The Life Sciences Law Review

Fifth Edition

Editor
Richard Kingham

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EDITOR'S PREFACE

The fifth edition of *The Life Sciences Law Review* covers a total of 37 jurisdictions, providing an overview of legal requirements of interest to pharmaceutical, biotechnology and medical device companies. The chapters are arranged to describe requirements throughout the life cycle of a regulated product, from discovery to clinical trials, the marketing authorisation process and post-approval controls. Certain other legal matters of special interest to manufacturers of medical products – including administrative remedies, pricing and reimbursement, competition law, special liability regimes and commercial transactions – are also covered. Finally, there is a special chapter on international harmonisation, which is of increasing importance in many of the regulatory systems that are described in the national chapters.

Now, more than ever, it is important for leaders in the pharmaceutical and medical device industries and their advisers to be knowledgeable about the laws and regulations in major jurisdictions around the world. In the past year, there have been significant developments in the regulation of drugs and medical devices, especially in the United States, where a new law – the 21st Century Cures Act – was passed at the end of 2016. There are prospects for further developments in the coming year. The new president and the Republican-controlled Congress will consider legislative measures affecting the pharmaceutical and medical device sectors, including proposed repeal of the Affordable Care Act, continuing inquiries into pricing of medical products and reauthorisation of user fee laws that fund a substantial part of the drug and device approval processes. The United Kingdom will initiate formal proceedings to begin the process of withdrawing from the European Union, with potential consequences for the medical products sectors. Other jurisdictions, including China and India, are considering reforms to their regulatory systems for medicinal products.

Each of the chapters has been written by leading experts within the relevant jurisdiction. They are an impressive group, and it is a pleasure to be associated with them in the preparation of this annual publication.

Richard Kingham
Covington & Burling LLP
Washington, DC
March 2017

Chapter 7

CHINA

Shaoyu Chen and John Balzano[1]

I INTRODUCTION

China's drug and device legislation has developed rapidly from simple laws and regulations enacted gradually up to 2000, to a substantial body of regulation covering the major areas of research and development, pre-market approval, manufacturing and post-marketing distribution and surveillance. This is an exciting time for drug and device regulatory reform in China. A growing body of healthcare regulation, including medical ethics, pricing and reimbursement, and standards for clinical research, is also emerging to influence the drug and device industries.

In 2013, China reorganised its State Food and Drug Administration into a more powerful ministry-level agency, referred to as the China Food and Drug Administration (CFDA), and reforms in all spaces have continuously expanded since that time. In 2014, China revised the entire medical device regulatory regime. Most recently China's State Council and the CFDA have worked to implement blueprints aimed at bringing higher quality drugs and devices that meet unmet medical needs to market faster. In this respect, for medical devices, the government has implemented significant GxP reform, a priority pathway for innovative devices, and other priority pathways for key disease areas, such as oncology and devices for paediatric and geriatric indications.

The reforms for drugs have been more concentrated in 2015 and 2016. China has established a new system of registration pathways for small molecule drugs under which generic drugs must demonstrate therapeutic and quality equivalence with what should typically be a fully evaluated reference product, and new drugs or innovations (e.g., dosage forms) must now meet a high standard of being 'new to the world'.[2] China has also implemented a pilot marketing authorisation holder programme (MAH Pilot) in certain

1 Shaoyu Chen is a partner and John Balzano is an of counsel at Covington & Burling LLP.

2 See Drug and Medical Device Registration Fee Regulations, Articles 3-4 (NDRC 2015); Drug Registration Fees Implementing Regulations, Article 3 (CFDA 2015).

cities that permits domestic research-based companies to hold the rights to the product, while contracting out manufacturing, subject to a set of obligations. The MAH programme has already begun to allow for smaller , research-based companies to undertake significant development efforts in China.

Other reforms are also aimed at improving patient access and encouraging innovation. These reforms include efforts to increase good clinical practice (GCP) compliance for both drugs and devices, new registration fees to provide greater resources for the CFDA, and other guidance documents and structural reforms within the CFDA to improve the speed of the marketing application review process.

This chapter provides an overview of the jurisdiction of the CFDA, the regulatory scheme for developing, manufacturing, and distributing drugs and medical devices. It also explores healthcare, antitrust and corporate considerations. It discusses the new reforms and the impact they are having, and it concludes with a discussion of future directions in these areas. The drug and device regulatory system will likely change and expand for many years to come.

