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Review on Drug Regulatory Science Promoting COVID-19 Vaccine Development in China

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ABSTRACT

Regulatory science is a discipline that uses comprehensive methods of natural science, social science, and humanities to provide support for administrative decision-making through the development of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated products. During the pandemics induced by infectious diseases, such as H1N1 flu, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), regulatory science strongly supported the development of drugs and vaccines to respond to the viruses. In particular, with the support of research on drug regulatory science, vaccines have played a major role in the prevention and control of coronavirus disease 2019 (COVID-19). This review summarizes the overall state of the vaccine industry, research and development (R&D) of COVID-19 vaccines in China, and the general state of regulatory science and supervision for vaccines in China. Further, this review highlights how regulatory science has promoted the R&D of Chinese COVID-19 vaccines, with analyses from the aspects of national-level planning, relevant laws and regulations, technical guidelines, quality control platforms, and post-marketing supervision. Ultimately, this review provides a reference for the formulation of a vaccine development strategy in response to the current pandemic and the field of vaccine development in the post-pandemic era, as well as guidance on how to better respond to emerging and recurring infectious diseases that may occur in the future.

1. Introduction

Vaccines are one of the greatest achievements in the medical field in the history of humankind. Vaccination is the most effective and economical method for preventing infectious diseases. Since China began nationwide implementation of planned immunization in 1978, and after several adjustments and expansions, China's national immunization programs include 14 vaccines to prevent 15 diseases, with a vaccination rate greater than 90% [1,2]. Vaccines have played an irreplaceable role in responding to public health emergencies, such as the pandemic H1N1 flu [3] and hand–foot–mouth disease [4,5]. Chinese vaccination has not only improved the overall health of Chinese people but also contributed to the progress of public health worldwide [1,2,6]. Since 2018, the vaccine management system, laws, and regulations in China have undergone major reforms. Further, vaccine supervision has become more scientific and stricter, effectively promoting the development of the vaccine industry.

The coronavirus disease 2019 (COVID-19) pandemic has undoubtedly increased the speed of global vaccine research and development (R&D), including in China. In one year after the beginning of the epidemic, more than one dozen COVID-19 vaccine candidates entered phase 3 clinical trials. Among them, massage RNA (mRNA) vaccines developed by BioNTech (Germany)/Pfizer (USA) and Moderna, Inc. (USA); adenovirus vectored vaccines by CanSino Biologics Inc. (China) and AstraZeneca (UK); and inactivated vaccines by Sinopharm (China) and Sinovac Biotech Co., Ltd. (China) were approved for conditional marketing. However, multiple variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have emerged successively and have spread rapidly worldwide since the beginning of the COVID-19 pandemic. Accordingly, this virus continues to challenge the vaccine industry and health system. As of 2021, five variants of concern (VOCs) were reported worldwide, including Alpha (B.1.1.7 and Q lineages), Beta

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(B.1.351 and descendent lineages), Gamma (P.1 and descendent lineages), Delta (B.1.617.2 and AY lineages), and the newly identified strain Omicron (B.1.1.529).

Vaccine regulatory science is also developing rapidly, which has played an irreplaceable role in the R&D of safe and effective COVID-19 vaccines for humans in a short period. China's vaccine industry has made rapid progress with the support of regulatory science, producing and providing effective preventive vaccines at home and abroad. As genetic lineages of SARS-CoV-2 emerge and circulate globally, scientific and efficient regulatory science is absolutely needed to support the entire life cycle of vaccine development in response to epidemics of new variants.

2. Overall state of the vaccine industry and R&D of COVID-19 vaccines in China

2.1. Overview of the vaccine industry in China

China is one of the few countries that can guarantee planned immunization with its own capabilities, and domestic vaccines account for more than 95% of vaccinations in China [7,8]. By the end of 2020, China granted approval for 55 vaccines to prevent 35 infectious diseases. As of 2020, 47 domestic vaccines with lot release were generated by 38 domestic companies in China. The doses of lot release for domestic human vaccines was 651 million in 2020. Further, the total output value of human vaccines in China was more than 60 billion CNY in 2020.

