fox conducted interviews with politicians, regulatory professionals, and FDA scientists about the critics of Accelerated Approval.[31] One viewpoint is that there is no clear statement about whether the drugs approved by Accelerated Approval is safe or not based on existing data. The "slowdown in overall approvals from 2001 to 2004 at FDA" is due to the political pressure from media and public concern about drug safety issue. [31] However, Davis's study implies the accelerated approval is fueled by industry interest rather than patients by taking the approval of Iressa as an example.[28] Davis claims the Accelerated Approval was part of "deregulatory regime", since it requires less resource and time to get market access, which is lucrative to drug sponsors.[28]

Interviews with FDA scientists indicate the "organizational pressure" and limited flexibility of approval are mentioned in both Fox and Davis studies. [28,31]

Richey et al hold a favorable attitude towards Accelerated Approval, concluding the oncology new molecular entities approved through Accelerated Approval are safe and effective.[32] However, not like its name indicated, the discrepancy in development time between Accelerated Approval and regular approval is slight (Accelerated Approval for 7.2 years vs regular approval for 7.3 years).[32] This statement is consistent with the viewpoint of Shea et al. that the criticism of oncology drug approval is exaggerated.[33]

Prasad et al investigate the approval case of Ponatinib including first approval, withdrawal and reintroduction. [34]In clinical trial, Ponatinib shows a high efficacy among patients with T3151 mutations, however, its first approval was for any patients with chronic myeloid leukemia. [34]After rapid withdrawal, Ponatinib is reintroduced to market only for those patients with T3151 mutations. [34]Prasad draw valuable lessons from the Ponatinib case - Instead of widely use, accelerated approval should be constricted to subgroup with high response rate or patients with no other therapy choice.[34] Similarly, Roberts et al. come up with a proposal named "selective approval", which refers to recognizing the subgroup have high efficacy in early phase of developing drugs.[35] This "selective approval" is beneficial to patients by providing more target therapy and less unnecessary spending, however, against interest of pharmaceutical companies who are willing to expand more market indications. [35] Prowell et al support the idea of approval in a more narrow subpopulation in their study.[36]

Both Kesselheim and Gaddipati focus on orphan drugs for cancer. Gaddipati et al define "rare cancer" as cancer with incidence rate less than 6 per 100,000 people. [37] Instead, Kesselheim

et al use “cancer” as a subcategory under orphan drug designation.[38] Kesselheim et al draw the conclusion that orphan drugs for cancer are more likely to be nonrandomized and smaller compared with non-orphan oncology drug. This conclusion is in accordance with Gaddipati study. [38] Gaddipati et al also concede the value and practicability of randomized trial designs in evaluating drug for rare cancer. [38]

Pariser, Kakkis (2015), Kakkis (2016) and Miyamoto mainly focus on drug approval for rare disease. [39-42]Miyamoto et al concentrate on cost-benefit analysis of expanding Accelerated Approval access for rare diseases and encourage Agency to develop some more comprehensive criteria for novel surrogate endpoint. [40] Kakkis (2015) proposes a framework to evaluate utilizing biomarker endpoint to improve current approval system for drug treating rare disease. [42]

Quality of the evidence

Quality of the evidence is shown in the ***Appendix 4***. In twenty-one included studies, ten were deemed to be of good overall quality. Four studies gain overall score below 6, which is considered as poor quality. The type of article is the main reason for not meeting the requirements of quality checklist. Chenoweth (2006) is an editorial to provide opinion towards the effectiveness of single-patient investigational design in new drug studies.[43] Fox (2005) is a news to discuss a label changing of Iressa due to not demonstrating significant survival advantage.[31] Prasad (2014) and Prowell (2012) are perspectives, which like general commentary. [36] Most studies (18 out of 21) include disclosure of potential conflicts of interest.

