

**Impact of China's regulatory reforms on
business operations in Chinese pharmaceutical market:
Perspectives and Challenges for
multinational pharmaceutical companies**

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Sofia Dust

aus Peking

Bonn 2018

Betreuer und 1. Referent: Dr. Michael Gebauer

Zweiter Referent: Dr. Santiago Figueroa-Perez

Table of Contents

List of abbreviations.	V
List of tables and figures.	VII
Summary.	IX
1 Introduction.	1
1.1 Aging Chinese population.	2
1.2 Change in China's disease profile.	3
2 Changing environment in China's drug regulatory system.	4
2.1 Impact of 2002 issued drug registration regulation on drug development process of multinational pharmaceutical companies in China.	4
2.1.1 Model of drug development and registration before 2002.	5
2.1.2 Model of drug development and registration since 2002.	7
2.2 Impact of latest IMCT Guidance on drug development and approval process of multinational companies in China.	10
2.3 Impact of recent major drug registration reforms on drug development process in China.	13
2.3.1 CFDA started major drug registration reforms in 2015.	14
2.3.2 Reform developments in 2017.	21
2.4 Impact of the reforms on multinational pharmaceutical companies' business operations in China.	26
3 Changing environment in China's state market regulatory administration.	28
3.1 Introduction.	28
3.1.1 Trends in healthcare expenditure and pharmaceutical spending.	28
3.1.2 Context of pricing and reimbursement in China.	29

3.1.3 Pathway from market authorization to market access.	31
3.2 Recent market regulation reforms and their impact on multinational companies' business operations in China	32
3.2.1 Adjustments to the NRDL.	32
3.2.2 Reform of drug pricing.	34
3.2.3 Increased number of private healthcare facilities.	36
4 Restructuring of China's government – Establishment of State Market Regulatory Administration	37
4.1 Key institutional changes in pharmaceutical and healthcare sector.	37
4.2 Impact on multinational pharmaceutical companies.	38
5 Conclusion.	39
6 References.	42

List of abbreviations

API	Active pharmaceutical ingredient
BE	Bioequivalence
BMI	Basic Medical Insurance
CAGR	Continuous annual growth rate
CDE	Center for Drug Evaluation
CFDA	China Food and Drug Administration
CRO	Contract research organization
CPP	Certificate of pharmaceutical product
CTA	Clinical trial application
DAL	Drug Administration Law
DRR	Drug Registration Regulations
EC	Ethics committee
EDL	Essential Drug List
FIH	First-in-human
GCP	Good clinical practice
GP	Government pricing
GGP	Government-guided pricing
HIF	Health Insurance Formulary
IDL	Import drug license
IMCT	International multi-center clinical trial
IND	Investigational new drug
IRB	Institutional review board
IRP	Internal reference pricing
KOL	Key opinion leader
MAA	Marketing authorization application
MAH	Marketing authorization holder
MOH	Ministry of Health

MOHRSS	Ministry of Human Resources and Social Security
MRCT	Multi-regional clinical trial
NCE	New chemical entities
NDA	New drug application
NDRC	National Development and Reform Commission
NHFPC	National Health and Family Planning Commission
NRDL	National Reimbursement Drug List
OECD	Organization of economic co-operation and development
OTC	Over-the-counter
R&D	Research and development
RMCT	Regional multi-center clinical trial
PRC	People 's Republic of China
PRDL	Provincial Reimbursement Drug List
SAMI	State Administration for Medical Security Insurance
SDA	State Drug Administration
SMRA	State Market Regulatory Administration
SDA	State Drug Administration
TCM	Traditional Chinese Medicine
THE	Total health expenditure
TPE	Total pharmaceutical expenditure
US FDA	United States Food and and Drug Administration
WTO	World Trade Organization
ZMU	Zero mark-up

List of tables and figures

Tables

Tab. 1: Registration classes of chemical drugs with the corresponding clinical trial requirements

Tab. 2: Selected anticancer drug approvals in China and in the USA

Tab. 3: CFDA old chemical drug classification system vs. new chemical drug classification system

Tab. 4: Changes in the purchase value of selected imported drugs in Sanming

Figures

Fig. 1: Annual drug expenditure and growth rate in drug expenditure in China, 2010–2020

Fig. 2: Comparison of China's population aged 65 and over with selected country populations, 2015 and predicted for 2050

Fig. 3: Development of China's population aged 65 and over, 1990-2015, predicted to 2050

Fig. 4: Percentage of the total deaths caused from the top five diseases in China's cities, 2003-2011

Fig. 5: Import drug registration pathway. In comparison with the timeframe of the global clinical development program

Fig. 6: Potential registration pathways since 2002 for global companies without manufacturing facilities in China

Fig. 7: Annual number of IMCT in China registered at clinicaltrials.gov, 2004-2015

Fig. 8: Impact of the 2014 issued IMCT guidance on drug registration pathway of global companies conducting MRCT involving study sites in China

Fig. 9: CFDA responses for 15 applications containing MRCT approach in 2014

Fig. 10: Comparison of the number of new drug applications (blue), applications waiting for approval (red) and completed applications (green), 2011-2014

Fig. 11: Comparison of the number of new drug applications for chemical drugs (blue), for TCM (red), for biologicals products (green) and for re-review (purple), 2011-2014

Fig. 12: Health expenditure in China, 1990-2012

Fig. 13: Total health and pharmaceutical expenditure in China, 1990-2012

Summary

As the second-largest in the world, China's pharmaceutical market is one of the most promising markets for multinational pharmaceutical companies. Not only due to its population size but also a rapidly aging population, rising per capita incomes and greater access to healthcare enhance the appeal of China's market to overseas companies.

However, China's drug regulatory system has been considered as a highly challenging one with heavy backlog of applications for both drug approval and clinical trial registration due to the complexity and length of the review and approval process, the volume of applications and understaffing of reviewer who are responsible to process these applications. To improve the process of drug review and approval, Chinese government recognized the integration of the Chinese clinical study into international multi-center clinical trial in the 2002 issued '*Drug Registration Regulation*'. The major drug registration reforms begun in 2015 with the announcement on several policies regarding review and approval of drug registration. China's efforts to reform the drug and medical device review and approval system culminated in the issuance of a central government directive in the end of 2017. This issuance is followed by a flood of CFDA implementation measures in a timely manner.

Besides the changing environment in China's drug regulatory system, major changes also take place in the environment of China's state market regulatory administration. Following widespread discontent at the healthcare situation in China due to rapid growth of drug expenditures which has contributed to serious burdens for patients as well as to combat the perverse incentives created by the 15% mark-up policy, China's central government officially issued significant reforms in 2009 with the goal to provide affordable and equitable healthcare for all. Since 2015, an ongoing series of reforms concerning regulation of Chinese pharmaceutical expenditure have been revised or developed, resulting in far-reaching impact on the pharmaceutical market in China.

In this master thesis, the changing environment of both China's drug regulatory system and China's state market regulatory administration are described. Here, the main focus is keeping on the impact of the announced reforms on multinational pharmaceutical companies' business operations in China, with a special emphasis on the opportunities and challenges with which the companies may be faced.

1. Introduction

Companies are steadily in search of new markets in order to generate higher profit margin. China's pharmaceutical market is one of the most promising market for multinational pharmaceutical companies. As the second-largest pharmaceutical market in the world, the People's Republic of China (PRC) offers many great opportunities towards foreign companies.

Drug expenditure in China has shown a continuous annual growth rate (CAGR) from 2010 through 2015, forecasted to grow from US\$108 billion in 2015 to US\$167 billion by 2020. The growth rate in drug expenditure in China has been predicted to slow to a CAGR of 6–9% over the next five years from 2015-2020 (Fig. 1) [1].

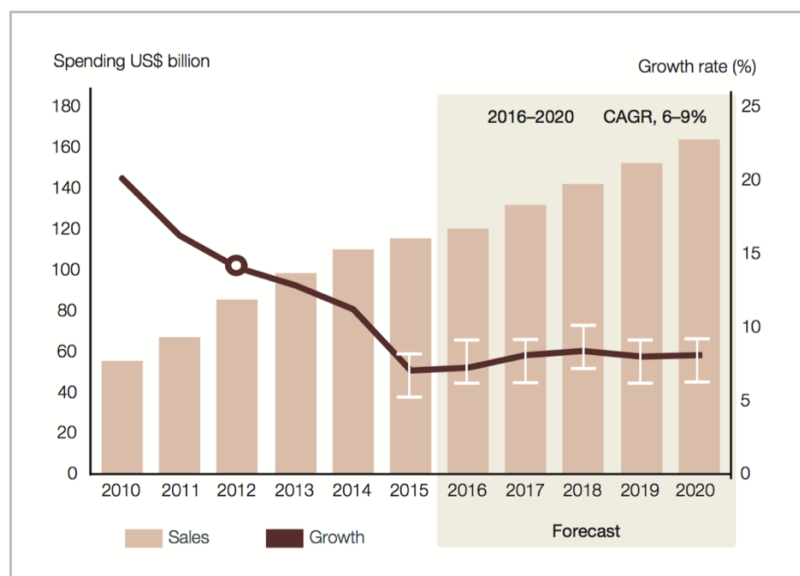


Fig. 1: Annual drug expenditure and growth rate in drug expenditure in China, 2010–2020 [1].

Not only due to its overwhelming population size but also the combined forces of economic and demographic development, ongoing healthcare reform to improve public access to healthcare and enhanced health awareness among the public lead to a great expansion of the Chinese pharmaceutical market, making it increasingly desirable for foreign companies.

While the pharmaceutical market in China is expected to grow in the future, China is faced with two trends that may threaten the long-term sustainability of China's system: China's rapidly aging population and increase of the rates of many chronic diseases.

1.1 Aging Chinese population

China has the largest elderly population in the world, which has been predicted to further increase over the next decades (Fig. 2) [2]. China's population aged 65 and over shows a continuous increase between 1990 and 2015. By 2050, it has been predicted that nearly 30% of China's total population will be over 65 (Fig. 3) [2].

Since elderly people have weaker immune systems and increasing physical wear, resulting in a higher incidence of illness, which is associated with an immense demand for medical treatment and services, they form a great target group for pharmaceutical companies.

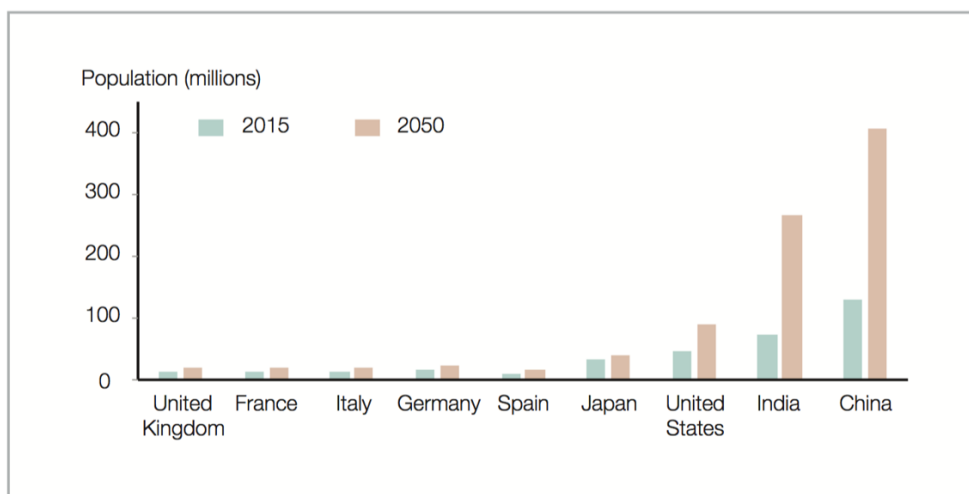


Fig. 2: Comparison of China's population aged 65 and over with selected country populations, 2015 and predicted for 2050 [3].

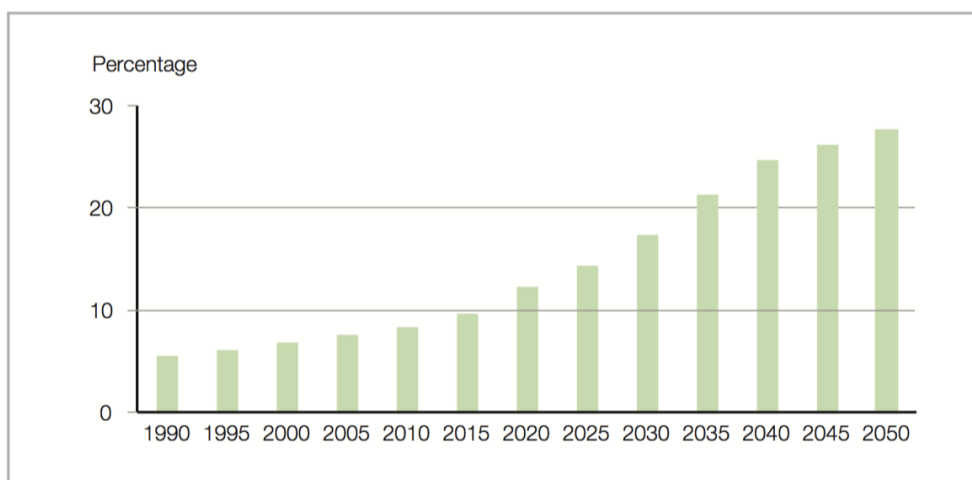


Fig. 3: Development of China's population aged 65 and over, 1990-2015, predicted to 2050 [2].

