Regulatory lessons from China COVID-19 vaccine policy and approval

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In the past five years the regulatory authorities have successively issued a series of supporting documents for implementation, continuously promoting the reform of the drug regulatory system to reconstruct the system of drug review and approval. In 2015, the State Council issued the “Opinions of the State Council on the Reform of Review and Approval System for Drugs and Medical Devices” (Notice No.44 of 2015) to resolve the backlog of drug registration applications, encourage innovation, and improve quality as a breakthrough to reform the drug review and approval system. The goals, tasks and specific measures of China's drug review system reform have been clarified for the first time.

On June 19, 2017, China Food and Drug Administration (CFDA) formally joined the International Human Drug Registration Technical Coordination Committee (ICH), marking the full integration of China's drug review and approval with international advanced standards. One year later, the NMPA of China was elected as a member of the ICH Management Committee. In 2017, China has further deepened the reform of the drug review system and encourage innovation. The General Office of the Central Committee of the Communist Party of China and the General Office of the State Council issued the “Opinions on Deepening the Reform of the Review and Approval System to Encourage Innovations in Drugs and Medical Devices” (General Office Notice No.42 of 2017) on October 8, 2017. The subject content of reviewing and approving, promoting drug innovation and generic drug development, strengthening drug life cycle management, and improving the regulatory mechanism proposes a systematic and complete pathway.

Supplement Table 1 7 Vaccines in WHO Emergency Use Listing

Manufacturer	Vaccine name	NRA of record	Platform	EUL decision
Pfizer/BioNTech	BNT162n2/COMIRNATY	European Medicines Agency	Nucieoside modified mRNA	Dec 31, 2020
Janssen	Ad26.COV2.S	European Medicines Agency	Recombinant, nonreplicating Ad26 vectored vaccine encoding the SARS-CoV-2 S protein	Mar 21, 2021
AstraZeneca /Univ. of Oxford	AZD1222	European Medicines Agency	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2	Apr 16, 2021
Serum Institute of India	Covishield	Drug Controller General of India	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2	Feb 15, 2021
Moderna	mRNA-1273	European Medicines Agency	mRNA-based vaccine encapsulated in lipid nanoparticle (LNP)	Apr 30, 2021
Sinopharm (CNBG) Beijing	SARS-CoV-2 Vaccine (Vero Cell), inactivated	China National Medical Products Administration	Inactivated, produced in Vero cells	May 7, 2021
Sinovac	SARS-CoV-2 Vaccine (Vero Cell), inactivated	China National Medical Products Administration	Inactivated, produced in Vero cells	Jun 1, 2021

Supplement Table 2 Vaccines list approved for use by at least one national regulatory authority[a] (up to Oct 20,2021)

Vaccine developer Country	No. in WHO EUL list	No. in Phase III or IV[1]	Approved vaccine	vaccine developer	Vaccine platform description	No. of approved countries or territory[2]
the 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-COV1901[b]	Medigen	Protein Subunit	1
			SARS-CoV-2 Vaccine (Vero Cells)	Minhai Biotechnology Co	Inactivated	1
			Shenzhen-LV-SMENP-DC	Shenzhen Genolmmune Medical Institue	Viral Vector	1
			IMB-Inactivated	IMBCAMS	Inactivated	1
			Inactivated (Vero Cells)	Sinopharm (Wuhan)	Inactivated	4
The United Kindom	2	2	Vaxzevria	Oxford/AstraZeneca	Non Replicating Viral Vector	92
India	0	2	Covaxin	Bharat Biotech	Inactivated	12

