Regulatory lessons from China’s COVID-19 vaccines development and approval policies

Jingshu Yang a,b,c and Yue Yang a,c,e,†

aSchool of Pharmaceutical Sciences, Tsinghua University, Beijing 100084, P. R. China
bTsinghua-Peking Center for Life Science, Beijing 100084, P. R. China
cKey Laboratory of Innovative Drug Research and Evaluation, School of Pharmaceutical Sciences, Tsinghua University, Beijing 100084, P. R. China
†Present address: Institute of Regulatory Science, Tsinghua University, Biomedicine Hall, Rm C104, Beijing 100084, China, Phone: +86.10.62780224
*Correspondence: yanghappy@mail.tsinghua.edu.cn

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ABSTRACT

Coronavirus disease 2019, responsible for a global pandemic, is caused by the severe acute respiratory syndrome coronavirus 2. Several vaccines have been developed and approved worldwide, particularly in China. As of Oct 17, 2021, four new coronavirus vaccines in China have been conditionally approved for marketing by the National Medical Products Administration, two of which have been authorized for emergency use in the Emergency Use Listing of the World Health Organization. Domestic vaccine R&D in China has relied on legal and regulatory support. This article summarizes the regulatory policy for vaccine development, review and approval. Vaccine approval laws have been continually improved, and regulations for special approval have been used to shorten the review time. China has coordinated pandemic-related needs, both domestically and with other countries, and made substantial progress in cooperative international anti-pandemic efforts.

Keywords: COVID-19 vaccines, R&D, regulatory science, approval

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was declared a pandemic in March 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance) and has led to severe morbidity and mortality worldwide. As of September 23, 2021, more than 231 million confirmed cases of COVID-19 and more than 4.7 million deaths have been reported worldwide (https://coronavirus.jhu.edu/map.html). The World Health Organization (WHO) declared COVID-19 a public-health emergency of international concern on January 30, 2020 (http://world.people.com.cn/n1/2020/0131/c1002-31565415.html). An overall case fatality rate of 2.3% has been reported in one of the largest studies on COVID-19 pneumonia [1]. At present, countries worldwide are in different stages of prevention and control of the COVID-19 pandemic. This review summarizes current laws and regulations on vaccine approval in China. Using Sinopharm/BIBP and Sinovac vaccines as examples, this review explains why China has been able to make substantial progress in vaccine research and development (R&D). Clinical-trial records were collected from the WHO COVID-19 vaccine tracker. Data on the countries in which certain vaccines have been approved were collected from UNICEF. Policy data were gathered from government websites. The search terms included vaccines, COVID-19, clinical trial, efficacy, adverse events and review report. Policies associated with drugs rather than vaccines were excluded. Chinese vaccines in the WHO Emergency Use Listing (EUL) were chosen for further discussion.

2. PROGRESS

Public-health emergencies may transcend national boundaries and greatly affect the political, economic and social stability of countries worldwide [2]. Globally, vaccines have become a major means of combating the COVID-19 pandemic, thus highlighting the importance of vaccines as public-health and pandemic preparedness tools, and of issues such as equitable distribution and the reliable supply of high-quality, affordable vaccines. The traditional timeline for vaccine development is 15–20 years. For COVID-19, researchers aimed to make vaccines available within 12–18
months [3]. As of June 22, 2021, approximately 1.5 years after the global pandemic was declared, 103 vaccines were in clinical development, 184 vaccines were in pre-clinical development (https://www.who.int/publications/m/item/draft-landscape-of-COVID-19-candidate-vaccines), and 7 vaccines (https://www.who.int/teams/regulation-prequalification/eul/covid-19) were authorized for emergency use in the EUL of the WHO (Supplement Table 1), including two types of inactivated SARS-CoV-2 vaccines developed by Chinese manufacturers, Sinopharm/BIBP and Sinovac. The successful development of vaccines in China has benefited from the early acquisition of viral strains. However, the effective prevention and control of the epidemic has hindered clinical trials in China. Therefore, clinical trials are being conducted overseas, thus posing challenges for regulatory authorities.