2.2. Progress in the internationalization of Chinese vaccines

The internationalization level of vaccine industry and related standards in China continues to improve. China's national vaccine regulatory system passed the assessment by the World Health Organization (WHO) in 2011 and 2014, and has been recognized by the WHO as a regulatory agency capable of fully performing its functions, which has laid the foundation for Chinese vaccines to enter the procurement catalog by the United Nations [9]. In 2013, the WHO Collaborating Center for Standardization and Evaluation of Biologicals was established in China for the first time, and the live attenuated Japanese encephalitis vaccine, which was made in China, became the first Chinese vaccine to pass the WHO Prequalification (PQ) [10]. Since then, China's influenza, hepatitis A, bivalent oral polio, and human papillomavirus vaccines have passed the WHO PQ and have been included in the global vaccine procurement list of the United Nations. After the beginning of COVID-19, China rapidly developed and industrialized COVID-19 vaccines based on multiple technology platforms. To ensure the accessibility of COVID-19 vaccines and the fairness of global distribution, international organizations, such as the WHO, the Global Alliance for Vaccines and Immunization (GAVI), and the Coalition for Epidemic Preparedness Innovations (CEPI) established the "COVID-19 Vaccines Global Access (COVAX)." Notably, China has joined the COVAX plan. The inactivated COVID-19 vaccines BBIBP-CorV of the Sinopharm (Beijing) [11] and CoronaVac of the Sinovac Biotech Co., Ltd. [12] have been listed for emergency use by the WHO. As of November 2021, China had provided more than 1.8 billion doses of COVID-19 vaccines and bulk to more than 110 countries or international organizations worldwide.

2.3. Overview of international R&D of COVID-19 vaccines

COVID-19 is the infectious disease that has had the greatest impacts on human health and society in a century. As of 3 December 2021, 262 866 050 COVID-19 cases were diagnosed, and 5 224 519 deaths from COVID-19 had been reported worldwide, according to the WHO data [13]. To rapidly respond to the COVID-19 pandemic, many countries have adopted multiple technical approaches for the development of different types of COVID-19 vaccines. With reference to the data published by the WHO, as of 30 November 2021, there were 329 COVID-19 vaccines under research worldwide, among which 135 have entered clinical trials [14]. More than ten COVID-19 vaccines have been approved for marketing or emergency use globally, including COVID-19 mRNA vaccines, inactivated COVID-19 vaccines, adenovirus vectored COVID-19 vaccines, and recombinant subunit vaccines for COVID-19 [15]. Further, by the end of November 2021, nearly 7.9 billion doses of COVID-19 vaccines had been administered globally [13], more than 2.5 billion doses had been administered and over 1 billion people were fully vaccinated against COVID-19 in China [16].

2.4. Overview of COVID-19 vaccine R&D in China

As early as February 2020, China deployed several technical routes in the R&D of COVID-19 vaccines, including inactivated vaccine, genetically engineered recombinant subunit vaccine, adenovirus vectored vaccine, nucleic acid vaccine, and attenuated influenza virus vectored vaccine [17]. China has conditionally approved the marketing of three inactivated COVID-19 vaccines developed by Sinopharm (Beijing), Sinopharm (Wuhan), and Sinovac Biotech Co., Ltd.; one adenovirus vectored COVID-19 vaccine developed by CanSino Biologics Inc.; and one recombinant protein subunit vaccine for COVID-19 developed by Zhifei Longcom (China). Among the inactivated vaccines, BBIBP-CorV developed by Sinopharm (Beijing) and CoronaVac developed by Sinovac Biotech Co., Ltd. finalized and passed the WHO PQ and supported global epidemic control [18] (Table 1). The inactivated COVID-19 vaccines developed by Shenzhen Kangtai (China) and the Institute of Medical Biology, Chinese Academy of Medical Sciences (China) have been approved for emergency use in China. Twenty-five Chinese COVID-19 vaccines have entered clinical stages.

3. Overview of the development of drug regulatory science

3.1. Definition and research content of regulatory science

Regulatory science is the basis of regulatory decision-making and aims to develop new tools, standards, and approaches to assess

Table 1
COVID-19 vaccines on the WHO emergency using list/PQ list.