Recommendations and Implications

Alternative Analysis adopted from Policy Assessment Criteria Table

Alternative	Cost Effectiveness	Efficiency	Cultural Competence /Equity	Ethical Considerations	Achievement of Intended Objectives	Administrative Feasibility
Using surrogate endpoint	N/A	✓+	✓+	✓	✓+	✓+
Identify subgroup who have higher response	✓+	✓	✓+	✓+	✓+	✓
Only 1 pivotal trial	✓+	✓+	✓	✓-	✓	✓+
Single arm, uncontrolled studies	✓+	✓+	✓	✓-	✓	✓
Post-marketing studies	N/A	N/A	✓+	✓+	✓+	✓-
Communication mechanism between sponsors and agency	✓+	✓+	N/A	N/A	✓+	✓+
Outside professional committee recommendation	N/A	N/A	✓	✓	✓	✓

* This is adopted from "Policy Assessment Criteria Table" designed by K. Wolff (*see Appendix 4*)

** The rating system includes poor' (✓-), 'adequate' (✓), 'strong' (✓+)

From the policy systematic review, the author finds 7 alternatives related to the four FDA expedited programs, which might be applicable to CFDA. Using surrogate endpoint is the basis of Accelerated Approval. The benefit of drug on survival needs long time to demonstrate, while the surrogate endpoint such as the effect on tumor growth is easier to measure in short period.[21] Most studies prove the efficiency of "using surrogate endpoint".[32] Second alternative is the idea of "selective approval" that raised by Robert et al.[35] "Selective approval" refers to the approval mechanism of targeted drug in subpopulation who are likely to have response.[35] The benefit of limitation of using approved drug in subpopulation with high response gain support by Prasad et al and Prowell et al.[34,36] The single-arm, uncontrolled study design requires less cost and time to complete. However, whether the outcome of this single-arm design conducting among small sample size is safe enough for patient provoke considerable controversy.[30] What is more, drugs can gain approval by conducting only 1 pivotal trial through expedited programs in the US. [44]

Several studies suggest that result of one, single-arm, uncontrolled study cannot approve the drug efficacy.[30] The necessity of implementation of post-marketing study are highlighted by several studies.[37] The single-arm, uncontrolled study design and using surrogate endpoint are the reasons to keep evaluating the drug benefit in larger population through post-marketing studies.[37] 6 studies emphasize the essential role of the early communication between sponsors and agency in facilitating new drug review. [28,39,45]

China Healthcare & Pharmaceutical Landscape

Chinese healthcare system remain problematic in two area:1) disparity between rural and urban healthcare, 2) a huge aging population accompanied with rising burden of chronic disease. [46] Improving the drug approval of oncology drug and orphan drug will solve the problem of the burden of cancer and rare disease.

Chinese government highly encourage innovation in drug R&D since 2007. In order to improve innovation of drug R&D, funding around $960 million has been provided by the national "New Drug Creation and Development Program" started in 2008.[47] Many multinational pharmaceutical companies such as Roche have built R&D center in China.[47] Besides scientific innovation, how to transform scientific advance into new drug therapy is also important.

One distinctive culture of drug industry in China is that hospitals largely rely on drug selling, account for 40% of total revenue.[48] Physician have financial incentive to over-prescribe and prescribing expensive drugs. Patients are the group to afford this burden, who pay for drugs out of pocket.

Multinational pharmaceutical corporations have strong motivation in investing innovative special drugs, while general drug market is full of fierce competition with local pharmaceutical companies.

Recommendation Framework

To respond to the unmet demand of patients with a life-threatening disease, CFDA should introduce regulations to expedite access of oncology and orphan drugs immediately.

First, CFDA should build a rationale to give criteria for which kind of drug is qualified to get into expedited approval program. Basic and comprehensive guidance for sponsors should be published in a clear manner and update timely when new regulatory launch. Specific terms and qualifying criteria need to be explicitly defined, just like *Guidance for industry: Expedited programs for serious conditions—drugs and biologics* published by FDA.