			Covishield (Oxford/AstraZeneca formulation)	Serum Institute of India	Non Replicating Viral Vector	73
			ZyCoV-D	Zydus Cadila	DNA	1
Cuba	0	2	Soberana plus	Finlay	Protein Subunit	1
			Soberana 2	Finlay	Protein Subunit	3
			CIGB-66	Center for Genetic Engineering and Biotechnology	Protein Subunit	3
Russian Federation	0	2	Covi-Vac	Chumakov Center	Inactivated	1
			SRCVB - EpiVacCorona	State Research Center of Virology & Biotechnology	Protein Subunit	3
			Sputnik Light	Gamaleya	Non Replicating Viral Vector	17
			Sputnik V	Gamaleya	Non Replicating Viral Vector	72
Kazakhstan	0	1	QazVac	Kazakhstan RIBSP	Inactivated	1
Iran (Islamic Republic of)	0	ND	COVIran Barekat	Shifa Pharmed Industrial Co	Inactivated	1
			SpikoGen	CinnaGen	Protein Subunit	1

[a] Vaccines approved for use include licensed vaccines and vaccines authorized for emergency/conditional use. [b] MVC-COV1901 was obtains Taiwan EUA approval due to MVC's COVID-19 vaccine has fulfilled following EUA standards set by Taiwan's regulatory agencies[3]

Supplement Table 3 Part of official documents related with vaccine review and approval

Laws or regulations	Published time	content
Special Review and Approval Procedure for	December 18, 2005	the State Food and Drug Administration may, according to law, decide to follow

Drug Registration of the State Food and Drug Administration[4]		the procedure to conduct special review and approval of drugs for public health emergencies in any of the following circumstances: (1) Where the President of the People's Republic of China declares a state of emergency or the State Council decides that certain areas within a province, autonomous region or municipality directly under the Central Government are in a state of emergency; (2) Where the contingency program for public health emer-gencies is initiated according to law; (3) Where the drug reserve department or the health administrative department of the State Council proposes a special review and approval for drugs having existing national drug standard; (4) Other circumstances applicable to special review and approval.
Vaccine Administration Law of the People's Republic of China	December 1, 2019	when particularly major public health emergencies or other emergencies which seriously threaten public health occur, the competent health department under the State Council shall propose recommendations on the urgent use of vaccines based on the need of disease prevention and control, and after evaluation organized by the drug regulatory department under the State Council, the permission for the urgent use within certain scope and period shall be granted by the drug regulatory department under the State Council **Article 70** in Chapter IX "Supervision and Management" requires that "the drug regulatory authorities and health departments shall conduct administration on the whole process of vaccine development, manufacture, distribution and immunization according to their respective responsibilities and supervise vaccine MAHs (Marketing Authorization

		Holder), disease prevention and control institutions, and immunization entities to fulfill their obligations according to law” the State organizes professional and specialized drug inspector teams at both national and provincial levels, and enhance supervision and inspection on vaccines.
Drug Registration Regulation	July 1,2020	**Article 72** in Chapter IV showed that “When the threat of public health emergencies occurs and after a public health emergency occurs, the State Drug Administration may decide in accordance with the law to implement special approval for the prevention and treatment drugs needed for the emergency response of public health emergencies” **Article 13**: “The National Medical Products Administration (NMPA) has established a drug registration system to accelerate the launch of drugs to support clinical value-oriented drug innovation. For qualified drug registration applications, applicants can apply for breakthrough therapy drugs, conditional approval, priority review and approval, and special approval procedures”
Drug Administration Law of the People's Republic of China	December 1, 2019	**Article 26** showed that “drugs used for the treatment of severe life-threatening diseases for which there is no effective treatment and drugs urgently needed available for public health, where the drug clinical trial data have shown their efficacy and predictable clinical results, may be conditionally approved, and the relevant information should be stated in the drug approval license”

Supplement Table 4 COVID-19 Vaccine Candidates in Phase III, IV (up to June 22, 2021)

