REGULATORY SHIFT IN CHINA: EVOLUTION OF NMPA

ABSTRACT

The paper aims to provide an outline and review of the major regulatory changes that NMPA has undergone in China since 2015 to speed up new products production and registration in accordance with international norms, as well as to raise the profile of Chinese medical products on a global scale. In the past, China's regulatory framework has been extremely difficult. Since 2015, China's health authority has been changing the organisational structure in China to bring Chinese therapeutic items up to international standards in terms of suitability, protection, and reliability, as well as to more likely locate individuals' general prescription drug requirement and expand access to new drugs and treatments from across the world. All the regulatory changes are making it easier to produce innovative products by implementing international standards and technological criteria, increasing review and approval transparency, and speeding up the new drug evaluation and approval, medical devices, and other products. The Chinese Ministry of Health has also issued guidance to help with drug production, including contact for drug development and technical assessment, introduction of electronic common technical documents, and post-approval safety surveillance. To promote the production of innovative products, regulations for priority review and approval, data protection regime, imported medical product registration, and new product classification are in place. China's regulatory system is constantly being reformed. It is possible to achieve simultaneous growth and approval in par with existing regulatory markets in the near future.

Keywords: NMPA, Regulatory, Reforms, Standards, innovative products, approval transparency

INTRODUCTION

China is considered to be an epitome where tradition meets technology. It is evident that cultural preservation and innovations towards an advanced future go hand in hand in this country. This can even be said about the health care system in place. Even though majority of

people still practice traditional medicine, the domestic demand for effective drugs, and novel medical devices have increased [1]. This can be due to the growing old-age population and the countries economical status on a global level. This has resulted in tremendous changes as the whole healthcare is evolving towards a new universal healthcare[2].

This also means that China is constantly changing and expanding with vast opportunities in terms of manufacturing, import and export of innovatory products, drugs, cosmetics, and medical devices. It is no secret that initially the walls around the Chinese market were looming high due to its language barrier and the regulations that were a bit difficult to comprehend and incorporate as it deviated so much from the harmonized approval process, it appears to be individual and tedious [3].

The product registration process varies from that of many other countries in that all imported drugs, whether sold internationally or not, must contain evidence from local clinical trials; in terms of quality, there are substantial differences between global standards and certain domestic products and suppliers; the period it takes to evaluate and approve new medicines is longer than in most other major countries[4].

Regional Chinese industries have historically been uninterested in the development of innovative new products due to strong competition in the generics market, and their current capacity for doing so is limited which can related to Indian market[5].

These companies have previously focused on bioequivalence (BE) trials for generic drug registration, but with due to the regulatory shift and the evolution of CFDA into NMPA new standards, they will have to begin focusing on generic consistency and efficacy. As a result, any data that is deemed incorrect or incomplete will not be accepted, potentially causing current licenses to be revoked. This can also pave way for the industries to consider new innovative products in future [6].

ADMINISTRATION IN CHINA

Pharmaceutical policy in China has historically been relatively disjointed and uncoordinated between provinces, autonomous regions and national levels. They have various levels of

authority based on the hierarchy. NMPA have published norms to dissolve and maintain a unified chain of command amongst the regions [7].

Below is a brief outline of the administration in China [8]:

Figure 1: Political Map of China

A three-level system division amongst the country currently exist namely provinces, counties, and townships. The country is divided into regions, independent nations, and municipalities, all of which report directly to the Central authorities. China is currently divided into 23 provinces, 5 autonomous regions, 4 municipalities directly subordinate to the Federal Government, and 2 special organizational entities.

Navigating legal documents can present to be a bit different since rule (guizhang) and regulations (xingzheng fagui) are published in forms of circulars, notice, decree and letters [9].

DISCUSSION

The aim of this shift is to encourage systemic change and improvise the pharmaceutical industry, bringing drugs, devices, and cosmetics which already on the market in China as well those that need to be formulated up to international effectiveness, protection, and quality standards [10].

These reforms aimed to:

- Rectifying the current accumulation of registration applications.
- Create a global-development environment that promotes research and innovation of novel medications;
- Increase the transparency & consistency of the evaluation and approval process [11].