Manufacturer	Vaccine candidate	Platform	Decision date
BioNTech/Pfizer	BNT162b2	Nucleoside modified mRNA	31 Dec 2020
AstraZeneca	ChAdOx1_nCoV-19 (AZD1222)	Recombinant ChAdOx1 vectored vaccine encoding the spike protein antigen of the SARS-CoV-2	16 Apr 2021
Janssen	Ad26.COV2.S	Recombinant, replication incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the SARS-CoV-2 spike protein	12 Mar 2021
Moderna	mRNA-1273	mRNA-based vaccine encapsulated in lipid nanoparticle	30 Apr 2021
Sinopharm (Beijing)	BBIBP-CorV	Inactivated, produced in Vero cells	7 May 2021
Sinovac Biotech Co., Ltd.	CoronaVac	Inactivated, produced in Vero cells	1 Jun 2021

the safety, efficacy, quality, and performance of regulated products throughout their life cycle. Regulatory science is a highly interdisciplinary discipline with an extensive research scope and application fields. This discipline resorts to the comprehensive methods of natural science, social science, and humanities to scientifically and effectively evaluate regulatory objects and provide support for administrative decision-making as society develops and new technologies and new products continuously emerge [19]. Regulatory science originated in the field of international environmental protection. After decades of development, research in regulatory science is currently focused on areas closely related to public health, such as food safety, medicine and health, and life sciences. The main research content of regulatory science includes the following three aspects: research and establishment of assessment methods and standards to ensure product quality; research and formulation of the technical guidelines required to guide product development and evaluation; and research and formulation of relevant laws and regulations based on scientific research and specific practices.

3.2. General state of regulatory science in Chinese vaccines

As vaccines are mainly used in healthy individuals, their evaluation and regulation are the most stringent among all medicines. Vaccines are also a key research topic in regulatory science. During the past 20 years, with the support of national projects in response to challenges faced in the evaluation of the safety and efficacy of vaccines, research has been carried out on quality control methods, quality specifications, related reference materials, and non-clinical safety evaluations for the target products to promote the type A H1N1 flu vaccine, EV71 vaccine for hand–foot–mouth disease, Ebola vaccine based on a mutant strain of Ebola virus in 2014, hepatitis E vaccine, and other innovative vaccines to be approved for marketing. At the critical moment of the 2009 H1N1 pandemic, China assumed the lead to successfully develop an H1N1 flu vaccine, which was approved for market use [20]. To support EV71 vaccine development, National Institutes for Food and Drug Control (NIFDC) worked closely with several laboratories at each step of R&D, including the screening of vaccine strains, establishment of reference standards for EV71 antigen and neutralizing antibodies, development of suitable evaluation methods for potency, and the statutory standards for quality control. China approved the EV71 vaccine in 2015 [21,22], which is the first vaccine available worldwide for hand–foot–mouth disease. The successful R&D of the H1N1 flu vaccine and EV71 vaccine developed in China are examples of regulatory science supporting innovative vaccine R&D [19], indicating that R&D and regulatory science study of Chinese vaccines has a solid foundation. In May 2019, China's NMPA launched the *Action Plan of Drug Regulatory Science*, signifying that China's drug regulatory science had entered a new stage.

3.3. Scientific supervision of vaccines supported by regulatory science

Regulatory science is the foundation of scientific supervision, which refers to the methods, guidelines, laws, and regulations formed on the basis of scientific research and emphasizes scientific research. While scientific supervision belongs to the category of administration to solve the problem of regulatory implementation. In 2019, on the basis of a comprehensive summary of the previous supervision experience in vaccines, China promulgated and implemented the *Vaccine Administration Law of the People's Republic of China* [23], in accordance with the *Opinions on Reforming and Improving the Vaccine Management System*, launching the most stringent supervision, avoiding loopholes in supervision, and ensuring supervision responsibilities. The *Vaccine Administration Law of the People's Republic of China* and the newly revised *Drug Administration Law of the People's Republic of China* [24], implemented in December 2019, have had a significant and positive impact in the field of vaccines. To implement these two laws, China's NMPA successively issued a series of supporting regulations and systems, established an inter-ministerial joint meeting system for vaccine management, dispatched inspectors to vaccine manufacturers, carried out routine inspections and patrols (additional risk-based inspection) at vaccine manufacturing sites to improve and implement vaccine lot release systems, and established and launched a vaccine tracking system.