On July 22, 2020, China officially approved the emergency use of several coronavirus vaccines, giving priority to the protection of medical personnel, epidemic prevention personnel, border inspection personnel and urban basic operations personnel (https://m.sohu.com/a/414476591162758). As of Oct 17, 2021, four new coronavirus vaccines in China were conditionally approved by the National Medical Products Administration (NMPA). Three are inactivated vaccines, and one is an adenovirus vector vaccine. As the demand for vaccination continues to expand while the currently marketed vaccines remain in short supply, the joint prevention and control mechanism of the State Council approved three coronavirus vaccines for emergency use according to the results of phase I/II clinical trials under the recommendation of the National Health Commission and the NMPA. These vaccines comprised two inactivated vaccines and one recombinant subunit vaccine (CHO cells).

China not only has been a leader (Table 1 and Supplement Table 2) in vaccine R&D, production, marketing and vaccination, but also has actively provided vaccine assistance to other countries and expanded its exportation of vaccines.

### 3. CHINESE LAWS AND REGULATIONS FOR VACCINES

Vaccine R&D and approval are influenced by medical-system reform and continual improvements in laws and regulations (Figure 1). Policies for infectious prevention and control have been introduced to support vaccine development to prevent and control infectious diseases. The first branch of these efforts involves legislation regarding infectious disease outbreaks, such as in the spring of 2003, after the first severe acute respiratory syndrome (SARS) outbreak worldwide, China was the main country affected by this global infectious disease outbreak, and has gained experience and learned lessons through prevention and control of the SARS epidemic. After 2003, China successively issued a series of laws, regulations and guidelines to respond to public-health emergencies (Figure 1 and Supplement Table 3). To prevent, control and eliminate the occurrence and prevalence of infectious diseases, and protect human health and public health, the Regulation on Public Health Emergencies was formulated on May 9, 2003 (http://www.gov.cn/zwgk/2005-05/20/content_145.htm) and revised in 2011. The Infectious Disease Prevention and Control Law was revised to reform the national infectious disease epidemic prevention and control system through legislation. In response to the shortcomings and weaknesses exposed in the prevention and control of the COVID-19 epidemic, the Infectious Disease Prevention and Control Law (Revised Draft for Solicitation of Comments) underwent targeted revisions on October 2, 2020.

The second branch of the efforts involves vaccine R&D. From the perspective of regulatory agencies, on August 15, 2020, under the NMPA, the Center for Drug Evaluation released several technical guidelines (Figure 1) to guide the clinical R&D of the new coronavirus vaccine in China, and to provide reference technical standards. Similarly, the U.S. Food and Drug Administration issued the Development and Licensure of Vaccines to Prevent COVID-19 in June of 2020. This guidance urged manufacturers to pursue traditional approval, on the basis of vaccine safety and efficacy evidence. Then the Emergency Use Authorization for Vaccines to Prevent COVID-19 was issued in October 2020 to accelerate approval of COVID-19 vaccines under investigation. From the perspective of funding, the Ministry of Science and Technology issued a series of guidelines for conducting R&D in key projects in response to the COVID-19 epidemic. On January 22, 2020, the first batch of emergency research projects of the Ministry of Science and Technology's Technological Response to the Novel Coronavirus Infection Pneumonia Epidemic was launched (http://www.gov.cn/xinwen/2020-01/24/content_5471938.htm). China has established a scientific and technological research team aiming to comprehensively utilize various resources; and perform simultaneous R&D, supervision, clinical research and production—working day and night to develop a new coronavirus vaccine as rapidly as possible. From the perspective of vaccine sponsors, such as Sinopharm (CNBG) and Sinovac, the mature inactivated vaccine R&D technology platforms developed since the SARS epidemic, production pathways, basic data and practical experience in SARS inactivated vaccines have been crucial to current research, thus advancing the rapid development and marketing of vaccines.