1.2 Change in China's disease profile

With the increase in the population of elderly people accompanied with changing lifestyles as well as air and water pollution, China's disease profiles have altered significantly. The aforementioned factors contribute to a rapid increase in the incidence of cancer, heart disease, diabetes and other chronic conditions. For example, China has already 110 million diabetics, three times the number in the United States, with many more undiagnosed cases [4]. In 2015, China reported 4.3 million new cancer cases, accounting for 20 % of the worldwide total [5]. From 2003 to 2011, the top four leading causes of death in China's cities are cancers, cardiovascular diseases, cerebrovascular diseases and respiratory diseases. Cancers caused the highest mortality in China over the years (Fig. 4) [6, 7, 8, 9, 10, 11, 12, 13].

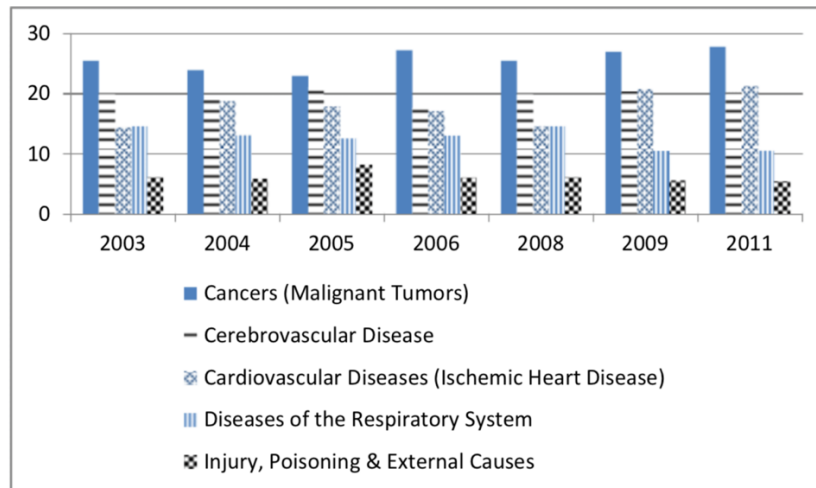


Fig. 4: Percentage of the total deaths caused from the top five diseases in China's cities, 2003-2011 [6, 7, 8, 9, 10, 11, 12, 13].

2 Changing environment in China's drug regulatory system

After China's reform and opening-up policy in 1978, China's healthcare sector has developed rapidly accompanied with its booming economy. Concomitant with the aging population and the change in China's disease profile new demands have been arisen in China's healthcare sector. To meet the demands of the Chinese population by avoiding the development of a health disparity towards other countries as well as to stay competitive in the global market, the Chinese government has launched several significant initiatives to reform the drug regulation. This recently announced reforms may have significant impact on pharmaceutical companies doing business in China.

2.1 Impact of 2002 issued Drug Registration Regulation on drug development process of multinational companies in China

Over the years, foreign companies intending to introduce their pharmaceutical products into the Chinese market have to face many regulatory hurdles. Especially the time required to successfully complete a drug registration application with the China Food and Drug Administration (CFDA) is one of the most critical issue in the registration procedure for the companies.

With China's membership in the World Trade Organization (WTO) in December 11, 2001, China has been integrated into the global economy and opens the door to a lucrative pharmaceutical market for overseas companies interested in doing pharmaceutical research and development (R&D) in China. Since some issues of the Chinese drug regulatory system do not conform to the WTO requirements, the State Drug Administration (SDA) issued the new '*Drug Registration Regulation (SDA, No. 35, 2002)*' [14], which is compatible with the WTO agreement and went into effect on December 1, 2002. representing a key milestone of the Chinese regulatory system.

In this chapter, the opportunities of drug development and registration in China for overseas companies before and after the release of the '*Drug Registration Regulation*' in 2002 will be explained.

2.1.1 Model of drug development and registration before 2002

Before the release of the new '*Drug Registration Regulation*' in 2002, the most traditional and direct approach to register a new drug for global companies without local manufacturing structures in China consists of filing an import drug application in order to apply for the Import Drug License (IDL).

In the scheme of import drug registration pathway, the process of marketing authorization application in China can only start following drug approval is obtained in overseas' markets. This means that the Certificate of Pharmaceutical Product (CPP) is needed for filing. Once the companies obtain the CPP, they can start the process by applying for a clinical trial authorization to conduct local clinical programs (Fig. 5).

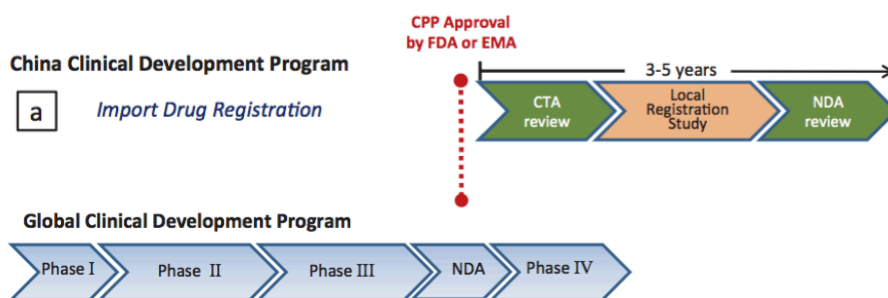


Fig. 5: Import drug registration pathway. In comparison with the timeframe of the global clinical development program [15].

The local clinical trial requirements for chemical drugs depend on the class (six classes) to which the drug belongs. They are announced in Annex 2 of the 2007 issued '*Drug Registration Regulation (SFDA Order No. 28, 2007)*' [16] as listed below (Tab. 1). In case of import drug registration, where the drug is already marketed abroad, the drug belongs to class 3. Here, for the local clinical program, > 100 pairs of Chinese patients are required for Phase III study and a local bridging pharmacokinetic study with 20–30 subjects is also needed.

Tab. 1: Registration classes of chemical drugs with the corresponding clinical trial requirements [17].

Class 1	Definition	New chemical entity never marketed in any country
		i. Drug substance and its preparations made by synthesis or semi-synthesis
		ii. Chemical monomer (including drug substance and preparation) extracted from natural sources or by fermentation
		iii. Optical isomer (including drug substance and preparation) obtained by chiral separation or synthesis
		iv. Drug with fewer components derived from marketed multi-component drug
		v. New combination products
	vi. A preparation already marketed in China but with a newly added indication not yet approved in any country	
Clinical requirement	Phase I: 20–30 cases/group for single and multiple ascending dose trials	
	Phase II: > 100 cases/group	
	Phase III: > 300 plus statistically significant consideration	
	Phase IV: > 2000	
Class 2	Definition	Drug preparation with changed administration route and not marketed in any country
		Clinical requirement
	Phase I: 20–30 cases/group for single and multiple ascending dose trials	
	Phase II: > 100 cases/group	
	Phase III: > 300 plus statistically significant consideration	
Phase IV: > 2000		
Class 3	Definition	Drug marketed ex-China, including:
		i. Drug substance and its preparations, and/or with changed dose form, but no change of administration route
		ii. Combination preparations, and/or with changed dose form, but no change of administration route
		iii. Preparations with changed administration route and marketed ex-China
	iv. A preparation already marketed in China but with a newly added indication approved ex-China	
	Clinical requirement	PK: 20–30 cases
		Phase III: > 100 pairs
Multiple indications: > 60 pairs		
Class 4	Definition	Drug substance and its preparation with changed acid or alkaline radicals (or metallic elements), but without any pharmacological change, and the original drug entity already approved in China
		Clinical requirement
	PK: 20–30 cases	
	Phase III: > 100 pairs	
For multiple indication: > 60 pairs		

Class 5	Definition	Drug preparation with changed dose form, but no change of administration route, and the original preparation already approved in China
	Clinical requirement	Oral solid preparation bioequivalence trials: 18–24 cases
		Non-oral preparation: clinical trial needed, > 100 pairs
		Sustained and controlled released preparations: PK of single and repeated doses needed; clinical trial: > 100 pairs
		Single active component Injection: > 100 pairs;
		Multiple component injection: > 300 pairs;
Microemulsions and liposome: Refer to Class 1 and 2.		
Class 6	Definition	Drug substance or preparation following national standard
	Clinical requirement	Oral solid preparation bioequivalence trials: 18–24 cases; If the quality of drug needs to be controlled by process and standards, clinical tests need 100 cases

As soon as the local study is completed, the applicant shall fill the application form for drug registration and submit the clinical data package along with other dossier for marketing approval and IDL.

Although this approach may go hand-in-hand with the following advantages,

- High probability of success - The new drug has already been approved abroad, where it has been used in a fairly big study population overseas and has passed the beginning years of high-risk stage [15].
- Low investment - The imported drug registration study can be a miniature of the pivotal Phase III trials conducted overseas [15].

the crucial disadvantage of this pathway is the significant drug lag.

2.1.2 Model of drug development and registration since 2002

To solve the issue of the massive drug lag introduced by the traditional imported drug registration pathway or at least to mitigate it the approach of integration of the Chinese clinical study into international multi-center clinical trial (IMCT) was formally recognized in the 2002 issued '*Drug Registration Regulation (SDA, No. 35, 2002)*' [14].

According to the regulation, multinational companies are now allowed to conduct global multi-regional clinical trial (MRCT) in China after the drugs had been approved or entered Phase II clinical trial overseas. The MRCT is performed simultaneously in multiple countries following an identical protocol and have to be conform with the relevant clinical trial regulations in China. Upon completion of the MRCT, the applicant has to submit the complete study data package of the MRCT to the CFDA. Since 2002, the common practice was the waiver of an independent local Phase III clinical trial based on MRCT data (if the China subgroup results are consistent with the overall global results), after submission of the clinical trial application (CTA) together with the application form for drug registration. Using the MRCT pathway, multinational companies are now allowed to initiate clinical program earlier in China before the overseas market approval has been obtained. Due to the parallel nature with the overseas clinical program, the registration approval in China can be shortened 3 to 4 years (Fig. 6).

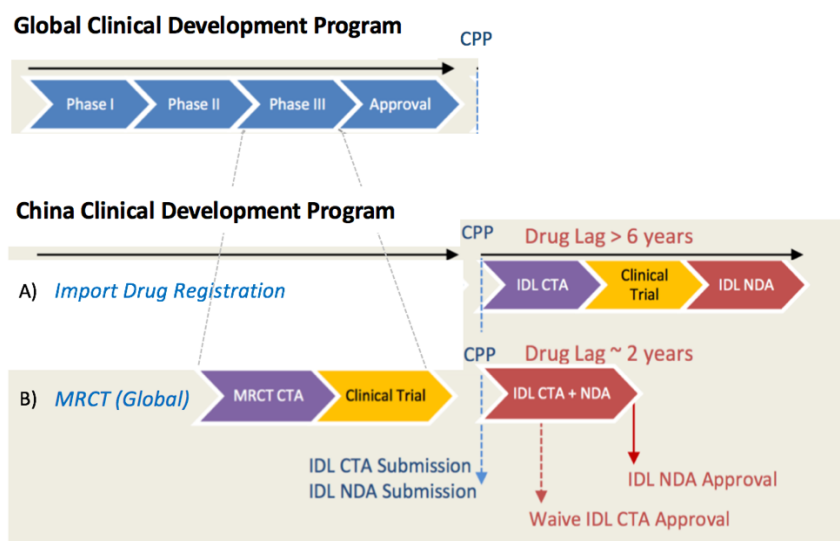


Fig. 6: Potential registration pathways since 2002 for global companies without manufacturing facilities in China. A) Import drug registration pathway; B) Global MRCT pathway. Purple process: file an IMCT application with the CFDA to integrate China in the global MRCT study. Orange process: China joins global Phase III study [19].

With the wish to accelerate new drug registration processes by bringing the timelines in proximity to the market approvals in other countries, the IMCT pathway for CTA was considered as the most common pathway taken by foreign companies in the past years. Based on the analysis of data from clinicaltrials.gov, the annual number of IMCT conducted in China has increased steadily since 2004 (Fig. 7) [20].

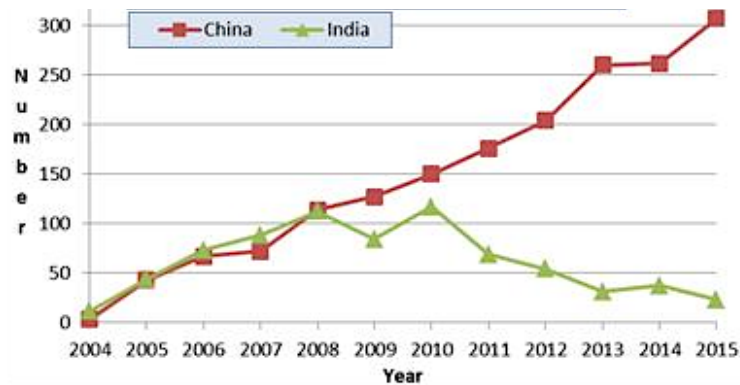


Fig. 7: Annual number of IMCT in China registered at clinicaltrials.gov, 2004-2015 [20].