4. Regulatory science promotes R&D of Chinese COVID-19 vaccines

COVID-19 vaccines R&D is the first R&D in history to involve hundreds of institutions or companies in the development of vaccines for a single disease. Further, multiple vaccine types are being developed in parallel. The rapid development of COVID-19 vaccines and successful vaccination over a short period have changed the mode of traditional vaccine R&D and applications. Such mass vaccination is also a unique event in the history of human vaccines and infectious disease prevention and control and is an embodiment of the achievements of modern molecular biotechnology and vaccine production technology.

4.1. China's national-level planning and multiple technical routes for the development of COVID-19 vaccines

An extremely ideal COVID-19 vaccine may have the following features [25]: safety (low risk, tolerable), effectiveness (high protection rate, ideally $\geq$ 70% and minimum 50%), durability (titer maintained for a long time), flexibility (boosted multiple times), universality (suitable for all age groups, including elderly people and individuals with underlying diseases), accessibility (can be mass-produced in a short time with low cost and globally accessible), and convenience (long-term storage at 4 °C or short-term stable storage at room temperature). However, at the beginning of the COVID-19 pandemic, it was impossible to predict the safety and effectiveness of various vaccine types for COVID-19 owing to the novelty of the pathogen. Therefore, China has deployed multiple strategies, including inactivated vaccine, recombinant subunit vaccine, adenovirus vectored vaccine, nucleic acid vaccine, and attenuated influenza virus vectored vaccine (Table 2). In China, inactivated vaccines and adenovirus type-5 vectored vaccines have been conditionally approved for marketing, and recombinant subunit vaccines have been approved for emergency use. Additional vaccine types, including mRNA, DNA, and attenuated influenza virus vectored vaccines, are at different stages of clinical trials [14]. Owing to the progress in diversified R&D technical routes, China has obtained technical reserves for the R&D of vaccines against variant strains. An additional vaccine targeting VOCs developed by SinoCellTech Ltd. (China) has already entered phase 2/3 clinical trials [14].

4.2. Relevant laws and regulations to promote the rapid development of vaccines in China

The *Vaccine Administration Law of the People's Republic of China* [23] stipulates that China supports basic and applied research on vaccines and promotes vaccine development and innovation by incorporating the development, production, and storage of vaccines for the prevention and control of major diseases into the national strategy. For vaccines that are urgently needed for major public health emergencies, the application for vaccine registration may be approved if the benefits of the vaccine are greater than the risks. Vaccines can be used urgently within a certain range and

Table 2
Technology platforms and major progress in COVID-19 vaccine development in China.

