"Regulatory Framework and Global Integration of the National Medical Products Administration (NMPA) in China"

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Abstract

The National Medical Products Administration (NMPA) of China, formerly known as the China Food and Drug Administration (CFDA), functions as the key regulatory body overseeing drug, medical device, food, and cosmetic safety. Established through a series of organizational reforms, NMPA was integrated into the State Administration for Market Regulation in 2018 to streamline processes and eliminate overlapping authorities. The agency is entrusted with responsibilities such as drafting laws, supervising manufacturing and quality standards, enforcing drug classification, overseeing ADR monitoring, and ensuring compliance with Good Manufacturing Practices. In alignment with global standards, China joined the International Council for Harmonisation (ICH) in 2017, facilitating harmonized drug registration processes. NMPA's regulatory framework encompasses a classification system for active pharmaceutical ingredients (APIs), a comprehensive dossier review process, and stringent registration requirements. Recent developments include reduced clinical trial requirements for quicker drug approvals, and enhanced policies to attract foreign investment by liberalizing the pharma market. Nevertheless, challenges such as regulatory loopholes and past corruption scandals have affected public confidence. Despite this, China's pharmaceutical sector is expanding rapidly due to rising healthcare demand, driven by population growth and aging. The NMPA continues to play a critical role in promoting public health, safeguarding product quality, and facilitating international collaboration for drug regulation and safety.

Keywords : National Medical Products Administration (NMPA), CFDA, drug regulation, China, food safety, medical devices.

Introduction

The agency had multiple former names, including **China Food and Drug Administration and State Food and Drug Administration.**The National Medical Products Administration was founded on the basis of the former State Food and Drug Administration (SFDA). In March 2013, the former regulatory body was rebranded and restructured as the China Food and Drug Administration, elevating it to a ministerial-level agency. In 2018, as part of China's 2018 government administration overhaul, the name was changed to National Medical Products Administration' and merged into the newly created State Administration for Market Regulation. The headquarters are in Xicheng, Beijing. In its first incarnation as the CFDA, the NMPA replaced a large group of overlapping regulators with an entity similar to the Food and Drug Administration of the United States, streamlining regulation processes for food and drug safety The National Medical Products Administration is directly under the State Council of the People's Republic of China, which is in charge of comprehensive supervision on the safety management of food, health food and cosmetics and is the competent authority of drug regulation in mainland China. On 10 July 2007, Zheng Xiaoyu, the former head of China's State Food And Drug Administration, was executed for taking bribes from various firms in exchange for state licences related to product safety.

Main responsibility

1. To organize relevant authorities to draft laws and regulations on the safety management of food, health food and cosmetics; organize relevant authorities to formulate comprehensive supervision policy, work plan and supervise its implementation.
2. To exercise comprehensive supervision on the safety management of food, health food and cosmetics in accordance with laws; organize and coordinate supervision work on the safety of food, health food and cosmetics carried out by relevant authorities.
3. To organize and carry out investigation and impose punishment on serious safety accidents of food, health food and cosmetics; delegated by the State Council, organize, coordinate and conduct specific law-enforcement campaigns over safety of food, health food and cosmetics nationwide; organize, coordinate and collaborate with relevant authorities in carrying out emergency rescue work on serious safety accidents of food, health food and cosmetics.

4. To draft law and regulations on administration of medical devices and supervise their enforcement; take charge of registration and regulation of medical devices; draft relevant national standards, draw up and revise professional standards of medical devices, manufacturing practice and supervise their implementation.
5. To be in charge of drug registration, draw up, revise and promulgate national standard of drugs; draw up criteria for marketing authorization of health food; review and approve health food; set up classification system for prescription drugs and OTC drugs; establish and improve ADR monitoring system; be responsible for drug re-evaluation, review drugs to be withdrawn and formulate a national essential medicines list.
6. To draft and revise good practices for drug research, manufacturing, distribution and use, and supervise their implementation.
7. To control the quality of drugs and medical devices in manufacturers, distributors and medical institutions; release national quality bulletin on drugs and medical devices on a regular basis; investigate and punish illegal activities of producing and selling counterfeit and inferior drugs and medical devices in accordance with law.
8. To regulate radioactive pharmaceuticals, narcotics, toxics, psycho -tropics, and other controlled drugs and devices in accordance with law.
9. To draw up and improve qualification system for licensed pharmacist, supervise and direct the registration of licensed pharmacist.
10. To direct national drug regulation and comprehensive supervision on the safety management of food, health food and cosmetics.
11. To carry out exchanges and cooperation in drug regulation, relevant safety management of food, health food and cosmetics with foreign governments and international organizations.
12. To undertake other work assigned by the State Council.
13. The State Food and Drug Administration is not responsible for regulating pharmaceutical ingredients manufactured and exported by chemical companies. This regulatory hole, which has resulted in considerable international news coverage unfavorable to China, has been known for a decade, but failure of Chinese regulatory agencies to cooperate has prevented effective regulation.[1]