Nevertheless, project management and study design will become more complex with China involved. There are significant hurdles multinational pharmaceutical companies should pay attention to if they decide to conduct IMCT. The hurdles involve particularly the “[...] differences caused by ethnic factors or healthcare system. Such differences could be directly related to the patient pharmacokinetic, pharmacodynamics profile or the patient sensitivities and tolerability. In addition, the comparatively long and unpredictable CTA approval time in China may significantly decrease the opportunities for China to join the global clinical program or cause an overall global timeline delay due to the limited recruitment window for patients” [15].

One possibility that may reduce the long CTA approval time is to take advantage of the ‘*Rules on Special Approval of New Drug Registration*’, also known as “Green Channel”, issued in 2009 by the CFDA [21]. This special channel can provide a fast-track review for new drugs that meet certain requirements. It includes a shorter approval process, additional opportunities to communicate with the CDE to enhance information exchange, as well as the opportunity to freely submit additional data during the review process [22]. Thus, if the drug of the overseas applicant meets the criteria and gets approval for special review procedure, it could provide a significant advantage concerning shorter timeline for China registration.

Another alternative strategy for overcoming the above mentioned limitations is to pursue the regional multi-center clinical trials (RMCT) strategy [15]. The overseas applicant may conduct RMCT in different countries within a region, such as in Asian countries only. Comparable with the global MRCT, the clinical development program designed for China with the surrounding countries can be initiated before the drug is approved overseas. Using the localized RMCT pathway, China can be precluded from participating in global MRCT, making it easier to overcome hurdles that may coming up in the MRCT pathway. One of the big advantages of the localized RMCT is that this pathway could meet the

CFDA registration requirement of the minimum number of recruited patients based on its China focused nature, which is often not meet in case of a global MRCT.

Generally, regardless whether MRCT or RMCT pathway will be chosen, multinational companies should initiate early consultation with the Chinese local key opinion leaders (KOLs), since many of them are CFDA reviewers of the corresponding medical fields. Therefore, an early and active communication promote by the companies may familiarize local KOLs with their products. Furthermore, an other critical factor for success in the IMCT pathway is the selection of appropriate contract research organization (CRO). Ideally, “[...] CRO should possess the global knowledge for clinical trial performance with strong local clinical trial experience in the corresponding fields” [15].

Overall, to be successful using the IMCT pathways, companies have to make their decision far ahead of the clinical development program to overcome potential hurdles. Early strategy development and decision making is key to facilitate early CTA submission and to resolve any potential scientific and operational issues in the study design and execution.

2.2 Impact of latest IMCT Guidance on drug development and approval process of multinational companies in China

Although there is a “strong interest in improving the participation of China in MRCT, there are accompanying concerns that the rush to MRCT for shorter approval could increase risks for patients, by omitting to consider potential differences in ethnicity” [23].

For this reason, the CFDA has officially issued a ‘*Draft Guidance for IMCTs (No. 698, 2014)*’ in November 2014 [24], effective since March 2015. This guidance aims to set clear requirements for MRCT involving study sites in China. Many concepts and requirements are consistent with the 2007 issued ‘*Drug Registration Regulation*’. Under Chapter 3, general requirements, the guidance stipulates that if IMCT data is used for application of drug registration in China, at least two countries, including China, have to be included. Involvement of ICH country is not a prerequisite and CFDA does not comment if Hong Kong or Taiwan can be considered as a country apart from China.

The CFDA also requested the addition of an extra submission and review step to the process. As shown in figure 8, the entire regulatory process was turned from a ‘2-submission-2-review’ process (submission and approval of MRCT-CTA followed by submission and approval of IDL-CTA+NDA and waiver of an independent local Phase III

clinical trial) into a ‘3-submission-3-review’ process (submission and approval of MRCT-CTA followed by submission and approval of IDL-CTA and waiver of an independent local Phase III clinical trial plus returning into start of queue for the submission and approval of IDL-NDA) [19]. In other words, prior to 2014, multinational companies have received an approval within 2 years after CPP is given. Recently, although the company was granted the waiver of an independent local Phase III clinical trial in China, they are asked to resubmit the application for drug registration. The dossier for resubmission will be returned to the start of the review queue, resulting in an addition of approximately 2 years to the approval process. Therefore, the total drug lag may be amounted to approximate 5 years [19].

For the waiver of an independent local Phase III clinical trial, the China subgroup results (> 100 pairs of Chinese patients are needed in the MRCT study) have to be consistent with the overall global results. In case the China subgroup results are not consistent with the overall global results, an independent local Phase III clinical trial with statistical significance is required to meet the China registration requirements [25].

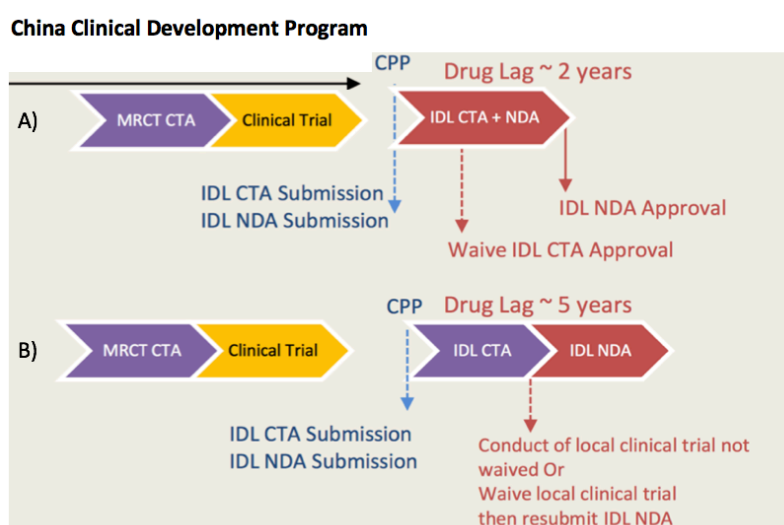


Fig. 8: Impact of the 2014 issued IMCT guidance on drug registration pathway of global companies conducting MRCT involving study sites in China. A) Regulatory process before 2014: ‘2-submission-2-review’; B) Regulatory process in 2014: ‘3-submission-3-review’ [19].

A survey with 33 multinational pharmaceutical companies, conducted by the Centre for Innovation in Regulatory Science (CIRS) in October/November 2014, demonstrated clearly that the CFDA acceptance of data derived from MRCTs declines significantly (Fig. 9) [19]. In case that companies have to undertake an independent Phase III clinical trial in China as a consequence of rejection of the waiver by CFDA, potential duplication in

scientific research may occur and the submission time of drug registration application as well as financial burden will increase significantly.

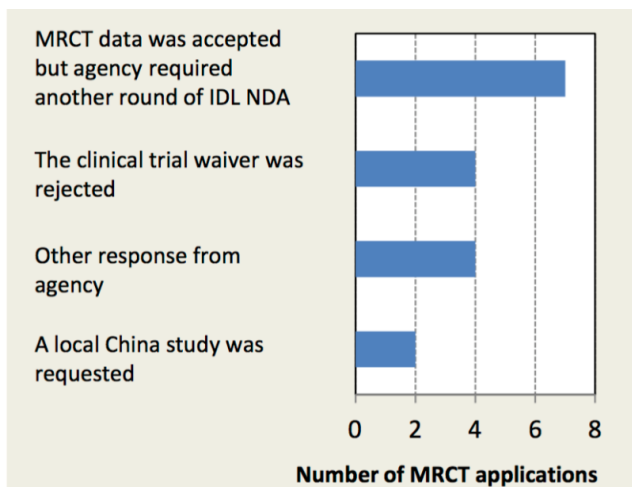


Fig. 9: CFDA responses for 15 applications containing MRCT approach in 2014 [19].

Under the 2014 issued guidance for IMCT, the CFDA encourages companies to develop drugs for unmet medical needs and for serious life-threatening diseases in China on the one hand. On the other hand, it also provides new substantive procedural requirements and strict criteria for the design and implementation of the MRCT that makes it challenging and time-consuming for multinational companies to use this pathway as part of their drug development program in China.

In the light of these regulatory changes in the MRCT pathway, companies should accordingly adjust their strategic planning of new drug development in China. Possibilities to overcome these limitations could be, for instance, setting the new drug in the category of drugs with urgent unmet medical needs or using the local class I development pathway if the company has local manufacturing facilities. The CFDA has issued a special review mechanism in February 2013 that was intended to accelerate review and approval process of drugs for diseases that need urgent treatment in China and for domestically developed new drugs [26].

However, the need for early planning as well as the lead time and the investment required to establish a local manufacturing structure should not be overlooked by the companies. Generally, they must be aware of the level of complexity to manage a local manufacturing project for a new drug, especially in parallel with global drug development. The entire procedure could be very challenging. In order to solve these issues, multinational companies can use a collaborative approach by arranging partnerships with Chinese domestic companies. This kind of partnerships can be formed through either licensing, co-

development partnerships or establishment of a joint venture company [15]. Domestic partners are particularly valuable because of the language skills and their firsthand understanding of China's steady changing regulatory environment. They also provide a wider breadth of expertise regarding the compliance of regulatory requirements. Moreover, this kind of partnerships will be treated similarly to local manufacturing companies, which might be particularly desirable for multinational companies without manufacturing facilities in China.

2.3 Impact of recent major drug registration reforms on drug development process in China

The issued guidance on MRCT is part of the comprehensive reforms on drug and medical device registration process in China begun in August 2015, when the China State Council officially announced the '*Opinions on Reforming the Review and Approval System of Drugs and Medical Devices (No. 44, 2015)*' [27].

This notification is the first significant response of the central government to the grievance of China's pharmaceutical regulatory environment: Heavy backlogs of drug applications, long regulatory review and approval timelines, quality issues of local drugs. In comparison with the United States Food and Drug Administration (US FDA), the approval date for urgently needed new drugs in China (such as anticancer drugs with notable effects) has been delayed for several years after their FDA approval (Tab. 2) [28].

Tab. 2: Selected anticancer drug approvals in China and in the USA [28].

Agent	Indication	FDA approval date	CFDA approval date
<i>Delayed approval</i>			
Dasatinib	Philadelphia-chromosome-positive leukaemia	June 2006	September 2011
Bevacizumab*	Advanced-stage NSCLC	October 2006	July 2015
Pemetrexed ‡	Non-squamous-cell carcinoma lung cancer	February 2004	December 2005
Everolimus	Advanced-stage renal cell carcinoma	March 2009	January 2013
Aprepitant	Chemotherapy-induced nausea and vomiting	March 2003	June 2013
Lenalidomide	Relapsed/refractory multiple myeloma	June 2006	December 2012
Axitinib	Renal cell carcinoma.	January 2012	April 2015

Based on the aspects mentioned above main intentions addressed by the reforms are to:

- eliminate the existing backlog of registration applications
- decrease the timeframe for review and approval processes that is longer than most major countries
- establish an environment for maximizing the quality of generic drugs because of significant quality differences between international standards and local products
- encourage R&D of innovative drugs in line with global standards

2.3.1 CFDA started major drug registration reforms in 2015

The *Opinions* announced by the China State Council are being implemented gradually by the CFDA. The following describes several major reforms of the CFDA that may have significant impact on multinational pharmaceutical companies doing business in China.

Announcement on several policies regarding review and approval of drug registration

With the November 11, 2015 release of the '*Announcement on Several Policies Pertaining to the Review and Approval of Drug Registration (No. 230, 2015)*' [29] and several draft implementation measures, the CFDA has unveiled significant implementation policies regarding improvements to the drug review and approval system by addressing following changes.

Elimination of drug application backlog

In the 2014 annual report, China's Center for Drug Evaluation (CDE) has reported a large rise in the backlog of drug registration applications, up by a third compared with the previous year [30]. At the end of 2014, 18597 applications were waiting for approval, which included new drug applications, renewals and change applications (for different dosage, alternative route of administration, or new indication). Although the number of completed applications increased from 2013 to 2014, there was also an increase of new drug applications with 8868 in 2014, compared with 7609 in 2013 (Fig. 10). Under the 8868 new drug applications, 7829 were for chemical drugs (Fig. 11)

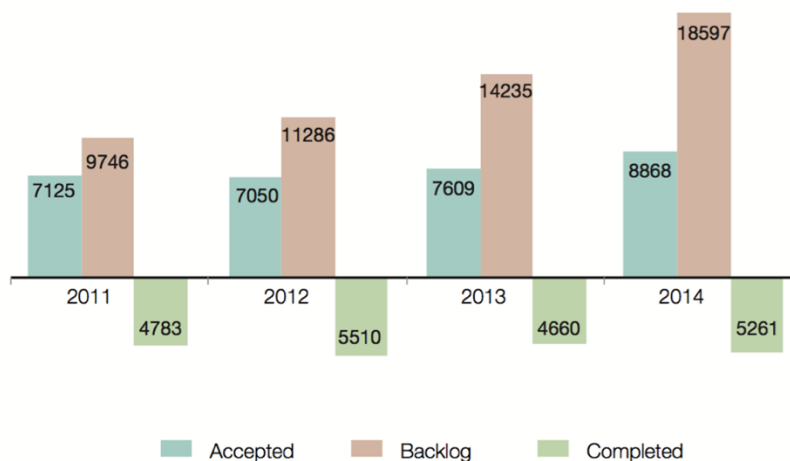


Fig. 10: Comparison of the number of new drug applications (blue), applications waiting for approval (red) and completed applications (green), 2011-2014 [30].