Vaccine platform	Vaccine	Doses	Schedule	Route	Developers	Status
Inactivated vaccine	BBIBP-CorV	2	Day 0 + 21	IM	Sinopharm (Beijing) + China National Biotec Group Co., Ltd. + Beijing Institute of Biological Products Co., Ltd.	Conditional approved
	CoronaVac	2	Day 0 + 14	IM	Sinovac Biotech Co., Ltd.	Conditional approved
	COVILO	2	Day 0 + 21	IM	Sinopharm (Wuhan) + China National Biotec Group Co., Ltd. + Wuhan Institute of Biological Products Co., Ltd.	Conditional approved
	KCONVAC	2	Day 0 + 28	IM	Shenzhen Kangtai Biological Products Co., Ltd.	Emergency use
	Inactivated vaccine (Vero cells)	2	Day 0 + 28	IM	Institute of Medical Biology, Chinese Academy of Medical Sciences	Emergency use
Protein subunit	ZF2001	3	Day 0 + 28 + 56	IM	Anhui Zhifei Longcom Biopharmaceutical Co., Ltd. + Institute of Microbiology, Chinese Academy of Sciences	Conditional approved
	Recombinant vaccine (sf9)	2	Day 0 + 28	IM	West China Hospital, Sichuan University	Phase 3
	SCB-2019	2	Day 0 + 21	IM	Clover Biopharmaceuticals Inc. + GlaxoSmithKline plc. + Dynavax Technologies Corporation	Phase 3
	SCTV01C targeting VOCs	1	Day 0	IM	SinoCellTech Ltd.	Phase 2/3
	Recombinant vaccine	3	Day 0 + 28 + 56	IM	Academy of Military Medical Sciences, Academy of Military Sciences + Zongyianke Biotechnology Co., Ltd. + Liaoning Maokangyuan Biotechnology Co., Ltd.	Phase 2
	Recombinant vaccine (V-01)	2	Day 0 + 21	IM	Guangdong Provincial Center for Disease Control and Prevention + Gaozhou Center for Disease Control and Prevention	Phase 2
	Recombinant vaccine (Chinese Hamster Ovary cell)	2	Day 0 As a booster	IM	National Vaccine and Serum Institute, China + Beijing Zhong Sheng Heng Yi Pharmaceutical Technology Co., Ltd. + Lanzhou Institute of Biological Products Co., Ltd.	Phase 1/2
	202-CoV	2	Day 0 + 28	IM	Shanghai Zerun Biotechnology Co., Ltd. + Walvax Biotechnology Co., Ltd. + CEPI	Phase 1
	ReCOV	2	Day 0 + 21	IM	Jiangsu Rec-Biotechnology Co., Ltd.	Phase 1
	PIKA-adjuvanted vaccine	2	Day 0 + 7	IM	Yisheng Biopharma Co., Ltd.	Phase 1
Viral vector	Ad5-nCoV	1	Day 0	IM	CanSino Biologics Inc.	Conditional approved
	DelNS1-2019-nCoV-RBD-OPT1	2	Day 0 + 28	IN	University of Hong Kong + Xiamen University + Beijing Wantai Biological Pharmacy Enterprise Co., Ltd.	Phase 3
Viral vector + antigen-presenting cell	COVID-19/aAPC vaccine	3	Day 0 + 14 + 28	SC	Shenzhen Geno-Immune Medical Institute	Phase 1
mRNA	ARCoV	2	Day 0 + 14 or Day 0 + 28	IM	Academy of Military Sciences + Walvax Biotechnology Co., Ltd. + Suzhou Abogen Biosciences Co., Ltd.	Phase 3
	mRNA vaccine	2	TBD	IM	Shanghai East Hospital + Stemirna Therapeutics Ltd.	Phase 1
	mRNA vaccine	2	TBD	IM	Zhuhai Lifanda Biotechnology Co., Ltd.	Phase 1
DNA	INO-4800	2	Day 0 + 28	ID + electroporation	Inovio Pharmaceuticals Inc. + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceuticals Co., Ltd.	Phase 3
	SARS-CoV-2 DNA vaccine	2	Day 0 + 21	IM + electroporation	The University of Hong Kong	Phase 1

IM: intramuscular; IN: intranasal; SC: subcutaneous; TBD: to be determined; ID: intradermal.

time limit in the event of a major public health emergency. The newly revised *Drug Administration Law of the People's Republic of China* also stipulates the conditional approval of urgently needed drugs. The *Management of lot release of biological products* [26] implemented on 1 March 2021, in China stipulates that biological products needed for national disease prevention and emergency control can be released simultaneously. To cope with the COVID-19 pandemic, the NMPA established an accelerated approval and lot release system for COVID-19 vaccines in China. To ensure safety and efficacy, COVID-19 vaccine R&D processes are sped up by rolling the submission of application materials and accelerating the review and approval processes. At present, China has marketed seven COVID-19 vaccines through the emergency use authorization and accelerated approval system.

4.3. Formulation of technical guidelines to promote COVID-19 vaccine R&D in China

With reference to the WHO and China's existing vaccine-related regulations and guidelines, combined with the characteristics of emergency R&D of Chinese vaccines for COVID-19, the NMPA issued five technical guidelines for COVID-19 vaccine R&D in China on 14 August 2020, including the *Technical guidelines on research and development of COVID-19 prophylactic vaccines (trial edition)* [27], the *Technical guidelines on pharmaceutical research of COVID-19 prophylactic mRNA vaccines (trial edition)* [28], the *Technical points for non-clinical studies and evaluation of prophylactic COVID-19 vaccines (trial edition)* [29], the *Technical guidelines on clinical research of COVID-19 prophylactic vaccines (trial edition)* [30], and the *Technical guidelines on clinical assessment of COVID-19 prophylactic vaccines (trial edition)* [31]. Since then, several guidelines for COVID-19 vaccine R&D have been formulated to promote COVID-19 vaccine R&D in China on the premise of ensuring safety and effectiveness without lowering standards. To maintain consistency between the Chinese vaccine R&D and international standards and consensus, the R&D and evaluation of the series of COVID-19 vaccines have referred to relative guidelines formulated by China and the WHO, and have been guided by constant communication with WHO, which ensured that the R&D of the vaccines was carried out on the basis of data related to quality, safety, and efficacy.