14. Objective

1) Integrate and centralise food safety regulatory authority

2) Streamline and strengthen responsibility of ministry, cooperation to ensnare food safety

3) Established and improve gram mot food and drug management safety

4) Consolidated food and drug regulatory authority

5) Transform and optimise government function

Registration for medical devices

Section I Product Research & Development

Section II Clinical Evaluation Section II Clinical Evaluation

Section III Registration System Verification

Section IV Product Registration [2]

Organisation structure

- Department of Administration

1. General Office

2. Dept. of Legal Affairs

3. Dept. of Food Safety Supervision

4. Dept of Drug and Cosmetics Registration (Dept of TCMs and Ethno-Medicines Supervision)

5. Dept. of Medical Device Registration

6. Dept of Drug Cosmetics Supervision

7. Dept of Medical Device Supervision

8. Bureau of Investigation and Enforcement

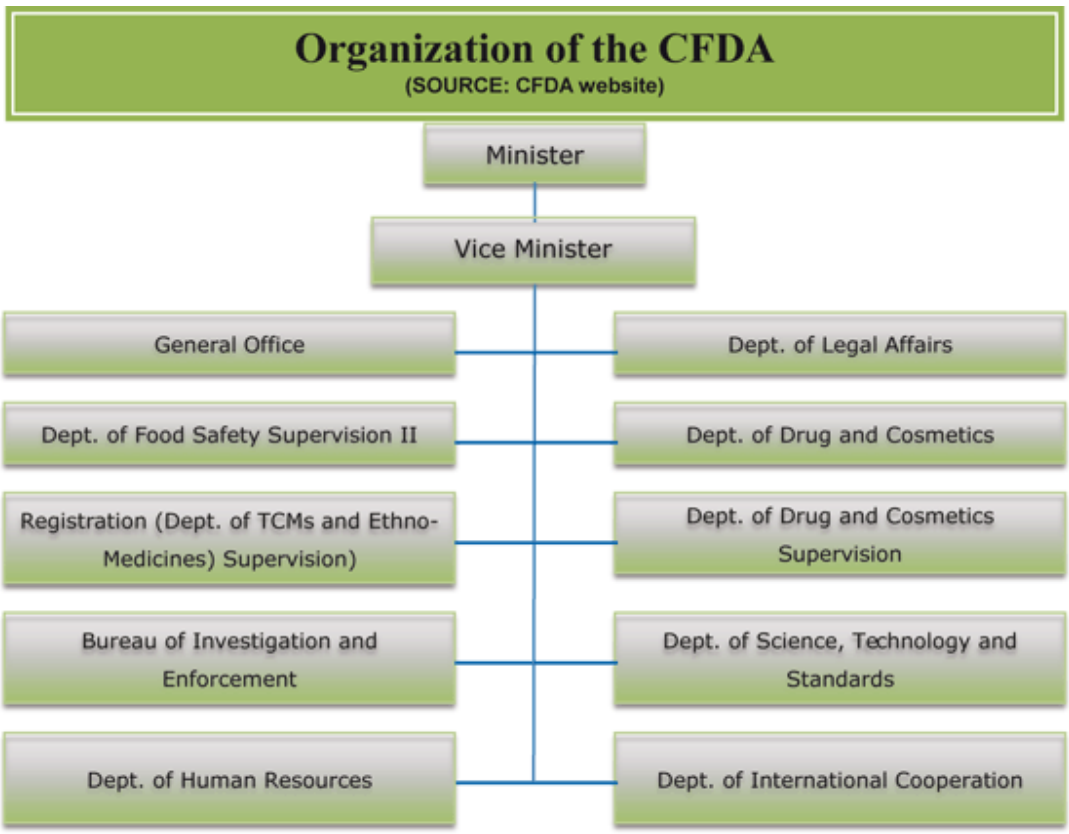
9. Dept of Emergency Management

10. Dept of Science, Technology and Standards

11. Dept of Media and Publicity

12. Dept. of Human Resources

13. Dept. of Planning and Finance [3]



Registration and licensing Requirements

- Regulatory Authority: National Medical Product Administration (NMPA)
- Website of regulatory Authority: http://www.nmpa.gov.in
- Fees for Drug Registration: 367.6 thousand RMB (57169 USD)
- Normal time taken for registration:3-5 Yrs
- Registration Requirements [Dossier Format): CTD
- Whether plant inspection is Mandatory: Yes
- Requirement of Local agent/Subsidiary: Local agent is sufficient

Recent activities

- In June 2017 NMPA joint ICH as 8th regulatory member
- CFDA renamed as National Medical Product Administration on 1st Sep 2018
- Administered by the State Administration for Market Regulation (SAMR)
- Registrant needs to use this name for future fillings.[4]

Functions Includes

- Registration review and approval of APIs, FDFs, Medical devices, Biologics And Cosmetics
- Review and publication and of national pharmacopeia's (CP)
- Drug classification based on the therapeutic category.
- Supervise and control registration procedures
- Inspection for domestic and outdoor facilities
- Promotion of national essential medicines and traditional medicines
- Established recall and disposal procedures.

NMPA reforms and actions

- New employment for the technical staff (sensors)
- Efforts to become ICH members
- Implementation of new policies