Fig. 11: Comparison of the number of new drug applications for chemical drugs (blue), for TCM (red), for biologicals products (green) and for re-review (purple), 2011-2014 [30].

The backlog has led to an estimated review time of 10 to 18 months for CTA and 12 to 15 months for new drug applications [31], which is significantly longer than the average review times of other countries.

The primary reason for the heavy backlog is the limited number of CDE reviewers, who are facing a yearly increasing workload. As one of the main sectors of the CFDA, the CDE is predominantly responsible for the review of all information provided by the applicant on the efficacy and safety of the drug, the approval of clinical studies, and assessments of clinical results. Before August 2015, the CDE had only 89 employees to review and approve all MAAs in China. In comparison, the US FDA has over 3000 employees working in this area [32]. To improve this situation, the State Council of China

is willing to provide increased funding to enable the CDE to hire and train more staff. Following a new hiring exercise, 600 drug reviewers had been employed by the end of 2016 with more hiring planned over the next few years [33].

Another reason for the heavy backlog of drug applications is the large number of “me-too” generic applications coming from China’s fragmented pharmaceutical manufacturing industry. Most of which are small or medium-sized enterprises with business mainly focus on generics and active pharmaceutical ingredients (APIs). The CDE 2014 annual report demonstrates that for eight compounds there are more than 100 different applications. For many other compounds (>1000), there are at least 10 or more identical generics seeking approval [30].

Furthermore, submission for marketing authorization in China is inexpensive. Companies may be tempted to submit more applications without a sufficient level of prior consideration, thus greatly increase the CDE workload and exacerbate the situation of drug application backlog. Before 2015, the fee of a new drug application made to the CFDA was approximately 25,000 yuan (US\$3,623). In comparison, the approximate cost of a similar approval application made to the US FDA was US\$569,000. In order to limit the total number of approval applications received and also to increase the financial resources, the CFDA steeply increased the registration fees for pharmaceuticals and medical devices by announcing the ‘*Notice of the State Administration of Food and Drug Administration on Issuing the Registration Fees for Drugs and Medical Device Products (No. 53, 2015)*’ [34] in May, 2015. The tremendous hike of the registration fees should help to deter spurious applications from generic manufacturers.

Self-inspection of clinical trial data

The most challenging step in the process of drug registration is that of clinical trials. Especially in case of generic drugs, it is challenging to declare a trial. But once a clinical trial is approved, it takes not much effort for a generic drug to get approval in China. As a result, clinical trials may not be treated seriously any longer after the trial has received the approval, leading to accumulated cases of clinical trial data falsification and submission of incomplete data.

The CFDA intends to reverse this situation by launching a self-inspection program for clinical data. This initiative began in July 2015, as the CFDA issued the ‘*Announcement of Self-Examination and Inspection of Drug Clinical Trial Data (No. 117, 2015)*’ [35]. If the applicant cannot guarantee the data’s reliability and efficiency, they can choose to actively

withdraw their application before the CFDA inspection without any consequences. Otherwise, if the data are found to be falsified, other drug registration applications from that same applicant will not be accepted by the CFDA for 3 years. In August 2015, CFDA issued that among the 1,622 registration applications pending approval, the applicants of a total of 1,094 registration applications submitted self-examination documents, accounting for 67%. 317 registration applications were withdrawn, accounting for 20% [36]. Overall, this self-inspection program not only guarantees clinical trial quality but also improves the backlog issue due to applicants who ultimately withdraw their applications if they have doubts.

Redefining the classification of chemical drugs

As an important part of the general reform initiated by China's State Council in August 2015, the CFDA formally launched a new classification system for chemical drugs with the release of the '*Reform Scheme of the Classification System for Registration of Chemical Drugs (No. 51, 2016)*' [37] on March 4, 2016.

The new classification scheme for chemical drugs differs considerably from the old one under the '*Drug Registration Regulations*' and is more closely aligned to other regulatory agencies. The Reform Scheme redefines "new drugs" and "generics." Under the old classification, the term "new drugs" referred to drugs never marketed in China, even if they had been marketed outside of China. Under the new classification, "new drugs" now refers only to new chemical entities that have never been marketed anywhere in the world, or improved new forms of known chemical entities that have never been marketed anywhere in the world.

Overall, chemical drugs are classified into five classes: Class 1 and 2 are for innovative and "improved" drugs not marketed anywhere. Class 3 and 4 are for China-manufactured generic drugs. The imported drugs now fall into a separate Class 5 (Tab. 3).

Tab. 3: CFDA’s old chemical drug classification system [38] vs. new chemical drug classification system [37].

Old Classification	Definition	New Classification	Definition
Class 1	New drugs not yet approved in any country	Class 1	Innovative new drugs not marketed anywhere in the world (<i>exclusivity period: 5 years</i>)
Class 2	Drugs seeking approval for a new route of administration and not approved in any country	Class 2	Improved new drugs not marketed anywhere in the world (<i>exclusivity period: 3-4 years</i>)
Class 3	Drugs approved in other countries but not in China	Class 3	Domestic drugs, with equivalent quality and efficacy to the originator’s drugs, that are marketed in other countries, but not yet in China (<i>exclusivity period: 0 years</i>)
Class 4	Drugs made by changing the acidic or alkaline radicals or metallic elements of the salt of a drug approved in China without changing the original pharmacological effects	Class 4	Domestic drugs, with equivalent quality and efficacy to the originator’s drugs, that are already marketed in China (<i>exclusivity period: 0 years</i>)
Class 5	Changed dosage form of a drug approved in China without changing the route of administration	Class 5	Imported drugs that seek to be marketed in China, including both the originator’s drugs and non-originator’s drugs (<i>exclusivity period: 0 years</i>)
Class 6	Generic form of a drug with existing national standards in China	-	-

Especially multinational companies with manufacturing facilities in China should draw their attention to the change that “new drugs” now only refer to drugs that have never been marketed anywhere in the world. This means, local manufactured drugs in China that are already marketed abroad but not in China would now enter the application procedure as a

Class 3 generic rather than a Class I new drug. This change will not only reduce a company's expenditure but also the approval timeline, since carrying out the entire drug development process in China in case of a Class I new drug application is much more time-consuming.

Furthermore, multinational companies should also keep in mind that while the new classification system will not have significant changes on the imported drug registration pathway, though it will likely impact China's domestic drug industry, where most of them have a business model based on generics. By the new classification system, the domestic manufacturers will now have more incentives to develop Class 1 and 2 new drugs, because of the advantages such as regulatory exclusivity period, expedited review and a more favorable standing in post-approval tendering and reimbursement. By this way, the new drug classification system may transform the competitive landscape between domestic and foreign pharmaceutical companies in China. Thus, foreign companies should always be alert to the business operations of the domestic manufacturers and always be prepared to revisit their global drug development strategies if necessary.

Piloting the marketing authorization holder (MAH) system

Under China's previous legal framework, only drug manufacturers are permitted to obtain regulatory approvals. Thus, R&D-based organizations such as universities must commit to a substantial investment in manufacturing facilities in order to commercialize their products. Under the CFDA's proposed MAH pilot program, R&D-based organizations can obtain and hold marketing authorization while taking responsibility for drug quality. Therefore, domestic R&D institutions can obtain regulatory approvals to commercialize their pharmaceutical products by completely outsource their actual manufacture. A three-year pilot program of the MAH system was first implemented in 10 provinces, effective as of December 1, 2015.

With this change, the CFDA aims to create a more supportive regulatory framework for domestic innovations in China by encouraging drug researchers to focus primarily on R&D instead to put effort into own manufacturing facilities.

Implementation of priority review

The lack of an effective approval mechanism to signal which drug should receive priority review is another factor contributing to the heavy lag of drug approvals. Since the CDE does not have a mechanism for prioritization, all applications are handled according to the same timeline, regardless of the nature of the drug concerned.

In February 2016, the CFDA published the '*Opinions on Implementing Priority Review and Approval to Solve Drug Registration Application Backlog*' [39]. This is a significant reform measure which introduces a prioritized review and approval pathway for certain drug applications. This document states in detail that drugs which can be used to prevent and/or treat serious diseases with obvious clinical benefits should be included for priority review and approval. After the CFDA has approved the priority review process request, applicants are given additional communication channels with the CDE and will also obtain quick feedback.

With the implementation of the priority review process, the CFDA also intends to encourage local and international new drug innovation in order to meet the demands of the Chinese population. That means, if multinational pharmaceutical companies intend to use this accelerated review and approval process in order to take the opportunity of an earlier market entry, they have to keep their focus on R&D of drugs which belong to the priority list.

Quality conformance evaluations of generic drugs

Due to the lack of confidence in the quality and therapeutic effects of domestic manufactured generic drugs, doctors and patients in China usually preferred to use imported brand-name drugs. The concerns about poor quality standards and pharmaceutical technologies were addressed when China's General Office of State Council issued the '*Opinions on Carrying out Quality and Efficacy Consistency Evaluation for Generic Drugs (GBF No.8, 2016)*' [40] in February 2016. With the increasing quality standard of domestic manufactured generics, a long-term challenge will arise for the imported brand-name drugs of overseas companies in the face of fierce competition in the Chinese pharmaceutical market.

2.3.2 Reform developments in 2017

At the end of 2017, China's efforts to reform the drug and medical device review and approval system culminated in the issuance of a central government directive, which represents a significant milestone of China's reform developments. This issuance is followed by a flood of CFDA implementation measures in a timely manner.

The “Innovation Opinion” - In-depth reform to encourage innovations

On October 8, 2017, the General Office of Chinese Communist Party's Central Committee and the General Office of China's State Council jointly issued the '*Opinion on Deepening the Reform of the Regulatory Review and Approval System to Encourage Innovations of Drugs and Medical Devices (No. 42, 2017)*' (“Innovation Opinion”) [41], proposing further reforms in the drug and medical device regulatory system to encourage innovations. Here, the *Opinion* officially adopted the four important draft policies announced by the CFDA in May 2017:

1. Reform to new drug and device approval process [42]

The *Opinion* allows early marketing in China by providing special conditional approvals for drugs and medical devices indicating for significant unmet medical needs, where early- or mid-stage clinical data can predict clinical benefits.

2. Reform of clinical trial management [43]

The *Opinion* seeks to streamline the clinical trial process by deregulating the process and removing certain governmental controls to encourage innovations and to shorten timelines.

3. Lifecycle management of drugs and medical devices [44]

The *Opinion* aims to enhance post-market supervision throughout product's life cycle.

4. Protection of innovator's rights [45]

The *Opinion* seeks to encourage innovations and protect innovators rights by establishing a patent linkage system and improving regulatory data protection

To fully implement the *Opinion*, implementation measures have to be carried out by the CFDA, including draft amendments to relevant laws and regulations governing the drug

and medical device approval systems. Shortly after the issuance of the *Innovation Opinion*, the CFDA issued first of all a decision on adjustment on imported drug registration, which is quickly followed by multiple implementation proposals by the end of the year. In the following, the legislative actions performed by the CFDA are listed in the order they were announced.

Decision on adjustment of imported drug registration

On October 10, 2017, two days after the *Innovation Opinion* was announced, the CFDA issued the '*Decisions Concerning the Adjustment of Imported Drug (No. 35, 2017)*' [46], which implemented changes to facilitate the review and approval process for imported drugs by removing certain restraints on clinical trials and registrations. The main objectives of the adjustment are to shorten the significant drug lag and to encourage foreign-developed new drugs to undergo clinical investigations within and outside China in parallel.

Following key changes are included:

Conduction of simultaneous Phase I clinical trials in China by opening first-in-human (FIH) Phase I trials to multinational companies

Previously, drug manufactured overseas had to be in a Phase II or Phase III clinical trial or must have received marketing authorization abroad before an IMCT could have been initiated in China. By the *Decisions*, multinational companies intending to conduct an IMCT in China are now permitted to launch a synchronized Phase I clinical trial inside and outside China (exception for preventive biological products). As of now, a full clinical development program can be performed inside China, starting from FIH to proof-of-concept trials, in parallel with the global development program. This means that foreign Phase I clinical trial data as part of the IMCT can be used for the approval application of imported drugs. This change enables multinational companies to generate a more comprehensive clinical data package as well as to receive more experience with the drug in clinical trials. Both factors could represent competitive advantages in the market place. Additionally, this change will greatly reduce the R&D costs by avoiding repeated clinical trials and will also open an FIH Phase I market in China. Generally speaking, this new model will greatly speed up the entire process of IMCT and the marketing of imported new drugs in China.