II THE REGULATORY REGIME

i Regulatory agencies and their jurisdiction

The CFDA is the primary pharmaceutical and medical devices regulatory agency in China. This includes biologics and combination products. It enjoys power over most aspects of pre-market approval and a substantial part of post-marketing activities. Under the current arrangement, the CFDA is organised into departments and affiliated centres. The departments have responsibility for administration and enforcement functions, while the affiliated centres are responsible for scientific review and for recommending decisions for the departments to adopt and implement.

For drugs, the primary departments and centres include the Department for Drug and Cosmetic Registration and the Department for Drug and Cosmetic Safety Supervision. The affiliated centres are the Centre for Drug Evaluation (CDE) and the Centre for Drug Re-Evaluation (CDR). The CDE evaluates clinical trial and marketing authorisation applications. The CDR includes the National Centre for Drug Adverse Event Monitoring, which is also responsible for device adverse event monitoring.

The CFDA similarly has registration and supervision departments for medical devices. The registration department is subdivided by whether the devices use electrical power or not, as well as including a department for supervising research and development. The supervision department is divided into divisions responsible for regulating manufacturing, distribution, and monitoring and evaluation. The Centre for Medical Device Evaluation (CMDE) is the affiliated centre responsible for organising the technical evaluation of medical devices.

With an official headcount of 345 at the national level (not counting contract personnel), the CFDA relies on provincial food and drug administrations (PFDAs) and similar food and drug regulatory authorities in the municipalities[3] to carry out various activities, including accepting applications, conducting on-site checks and inspections,

3 While varying from year to year, the local food and drug agencies and affiliated organisations at PFDAs and municipalities have a total approximate headcount of 80,000 (direct and affiliated).

collecting samples, and issuing manufacturing and distribution licences. These provincial agencies receive their budget and their personnel allocation from the provincial governments, and they can vary in terms of capacity. State accredited laboratories and clinical trial sites (i.e., in state-owned hospitals) also play a role in drug and device regulation in China. China has worked since 2015 to provide the review agencies (CDE and CMDE) with more reviewers. Real numbers are difficult to determine, but the CDE's 2015 annual report indicates that it added approximately 146 reviewers in that year, indicating that the number of reviewers has grown into the hundreds, from approximately 60–70 a few years ago.[4] The CMDE has similarly been adding reviewers but has a lower number of about 135 as of 2016.[5] The increases in staff have been and will continue to be an important step to resolving delays.

Although the CFDA is the primary agency for pre-approval, other government agencies also play important roles in the pharmaceutical regulatory framework. For example, the National Development and Reform Commission (NDRC) plays a key role in articulating drug and device pricing policy. The State Administration for Industry and Commerce (SAIC) plays a significant role in enforcing advertising and promotion and other consumer protection laws. The National Health and Family Planning Commission (NHFPC) (formerly the Ministry of Health) oversees all aspects of the medical profession and hospitals (which include CFDA-accredited clinical trial sites for drugs and devices), and it plays a role in determining the essential drugs that may be reimbursed under China's state insurance plans. The Ministry of Personnel and Human Resources also plays a role in setting the formularies for these insurance plans. For imported drugs, two additional government agencies, the Chinese Customs and the Administration of Quality Supervision, Inspection and Quarantine, are involved in product-quality inspections and customs clearance. This sharing of responsibility creates a complex system in many respects.

ii Primary statutes and regulations

The CFDA administers laws, State Council regulations, rules, and guidance documents related to drugs and devices. The primary statute regulating drugs (including biologics) in China is the Drug Administration Law (DAL), which was enacted by China's national legislative body, the National People's Congress, in 1984 and then subsequently amended in 2001.[6] Small amendments were made to the DAL in 2013 and in 2015 to support what China considered to be more pressing regulatory reforms, such as drug pricing. The State Council has enacted one general set of implementing rules for the DAL, referred to as the DAL Implementing Regulations (DALIR). The CFDA (and its predecessor agency, the SFDA) promulgated several agency rules under the DAL and DALIR to govern various activities, such as development, registration, manufacturing and marketing of drugs. These include GxPs on manufacturing, distribution, clinical development and laboratory work. The core regulation governing clinical trials and drug and biologic registration are the Provisions on Drug Registration (PDR), and the more recent reference product and MAH reforms are written into scattered State Council and CFDA documents that supersede provisions

4 Annual Report of the Center for Drug Evaluation (3 March 2016).

5 This statistic was compiled by reviewing multiple hiring announcements on CMDE's website, www.cmde.org.cn.

6 Drug Administration Law (amended February 2001), http://eng.sfda.gov.cn/WS03/CL0766/61638.html.

in the PDR. These reforms may be incorporated into the DAL or the PDR (or both) once they proceed past the experimental stage. The CDE also issues its own rules and guidance documents related to drug development and registration, priority pathways and supplemental applications.