- Waiver for the clinical trials and bio studies (BE) for fast approvals and to

Regulatory authorities relating to Drug Administration

- National Institutes for Food and Drug: Verify the drug specification and test the sample Control (NFDC)
- Centre for Food and Drug Inspection (CFDI): Inspect the manufacturing facility of the drug
- Central For Drug Evaluation (CDE): Conducts Drug evaluation
- Centre for Drug Re-evaluation (CDR)

Laws, Regulations and Guidelines

(1) Drug Administration Law of the People's Republic of China the Peoples Republic of China (No. 45)

- First amendment on Dec 28th, 2013
- Second amendment on Apr. 4th, 2015
- Draft amendment released

(2) Basic regulation of drug registration in China

(3) Provisions for Drug Registration SFDA

Service guide

- 30024-1 Service guide for approval of IDL
- 30024-2 Service guide for approval of Re
- 30024-3 Service guide for the approval of changes specified in IDL, with attachment

(4) Good Manufacturing Practice for Drugs (2010 Revision)

(5) Registration dossier's requirements

chemicals drug registration with new classification (No 80, 2016)

Drug Classification System

Class-1-New chemical entity

Class-1-New chemical entity with new therapeutic indication

Class-3-Generic drug for the innovator not marketed in China

Class-4-Generic drug of innovator marketed in China

Class-5-Imported drugs

Class 5.1-for innovator drug enter into the China

Class 5.2-for the generic drug enter into the China

Table 1:Difference between previous and current policies for registration of API

Previous	Current
Import Drug Licence (IDL) Country specific requirement	Joint application policy (Effective from 1st January) Similar to USFDA system
Use to be valid for 5 years	Valid till entire product cycle
Long review cycle and approval	Fast review cycle and approval
No initial assessment	Formal initial assessment (as per No. 80 order)
No need of costumer activation	Need costumer activation

CTD Module

- Based on the quality safety and efficacy
- The content is equivalent
- Based on number 80 article by CFDA

NMPA's expectations for importers:

- Appointment of local agent for easy communication (if applicable)
- Regional requirements should be strictly followed
- Stringent controls should be adopted irrespective of the CP pharmacopeia
- Supply of samples and documentation support during sample evaluation
- Cooperation from supplier during port inspection and sampling (if required)
- Extension of the USDMF and CEP to China market sometimes cannot be considered.[4]