Simplifying the approval process of IMCT pathway

As mentioned above, the regulatory process of the IMCT pathway for global companies without manufacturing facilities in China was a '3-submission-3-review' process as a consequence of the 2014 issued CFDA Guidance for IMCT. Under the *Decisions*, there is no longer a need for the submission to request an independent local Phase III clinical trial. Thus, upon the completion of the IMCT, the applicant can directly apply for marketing authorization in China without submitting a separate application to waive the local China-based trial first.

CPP no longer required for MAA submission

Additionally, the *Decisions* removes the previous restriction that a foreign-developed drug must be approved in another country and had to wait for the CPP first before proceed to China for MAA submission, even if there are MRCT data in China. In this manner, after completion of the MRCT and with the relevant clinical study report, the sponsor can make an MAA submission to CFDA without CPP. This means, theoretically, China MAA approval can be in parallel with or even earlier than foreign MAA approval.

Guidance on acceptance of foreign clinical trial data

On October 20, 2017, the CDE issued a draft guidance to the '*Technical Requirements for the Acceptance of Foreign Clinical Trial Data*' [47]. The proposed guidance aims to allow clinical trial data generated in an IMCT to be used to support registration of drugs and medical devices in China, including bioequivalence (BE) study for generic drugs approved in the US, EU or Japan. The CDE could choose to accept, partially accept, or reject the foreign clinical data.

The draft guidance provides detailed requirements for acceptance of foreign clinical data, which include following:

- Foreign clinical data should be complete and meet the requirements under the ICH GCP and China GCP.

Although China's GCP standards are mainly the same as those set in the ICH E6 guideline, there are still some differences. For example, in case of ICH E6 GCP, investigators have to report only unexpected and serious adverse events to institutional review board (IRB) and ethics committees (ECs). However, the China

GCP (Chapter 3, Article 10) states that, “any serious events that occur during the trials shall be reported to the Ethics Committee.” [48].

- Clinical trials should pass CFDA’s on-site audits
- Provision of clinical data to prove that no ethnicity difference affects the product’s safety and efficacy

Amendments to Drug Administration Law and Provisions for Drug Registration

On 23 October 2017, CFDA published the ‘*Draft Amendment of the Drug Administration Law*’ [49] and ‘*Draft Administrative Measures for Drug Registration*’ [50] for public consultation. The two drafts indicate the government’s priority for the reform of the new drugs approval system, especially for original drugs, in order to enhance innovation. The proposed amendments aim to change the regulatory review and approval process relating to clinical trials, marketing authorization and the efficiency of approval processes.

The amendments include for example:

Establishment of a notification system for CTA

As mentioned before, previously, clinical trial applicants require express approval for CTA, which has been a cause for delay in the clinical development process in China. The new established notification system for CTA (or implicit approval) is comparable with the IND mechanism in the US FDA. Here, the applicant only need to wait for 60 working days before initiating the study after submission the CTA to the CDE unless the CDE rejects the application or issues a deficiency notice during this 60-day period. This amendment has a great positive impact on multinational companies who intent to initiate IMCTs in China, since unpredictable CTA approval timelines are one of the primary reason that China often can not participate in IMCTs.

Improvement in ethics committee reviews

Under the previous system, EC review and approval is subsequent to the CDE’s clinical trial authorization process. According to the proposed amendments, companies can now apply for EC review and approval in parallel to the CTA, provided the possibility that the clinical study protocols can be approved by the EC before submission of the CTA

to the CDE. In the event of IMCT, the proposed policy encourages mutual recognition of EC approvals. After the EC approval by the lead site, other sites can accept the lead site's approval without repeating review. This will significantly shorten the EC approval time. Moreover, With the upstream process of EC review, CFDA/CDE reviewers will be able to review comments from EC sites, including those on clinical trial design. In this way, the relevance of the ECs will be emphasized and thus encourage more active review of protocols by the ECs.

Removal of separate reviews and approvals within a drug application

Under the proposed amendments, separate reviews and approvals for a drug, its APIs and excipients are removed. Instead, applications for drug and its API, excipients and packaging material are required to be linked and reviewed together.

Draft rule on regulation of clinical trial sites

On October 27, 2017, the CFDA released a draft rule on the regulation of clinical trial sites [51]. Under the previous system, hospitals need to be certified by the CFDA and the National Health and Family Planning Commission (NHFPC) in order to become qualified clinical trial sites. Here, they have to go through a more stringent accreditation process, including passing CFDA's pre-approval inspection.

The proposed change seeks to revoke this certification system by opening clinical sites to all qualified hospitals that have the necessary infrastructure to conduct clinical trials. It requires only an online filing via CFDA's website before the trial can begin. Additionally, it requires the sites to update its information if any changes occur or receive an inspection notice from an overseas regulatory authority. The CFDA retains responsibility for site inspections. This draft rule, if finalized, will replace the current *Accreditation Measures for Clinical Trial Sites (No. 44, 2014)*. Generally, this new system will open the door for more qualified domestic hospitals/institutions to conduct clinical trials in China, leading to a likely increase in the number of sites able to meet the need of the steadily rising number of clinical trials in China.

Publication of the Chinese "Orange Book"

On December 28, 2017, the CFDA issued a '*Notice concerning Publication of the China Marketed Drug Catalogue (No. 172, 2017)*' [52]. By this way, China has implemented its equivalent of the U.S.-styled "Orange Book. In the U.S., reference drugs, such as off-patent originators, have been codified into the US FDA's Orange Book. It is mandatory that generics are tested against the right reference drug concerning quality, efficacy and safety. As China did not have such a reference resource for comparison, quality concerns were always present in bioequivalence testing. The purpose of the Chinese version is to encourage R&D of innovative drugs while rewarding generic manufacturers, especially domestic manufactures, producing high-quality products. The Chinese Orange Book includes a list of originator drugs and their generic substitutes. The catalogue is expected to provide a full record of all newly listed drugs and will be updated as new drugs are approved. Patent information related to marketed chemical drugs is also listed in the Catalog. Moreover, it includes links to other databases with more information about the drugs and related patents. This Chinese version of the Orange Book is a key part of the CFDA's overarching drug reforms and may represent the first step in establishing a patent linkage system in China.

2.4 Impact of the reforms on multinational pharmaceutical companies' business operations in China

The afore-mentioned changes in China's policy environment reflect the government's clear determination to modernize the regulatory environment by decreasing the review and approval timelines, stimulating innovation and issuing more global harmonized requirements and processes. The rapid implementation of the *innovation Opinion* by the CFDA demonstrates clearly how seriously China takes these reforms and how fast they can be implemented in practice.

The reforms would not only significantly change China's regulation landscape of clinical trial and drug approval processes, but also especially influence the strategic planning of multinational pharmaceutical companies doing business in China. Since these changes align China more closely to global standards, processes and timelines, many burdens previously hampered global companies to involve China in their international development program have been eliminated. More and more companies will be attracted to enter the Chinese market. Here, multinational companies should adapt their business model to the

newly designed regulatory landscape, for example, by exploring early-phase concurrent drug development opportunities for innovative drugs in and outside of China or refining the product portfolio to specifically keep focus on Chinese disease demographics and public health priorities.

The reformed drug approval process provides great opportunity for the development of clinical trials in China. The issued changes are expected to improve the overall standards of clinical trials in China by providing reliable and high-quality trial data that can be used worldwide. It can be expected that more and more foreign companies will consider to include China into their IMCTs by conducting a full clinical development program inside China, intending to obtain the CFDA marketing authorization approval in parallel with the US, EU or any other country's approval.

Furthermore, they should integrate China more into their drug R&D strategies, as in-country research offers a general low cost base, a large patient pool and increasing scientific capabilities. Additionally, China's rich genetic resources accompanied with its traditional and local industry's knowledge, especially in the field of generic drugs, can be exploited for drug research as well. It is often more to the foreign company's advantage to have a local partner speaking the language and having local manufacturing sites. Moreover, involving local research staff in the design and discussion of clinical trial protocols from early stage may provide a significant benefit to meet the CFDA requirements regarding specific trial design for Chinese patients. Here, different business strategies can be performed such as collaborating with local CROs or establishing own research centers in China with local research staff.

3 Changing environment in China's state market regulatory administration

3.1 Introduction

3.1.1 Trends in healthcare expenditure and pharmaceutical spendings

China's total health expenditure (THE) has been growing rapidly over the past several years. From 2005 to 2012, THE grew from RMB866 billion to RMB2812 billion [53] (Fig. 12).

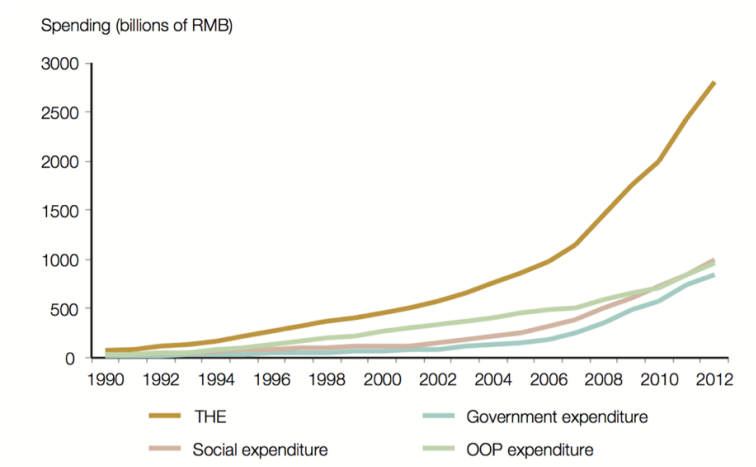


Fig. 12: Health expenditure in China, 1990-2012 [53].

The surging costs of healthcare in China is highly related to the high expenses in pharmaceutical costs. In 2008, total pharmaceutical expenditure (TPE) accounted for as high as 42.67% of THE (Fig.13) [53]. China spends more on pharmaceuticals than the OECD average of 20% [54]. Drug expenditure per capita grew rapidly from 36.59 Yuan to 467.04 Yuan between 1990 and 2008, with an annual growth rate of 15% [55].

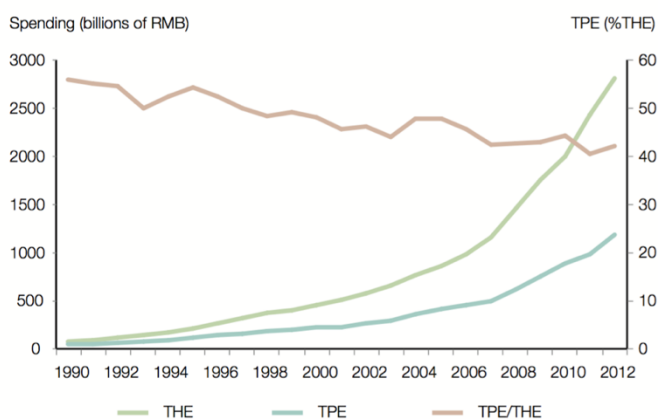


Fig. 13: Total health and pharmaceutical expenditure in China, 1990-2012 [53].

The severely growth of pharmaceutical expenditures is a result of China's 1978 Reform and Opening-up policy. In the past, public hospitals owned by China's governments are funded through a variety of channels (government subsidy, drug revenue, and medical service fees) [56]. However, since the reform, the government largely reduced its funding for public hospitals. The proportion of government subsidy out of total hospital revenue had fallen from about 60% in the 1980s to 10% in 2009 [57]. In order to help hospitals and physicians to have another source of income to compensate the financial loss due to reduced funding, the government set up the 15% drug mark-up policy. This policy allows hospitals to earn a 15% mark-up on the sale of pharmaceutical products [58]. As a consequence, driven by financial incentives, physicians tend to prescribe expensive drugs or overprescribe drugs to patients. Thus, drug sales became an important source of hospital revenues [59]. In 2009, drug sales accounted for 42% of the total income for public hospitals on average [60]. This profit-driven behavior accompanied with the irrational use of pharmaceuticals were considered as the major cause for high health expenditure in China.

3.1.2 Context of pricing and reimbursement in China

Pricing and reimbursement policies belong to the most rapidly evolving aspects in China. While drug reimbursement in China is very important for pharmaceutical companies since it can greatly expand the potential market of a drug by making it more accessible and affordable to middle and lower income earners, drug pricing in China is an entirely separate topic from drug reimbursement. It is the process to set the ultimate price a hospital pays for the procurement of drugs.