Reforms	
2016	Self-inspection of clinical data
	Priority review
	Additional capacity at CDE
	Marketing Authorization Holder rationalization/new classification/definition of new drugs
	Generic drug quality and efficacy consistency Evaluation (GQCE)
2017	Opening up of first-in-human (FIH) Phase I trials to global development
	Simplified process for gaining a marketing approval
	Clinical trial management
	Acceleration of drug and medical device registration review process
	Drug and medical device life cycle management
	Protecting innovators' rights
2018	NHC Rare Disease list
	NMPA elected member of ICH Management Committee
	Technical Guideline for Acceptance of Overseas Drug Clinical Trial Data
	Adjusting the Approval Process for Drug Clinical Trial Evaluation (Circular 50)
	MAH pilot project extended one year
	Accelerated approval
	Independent Vaccine Administration Law
	CDE website
2019	Medical device site qualification notification
	MAH ADR direct reporting system online
	Oncology and rare disease drugs
	eCTD implementation progress and plan

Figure 2: List of major reforms in NMPA during the 13th 5-year plan **[12]**

Table 1: Rules and Regulations published under NMPA during the 13th 5-year plan for drugs [13]

Drugs				
FILE	**NAME**	**PHASE**	**IMPLEMENTED BY**	**ISSUE DATE**
General Decree				
Decree No. 28 of 2020	Approaches for Drug Manufacturing Control and Management	Implemented	NMPA	January 22, 2020
Decree No. 39 of 2017	Administrative Measures for Batch Issuance of Biological Products	Implemented	SFDA	December 29, 2017
	Approaches for Drug Manufacturing Control and Management	Implemented	NMPA	November 21, 2017
	Measures for the Administration of Internet Drug Information Services	Implemented	NMPA	November 21, 2017
	Measures for the Administration of Pharmaceutical Business Licenses	Implemented	NMPA	November 21, 2017
	Provisions for Administering the People's Republic of China's Drug Administration Law	Implemented	SFDA	February 6, 2016

Registration/Filling				
Notice No. 119 of 2020	Online application of drug registration	Implemented	Comprehensive Department of the State Drug Administration	
Notice No. 2 of 2020	The filing procedures and requirements of provincial-level Chinese herbal medicine preparation specifications	Implemented	NFDA	
Notice No. 193 Of 2015	The filling out relevant items in the Drug Production License	Implemented	SFDA	
GMS/QMS				
Notice No. 160 of 2016	Guiding Principles for On-site Inspection of Good Drug Management Practices	Implemented	SFDA	December 14, 2016
	Pharmaceutical business quality management practices	Implemented	SFDA	June 30, 2016
Clinical Evaluation				
Notice No. 108 of 2019	The Principles and Procedures of Drug Sampling and Other Documents	Implemented	Comprehensive Department of the State Drug Administration	December 26, 2019
Notice No. 34 of 2016	Clinical trial data verification work procedures	Implemented	SFDA	March 28, 2016

Post Market Surveillance				
Notice No. 78 of 2015	Guidelines for Reporting, Monitoring and Inspection of Adverse Drug Reactions	Implemented	SFDA	July 2, 2015

Table 2: Rules and Regulations published under NMPA during the 13th 5-year plan for medical devices [14], [15][16][17]

Medical Device				
FILE	**NAME**	**PHASE**	**IMPLEMENTED BY**	**ISSUE DATE**
General Degree				
MJPRC-20180825-1	Amended Regulation on Supervision and Management of Medical Devices of Medical Devices (Draft)	Draft	Ministry of Justice	June 25, 2018
Decree No.7 CFDA, 2017	Measures for Supervision and Administration of Medical Device	Implemented	CFDA	November 21, 2017