Dossier assessment criteria

- Should comply with the no 80 article requirement by NMPA.
- Administrative/regional requirements should be suffice.
- Ex, Administrative documents should be legalised and notarized.
- Specification should not be less than the local standards
- Formality check should pass [4]

Consolidated review procedure

- Firstly, submit registration dossiers and get a
- holder/Manufacturer of AM or Secondly, try to associate with DPs by holder/Manufacturer of All (or) DP or agent
- Thirdly, consolidated review by CDE
- Finally, activate the status of API depending on the result of DF evaluation by CDE

Status of APIs

- A-Approved for using in marketed DP's
- A*- Has passed the technical evaluation independently but not joint with DPs
- A#-API has approved for wing in marketed IPs, but have major (major changes in manufacturing process, changes on manufacturing product and has not passed consolidated review DMF section with some special requirement Section 3.2.5.1.3
- Polymorphism report should be provided (If applicable)

Section 3.2.5.22

- Process should at least have 3 chemical conversions. (CMO acceptable)
- (Purification and salt formation cannot be considered as chemical step)
- If process has reprocessed and discussion validation and batch equivalency data should be provided [4]

Section 3.2.5.23

- KSM should be justifying in accordance with ICH Q7
- It should procure from at least GMP compliant facility
- Audit and compliance report of vendor should be provided
- Quality inducative methods (RS/Assay) should be added in KSM spec (As applicable)
- Complete AMV should be carried out. Partial validation shall not be considered.
- KSM should be well characterized
- CMC information of KSM (II required).

Section 3.2.5.2.4

- All in-process and intermediate specs should be quality compliant AMV (complete/partial) should be performed.
- Critical process parameters should be justified (Negative experimental studies)

Section 3.2.5.2.5

- Executed process validation protocol and report should Blank Master Batch Product

Section 3.2.5.2.6

- Rational for selection of the manufacturing process from lab, pilot, commercial butches
- Supported with literatures/ patents should be included

Section 3.2.5.3.1

- API had better be characterized against the pharmacopeial standard [4]

Some specific regional requirement (Special requirements from NMPA)

(1) Master blank manufacturing records

- For all the APIs, blank BMRs should be provided for all the
- Except for sterile DPs and DPs manufactured by special process, BMRs should be provided
- For the samples used for Clinical trial and BE studies, the BMRs should be provided

(2) Complete validation

- For API, provide the validation documents of each test method one by one, the validation results, and provide validation data &chromatograms
- For DP, the requirements for method validation are the same with API's

(3) Comparison with innovators

- For API, compare the Assay, Related Substances unspecified impurity, total impurity), Polymorphism and so on
- For DP, compare the design, screening & optimization and determination of formulations. Compare the quality characteristics (including Assay, related substances, packing conditions)

(4) The information on KSM (s)

- Audit reports for outsourced KSM(s) for outsource care plan should be established, and audit reports should be provided

Control of KSM (s)

Detailed manufacturing process Specified impurities solvents and Necessary method validation

(5) Reaction steps of production of API

- At least three steps acquiescently purification are not counted the production of KSMs should also conforms to GMP The requirements of quality control on KSM almost the same as that of final API

(6) Stressing test/Affecting factors testing

a. Stress testing (API)

Purpose elucidates the intrinsic stability of the API Conditions under more severe conditions than those used for accelerated testing

b. Affecting factors testing

Purpose investigates the intrinsic stability of the API Conditions under more severe conditions than those used for accelerated testing

c. Stress testing (DP)

Purpose: assess the effect of severe conditions on the drug product

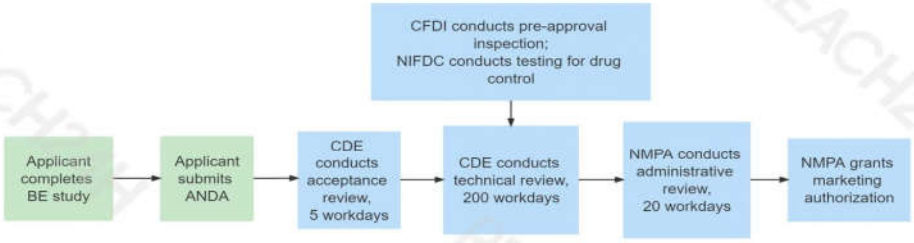
Condition: include photostability testing and specific testing on certain products, metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products)

d. Affecting factors testing Purpose: investigate the rationality of the formulation, manufacturing processes and Packing conditions