Drug pricing

Drug pricing in China is based on a combination of free market and state control mechanisms, which is regulated by the National Development and Reform Commission (NDRC) and provincial Pricing Bureaus. Defining the price of imported drugs is different from the process of setting the price for domestically manufactured drugs. A newly imported drug that has just entered the Chinese market, without its patent holder selling the same substance in China, will likely receive a price close to its free-market price. An imported generic drug will usually be given a price that is lower than the imported patented drug but higher than the price of domestic manufactured generics. The actual selling price to patients is mainly determined through tendering or direct negotiations for

off-patent and patent drugs, respectively. Since most pharmaceuticals in China are purchased at hospitals, the focus of tendering is keeping on hospitals. After completion of the tendering process, individual hospitals will further engage with individual manufacturers in a process known as secondary negotiation. Here, hospitals often negotiate a drug selling price that is lower than the listed tender price [61].

Reimbursement drug lists

For drugs to become eligible for reimbursement under the national health insurance system, they must be listed on one of the three major drug reimbursement lists: the national Essential Drug List (EDL); the National Reimbursement Drug List (NRDL), List A and List B; and the Provincial Reimbursement Drug List (PRDL), which varies from province to province.

The EDL is issued once every three to five years by China's Ministry of Health (MOH). It includes mostly old generic drugs: Western drugs as well as traditional Chinese pharmaceuticals that are judged to be essential to China's healthcare system. Drugs on the EDL will be 100% reimbursed by the government. The retail price for EDL drugs are set by the NDRC.

The NRDL is set by central government agencies including NDRC, CFDA, Ministry of Human Resources and Social Security (MOHRSS) and Ministry of Finance. It is issued once every four to five years through a four-step process with expert committees vote regarding the inclusion of drugs on the NRDL. Pharmaceutical companies cannot apply for inclusion and are also not involved in the NRDL review process. The NRDL is separated into two lists: List A and List B. List A consists of more basic drugs (mostly old, generic drugs) that will be 100% reimbursed to patients according to the Basic Medical Insurance (BMI) Fund regulations. List B includes premium and innovative drugs that receive relatively higher prices. The retail price for drugs on list B is set by the NDRC and the relevant Provincial Pricing Bureau. Here, patients' co-pays can be quite high for some drugs, ranging from 10% - 90%. Pharmaceuticals on List B are categorized by their API, not by their brand name. That means, reimbursement is determined for each API, where the same percentage of the drug price is reimbursed by BMI regardless of the total drug price. By this way, many Western versions of drugs have become much more affordable to Chinese patients than they would be otherwise.

If a drug fails to make it onto the NRDL, it is still possible for pharmaceutical companies to get it listed on the various PRDLs. PRDLs are set by provincial government entities

including the price bureau, the provincial bureau of MOHRSS and the provincial finance bureau. In order to address local needs, provinces have the option to replace 15% of the drugs on List B creating their own PRDL. They can also use money from its own budget to support the reimbursement of additional drugs.

3.1.3 Pathway from market authorization to market access

After a pharmaceutical product has been approved by the CFDA, it mostly takes another few months before it can be prescribed by a doctor. Generally, three steps are required to get drugs on the Chinese market [62]:

The first step is drug price approval. After a drug is approved by the CFDA, the retail price of a drug must receive official approval before the drug can be offered in any tendering or bidding process. The price of a drug is set by NDRC if the drug is listed on the NRDL. If the drug is not listed on the NRDL, pharmaceutical companies are supposed to apply to the local provincial pricing bureau for pricing approval. Each provincial government's pricing bureau must approve the proposed retail price. That means for each province, where the company intends to sell the drug, a separate application has to be submitted to the respective pricing bureau.

The second step is the process of provincial bidding, which usually happens once or twice a year. Regardless whether the drug is listed on the NRDL or a PRDL, it must take part in provincial bidding before it can be sold in a hospital. Like drug price approval, bidding takes place on a province-by-province basis. After receiving bids, a tendering committee, composed of local government officials, NDRC representatives and pharmacists, determines which companies are allowed to distribute their pharmaceuticals in the province concerned. Usually two to five suppliers of each drug are selected.

The final step is hospital listing. Following winning a tender, the drug must be listed by each individual hospital before it can be prescribed by physicians working there. Like the bidding process, hospital listing happens on an individual basis. Each large hospital forms a committee once or twice a year to approve new drugs for its formulary. Only drugs listed on the formulary can be purchased by the hospital and prescribed to patients by physicians.

Generally, the way how a company approaches the reimbursement drug lists, bidding process and hospital listing is crucial for a successful access of the drug to the Chinese pharmaceutical market.

3.2 Recent market regulation reforms and their impact on multinational pharmaceutical companies' business operations in China

The rapid growth of drug expenditures has contributed to serious burdens for patients, especially for inpatients in rural areas [63]. Following widespread discontent at the healthcare situation in China and in order to combat the perverse incentives created by the 15% mark-up policy, China's central government officially issued significant reforms in 2009 with the goal to provide affordable and equitable healthcare for all.

Since 2015, an ongoing series of reforms concerning regulation of Chinese pharmaceutical expenditure have been revised or developed, resulting in far-reaching impact on the pharmaceutical market in China. The most recent reforms that may affect business operations of multinational pharmaceutical companies in China are provided in the following.

3.2.1 Adjustments to the NRDL

The NRDL has remained unchanged since the last update in 2009. That means, drugs approved since then have not been added to the NRDL. Due to the long period between the NRDL updates, new drugs undergo significant delays between approval and reimbursement. In February 2017, the MOHRSS published the updated NRDL [64]. In comparison to the 2009 version, the 2017 version added 339 new medications with an increase of 15.4%. With the update of the NRDL, MOHRSS also announced that 45 drugs are set on a "negotiation"-list. Most of these drugs are on-patent with high clinical value but they could not be added directly to the NRDL due to their high costs. To have these drugs listed in the NRDL, the pharmaceutical companies concerned have to confirm their willingness to negotiate a lower price in order to start drug pricing negotiation process with MOHRSS. The price negotiations were conducted with manufacturers of 44 innovative drugs and was completed by the end of July 2017 [65]. As a result, 36 drugs passed the negotiation and are listed on list B of the NRDL. However, the results of the negotiation processes indicated significant price cuts with an average of 44 % compared to their previous tender prices.

Although the negotiated prices lead to a reduction of the profit margin, companies should expect a great increase in the uptake of the listed drugs nonetheless. More patients can afford the discounted drugs now because of the reduced financial burden. In the past, these drugs were mostly financed by out of pocket payments with a small target group of

patients. Thus, the increase of the sales volume is likely to offset the reduction in prices if considering the size of the Chinese population. This opened up a significant marketing opportunity for pharmaceutical companies to increase profit margin if they are able to find a tradeoff between sales price and volume. Apart from that, doctors often care about the affordability of drugs and some patients also prefer a reimbursed prescription instead of a non-reimbursed one. These aspects give reimbursed drugs further advantages in the market competition [66].

Based on the fact that companies cannot apply for reimbursement directly, they should keep their focus on convincing Chinese KOLs on the clinical benefits of their product, who will be requested by the government to make recommendations for reimbursement. By this way, the products may more likely to be considered during the selection process.

Companies should also take note that for certain very expensive drugs, become part of the NRDL might not be a profit-maximizing strategy. The reimbursement ratio can be as low as 10% for very expensive drugs. Thus, it has to be assessed prospectively by the companies if the potential increase in sales volume would be large enough to offset the reduction of profit margins by price cutting. They have to determine the exact level of discounting they can offer while remaining competitive in the Chinese pharmaceutical market. For certain premium drugs (e.g. oncologicals) the best profit-maximizing strategy may be a cash-pay system just targeting a small group of patients who can afford the drugs [66].

Companies who could not reach an agreement regarding the proposed discounts and thus remained off the NRDL have the option of negotiation with the provinces individually. They can determine their own retail prices, which have to be approved by the local Pricing Bureau. However, due to the fact that every province in China has to be approached one by one, this process could be extremely time-consuming, resulting in delayed and fragmented market access.

Generally, the update issued to the NRDL in February 2017 accompanied by the secondary reimbursement negotiations in July 2017 represent a milestone in China's effort to improve the healthcare situation. For pharmaceutical companies, a frequently update of the NRDL in the future will minimize the gap between drug approval and reimbursement, with the result that newer therapy opportunities are gaining consideration earlier.

3.2.2 Reform of drug pricing

In May 2015, the NDRC and other administrative authorities jointly announced with the release of the '*Circular Concerning Opinions on Advancing the Drug Pricing Reform (No. 904, 2015)*' [67] a groundbreaking reform of the drug pricing system in China.

Previously, direct participation in the pricing control of reimbursable drugs as established under the 'Circular concerning Opinions on Reforming Drug Price Administration' issued in July, 2000 was the key government strategy for constraining drug expenditures [68]. The NDRC set exact retail prices for certain drugs that belong to the government programs of planned supply, so-called government pricing (GP) and maximum retail prices or price caps for the remaining reimbursable drugs, so-called government-guided pricing (GGP).

With the 2015 issued reform, the government intends to remove many of the constraints on drug prices by gradually establish a market-driven drug pricing system to give companies more freedom to set market prices with minimal direct control from the government. The reform especially aims to abolish GP and GGP for most drugs by introducing new price control mechanisms. Here, it announced the introduction of a form of internal reference pricing (IRP), named 'reimbursement standard'. It will be used as a guide for market prices of drugs with market competition listed in the Health Insurance Formulary (HIF: including the NRDL and PRDL). For drugs listed in the HIF with little or no market competition, such as in-patent drugs and drugs with exclusive sources of supply, this reimbursement standard will not be used. For these products, retail prices will be determined with the pharmaceutical industry and other stakeholders through a transparent and multilateral negotiation mechanism. For blood products not listed in the HIF and drugs procured and subsidized by the government, such as vaccines, HIV/AIDS drugs, contraceptives, retail prices will be determined either through tenders or negotiations. For drugs not in any of the above categories, the prices will be set by the manufacturers based on the production costs as well as market demand and supply.

In order to test various pricing approaches and their impact on future pricing behaviors, China is currently running pilot projects in several cities. Two pilot projects, in the cities of Sanming and Shaoxing, were initiated before the 2015 issued reform and are still in operation.

Pilot project - Sanming

Sanming, a city in Fujian Province, is piloting a form of IRP for drugs with the same active ingredient and dosage form [69]. The reimbursement standard is set at the procurement price of the cheapest generic. The price difference between the cost of the chosen drug and the preset reimbursable amount has to be managed by the hospital. In this case, the excessive drug cost must be paid by patients as out-of-pocket expenses in a form of co-payment.

As a result of changing preference towards cheaper, locally produced generics, the overall purchase value of selected imported drugs dropped down by approximately 12 to 54% (Tab. 4), suggesting the replacement of imported drugs by locally produced generics [70].

Tab. 4: Changes in the purchase value of selected imported drugs in Sanming [69].

Active ingredient	Brand; manufacturer	Dosage form	Change in market share from February 2015 to March 2015 ¹ (by value)		
			Feb 2015 [USD]	Mar 2015 [USD]	Δ
Amlodipine	Norvasc; Pfizer	5 mg × 7 tab	45,910.00	40,345.20	– 12.1%
Cefoperazone/Sulbactam	Sulperazon; Pfizer	1500 mg × 1 vial	52,635.10	44,841.50	– 14.8%
Aspirin	Aspirin; Bayer	100 mg × 30 tab	23,987.40	19,630.00	– 18.2%
Acarbose	Glucobay; Bayer	50 mg × 30 tab	68,822.60	55,119.00	– 19.9%
Cefuroxime	Monocef; Esseti Farmaceutici	1500 mg × 1 vial	978.20	677.20	– 30.8%
Atorvastatin	Lipitor; Pfizer	20 mg × 7 tab	79,886.50	36,573.30	– 54.2%

¹The reported period is the one for which data were collected through the primary research; data for the overall piloting period or other time spans were not available.

Pilot project - Shaoxing

Shaoxing, a city in Zhejiang Province, is piloting an approach called ‘second price negotiation’, which allows hospitals to directly negotiate discounts with manufacturers [69]. Local procurement prices obtained via the tendering process serve as both price caps in negotiations and reimbursement standards. After the first month of implementation, the prices of most drugs’ in Shaoxing had been discounted by approximately 2 to 10%. Some high priced products were reported to be withdrawn from the local market [71]. For instance, the use of 14 drugs was discontinued or limited by Shaoxing 7th People’s Hospital. Most of them are imported drugs from multinational companies (e.g. Pfizer’s Cefoperazone/Sulbactam, Wyeth’s Venlafaxine, Lundbeck’s Escitalopram) [72]. Shaoxing is not the only city piloting the second price negotiation. Until June 2015, 100 cities were allowed to pilot the second price negotiation approach and took part in the general healthcare reform [73, 74].

The results of the pilot projects have shown a remarkable trend for drug budget saving, especially in case of imported drugs. Previously, the insurers would be reimbursed with the same percentage of the market price regardless of brand-name drugs or generic drugs. With the new policy, high out-of-pocket payments for brand-name drugs will significantly decrease drug affordability for patients. As a consequence, the sales volume of brand-name imported drugs will decrease sharply. Thus, it is crucial for companies with brand-name drugs in China to adjust their development models and marketing strategies accordingly in order to counteract the loss of both purchase value and sales volume caused by the drug pricing reform.