The third branch of the efforts is vaccine licensure. On the basis of the 2001 Drug Administration Law of the People's Republic of China, the 2002 Regulations for the Implementation of the Drug Administration Law of the People's Republic of China, the 2003 Regulations on Public Health Emergencies and the 2004 Infectious Disease Prevention and Control Law of the People's Republic of China, as well as other laws and regulations, the Special Review and Approval Procedure for Drug Registration of the State Food and Drug Administration (http://www.
Table 1 | Vaccines approved for use by at least one national regulatory authoritya (through October 20, 2021)

| Vaccine developer's country | No. in WHO EUL list | No. in phase III or IV | Approved vaccine | Vaccine developer | Vaccine platform description | No. countries or territories with approval |
|-----------------------------|---------------------|-----------------------|------------------|------------------|-----------------------------|------------------------------------------|
| United States               | 3                   | 4                     | mRNA-1273        | Moderna           | mRNA                        | 65                                       |
|                             |                     |                       | Comirnaty        | Pfizer/BioNTech   | mRNA                        | 94                                       |
|                             |                     |                       | Ad26.COV2.S      | Janssen (Johnson & Johnson) | Non-replicating Viral vector | 67                                       |
| China                       | 2                   | 8                     | BBIBP-CorV (Vero cells) | Sinopharm (Beijing) | Inactivated                  | 54                                       |
|                             |                     |                       | CoronaVac        | Sinovac           | Inactivated                  | 33                                       |
|                             |                     |                       | ZF2001           | Anhui Zhifei Longcom | Protein subunit             | 4                                        |
|                             |                     |                       | Ad5-nCoV         | CanSino           | Non-replicating viral vector | 9                                        |
|                             |                     |                       | MVC-COV1901b     | Medigen           | Protein subunit             | 1                                        |
|                             |                     |                       | SARS-CoV-2 Vaccine (Vero cells) | Minhai Biotechnology Co | Inactivated                  | 1                                        |
|                             |                     |                       | Shenzhen-LV-SMENP-DC | Shenzhen Genoimmune Medical Institute | Viral vector | 1 |
|                             |                     |                       | IMB-Inactivated  | IMBCAMS           | Inactivated                  | 1                                        |
|                             |                     |                       | Inactivated (Vero cells) | Sinopharm (Wuhan) | Inactivated                  | 4                                        |
| United Kingdom              | 2                   | 2                     | Vaxzevria        | Oxford/AstraZeneca | Non-replicating viral vector | 92                                       |

aVaccines approved for use include licensed vaccines and vaccines authorized for emergency/conditional use. bMVC-COV1901 obtained Taiwan EUA approval because the MVC's COVID-19 vaccine fulfilled the EUA standards set by Taiwan's regulatory agencies (https://www.medigenvac.com/public/en/news/detail/83?from_sort=2). Information adapted from https://www.unicef.org/supply/covid-19-vaccine-market-dashboard.
gov.cn/gongbao/content/2006/content_421808.htm) was formulated and published on December 18, 2005. This document describes circumstances for special review and approval of drugs for public-health emergencies in the supplementary information. In early stages of the COVID-19 pandemic, some vaccines were used in China according to this procedure. The NMPA established four pathways (Figure 2) to accelerate the launch of new drugs to support clinically valuable drug innovation in the 2020 version of the Drug Registration Regulation (http://www.gov.cn/zhengce/zhengceku/2020–04/01/content_5498012.htm), addressing conditional approval, breakthrough therapy, priority for drug marketing authorization review and approval, and special review. These pathways further improved the original special approval procedures, and stipulated special inspection.

Figure 1 | Official documents related to vaccine review and approval. Data available at https://www.nmpa.gov.cn/yaopin/ypggtg/ypqtg/20200708151701834.html.

Figure 2 | Comparison of standard review and accelerated approval processes.
and approval conditions in principle. The US FDA has designed four expedited programs in Prescription Drug User Fee Act (PDUFA) I–VI, for fast-tracking, breakthrough therapy, accelerated approval and priority review based on the clinical value of new drugs (https://www.fda.gov/media/86377/download).