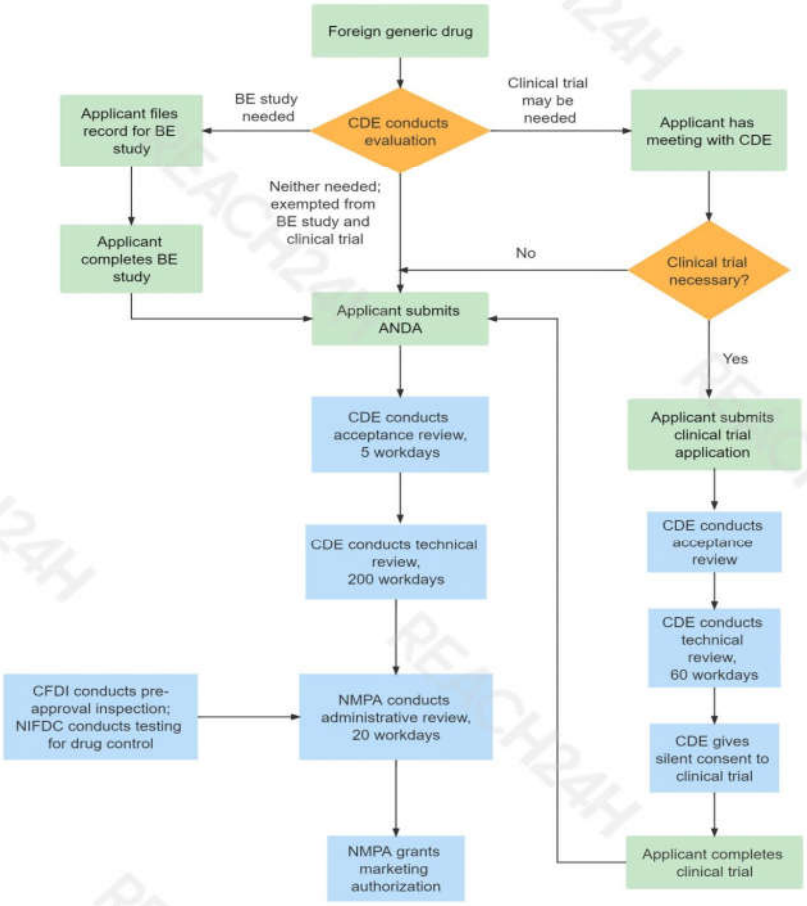
Abbreviated New Drug Application

NMPA: National Medical Products Administration;
CDE: Center for Drug Evaluation;
CFDI: Center for Food and Drug Inspection of NMPA;
NIFDC: National Institutes for Food and Drug Control.

For domestic generic drugs manufactured in China:



For foreign generic drugs imported to China:



Introduction of China Market

China's Pharma market is estimated at $ 140.3 billion in 2017 having grown by 29% as per BMI report. It is the largest market in Asia Pacific Region and second largest in the world. In 2018 the market is expected to reach $ 142.26 Billion. China's rapid ageing of the population and rising incomes will lead to a surge in demand for medicines and quality healthcare services. Forecast of pharmaceutical sales show market may reach.

USD372.4bn in 2027 with a Cagr of 9% Government is unable to cope with such stroto open up the domestic market further to both private and foreign players. On March 5 2018, Premier Li stated that the Chinese government will remain committed to opening up the economy to foreign companies. As a result, it is believed, Beijing to adopt the negative list management system, which provide guidelines on sectors where foreign investors cannot invest in, or can only invest in under certain restrictions. Foreign companies earlier were to seek before they were allowed to invest in China, However, with the changes to the negative list taking effect, foreign enterprises only need to register their activities with the authorities in the same way as their domestic peers, so long as their intended activities are not on the negative list the new system will benefit foreign companies, including drug makers as it will help to cut red tape. Pharma journals like BMI feel the regulatory issues that plague the will continue to pose a significant barrier to innovative multinational pharmaceutical firms' revenue growth. While the business environment is certainly showing signs of improvement, backed by the implementation of progressive reforms, the country's medicine market will continue to be met with challenges presenting a key market access barrier [4]