Second, CFDA should develop a dialogue mechanism between sponsors and agency. Dialogue need to start early before application and continue in the approval process. CFDA takes responsibility of giving immediate feedback or schedule a meeting when sponsors request.

Third, post-approval confirmatory studies need to be conduct carefully. Some drugs approved by expedited programs are on basis of limited data in single, uncontrolled trial. Once the post-marketing studies fail to demonstrate the clinical benefit, the approval can be withdrawn from the market.

One distinctive culture of drug industry in China is that hospitals largely rely on drug selling, account for 40% of total revenue.[48] Physician have financial incentive to over-prescribe and prescribing expensive drugs. Patients are the group to afford this burden, who pay for drugs out of pocket. Oncology and orphan drug are high price. To make oncology and orphan drug more affordable for patients, the future study should be focus on introducing the reimbursement related to the expedited approval.

Conclusion

The unmet demand of patients with cancer and rare disease is urgent and enormous in China. There is many similarity of pharmaceutical market environment and new drug approval between China and the US. Additionally, the US have experience in implementation of expedited programs for approval. CFDA should introduce regulations to expedite access of oncology and orphan drugs immediately by adopting the FDA expedited programs.

Appendix 1. Evidence Results

Author(year)	Study Design	Focus Drugs	Key Finding	Comments
Davis (2011)	Case study analysis	Oncology drug	The development of "fast" approval regulations for oncology drugs should be considered as "part of a deregulatory regime". Speeding up the drug approval is motivated by the pharma companies' interest rather than patients need.	This study focus on analysis the sociological factors affects the expedited approval. It provides a new perspective to evaluate the accelerate approval and mention the poor conduction of post-market studies. The limitation is the case study is lack to generalization.
DiMasi (2007)	Review	Oncology drug & Orphan drug	Many cancer drug approved by priority review. The development of oncology drugs indicates a higher cost because the rate of failure in Phase 3 is higher than other drugs.	This study evaluates oncology drug approval through economic perspective. DiMasi calculate the phase transition possibility and clinical success rate. They also discuss the attribution in global market.
Chenoweth (2006)	Editorial	Oncology drug	The single-patient IND studies should be allowed and available through a cooperative compassionate use program, which might be beneficial to patients with the same risks in Phase I studies testing for other indications.	The author's attitude is very positive and encouraging the pharmaceutical companies to widely use the single-patient IND studies in cancer patients.
Esserman (2014)	Clinical Research	Oncology drug	FDA should encourage the accelerated approval of oncology drug in the neoadjuvant treatment, which is smaller, cheaper, faster trials.	Esserman et al evaluate the approval of Pertuzumab in neoadjuvant setting and bring the questions to the clinical implication. Eseerman et al mention oncologist cannot change their standard of care, because full approval is waiting to be confirm after adjuvant trial.
Fox (2005)	Commentary	Oncology drug	Some criticism claims that industry fails its obligations of conducting post marketing studies. An interview with FDA scientists implies the approval decision is largely affected by recommendation from expert committee and	This commentary provides with some discussion about safety standard of FDA approval among industry, agency and scientists after the Gefitinib not producing a significant survival advantage over placebo.