3.2.3 Increased number of private healthcare facilities

With the aim to relieve the increasing burden on current healthcare system, the government has opened up the system to private investments as outlined in its 13th five-year plan [75]. The private sector is viewed as a solution to address the issue of how the Chinese healthcare system can deal with the rapidly aging population and the overcrowded public facilities.

As set in the 13th Five-Year Plan, the government allowed up to 100% foreign ownership in private hospitals, which previously required a minimum of 30% Chinese ownership. It also encouraged private services for elderly and home care. The rising wealth of China's growing middle and upper classes drive an unprecedented opportunity for private healthcare growth. In particular, increase in number of healthcare facilities in private sector reflects greater out-of-pocket and private insurance healthcare payment behaviors. This provides a promising opportunity for companies with expensive innovative drugs to increase their profit margins by entering the private sector. Either way, due to the strong measures ordered by the State Council of China to control drug expenses in public hospitals, companies can no longer rely solely on public hospitals for revenues. Here, the increasing private sector can be considered as a new market direction. In order to take advantage of this favorable situation, companies should be prepared to enter the private sector by addressing the different needs located there.

4 Restructuring of China's government – Establishment of State Market Regulatory Administration

On March 17, 2018, China's National People's Congress approved a government restructuring plan as an improvement measure for the weak and fragmented healthcare governance structure [76]. The restructuring will result in the reduction of eight central level ministries and seven vice-ministerial agencies. It mainly intends to remove duplications of responsibilities between existing ministries and agencies and to remove institutional obstacles hindering intra-government collaboration.

As part of the new plan, China has established a new super-administration, the State Market Regulatory Administration (SMRA), which will among others merge and undertake the responsibilities previously held by the CFDA and other healthcare agencies. In contrast to CFDA, the new administration will also have a variety of other responsibilities that are not related to science-based aspects in conjunction with product safety and effectiveness. With the establishment of the SMRA, the Chinese government has generated a single powerful market regulator which will have a wide-ranging oversight of issues regarding drug and food safety, protection of intellectual property and product quality in general.

4.1 Key institutional changes in pharmaceutical and healthcare sector

Under the recent restructuring plan, three new regulatory authorities will be established in the pharmaceutical and healthcare sector:

State Drug Administration (SDA)

The SDA, supervised by the SMRA, will replace the pharmaceutical-related regulatory power of the CFDA. At the local level, there will also be provincial drug administrations but at the city/county level, the relevant regulatory functions will be directly within the local branches of the SMRA.

State Administration for Medical Security Insurance (SAMI)

The SAMI is responsible for drug pricing regulation, regulation and supervision of the bidding process for drug and medical supply procurement as well as regulation of the drug and medical services pricing.

National Health Commission

China's current National Health and Family Planning Commission ("NHFPC"), which regulates both family planning and the healthcare system, will be merged into a new authority known as National Health Commission. According to the restructuring plan, the new authority will not be further responsible for family planning but among others responsible for the supervision of hospitals and medical services and policy formulation for drugs, medical treatment and elderly care.

4.2 Impact on multinational pharmaceutical companies

A huge effort was taken to reshape China's government structure in order to establish a new structure that is better-structured, more efficient and service-oriented than the old one. However, merging several large bureaucratic institutions also raises a number of challenges with which multinational companies may be confronted.

New structuring includes that the new ministries and agencies will need to be assigned new roles and responsibilities, which is accompanied by personnel and internal restructuring. Additionally, new leadership is often associated with new ambitions, resulting in the release of new policies. It can be assumed, indeed, that the new SDA body under the SMRA will continue to implement the previous CFDA reform initiatives issued since October 2017. However, personnel reshuffle might delay implementation of these initiatives, making it not clear to what extent the new authority will continue to develop the draft rules proposed by the CFDA. Thus, companies have to closely monitor the policy announcements by the new SMRA leadership to get familiar with its new priorities and ambitions.

Generally, during the transitional period, foreign companies doing business in China need to be prepared for possible delays in filing, review or approval processes due to the uncertainties brought by the restructuring plan. They should remain particularly vigilant in

the development of how fast new policies will be released and how responsibilities within the new regulatory authorities will be organized.

Besides the possible challenges potential benefits also arise through the merger. As many regulatory functions are now together within one authority, the structure becomes less fragmented and inter-departmental communication will most likely increase, resulting that different procedures in view of drug regulatory may become simplified and uniform. Moreover, it will allow companies to communicate with only one regulatory body to resolve operational issues in China instead with many different agencies, as it used to be common in the past.

5 Conclusion

The latest rounds of healthcare reform in China reflect the tremendously effort of the Chinese government to modernize and improve the regulatory landscape of drug review and approval, health insurance and healthcare in China. While the impact of the major reforms already starting to become visible, the resulted changes are considered to bring new opportunities to multinational pharmaceutical companies doing business in China or interesting in participating in the Chinese pharmaceutical market. At the same time, China's evolving regulatory system also imply challenges to the overseas industry.

Over the past few decades, different aspects concerning approval and conduction of clinical trials in China have been improved considerably. Participation in IMCTs enables companies to initiate clinical program earlier in China before the overseas market approval has been obtained, shorten the timeframe of registration approval significantly. Additionally, it also enhances the capacity and inclusion of Chinese clinical research centers.

Heavy drug application backlogs and long timeframe for review and approval processes in China have been a major issue until 2014, resulting in delays on the initiation and implementation of innovative drug development programs, leading to delay of market entry and thus creating serious public health implications for the Chinese population. In response to the grievance, CFDA begun in 2015 with the announcement of several policies and measurements regarding review and approval of drug registration. These include e.g. increasing of human capacity at the CDE, increasing registration fee to decrease thoughtless applications, re-categorizing how drugs are approved, a pilot market authorization holder system, self-inspection of clinical trial data and implementation of

priority review. These changes improve the efficiency and speed of the drug review and approval process, particularly for innovative drugs.

In 2017, the *'innovation opinion'* was announced, which proposed further reforms to encourage innovation on drugs and medical devices by adopting the four important CFDA draft policies. To fully implement the *'innovation opinion'*, the CFDA announced its decision to change the requirement on import drug registration by removing certain restraints on clinical trials and registrations to simplify the review and approval process, encouraging foreign companies to undertake global studies in China. It is now significantly easier for foreign-developed new drugs to undergo clinical investigation within China and overseas in parallel, thus shorten the drug lag between approval outside and inside China. With China's accession to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) in June 2017, China reinforce its intention to create a regulatory standard that will narrow the gaps between China and other countries.

The reforms outlined above create a flexible and modern framework that will more closely align China's regulatory environment to global standards. The benefits of the reforms to multinational companies include minimization of the drug lag, shortening of the drug review and approval timeline, clinical investigation with other countries in parallel, improvement of transparency and establishment of a stronger quality control regarding generic drugs and clinical data. Besides the arising benefits for global companies, it should also keep in mind that the issued reforms will also have a profound impact on China's pharmaceutical industry. From the government's site, there is also a major incentive to restructure the local pharmaceutical industry by promoting local companies to develop innovative new drugs instead of generics. From that point of view, companies must be aware that the reforms will also transform the competitive landscape between domestic and foreign pharmaceutical companies in China.

Further development opportunities arise for multinational companies through the latest revision of the NRDL and the increased number of private hospitals, which will increase the profit margin by increasing the sales volume and opening a new market direction. At the same time, they are faced with the challenges caused by the announced implementation of changes to the current pricing model. These include among others a stringent control of drug prices in public hospitals and health insurance and new systems regarding procurement and price negotiation. Although the drug pricing reform aims to remove constraints on drug prices by gradually establish a market-driven drug pricing

system, abolishment of GP and GGP, as such, is not expected to affect drug prices, as other mechanisms of price control still remain in place.

The government restructuring plan issued in March this year may simplify the entire drug regulatory process based on the establishment of a new structure intending to be less fragmented, more efficient and service-oriented than the old one. In the future, multinational companies should pay close attention to further organizational and political actions of the SMRA in order to see if the policy course set by its predecessor agencies will be preserved.

In view of these opportunities and challenges, multinational pharmaceutical companies must gain a better understanding of the current landscapes, upcoming changes and their implications. Overall, they need to closely monitor the ongoing changes and the emerging trends in the Chinese pharmaceutical market, adjusting their development strategies accordingly by taking pertinent countermeasures proactively and ensuring a timely communication to all relevant stakeholders.

6 References

- [1] "Global medicines use in 2020. London, IMS Health.," 2015.
- [2] "World population prospects, the 2015 revision. New York, United Nations," 2015. [Online]. Available: https://esa.un.org/unpd/wpp/publications/files/key_findings_wpp_2015.pdf. [Accessed 10 October 2018].
- [3] "National data. Beijing, National Bureau of Statistics," 2015. [Online]. Available: <http://data.stats.gov.cn/english/>. [Accessed 10 October 2018].
- [4] "China's diabetes boom promises \$23 billion pot for drug makers," 21 March 2016. [Online]. Available: <https://www.marketwatch.com/story/chinas-diabetes-boom-promises-23-billion-put-for-drug-makers-2016-01-15>. [Accessed 24 August 2018].
- [5] C. W., "Cancer Statistics in China, 2015," *CA Cancer J Clin*, vol. 66, March/April 2016.
- [6] "China Health Statistics. In. Beijing.," Ministry of Health of the People's Republic of China. , 2004.
- [7] "China Health Statistics. In. Beijing.," Ministry of Health of the People's Republic of China. , 2005.
- [8] "China Health Statistics. In. Beijing.," Ministry of Health of the People's Republic of China. , 2006.
- [9] "China Health Statistics. In. Beijing.," Ministry of Health of the People's Republic Of China., 2007.
- [10] "China Health Statistics. In (pp. 23). Beijing.," Ministry of Health of the People's Republic Of China., 2008.
- [11] "China Health Statistics. In. Beijing.," Ministry of Health of the People's Republic Of China., 2009.
- [12] "Chinese Health Statistical Digest. In (pp. 25). Beijing.," Ministry of Health of the eople's Republic Of China, 2010.
- [13] "China Health Statistical Yearbook 2012. In. Beijing.," Ministry of Health of the eople's Republic of China., 2012.
- [14] "Measures for the Administration of Drug Registration, Decree of the State Drug dministration (No.35)," 1 December 2002. [Online]. Available: <http://www.asianlii.org/cn/legis/cen/laws/mftaodrti762/>. [Accessed 14 October 2018].
- [15] M. Q. Lu, "Strategic drug development in China and surrounding countries," in *Approaching China's Pharmaceutical Market*, Springer International Publishing, 2015, p. 507–532.

-
- [16] "Provisions for Drug Registration (SFDA Order No. 28)," 2007. [Online]. Available: <http://eng.sfda.gov.cn/WS03/CL0768/61645.html>. [Accessed 12 October 2018].
- [17] M. Q. Lu, *Approaching China's pharmaceutical market. A fundamental guide to clinical drug development*, Springer International Publishing, 2015.
- [18] "China to accept overseas trial data in bid to speed up drug approvals.," 9 October 2017. [Online]. Available: <https://www.reuters.com/article/us-china-pharmaceuticals/china-to-accept-overseas-trial-data-in-bid-to-speed-up-drug-approvals-idUSKBN1CE080>. [Accessed 14 October 2018].
- [19] "Understanding the dynamics of china's medicine regulatory environment," Centre for Innovation in Regulatory Science (CIRS), June 2015. [Online]. Available: http://www.cirsci.org/sites/default/files/CIRS_RD_Briefing_56_15062015.pdf. [Accessed 17 October 2018].
- [20] "Clinical Trials in Asia: Tale of the Tiger or Tiger by the Tail? Part IIIa – India and China," 13 September 2016. [Online]. Available: <https://www.clinicaltrialsarena.com/news/clinical-trials-arena/clinical-trials-in-asia-tale-of-the-tiger-or-tiger-by-the-tail-part-iii-a-india-and-china-5004390-2/>. [Accessed 14 October 2018].
- [21] "SFDA issues Requirements on Special Approval of New Drug Registration," 12 January 2009. [Online]. Available: <http://eng.sfda.gov.cn/WS03/CL0757/62177.html>. [Accessed 15 October 2018].
- [22] J. Yan, "New drug regulation and approval in China," in *A Comprehensive Guide to Toxicology in Preclinical Drug Development*, London, Academic Press, 2013, p. 713–723.
- [23] P. Lattanzi, "China's legal framework for pharmaceutical products: challenges and opportunities for EU companies," *Int. J. Healthcare Technology and Management*, Vols. 16, Nos. 1/2, 2017.
- [24] "Guidance for International Multicenter Clinical Trials (IMCT) (Trial), Draft for Public Comment, No. 698," CFDA, 2014.
- [25] "Guidance for International Multicenter Clinical Trials (IMCT) (Trial), Draft for Public Comment (No. 698, 2014)," CFDA, 2014.
- [26] "SFDA Proposes New Review Channel for Innovative Drugs," *PharmAsia News*, 15 January 2013. [Online]. Available: <https://scrip.pharmaintelligence.informa.com/SC082406/SFDA-Proposes-New-Review-Channel-For-Innovative-Drugs>. [Accessed 21 September 2018].
- [27] "Opinions of the State Council on Reforming the Examination and Approval System