The fourth branch of the efforts involves the promulgation of special laws and regulations for vaccines. Led by the NMPA–State Administration for Market Regulation and the National Health Commission, the law on vaccine administration began to be drafted in the fourth quarter of 2018. State Council Order No. 70 (an order issued by the State Council) demanded a national vaccine strategy to provide guidance for industrial development and cross-ministerial regulation. Vaccine-related initiatives were prioritized in terms of funding and resources, thus making vaccines a strategic issue linked to national stability. This legislation marked a new era for the vaccine industry and its regulation. On June 29, 2019, the Vaccine Administration Law was passed by the National People’s Congress, thus making China the first country worldwide to enact a separate comprehensive law on vaccines. In contrast to the previous rules for immunization at vaccination stations set up by the Chinese Center for Disease Control and Prevention, medical institutions with practice licenses were allowed to perform inoculation with non-immunization and immunization programs vaccines according to the Vaccine Administration Law. For vaccines addressing major public-health emergencies or other vaccines that are urgently needed, as identified by the competent health department under the State Council, the drug regulatory authority under the State Council may grant conditional approval of an application for registration if the benefits of a vaccine outweigh its risks, according to evaluation (http://www.npc.gov.cn/npc/c30834/201907/11447c85e05840b9b-12c62b5b645e9d.shtml). Conditional approval for vaccines requires the marketing authorization holder (MAH) to continue relevant research and submit follow-up research results in a timely manner to supplement the safety and effectiveness data on the vaccine and complete the conditional requirements. On December 1, 2019, the Vaccine Administration Law and the newly revised Drug Administration Law (http://www.npc.gov.cn/npc/c30834/201908/26a6b28dd83546d79d1f90c62e59461) were formally implemented, thus incorporating the experience and effective measures from the reforms of the drug review and approval system into law. Several new systems were later introduced, including the MAH system and passive approval for clinical-trial applications. To date, the drug application backlog has already been cleared; R&D and marketing approval of new drugs have become faster; and the number of new drugs entering the market has markedly increased. On July 8, 2020, the NMPA issued several departmental rules (Figure 1) to provide a basis for accelerating the review and approval of drugs in China. For drugs (including vaccines) given conditional approval, MAHs must use corresponding risk management measures and complete relevant studies within a stipulated period, in accordance with the regulations. If MAHs are unable to complete the study within the stipulated period as required or are unable to demonstrate that the benefits outweigh the risks, the drug regulatory authority under the State Council handles the matter in accordance with the law, and the drug approval license is revoked. The conditional approval process is similar to the FDA’s accelerated approval process [4].

Under normal circumstances, all vaccine development processes are generally performed in series. During the COVID-19 pandemic, when the safety and effectiveness of the vaccines had not yet been determined, China used a parallel pathway, in which relevant departments quickly reviewed the available information and approved decisions in accordance with the regulations for special approval. Research was performed early and simultaneously with R&D departments and enterprises. For example, the technical standards department of the National Institutes for Food and Drug Control, the Center for Drug Evaluation of NMPA, follows up promptly to ensure that the scientific research data meets the standards [5]. Because of the strict control of the epidemic situation in China, large-scale phase III clinical trials of vaccines cannot be conducted. Therefore, most of the new coronavirus vaccines are undergoing clinical trials overseas, thus posing a challenge.

From December 2020 to May 2021, four new coronavirus variants, Alpha, Beta, Gamma and Delta, appeared in the United Kingdom, South Africa, Brazil and India, respectively. The effectiveness of the vaccines toward the variant strains is in question, and the new variant strains must urgently be targeted. New coronavirus vaccines with greater effectiveness must be developed and marketed. At present, the R&D on China’s coronavirus vaccines is focused on searching for correlates of protection; using surrogate endpoints to shorten the vaccine development and production cycle; improving emergency vaccine production capacity; ameliorating vaccine immunogenicity and protection efficiency, as well as vaccine delivery methods; and enhancing the vaccine immune protection spectrum and adjuvant use. In addition, to cope with the various mutations that may occur in the new coronavirus, a universal vaccine that can induce broad-spectrum and durable immunity is being designed and prepared, targeted to the highly conserved gene sequences and epitopes in the viral genes [6].

However, some shortcomings remain. First, the domestic technology route is a single pathway. Although a mature inactivated vaccine technology platform has been established, new technology routes, such as nucleic acid vaccines, lack reserves of technology; moreover, the R&D strength for domestic vaccines is far from reaching the international leading level. Second, the government implements a strict access system for vaccine manufacturing, thus resulting in deficiencies for vaccine manufacturers. Emergency expansion capabilities are restricted by laws and regulations. Vaccine MAHs are entities that
obtain drug registration certificates for vaccines and drug manufacturing certificates. The law strictly reviews vaccine MAHs and does not permit cooperative production at scattered sites except those within a single company, thus making venue changes very difficult. This aspect differs from the rules of international regulatory authorities. Third, lot release has greater restrictions for non-vaccine manufacturers when compared with vaccine manufacturers on parties that are not vaccine manufacturers, e.g., contract development and manufacturing organization companies, thus influencing vaccine export and restricting the vaccine development process. Vaccines for export are provided by MAHs according to the Vaccine Administration Law. The importation and exportation of semi-finished products produced by contract development and manufacturing organizations are restricted. The government implements the most stringent regulatory system for vaccines and adheres to principles of safety first and risk management; consequently, human challenge trials are not allowed in China. To solve these problems, more data must be collected to evaluate policies. On the basis of comparison of the procedures of advanced regulatory agencies and the Chinese NMPA, the reasons for the decisions must be made clear to policy makers, instead to copying experience.