			senior management.	
Gaddipati (2012)	systematic analysis of clinical trials	Drug for "rare cancer"	Gaddipati et al investigate the characteristics of clinical trial of drugs for rare cancer. Overall objective response rate is used in 69% of approvals as primary efficacy endpoint.	This study brings up a new concept of rare cancer, which is less than 6 new cases per 100,000 people per year. Gaddipati et al provide plenty of suggestions to sponsors about trial design.
Kakkis (2016)	Commentary	Orphan drug	Biomarker qualification process for rare diseases is not well defined, which makes the accelerated approval is hard to conduct. Kakkis offers some key consideration to improve the biomarker qualification as surrogate endpoint.	This commentary is professional and well-organized, including two tables are quite clear and informative.
Kakkis (2015)	White paper	Orphan drug	Kakkis et al recommend having a scientific framework to evaluate the biomarker endpoint, which could increase the available treatment for non-cancer rare disease.	This white paper is focus on providing recommendation to approval of non-oncology orphan drugs. Kakkis et al analyze in a well-organized approach including disease characteristic, drug, experiment data etc.
Kesselheim (2011)	Review (case study)	Orphan and Non-orphan drugs for cancer	The median FDA review time is similar between non-orphan oncology drugs and orphan oncology drugs. However, non-orphan cancer drugs are more likely to be nonrandomized, unblended and have smaller sample size.	Comparing the clinical trial between orphan oncology drugs and non-orphan oncology drugs, this study is focus on the effect of the Orphan Drug Act of 1983 on clinical trial of oncology drug approval.
Miyamoto (2011)	Cost-benefit analysis	Drugs treating ultra-rare disease	Miyamoto et al. explore the cost of developing orphan disease and their market return. This study implies AA process reduce the cost of developing those drugs and increase the NPV.	This is a cost-benefit analysis for orphan drug development, which is quite innovative in this field. The estimation of cost is more precise than the return, since the market size is hard to gain precise data. One highlight is this study bring a thought to me for further study specially to estimate the cost-benefit of accelerated approval in China market.

Pariser (2012)	Review	Orphan drug	This study investigates relationship between application characteristic of orphan drugs, such as rare disease prevalence, company size, and the approval rate. This study suggests more orphan drugs approved by priority review. It also mentions the correlation between company size and approval rate	Pariser et al evaluate 177 new drug submission between 2006 and 2010. One limitation might be this characteristic only reflect a feature of this period. It might be better to combine with application after 2010 to reveal a tendency of orphan drug approval.
Prasad (2014)	Viewpoint	Oncology drug	Ponatinib was withdraw by FDA after gaining approval and then reintroduced to market in a narrow population. Prasad et al. taking the approval history of Ponatinib as an example to analysis the mechanism of accelerated approval.	The case analysis of Ponatinib reflects some complicated unsolved problems of AA in simple language. Prasad et al come up with four ideas to improve the approval process and communication between physician and patients, which is worth considering.
Prowell (2012)	Perspective	Drugs for Early Breast Cancer	Prowell et al. discuss the utilization of pathological complete response in AA process. This study also suggests to strictly limit subgroup who has higher recurrence using drugs approved by AA.	It focuses on analyzing ability of endpoint to predict long term clinical benefit. It mentions the plenty of advantages of using pathological complete response as an endpoint and lists its problems briefly.
Richey (2009)	report	Oncology drug	Richey et al find the median development time for drugs that received AA and regular approval are similar, which indicate the AA doesn't shorten the time to approval drugs.	This report claims the most oncology drug granted AA have clinical benefit, which is confirmed in subpart H trial. This report also compared approval between oncology drug with orphan drug indication and non-orphan drug indication, which is meaningful.
Roberts (2004)	Perspective	Oncology drug in Fast-track program	Roberts et al. proposed a "selective approval", which means targeting subgroups who are likely to response to approved drug which might helpful to decrease cost of ineffective treatment. Even this process might be	This study comprehensively probes current problems of drugs approved by fast track and bring about an approach to solve these. Drug developers play important role in improve and conduct the new policy. How to