-
- for Drugs and Medical Devices – Country Law (No. 44, 2015)," China Food and Drug Administration, State Council, People's Republic of China, 9 August 2015. [Online]. Available: <http://samr.sda.gov.cn/WS01/CL0056/126821.html>. [Accessed 10 September 2018].
- [28] Q. Zhou, "The changing landscape of clinical trial and approval processes in China," *Nature Reviews, Clinical Oncology*, 2017.
- [29] "Announcement on Several Policies Pertaining to the Review and Approval of Drug Registration (No. 230 of 2015)," China Food and Drug Administration, State Council, People's Republic of China, 11 November 2015. [Online]. Available: <http://samr.sfda.gov.cn/WS01/CL1278/134665.html>. [Accessed 5 September 2018].
- [30] "2014 CDE annual report," Center for Drug Evaluation, CFDA, 13 March 2015. [Online]. Available: <http://www.cde.org.cn/news.do?method=viewInfoCommon&id=313425>. [Accessed 16 September 2018].
- [31] L. Su, "Drug development models in China and the impact on multinational pharmaceutical corporations," *Food and Drug Law Institute Update*, p. 19–23, September/October 2013.
- [32] "How many people are employed by FDA and in what areas do they work?," Washington, DC, US Food and Drug Administration, 2015. [Online]. Available: <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm213161.htm>. [Accessed 23 August 2018].
- [33] B. Wang, "An overview of major reforms in China's regulatory environment," *Regulatory Rapporteur*, Vols. 14, No 7/8, July/August 2017.
- [34] "Notice of the State Administration of Food and Drug Administration on Issuing the Registration Fees for Drugs and Medical Device Products (No. 53, 2015)," China Food and Drug Administration, State Council, People's Republic of China, 27 May 2015. [Online]. Available: <http://samr.sfda.gov.cn/WS01/CL1411/120201.html>. [Accessed 4 September 2018].
- [35] "China Food and Drug newsletter," *China Center for Food and Drug International Exchange & Servier (Tianjin) Pharmaceutical Co., Ltd.*, vol. 9, 24 July 2015.
- [36] "Inspection Report for Drug Clinical Trial Data," Center for Food and Drug Inspection of CFDA, 22 July 2016. [Online]. Available: <http://www.cfdi.org.cn/resource/news/8689.html>. [Accessed 2 September 2018].
- [37] "Notice of the General Administration of the People's Republic of China on the Publication of the Work Plan for the Classification of Chemical Registration (No.

-
- 51, 2016)," China Food and Drug Administration, State Council, People's Republic of China, 4 March 2016. [Online].
Available: <http://samr.sda.gov.cn/WS01/CL0087/146140.html>. [Accessed 12 September 2018].
- [38] "Optimizing Drug Registration in China: Category I Route," Wilmington, NC, Pharmaceutical Product Development, 2013. [Online]. Available: http://www.ppd.com/drug-registration-china/China_CategoryI-Registration-PPD_White%20Paper.pdf. [Accessed 25 August 2018].
- [39] "Implementing Priority Review and Approval to Solve Drug Registration Application Backlog," Leawell international LTD., 11 November 2016. [Online]. Available: <http://en.leawell.com.cn/a/270.html>. [Accessed 20 October 2018].
- [40] "Quality and Efficacy Consistency Evaluation for Generic Drugs," Leawell international LTD., 16 May 2016. [Online].
Available: <http://lwen.lly360.com/a/231.html>. [Accessed 21 October 2018].
- [41] "Opinions of the State Council on Promulgating the Reform of Review and Approval System for Drugs and Medical Devices to Encourage Innovation (No. 42, 2017)," Chinese Communist Party's Central Committee and State Council, People's Republic of China, 8 October 2017. [Online]. Available: <http://samr.sda.gov.cn/WS01/CL1747/178283.html>. [Accessed 26 August 2018].
- [42] "China Food and Drug Administration Announcement Seeking Public Comments on Relevant Policies on Accelerating Evaluation and Approval for the Marketing Authorization of New Drugs and Medical Devices to Encourage Innovation in Drugs and Medical Devices (Draft for Public Comment) (2017 No. 52)," Covington & Burling LLP, 11 May 2017. [Online]. Available: https://www.cov.com/-/media/files/corporate/publications/file_repository/alert_circular_52.pdf. [Accessed 14 August 2018].
- [43] "China Food and Drug Administration Announcement on Seeking Public Comments regarding Relevant Policies on Reforming the Administration of Clinical Trials to Encourage Innovation in Drugs and Medical Devices (Draft for Public Comment) (2017 No. 53)," Covington & Burling LLP, 11 May 2017. [Online]. Available:
https://www.cov.com/-/media/files/corporate/publications/file_repository/alert_circular_53.pdf. [Accessed 14 August 2018].
- [44] "China Food and Drug Administration Announcement Seeking Public Comments regarding Relevant Policies on Implementing Drug and Medical Device Lifecycle

-
- Management to Encourage Innovation in Drugs and Medical Devices (Draft for Public Comment) (2017 No. 54)," Covington & Burling LLP, 11 May 2017. [Online]. Available:https://www.cov.com/-/media/files/corporate/publications/file_repository/alert_circular_54.pdf. [Accessed 14 August 2018].
- [45] "China Food and Drug Administration Announcement Seeking Public Comment regarding Relevant Policies on Protecting Innovator Interests to Encourage Drug and Medical Device Innovation (Draft for Public Comment) (2017 No. 55)," Covington & Burling LLP, 12 May 2017. [Online]. Available: https://www.cov.com/-/media/files/corporate/publications/file_repository/alert_circular_55.pdf. [Accessed 14 August 2018].
- [46] "Decisions Concerning the Adjustment of Imported Drug Registration (No. 35, 2017)," China Food and Drug Administration, State Council, People's Republic of China, 10 October 2017. [Online]. Available: <http://samr.sfda.gov.cn/WS01/CL1033/178362.html>. [Accessed 18 August 2018].
- [47] "Technical Requirements for the Acceptance of Foreign Clinical Trial Data," Center for Drug Evaluation, CFDA, 20 October 2017. [Online]. Available: <http://www.cde.org.cn/news.do?method=viewInfoCommon&id=314075>. [Accessed 28 August 2018].
- [48] L. Zhao, "Bridging the gaps of China GCP regulation compared to ICHGCP to effectively conduct multinational clinical trials (MCTs)," *J Develop Drugs*, vol. 2:4, 2013.
- [49] "Draft Amendments to the Drug Administration Law," China Food and Drug Administration, 23 October 2017. [Online]. Available: <https://web.archive.org/web/20171224062932/http://www.sda.gov.cn/WS01/CL0050/178902.html>. [Accessed 21 October 2018].
- [50] "Legal Debriefs – the Revised Administrative Measures for Drug Registration (Draft for Comment)," Zhong Lun, 23 November 2017. [Online]. Available: <http://www.zhonglun.com/Content/2017/11-23/1743470273.html>. [Accessed 21 October 2018].
- [51] "Chinese Government Initiates Significant Drug and Device Regulatory Reforms," Covington & Burling LLP, 6 November 2017. [Online]. Available: https://www.cov.com/-/media/files/corporate/publications/2017/11/chinese_government_initiates_significa

-
- nt_drug_and_device_regulatory_reforms.pdf. [Accessed 25 September 2018].
- [52] "Notice concerning Publication of the China Marketed Drug Catalogue (No. 172, 2017)," China Food and Drug Administration, 29 December 2017. [Online]. Available:
<https://web.archive.org/web/20180113220624/http://www.sda.gov.cn/WS01/CL0050/220786.html>. [Accessed 21 October 2018].
- [53] "China national health accounts report," National Health Development Research Center, Beijing, 2013.
- [54] "Health at a glance 2015: OECD indicators," Organization for Economic Co-operation and Development , Paris, 2015.
- [55] M. Wenhui, "China: The zero mark-up policy for essential medicines at primary level facilities," World Health Organization, 2015.
- [56] Y. H, "The evaluation of medical care income of hospital in different rank of Shanghai city," *Chinese Hospital Management* , vol. 23(5), pp. 11-13, 2003.
- [57] "Chinese Health Statistics Yearbook," Xiehe Medical University Press, Beijing, 2010.
- [58] "China National Health Accounts Report," China National Health Development Research Center, Beijing, 2009.
- [59] J. Q, "Outpatient prescription practices in rural township health centers in Sichuan Province, China," *BMC health services research*, vol. 12(1), p. 324, 2012.
- [60] Z. X, "The effect of the National Essential Medicines Policy on health expenditures and service delivery in Chinese township health centers: evidence from a longitudinal study," *BMJ Open*, vol. 4, p. e006471– e006471, 2014.
- [61] E. Mossialos, Pharmaceutical policy in China. Challenges and opportunities for reform, World Health Organization , 2016 .
- [62] "Market Access in China: Drug Listing, Bidding, Pricing and Reimbursement," Pacific Bridge Medical, 11 June 2014. [Online]. Available:
<https://www.pacificbridgemedical.com/publication/gaining-market-access-in-china-the-complex-process-of-drug-listing-bidding-pricing-and-reimbursement/>. [Accessed 23 September 2018].
- [63] M. W, "Systematic review on irrational use of medicines in China and Vietnam," *PloS one*, vol. 10(3), p. e0117710. pmid:25793497, 2015.
- [64] "China's update on the National Reimbursement Drug List for Basic Medical Insurance, Employment Illness Insurance, and Maternity Insurance (NRDL 2017 edition)," Ministry of Human Resources and Social Security, People's Republic of

-
- China., 23 February 2017. [Online].
Available:http://www.mohrss.gov.cn/SYrlzyhshbzb/dongtaixinwen/buneiyaowen/201702/t20170223_266787.html. [Accessed 22 October 2018].
- [65] "Announcement on 36 medicines newly added to the B List of China National Formulary," Ministry of Human Resources and Social Security, People's Republic of China, 13 July 2017. [Online].
Available:http://www.mohrss.gov.cn/SYrlzyhshbzb/shehuibaozhang/zcwj/201707/t20170718_274153.html. [Accessed 22 October 2018].
- [66] "China regulatory and market access pharmaceutical report 2014," Pacific Bridge Medical, Bethesda, 2014.
- [67] "Circular Concerning Opinions on Advancing the Drug Pricing Reform (No. 904, 2015)," National Development and Reform Commission, 4 May 2015. [Online].
Available:http://www.ndrc.gov.cn/zcfb/zcfbtz/201505/t20150505_690664.html.
[Accessed 22 October 2018].
- [68] "Regulation of drug pricing policy for health providers. Policy Document No. 391.," Ministry of Health, China, Beijing, 2000.
- [69] C. Yixi, "Drug pricing reform in China: analysis of piloted approaches and potential impact of the reform," *Journal of Market Access & Health Policy*, 2016.
- [70] "Secret: Sanming healthcare reform, how to succeed?," Xinhua News Agency, 2015. [Online]. Available:
http://www.sm.gov.cn/ztl/shyywstzgg/gzdt/201502/t20150208_285631.htm.
[Accessed 17 August 2018].
- [71] "The 2nd price negotiation: Drugs will be stopped if do not accept the price decreasing," HC Pharmaceutical Industry Network, 21 January 2015. [Online].
Available: <http://info.pharmacy.hc360.com/2015/01/210952545605.shtml>. [Accessed 25 October 2018].
- [72] "14 imported drugs have been stopped or restricted to use in Shaoxing Tier 3 hospitals," Yangming Situ, 30 January 2015. [Online]. Available:
<http://www.chinamsr.com/2015/0130/83929.shtml>. [Accessed 25 October 2018].
- [73] "State Council guidance on improving public hospitals centralized drug procurement," State Council, 28 February 2015. [Online]. Available:
http://www.gov.cn/zhengce/content/2015-02/28/content_9502.htm. [Accessed 24 October 2018].
- [74] "Arguments on 2nd pricing, many areas releasing 'yes' signal," China Eco Net, 4 June 2015. [Online]. Available:

-
- http://finance.ce. cn/rolling/201506/04/t20150604_5543625.shtml. [Accessed 23 October 2018].
- [75] "The 13th five-year plan for economic and social development of the People's Republic of China (2016–2020)," People's Republic of China, [Online]. Available: <http://en.ndrc.gov.cn/newsrelease/201612/P020161207645765233498.pdf>. [Accessed 25 October 2018].
- [76] "The Reform Plan of the Institutions of the State Council," Xinhua News Agency, 17 March 2018. [Online]. Available: https://web.archive.org/web/20180829202216/http://www.gov.cn/guowuyuan/2018-03/17/content_5275116.htm. [Accessed 25 October 2018].

Eidesstattliche Versicherung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Ort, Datum

Unterschrift