	Production			
Decree 4 CFDA, 2014	Provisions for Medical Device Registration	Implemented	CFDA	July 30, 2014
Registration/Filling				
Notice, CMDE-20190103	Operation Specification for Record Filing of Medical Device Master Files	Draft	CMDE	January 3, 2019
Notice, CMDE-20190103	Record Filing Requirement of Medical Device Master Files	Draft	CMDE	January 3, 2019
Notice, CMDE-20190103	Guideline for Record Filing of Medical Device Master Files	Draft	CMDE	January 3, 2019
Notice, CMDE-20190103	Announcement on Record Filling of Medical Device Master Files	Draft	CMDE	January 3, 2019
Notice, No. 83, NMPA, 2018	Innovation Device Approval Procedure	Implemented	NMPA	November 5, 2018
Notice, NMPA-20180822	Unique Device Identification (UDI) Implementation Plan	Draft	NMPA	August 22, 2018
Notice, No.131, CFDA, 2017	Using Chinese Name for Registrant or File Submitter of Imported Medical Devices	Implemented	CFDA	November 2, 2017
Decree 6, CFDA, 2014	Regulation on Instructions for Use and Labels of Medical Devices	Implemented	CFDA	July 30, 2014
GMP/QMS				

Notice No.101 NMPA, 2018	Regulations for the Administration of Overseas Inspection of Pharmaceutical & Medical Devices	Implemented	NMPA	December 26, 2018
Notice No.19 CFDA, 2016	Good Manufacturing Practice in Class III Medical Device Manufacturers	Implemented	NMPA	February 5, 2016
Notice No.218 Annex 3, CFDA	Good Manufacturing Practice Guidelines for Onsite Inspection of Implantable Medical Devices	Implemented	CFDA	September 25, 2015
Notice No. 218 Annex 2, CFDA	Good Manufacturing Practice Guidelines for Onsite Inspection of Sterile Medical Devices	Implemented	CFDA	September 25, 2015
Notice No.218 Annex 1, CFDA	Good Manufacturing Practice Guidelines for Onsite Inspection	Implemented	CFDA	September 25, 2015
Notice, No.103, CFDA, 2015	Good Manufacturing Practices on In Vitro Diagnostic Reagents	Implemented	CFDA	July 10, 2015
Notice, No.102, CFDA, 2015	Good Manufacturing Practice for Implantable Medical Devices	Implemented	CFDA	July 10, 2015
Notice, No.64, CFDA, 2014	Good Manufacturing Practice for Medical Devices	Implemented	CFDA	December 29, 2014
<u>Clinical Evaluation</u>				

Notice CMDE-20181122-2	Technical Guideline for Comparing the Same Variety of In-vitro Diagnostic Reagents Exempted from Clinical Trials (Draft)	Draft	CMDE	November 22, 2018
Notice CMDE-20181122-1	Guidelines for Clinical Trials of In Vitro Diagnostic Reagents (Draft)	Draft	CMDE	November 22, 2018
Notice No.6, CFDA, 2018	Medical Device Clinical Trial Design Guideline	Implemented	CFDA	January 8, 2018
Notice No. 179, CFDA, 2017	Basic Requirements for Clinical Evaluation Materials of IVD Exempted from Clinical Trial (Draft)	Implemented	CFDA	November 8, 2017
Decree 25, CFDA, 2016	Good Clinical Practice for Medical Device	Implemented	CFDA/National Health Commission	March 23, 2016
<u>Guideline & Standard</u>				
	Current China NMPA Clinical Pathways for Medical Device Registration (Draft)			November 18, 2020
	Drug-Medical Device Combination Products in China (Draft)			September 21, 2020
Notice No.7, CMDE, 2019	Guideline on AI-Aided Software	Implemented	CMDE	July 3, 2019
Notice No.50,	Guideline for Technical Review of Medical Device	Implemented	CFDA	August 18, 2015

CFDA, 2015	Software Registration			
Post Market Surveillance				
Decree 1 Annex 9, NMPA, 2018	Guidance on Inspecting Medical Device Adverse Event Monitoring Activity	Draft	NMPA	September 20, 2018
Decree 1 Annex 7, NMPA, 2018	Guidance on Focus Points when Monitoring Medical Device Adverse Events	Draft	NMPA	September 20, 2018
Decree 1 Annex 5, NMPA, 2018	Guidance for License Holder on Collecting and Reporting Individual Cases of Medical Device Adverse Event	Draft	NMPA	September 20, 2018
Decree 1 Annex 3, NMPA, 2018	Guidance on Medical Device Adverse Event Monitoring Scope	Draft	NMPA	September 20, 2018
Decree 1 Annex 1, NMPA, 2018	Guidance on Medical Device Adverse Event Monitoring	Draft	NMPA	September 20, 2018
Decree 1, NMPA, 2018	Measures for the Administration of Medical Device Adverse Event Monitoring and Re-evaluation	Implemented	NMPA	August 31, 2018
Decree 29, NMPA, 2018	Measures for the Administration of Medical Device Recall	Implemented	CFDA	January 25, 2017