4. COVID-19 VACCINES STATUS

4.1 COVID-19 vaccine platform

As of June 22, 2021, according to a WHO report, ten vaccine platforms for 103 vaccines were in clinical development. Among them, the protein subunit platform accounted for 32% of the vaccines (n=33), followed by non-replicating viral vectors (16%, n=16), inactivated viruses (16%, n=16) and RNA (16%, n=16) platforms (Table 2 and Figure 3).

Table 2 | Candidates in clinical trials (through June 22, 2021)

| Platform                  | No. candidate vaccines |
|---------------------------|------------------------|
| PS (protein subunit)      | 33                     |
| VVnr (viral vector, non-replicating) | 16               |
| DNA                       | 10                     |
| IV (inactivated virus)    | 16                     |
| RNA                       | 16                     |
| VVr (viral vectors, replicating) | 2              |
| VLP (virus like particle) | 5                      |
| VVr + APC (VVr + antigen presenting cell) | 2            |
| LAV (live attenuated virus) | 2                |
| VVnr + APC (VVnr + antigen presenting cell) | 1          |

Data available at https://www.who.int/publications/m/item/draft-landscape-of-COVID-19-candidate-vaccines.

At present, China is advancing technical research on new coronavirus vaccines through five technical routes: inactivated vaccines, genetically engineered recombinant subunit vaccines, adenovirus vector vaccines, attenuated influenza virus vector vaccines and nucleic acid vaccines. Both adenovirus vector vaccines and influenza virus vector vaccines are viral vector vaccines, and nucleic acid vaccines are divided into mRNA vaccines and DNA vaccines. Many inactivated virus vaccine R&D companies/institutions exist in China, whereas foreign companies/institutions focus primarily on mRNA vaccines (Table 1).

Two of the seven vaccines (BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna]) authorized for emergency use in the WHO EUL are RNA vaccines, whereas three (AZD1222 [AstraZeneca], Ad26. COV2. S [Janssen] and Covishield [Serum Institute of India PVT. Ltd.]) are non-self-replicating virus vector platform vaccines. Another two inactivated SARS-CoV-2 vaccines (Vero cells) have been developed by Sinopharm and Sinovac in China. A total of 23 vaccine candidates are in phases III or IV (Supplement Table 4), eight of which were developed by Chinese manufacturers.

4.2 Vaccine distribution in China

Owing to differences in technology and economic capabilities, the R&D for new coronavirus vaccines is highly concentrated in several countries. Regardless of which country’s vaccine R&D efforts are successful, the developed vaccines should become an international shared public resource. Therefore, vaccine R&D cannot be separate from international cooperation. The efforts of scientific researchers have made China a world leader in vaccine R&D progress. Two vaccines developed by domestic companies have been included in the WHO EUL list and shared worldwide, particularly in developing countries where the pandemic is severe. At present, through expansion efforts, China’s vaccine production, raw materials and auxiliary materials are supplied in an orderly manner, and the stable production system is able to meet the current and future needs of large-scale vaccine production. This aspect is the most important factor ensuring large-scale vaccine production and the ability to meet vaccination demand.

Domestically, communities have set up temporary vaccination sites to rapidly expand the scope of vaccination at citizens’ discretion.