			beneficial to patients and public, the main obstacle is the lack of financial incentive of pharma companies.	encourage them to eagerly participate in is an important question worth considering.
Shah (2013)		Antineoplastic Tyrosine Kinase Inhibitors(TKIs)	This study finds the review and approval time for TKIs is average 205.3 days in FDA, while the priority review drugs take 167.1 days. Shah et al. conclude even the review time in FDA is shorter than EU, however, the active review time is similar.	This study is focus on comparing the TKIs application and approval process between US and EU. Shah et al. take the agency system characteristic, approval process into consideration. This study also uses two drugs- gefitinib and lapatinib to uncover the reasons behind the difference in approval time.
Shea (2013)		Oncology drugs	About 40% oncology drugs approved by regular approval is using OS as an endpoint while 80% approved by AA using RRs. There is a tendency of increasing number of indication using OS as endpoint, which is associated with increasing regular approval.	This study aims to exploring the flexibility of FDA in approving oncology drugs by investigating utilization of endpoint. Authors recommend raise the AA used in early stage cancer and claim the blames and anxiety about FDA police is unnecessary.
Yao(2013)	Perspective	Oncology drugs	This study indicates when type I error in Phase II becomes more precise, the predictive value is higher. Yao et al suggest to conduct collaborative process instead of linear approval process.	This study evaluates the limitations of single arm study with small size, which strongly support the suggestion of conducting collaborative approval process. However, Yao et al only give a vague direction, further in-depth and detailed recommendation is required to apply.
Dagher (2004)	Review	Oncology drugs	From 1992 to 2004, there are 22 oncology drugs are approved by FDA and major of them evaluated by single-arm studies. This article suggests using OS as indicator is increasing as increasing in regular	This study provides a regulatory history of oncology drug approval and evaluates two type of trial design, single-arm study and randomized study. This is a comprehensive overview with strong evidence and an

			approval.	approach to evaluate approved drug. The limitation is the data only limit to 1992 - 2004.
Leyens (2015)	Report		This report compares the approval process between EU and US.	Leyens et al focus on analyzing endpoints used in AA and regular approval to evaluate the flexibility of FDA in oncology drug approval. However, the relationship between multiple endpoints and regulatory flexibility is not clarified.
Tibau (2016)	Retrospective analysis of meeting transcripts	Oncology drugs	There is strong association between ODAC committee proposals and oncology drug approval. Efficacy is the major reason for individual ODAC member voting for approving. How many trials supporting the application is an essential indicator of promising voting.	This study reveals the relationship between ODAC and FDA approval, which might inspire CFDA to learn from it. How to combine outside professional advice and recommendation into the approval process is important in making improvement.

Appendix 2. Methodological Quality Assessment Form Adopted from STROBE Statement

Methodological Quality Assessment Form Adopted from STROBE Statement

Title and abstract	1	Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Data sources	5	Give sources of data and details of methods of assessment (measurement)
Statistical methods	6	Describe all statistical methods
Results		
Outcome data	7	Report numbers of outcome events or summary measures over time
Main results	8	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and heir precision (eg, 95% confidence interval).
Other analyses	9	Report other analyses done
Discussion		
Key results	10	Summarise key results with reference to study objectives
Limitations	11	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	12	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	13	Discuss the generalisability (external validity) of the study results
Other information		
Funding	14	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

** The original STROBE checklist is from https://strobe-statement.org/index.php?id=available-checklists*

Appendix 3. Comparison of First Approval Time of 10 World Most Sold Oncology Drugs between the US and China

TABLE. APPROVAL TIME OF 10 MOST SOLD CANCER DRUGS IN WORLD

Drug Name	Brand Name	Cancer Indications	Company	First Approval in US	First Approval in China	Delay Time
Rituximab	Rituxan/MabThera	non-Hodgkin's lymphoma, chronic lymphocytic leukemia	Genentech/Roche	1997	2001	4 years
Bevacizumab	Avastin	colorectal, lung, kidney, and glioblastoma	Genentech/Roche)	02/26/2004	March. 2010	6 years
Trastuzumab	Herceptin	breast, esophageal, and gastric	Genentech/Roche	09/01/1998	2002	4 years
Imatinib	Gleevec	variety of leukemias and gastrointestinal stromal tumors	Novartis	05/01/2001	2001	0
Pegfilgrastim	Neulasta	febrile neutropenia	Amgen	01/13/2002	Not Available in China Market	-
Lenalidomide	Revlimid	multiple myeloma, mantle cell lymphoma, myelodysplastic syndromes	Celgene	12/27/2005	N/A	-
Pemetrexed	Alimta	lung	Eli Lilly	06/20/2004	2005	1 year
Bortezomib	Velcade	multiple myeloma, mantle cell lymphoma	Takeda/Johnson & Johnson	10/14/2003	Not Available in China Market	-
Cetuximab	Erbitux	colorectal, head and neck	ImClone and Merck	02/12/2004	2006	2 years
Abiraterone	Zytiga	prostate	Johnson & Johnson	04/28/2011	08/18/2015	4.3 years