No.	Vaccine platform acronym	Vaccine platform description	Type of candidate vaccine	Number of doses	Schedule	Route of administration	Developers	Phase
1	IV	Inactivated virus	CoronaVac; inactivated SARS-CoV-2 vaccine (vero cell)	2	Day 0 + 14	IM	Sinovac Research and Development Co., Ltd	IV
2	IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	2	Day 0 + 21	IM	Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products	III
3	IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell), vaccine name BBIBP-CorV	2	Day 0 + 21	IM	Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products	III
4	VVnr	Viral vector (Non-replicating)	ChAdOx1-S - (AZD1222)	1-2	Day 0 + 28	IM	AstraZeneca + University of Oxford	IV
5	VVnr	Viral vector (Non-replicating)	Recombinant novel coronavirus vaccine (Adenovirus type 5 vector)	1	Day 0	IM	CanSino Biological Inc./Beijing Institute of Biotechnology	IV
6	VVnr	Viral vector (Non-replicating)	Gam-COVID-Vac Adeno-based (rAd26-S+rA	2	Day 0 + 21	IM	Gamaleya Research Institute; Health Ministry of	III

			d5-S)				the Russian Federation	
7	VVnr	Viral vector (Non-replicating)	Ad26.COV2.S	1-2	Day 0 or Day 0 +56	IM	Janssen Pharmaceutical	III
8	PS	Protein subunit	SARS-CoV-2 rS/Matrix M1-Adjuvant (Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M)NVX-CoV2373	2	Day 0 + 21	IM	Novavax	III
9	RNA	RNA based vaccine	mRNA-1273	2	Day 0 + 28	IM	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	IV
10	RNA	RNA based vaccine	BNT162b2(3 LNP-mRNAs),also known as “Comirnaty”	2	Day 0 + 21	IM	Pfizer/BioNTech+ Fosun Pharma	IV
11	PS	Protein subunit	Recombinant SARS-CoV-2 vaccine (CHO Cell)	2-3	Day 0 + 28 or Day 0 + 28 + 56	IM	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	III
12	RNA	RNA based	CVnCoV	2	Day 0 +	IM	CureVac AG	III

		vaccine	Vaccine		28			
13	IV	Inactivated virus	SARS-CoV-2 vaccine (vero cells)	2	Day 0 + 28	IM	Institute of Medical Biology + Chinese Academy of Medical Sciences	III
14	IV	Inactivated virus	QazCovid-in® - COVID-19 inactivated vaccine	2	Day 0 + 21	IM	Research Institute for Biological Safety Problems, Rep of Kazakhstan	III
15	DNA	DNA based vaccine	nCov vaccine	3	Day 0 + 28 + 56	ID	Zydus Cadila	III
16	IV	Inactivated virus	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152)	2	Day 0 + 14	IM	Bharat Biotech International Limited	III
17	PS	Protein subunit	VAT00002: SARS-CoV-2 S protein with adjuvant	2	Day 0 + 21	IM	Sanofi Pasteur + GSK	III
18	IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	2	Day 0 + 28	IM	Shenzhen Kangtai Biological Products Co., Ltd.	III
19	PS	Protein subunit	FINLAY-FR-2 anti-SARS-CoV-2 Vaccine (RBD chemically conjugated to tetanus toxoid plus	2	Day 0 + 28	IM	Instituto Finlay de Vacunas	III

			adjuvant)					
20	PS	Protein subunit	EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19)	2	Day 0 + 21	IM	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	III
21	RNA	RNA based vaccine	SARS-CoV-2 mRNA vaccine (ARCoV)	2	Day 0 + 14 or Day 0 + 28	IM	Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences	III
22	PS	Protein subunit	CIGB-66 (RBD+aluminium hydroxide)	3	Day 0 + 14 + 28 or Day 0 +28 + 56	IM	Center for Genetic Engineering and Biotechnology (CIGB)	III
23	IV	Inactivated Virus	VLA2001	2	Day 0 + 21	IM	Valneva, National Institute for Health Research, United Kingdom	III

REFERENCE

[1] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

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[3] https://www.medigenvac.com/public/en/news/detail/83?from_sort=2
[4] State Administration of Market Order No. 21. Available at: http://www.gov.cn/gongbao/content/2006/content_421808.htm. Accessed May 23, 2021.