As required in Article 98 in the Vaccine Administration Law of the People’s Republic of China, “The State encourages vaccine manufacturers to produce and export vaccines to meet the international demand. Exported vaccines shall meet the standards of the importing country (region) or contractual requirements.” After China’s vaccine was conditionally approved, the first batch of vaccines was sent as aid to Pakistan on January 31, 2021, with the aim of making COVID-19 vaccines a global public good.
On October 8, 2020, China signed an agreement with the Global Alliance for Vaccines and Immunization to formally join COVAX [7], a worldwide COVID-19 vaccination global initiative. This is an important measure enabling China to support the human health community and fulfill its commitments to promote vaccines as global public products. China maintains close communication with COVAX and has joined COVAX to promote the fair distribution of vaccines actively and ensure that vaccines are provided to developing countries. Simultaneously, more countries will be encouraged to join and support COVAX. Through COVAX, China will also strengthen its cooperation with other countries in vaccine efforts.

According to China’s International Development Cooperation Agency (http://en.cidca.gov.cn), since 2019, China has performed the most concentrated and largest emergency humanitarian relief operation in the history of the People’s Republic of China. Among all countries, China has provided the most vaccines worldwide, supplying various anti-epidemic and disaster relief supplies to more than 150 countries and 13 international organizations, including more than 480 million doses of vaccines. After the conditional approval for marketing China’s first vaccine, China took domestic and foreign needs into account, and also provided vaccine assistance to 88 developing countries with urgent needs, including Laos, Timor-Leste, Thailand and Gabon, and four international organizations. These vaccines are also being used in other countries including Indonesia, Pakistan, Russia, Turkey, Egypt, Jordan, the United Arab Emirates, Morocco, Brazil, Chile, Argentina, Peru and Mexico. China has risen to the challenges of international anti-pandemic cooperation and made substantial progress.

### 4.3 Efficacy and safety data for vaccines marketed in China

Several vaccines marketed in China have been evaluated in large, placebo-controlled trials and found to be both safe and effective. Adverse events have comprised mild to moderate local reactions, and transient systemic symptoms, such as fatigue, nausea and headache.

The Sinopharm/BBIBP COVID-19 vaccine is a two-dose β-propiolactone-inactivated, aluminum hydroxide-adjuvanted COVID-19 vaccine, which is administered on a 0/21–28-day schedule for the prevention of COVID-19. It was authorized by China’s NMPA on December 31, 2020, and has since been authorized by 45 countries/jurisdictions for use in adults ≥18 years of age. More than 65 million doses have been administered through emergency-use programs. The vaccine’s efficacy is as high as 78.1% (95%CI 64.9, 86.3; Table 3).

During clinical development, 16,671 participants received any dose/schedule of the BBIBP-CorV product, 97% of whom received the authorized dose/schedule. No safety concerns were identified from pre-clinical or reproductive toxicology studies, and the most common adverse events were pain at the injection site, headache and fatigue. Two serious adverse events were found to be possibly associated with vaccination (serious nausea and inflammatory demyelination syndrome/acute disseminated encephalomyelitis). One death occurred in the phase III trial in the placebo group. One participant with a diagnosis of thrombus was identified in the phase III trial in the BBIBP-CorV group.
As of December 30, 2020, the post-authorization safety data limited to domestic use in China were based on 5.9 million people. A total of 1,453 adverse events have been reported, with a reporting rate of 24.6/100,000 doses. The 108 local reactions reported included two reports of severe induration, and six reports of severe redness and swelling. Of 202 cases of fever reported, 86 were classified as severe (≥38.6 °C).

All 11 cases of facial nerve symptoms were assessed to be unrelated to the vaccine. Other reports included allergic rash/urticaria.

The Sinovac/CoronaVac COVID-19 vaccine is also a two-dose β-propiolactone-inactivated, aluminum hydroxide-adjuvanted COVID-19 vaccine, which is administered on a 0/14–28-day schedule for the prevention of COVID-19. It was authorized by China’s NMPA on February 6, 2021, and authorized by 32 countries/jurisdictions for use in adults ≥18 years of age, with variations in indications by age. On June 7, 2021, China approved emergency use of the Sinovac vaccine to expand the age range above 3 years of age. A total of 260 million doses have been distributed to the public domestic and overseas markets. The vaccine’s efficacy is as high as 50.7% (95% CI 35.9, 62.0) (Table 4).