The world most sold cancer drugs in 2015. http://www.pharmaceutical-technology.com/features/featurethe-worlds-most-sold-cancer-drugs-in-2015-4852126/

Appendix 4. Quality Assessment

		Davis (2011)	DiMasi (2007)	Chenoweth	Esserman (2014)	Fox (2005)	Gaddipati (2012)	Kakkis (2016)	Kakkis (2015)	Kesselheim	Miyamoto	Pariser (2012)	Prasad (2014)	Prowell (2012)	Richey (2009)	Roberts (2004)	Shah (2013)	Shea (2013)	Yao (2013)	Dagher (2004)	Leyens (2015)	Tibau (2016)
1	Title & abstract	√	√				√		√	√	√				√		√	√		√	√	√
2	Background /rationale	√	√	√	√	√	√	√	√	√	√	√	√		√	√	√	√	√	√	√	√
3	Objectives	√			√		√	√	√	√	√	√					√	√			√	√
4	Study design	√					√		√	√					√							√
5	Data sources	√	√				√	√	√	√	√	√			√		√	√	√	√		√
6	Statistical methods	√	√				√	√		√	√	√			√			√	√			√
7	Outcome data	√	√				√	√		√	√	√			√	√	√	√	√	√	√	√
8	Main results	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√
9	Other analyses	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√	√
10	Key results	√					√		√		√	√			√		√	√		√		√
11	Limitations									√		√			√			√				√
12	Interpretation	√	√				√		√	√	√	√			√	√	√	√		√	√	√
13	Generalizability				√			√	√		√	√			√			√		√	√	√
14	Funding	√	√		√		√	√	√	√	√	√	√	√	√	√	√	√	√		√	√
	Overall Score	**12**	**9**	**3**	**6**	**3**	**12**	**9**	**11**	**12**	**11**	**12**	**4**	**3**	**13**	**6**	**10**	**13**	**6**	**8**	**9**	**14**

*Quality Assessment Form is adopted from STROBE Statement

Appendix 5. Policy Assessment Criteria Table

Cost Effectiveness – the likelihood the policy meets its stated objectives cost and benefits in terms of monetary costs and benefits.
Efficacy – the optimal utility from policy implementation using the minimal amount of resources. This includes but is not limited to social and political factors, physical and psychological resources as well as intangibles like time and previously allocated resources (sunk and opportunity costs).
Cultural Competency/Equity – this is about how well the policy is targeted toward the specific needs of a population. Ideally the recipients of the assistance or those impacted directly by the policy should be involved in the decision-making process of policy implementation and design. Included in this is if the policy reflects the population – i.e. if the group being impacted is from Argentina, are materials for the population printed in Spanish?
Ethical Considerations/Equity – simply, is the policy or program ethical? Are an individual's Constitutional and civil rights as well as their human dignity, quality of life recognized, and are they treated with respect?
Achievement of Intended Objectives – is the policy or program effective in meeting the goals it aims to meet? Are there barriers to achieving the goals?
Feasibility: Political, Economic, and Administrative – feasibility is about the ease of implementation and operation of the policy, ease of enforcement / following regulations and flexibility of the policy.

Policy Alternative	Cost Effectiveness	Efficiency	Cultural Competence /Equity	Ethical Considerations	Achievement of Intended Objectives	Administrative Feasibility

* This is "Policy Assessment Criteria Table" designed by K. Wolff (*see Appendix 4*)
** The rating system includes poor' (✓-), 'adequate' (✓), 'strong' (✓+)

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