4.4. Complete quality control and evaluation technology platform to ensure the safety and effectiveness of vaccines

China relied on national vaccine quality control laboratories, related inspections, and scientific research institutions to study and develop relevant animal models [32–37], quality control methods [38], reference materials [39], and quality specifications for innovative vaccine R&D for COVID-19 immediately after the outbreak [40]. Through laboratory work, such as virus seed verification, cell bank verification, product verification, and clinical serum testing, Chinese researchers have ensured the safety and effectiveness and promoted the R&D of COVID-19 vaccines. The evaluation method of vaccine efficacy is important for vaccine quality control; for example, at the beginning of the COVID-19 epidemic, the NIFDC established a SARS-CoV-2 neutralization assay based on a pseudotyped SARS-CoV-2 virus [38,41] and a transgenic mouse model expressing humanized SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) [32]. These evaluation tools have been widely used in preclinical and clinical evaluations of the COVID-19 vaccine candidates, which promotes the research and development of COVID-19 vaccines in China. Because of its flexibility and availability, the SARS-CoV-2 pseudovirus has also been widely employed in the investigation of infectivity and antigenicity of SARS-CoV-2 variants [42–45], which is helpful to illustrate the current vaccine efficacy against the circulating variants and to design future broad-spectrum vaccines for the continuing pandemic. To ensure the emergency use of COVID-19 vaccines, 13 provincial drug quality control agencies were authorized to undertake the lot release task to provide quality assurance for vaccine inoculation in China.

4.5. Strengthening post-marketing supervision to promote the quality and supply of Chinese vaccines for COVID-19

Chinese vaccines for COVID-19 have brand-new characteristics, including the largest vaccine production, distribution, and administration in human history. China has promptly issued a workflow for increasing production and line expansion, as well as technical guidelines for COVID-19 vaccines, including regulatory requirements for COVID-19 vaccine expansion and production, workflow for post-marketing changes in the registration and management of COVID-19 vaccine expansion and production, research on post-marketing changes in the assurance of quality and supply of COVID-19 vaccines, key considerations for commissioned production technology, and key technical points for research on the increase of multiple doses of COVID-19 vaccines (without preservatives), to clarify the specific circumstances and workflow of the changes after the increase in production and expansion lines. The NMPA has implemented a stationed inspection system for vaccine manufacturers to coordinate the stationed work with the production plans of the companies and align the dispatched inspection with the production batches of the enterprises, thereby ensuring that enterprises fulfil their responsibility for vaccine quality under large-scale and heavy-duty conditions in China. In addition to establishing a tracking and regulatory system for vaccine information, China has urgently developed an independent tracking and regulatory system for COVID-19 vaccines to ensure that the sources and destinations of COVID-19 vaccines are traceable.

5. Conclusions

Since the beginning of COVID-19, the global vaccine R&D system, patterns, and capabilities have undergone significant changes. Further, vaccine R&D, production, and supervision in China have also markedly changed. The administration of COVID-19 vaccines has effectively reduced the number of hospitalizations, severe illnesses, and deaths from COVID-19. Authorities have accumulated experience in the global vaccine supply, distribution, administration, and real-world monitoring of the safety and efficacy of COVID-19 vaccines.

To cope with the major threats to human health caused by new and recurring infectious diseases in the future, rapid vaccine R&D should be promoted under the overall framework of promoting regulatory science, where focus should be given to basic research on pathogens, pathogen epidemiology and molecular epidemiological research, basic vaccine research, key technologies for vaccine industrialization, vaccine evaluation and approval mechanisms, and the internationalization of vaccines.

Compliance with ethics guidelines

Zhiming Huang, Zhihao Fu, and Junzhi Wang declare that they have no conflict of interest or financial conflicts to disclose.

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