Latest Updates

- In August 2018, it was reported that representatives of leading Chinese pharmaceutical firms are exploring chances of co
- In March 2018, Merck Kraal announced its plans of building a single operation in Wiro to target the biosimilars market
- Scandals regarding substandard pharmaceutical drugs will jeopardise China's a become an international pharmaceutical leader The current furore erupted in July 2018 after a rabies vaccine for humans manufactured by Changchun Chang sheng Biotechnology, one of China's largest vaccine makers, was found to have violated safety

- On July 18 2018, Takeda announced the company's ambitions for its China business make the country the second wow regards China as a core country for its business practice

Proposed Changes

- ## Hospital Sector

At present most of the health care is with the government. This is also expected to change. There are 14,500 private hospitals in the country, accounting for 52.6% of total hospitals. Premier Li pledged in his government work report, to set up closely liked medical alliances across the country to solve the problem of 'difficult medical treatment, expensive medical treatment', opening up new investment opportunities. [4]

- ## Medical coverage

On March 5, Chinese Premier Li Keqiang, announced that the government subsidy on basic medical insurance will increme by USD6.3 per capita to USD77.7 per capita, from USD71.3 per capita currently. This will enable a significant improvement in healthcare a increased demand for medicines, providing an improved outlook for healthcare providers and pharmaceutical firms. The government has also set a target to enroll more than 20han people under the critical illness insurance scheme, an March 20 2018, Premier Li stated that the government plans to lower import tariffs on cancer drugs, potentially to 0%, from around 5% to 6% currently, to increase affordability

Import Tariff

The proposed changes to China's import tariff policy for foreign cancer medicines will provide a boost multinational pharmaceutical firm and the increased reimbursement of these medicines will increase patient access to innovative oncology therapeutics also expanded the list of medicines covered by the basic medical insurance to include 339 additional drugs.

- **Regulatory** Registration and approval for drugs and medical devices will also be consolidated in a new drug administration that will be established and managed under the newly formed National Market Supervision Administration which will absorb the China Food and Drug Administration (CFDA) and related responsibilities from the State Administration for Industry the General Administration of Quality Supervision, Inspection and Quarantine

(AQSIQ) The CFDA, SAIC, and AQSIQ will cease to exist. Announcement in late June 2017, accepting of the IHC implies, that China's drug regulation will now be in line with international standards and this will in turn boost the sale of Chinese pharmaceutical products internationally IC11, set up by the US, ELI and Japan in 1990, is an international organisation that standardises global drug registrations and mission is to ensure development and registration of safe, effective, and high quality medicines in a resource efficient manner. The drug regulatory authorities, the pharmaceutical industry and research and development institutes will actively

participate in the formulation of international rules and promote quicker domestic application of new drugs. Commenting on this, Yaan Lin, director general

- **Epidemiology**

With China's rapid economic development, the disease burden has changed in the country. Cardiovascular diseases and cancer have become the leading causes of death among Chin Hypertension and cigarette smoking are the leading preventable causes of death in China. To this end, the burden imposed by non burden of communicable conditions is on the decline. [4]

- ## Generic Market

The financial sustainability of China's universal healthcare scheme will be a central issue underpinning the government's austere approach. Moreover, rising demand for medicines in the country will push the government to focus on cost pricing pressures, a focus on cost continue over the coming years. These factors would help Generic component of China's market move faster. Generic drug market spending to increase from USD 76.27 bn in 2017 to USD125 bn by 2022, with a CAGR of 10% In 2017, generic drugs accounted for 63.47% of total sales. Latest forecasts show that by 2018 ending market is likely to touch 590 6 bn with 18% growth

- ## Pharma Trade

As one of the largest pharmaceuticals markets in Asia Pacific, China continues to present a highly dynamic pharmaceutical trade environment. Imports increases as China's demand for medicines, especially innovative treatments, continues to grow healthcare modernisation Exports are also expected to grow as Chinese pharmaceutical firms continue to look beyond the local market. In