During clinical development, 8,840 participants received any dose/schedule of the Sinovac vaccine, of whom 94% received the authorized dose/schedule. No safety concerns have been reported from pre-clinical or repro/tox studies. The most common adverse events were pain at the injection site, headache, fatigue and myalgia. During the phase III trial in Brazil, no differences in the number of reported serious adverse events or grade 3+ adverse events between the vaccine and placebo groups were found. All serious adverse events were classified as “unlikely” or “unrelated” to vaccination, and few allergic reactions were observed. A total of three deaths have been reported in the trial: two in the placebo group (COVID-19 and cardiopulmonary arrest) and one in the vaccine group (suicide).

No unexpected signals from post-authorization passive surveillance have been identified for Sinovac, on the basis of limited data from China, Indonesia, Brazil and Chile. Among 35.8 million doses distributed in China, 49 serious adverse events have been reported, including anaphylaxis, Henoch-Schönlein purpura, laryngeal edema, demyelination and cerebral hemorrhage (n=6). Of the ~17 million doses distributed in Brazil/Indonesia, 162 serious adverse events have been reported, including fever, dyspnea, death and headache (n=16).

Among 3.7 million doses distributed in Chile, 90 serious adverse events have been reported, most commonly

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Table 3 | Vaccine efficacy in multi-country phase III trial for Sinopharm/BBIBP COVID-19 vaccine (median follow-up time: 112 days)

| Group/subgroup | BBIBP-CorV group | Placebo group | Vaccine efficacy percentage (95%CI) |
|----------------|------------------|---------------|-------------------------------------|
|                | No. at risk | No. cases | No. at risk | No. cases |                |
| Overall        | 13,765      | 21        | 13,765      | 95        | 78.1 (64.9, 86.3) |
| Hospitalization| 13,765      | 3         | 13,765      | 14        | 78.7 (26.0, 93.9) |
| Severe         | 13,765      | 0         | 13,765      | 2         | NE |
| Sex            |               |            |            |            |                |
| Male           | 11,598      | 18        | 11,642      | 83        | 78.4 (64.1, 87.0) |
| Female         | 2,167       | 2         | 2,123       | 13        | 75.6 (13.3, 93.1) |
| Age group      |               |            |            |            |                |
| 18–59 years    | 13,556      | 21        | 13,559      | 95        | 78.1 (64.9, 86.3) |
| ≥60 years      | 209         | 0         | 206         | 0         | NE |
| Comorbidities  |               |            |            |            |                |
| Hypertension   | 374         | 0         | 367         | 4         | NE |
| Diabetes       | 300         | 2         | 308         | 4         | 63.7 (~79.8, 92.7) |
| Obesity        | 3,040       | 7         | 3,080       | 36        | 80.7 (56.7, 91.4) |
| Baseline SARS-CoV-2 serostatus | | | | |
| Baseline positive | NR | 0 | NR | 1 | NE |
| Baseline negative | NR | 16 | NR | 83 | 80.8 (67.2, 88.8) |

NE=not estimated; NR=not reported. Data available at https://cdn.who.int/media/docs/default-source/immunization/sage/2021/april/2_sage29apr2021_critical-evidence_sinopharm.pdf?sfvrsn=3fe32c1_5.
clinical symptoms of anaphylaxis, with a low reporting rate of 1.7/100,000 doses.

5. CONCLUSION

Laws and regulations associated with vaccine approval, and regulations for special approval have played important roles in health protection and scientific understanding of the causes of diseases and preventive measures, particularly in response to public-health emergencies. Several regulatory lessons have been learned since the SARS epidemic. First, the acceleration of COVID-19 vaccine R&D relied on refinement of the guidelines for responding to public-safety incidents, the establishment of special laws for vaccines, incentives for developing emerging technologies and an emphasis on experience and technology accumulation. Second, some acceleration measures can be used only in emergency situations, and accelerating the licensure of vaccines requires original innovation. Third, regulatory agencies are advised to focus on accelerating review and approval process from the whole drug life cycle. Guidance for innovated technologies are also needed. Fourth, some shortcomings of vaccine policies remain to be solved. Vaccine regulation must consider not only public health and safety, but also respect for the principles of science to achieve safety and efficacy [8]. Along with the promulgation of the Vaccine Administration Law and the Drug Administration Law, related regulations and further guidance are also needed to solve current issues.

AUTHOR CONTRIBUTIONS

The manuscript was written on the basis of contributions of all authors. All authors have approved the final version of the manuscript.

COMPETING INTERSTS

The authors declare no competing interests.

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