Table 3: Rules and Regulations published under NMPA during the 13th 5-year plan for Cosmetics [18][19][20]

Cosmetics				
FILE	**NAME**	**PHASE**	**IMPLEMENTED BY**	**ISSUE DATE**
General Decree				
Announcement No. 265 of 2015	Cosmetics Production licensing	Implemented	SFDA	December 15, 2015
	Cosmetics Supervision and Administration Regulations	Draft	CSAR	June 30, 2020
Registration/Filling				
Drug Administration Letter (2020) No. 105	Administrative Measures for Cosmetics Labeling	Draft	NMPA	September 21, 2020
	Administrative Measures for Cosmetic Supplementary Inspection Methods	Draft	CSAR	November 12, 2020
	Cosmetic Sampling Inspection Management Regulations	Draft	CSAR	September 27, 2020

Announcement No. 195 of 2017	General Administration on Regulating the Registration and Filing of Cosmetics Related Matters	Implemented	SFDA	November 30, 2017
Announcement No. 31 of 2018	Pilot Implementation of the Filing Management of Imported Non-Special Purpose Cosmetics	Implemented	SFDA	March 8, 2018
Drug Administration Letter (2020) No. 105	Administrative Measures for Cosmetics Labeling	Draft	NMPA	2020-09-21
GMS/QMS				
	Cosmetic Production Quality Management Standards	Draft		September 27, 2020
Notice No. 4 (2018)	Regulating the Risk Monitoring of Cosmetics	Implemented	SFDA	January 5, 2018
Guidelines and Standards				

Drug Administration Letter〔2020〕82	Technical Guidelines for Safety Assessment of Cosmetics	Draft	Department of Cosmetics Supervision, National Food and Drug Administration	July 29, 2020
Drug Administration Letter (2020) 82	Rules for Classification of Cosmetics and Classification Catalogue	Draft	Department of Cosmetics Supervision, National Food and Drug Administration	July 29, 2020
Post Market Surveillance				
Notice No. 94 (2020)	Cosmetics Adverse Reaction Monitoring Management Measures	Draft	SFDA	September 27, 2020

CONCLUSION

Few changes over the course of these 5 years speaks for itself taking into consideration that in China, there have been an increase in the number of clinical research centres and clinical organisations. In April 2016, China only had 478 clinical trial institutions. In 2019, there were 886 authorized clinical study organizations, an 185 percent rise over the past year.

By introducing in November2019 the record-setting system for registering and administering clinical trials institutions in China, more and more healthcare facilities will be qualified for clinical trials. This will allow China to address the growing number of clinical trials ongoing in the country, as well as encourage the drug development.

In 2017, the Chinese regulator, the National Medical Products Administration (NMPA) joined ICH, highlighting the convergence of the Chinese regulatory system with international norms.

China is a prominent advocate and defender of globalisation as the world's second largest economy. Chinese pharmaceutical innovation can only be globalised by mutual recognition of clinical trials data from China and the world. Between new medicine licences in the United States and China there existed a delay between five and seven years before 2015. Due to the above-mentioned Chinese pharmaceutical reforms, this time lag was decreased to one or two years, and in certain situations to few months. As part of this internationalisation process, Chinese domestic innovation capacities and achievements are rising rapidly.

China was appointed in 2018 to McKinsey's second-level innovator list, alongside Europe and Japan's creative markets, representing China's remarkable success in pharmaceutical innovation. Previous limits on drug and medical-device innovation have been lifted as the breadth of these reforms' spreads across multiple stages of the products life cycle.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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