2017, pharmaceutical (Only finished dosage forms) imports were valued a forecast to grow to USD36 2 ban by 2022 with a five the rise in China's pharmaceutical exports is driven by two main trends First, given the attractiveness of China to multinational drug makers, & firms have be country In comparison, China's pharmaceutical esport value was USD4 3bn in 2017

- **Pricing Regime**

Prices of drugs on The Essential Drugs List are set by the government, while most other drug prices Are set after negotiations between the government and the manufacturer

In place of price controls, the Chinese authorities have introduced a tendering system that has been the source of significant pressure While a "double envelope approach is adopted Authorities consider both the quality of a product and its price during the decision-making process Reports suggest that firms have been asked to provide discounts The introduction of national Affected were AstraZeneca's Iressa (getfitnib) and Zhejiang Beta Pharma's

Conmana (icotimb) and Vircad (tenofovir), which saw price cut Moreover, in July 2017 it was announced that 36 new drugs will be added to the national insurance Programme including novel pharmaceuticals. To lower their prices, manufacturers went through Rounds of negotiations with China's Ministry of Human Resources and Social Security. For example, GlaxoSmithKline's (GSK) breast cancer drug Tyler (lapatinib) was added to the list after a price Cut of 42%, Bayer's liver and kidney cancer drug Nexaver (sorafenib) was reduced by 51 Roche slashed the price by an average of 59% to get three monoclonal antibodies (rituximab), Herceptin (trastuzumab) and Avastin (bevacizumab) Negotiations are set to shope the Health technology assessment (HTA) become more prominent in the country. China has been Steadily building up its expertise with a total of five ITA institutes

Organisation Falling under the Formed partnerships with leading organizations such as the relationship between the China National Health Development Research Centre and UK's National Institute for Health and Clinical Excellence (NICE) among others Data limitations are an impediment but it is expected that to be gradually Alleviated as more studies are conducted The National Drug Reimbursement List, for example, notes That the cost and benefits of products will be compared using National Development and Reform. Commission's 'Guideline for reform of

drug and medical service Pricing further chines with this view, highlighting that pricing for pharmaceuticals should gradually Adopt pharmacoeconomic evaluation

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The national-level tendering in May 2016 placed pressure on prices Products Affected were AstraZeneca's Iressa (getfitnib) and Zhejiang Beta Pharma's Conmana (icotinus) and Viread (tenofovit), which saw price cuts of 53% 54% and 67% respectively. Moreover, in July 2017 it was announced that 36 new drugs will be added to the national imutance II China's Monistry of Human Resources and Social Security For example, GlaxoSmithKline's (GSK) breast cancer drug Tykerb lapatinibi was added to the list after a price Cut of 424 Bayer's liver and kidney cancer drug Nesavar (sorafenib) was reduced by 51 Roche slashed the price by an average of 59% to get three monoclonal antibodies (rituximab), Herceptin (trastuzumab) and Avastin (bevacizumab)- onto the list. Whole price Negotiations are set to shape the immediate business environment, the longer Health technology assessment (HTA) become more prominent in the country China has been Steadily building up its expertise with a total of five IITA institutes-Falling under the National Health and Family Planning Commission

It has also formed partnerships with leading organisations such as the relationship between the China National Health Development Research Centre and UK's National Institute for Health and Clinical Excellence (NICE) among others Data limitations are an impediment but it is expected that to be gradually alleviated as more studies are conducted. The National Drug Reimbursement List, for example, notes that the cost and benefits of products will be compared using pharmacoeconomic principles. The National Development and Reform Commission's 'Guideline for reform of drug and medical service pricing [4]

Case Study

Zheng Xiaoyu the former director of China's State Food and Drug Administration (SFDA), was executed in July 2007 for taking bribe and approving untested medicine which led to death of at least 10 people

Mr. Zheng was director of the regulatory agency since its formation in May 2003 until mid-2005. Before that he was head of the state pharmaceutical administration from1994to 1998 and head of the state drug administration from 1998 to 2003

Court documents quoted pleaded guilty to the charges that he 'sought benefits' from eight domestic countries in exchange for approval of drugs and medical devices between 1997 and December 2006. [5]

Zheng Xiaoyu

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