China has not enacted a statute covering medical devices, but the State Council has enacted a framework regulation, the Regulations for the Supervision and Administration of Medical Devices (RSAMD). And, as with drugs, the CFDA has enacted a number of implementing rules covering registration, production and distribution.[7] In 2014, the State Council revised the RSAMD, and the CFDA subsequently issued an entirely new set of substantially revised implementing regulations, governing device registration, manufacturing and distribution. These reforms continued well into 2016, and CFDA has not yet finalised certain rules, such as those on adverse event reporting and monitoring, recalls, and device advertising and promotion. Like the CDE, the CMDE issues its own rules and product specific guidance documents.

iii Product classification and definitions

Drugs

The DAL defines 'drugs' broadly as:

> *articles which are used in the prevention, treatment and diagnosis of human diseases and intended for the regulation of the physiological functions of human beings, for which indications, usage and dosage are established, including Chinese crude drugs, prepared tranches of Chinese crude drugs, traditional Chinese medicine preparations, chemical drugs substances and their preparations, antibiotics, biochemical drugs, radioactive pharmaceuticals, serum, vaccines, blood products and diagnostic agents.*[8]

The CFDA has significant discretion to determine whether a substance constitutes a drug or fits into another regulatory regime. As will be discussed below, the CFDA does recognise some category overlap. When products may be considered drug and device combination products, the CFDA and a combination of experts from either the CDE, CMDE or both will make a decision as to whether to regulate the product as a drug or as a device.

Once determined to be a drug, the regulatory requirements applicable to a product will be determined by its pathway and its features. The primary pathways are either a domestically manufactured drug or an imported drug.

Before a company can market a drug in China, the DAL requires that the company submit and obtain government approval of a drug registration application, which may be divided into two parts: (1) a clinical trial application; and (2) a subsequent application for approval to market the drug.[9] If the drug is to be manufactured in China, the company must also submit a manufacturing licence application and obtain a good manufacturing

7 RSAMD, www.cfda.gov.cn/WS01/CL0784/97814.html. These regulations cover *in vitro* diagnostic reagents (IVDs), but IVDs are regulated separately under a specialised set of implementing regulations. Throughout this chapter, references to medical devices refer to non-IVD devices, unless otherwise indicated.

8 Article 102 of the DAL.

9 Article 29 of the DAL.

practice (GMP) certification of its facilities.[10] If the drug is to be manufactured abroad, the company must apply for an import drug licence.[11] In either event, approval requires a robust demonstration of safety and efficacy, showing that the drug's benefits outweigh its risks. After approval, a drug manufacturer is required to conduct pharmacovigilance and follow rules on advertising and promotion, as discussed in the sections below.

The DAL and PDR[12] classify a drug either as a domestic drug or as an imported drug, depending on whether the finished dosage form of the drug is manufactured inside or outside China. The PDR then classifies domestic drugs into three types: traditional Chinese medicines and natural drugs, chemical drugs and biological drugs. Within each classification, drugs are then placed into categories and subcategories. These classifications and sub-classifications determine the clinical data and other requirements necessary for registration.

In March 2016, pursuant to authorisations from the National People's Congress and the State Council, the CFDA restructured the registration categories for chemically synthesised drugs. These new categories were intended to reduce confusion about the registration process, integrate the new reference product system for generics and encourage innovation. The five categories under this system are as follows:

a Category 1: innovative drugs. These drugs have an active ingredient that has a clear structure and is clinically valuable. The ingredient must be new to the world, not just new to China.

b Category 2: improved innovative drugs. These drugs have an improvement that is clinically valuable and new to the world, such as certain structural changes, dosage forms, routes of administration, strengths and indications.

c Category 3: generics with foreign reference products. This category is for generic drugs that use fully evaluated drugs (typically originator drugs), which are marketed abroad but not in China, as their reference products.

d Category 4: generics with domestic reference products. The opposite of Category 3, this category is for generics that use fully evaluated drugs that are marketed in China as their reference products.

e Category 5: foreign drugs. Following on from the separation between imported and domestic drugs described above, this category is either for originator drugs that are already marketed abroad (5.1) or generic drugs marketed abroad (5.2). These drugs use the import licence pathway.[13]

Biologics have not undergone a similar reform. They are under the original categorisation contained in the PDR, Appendix Three. Under the PDR, all biologics proceed along the new drug pathway, even if they might be considered biosimilars. In terms of application pathways, in Appendix III, biologics are classified as either therapeutic or preventive, then further classified into 15 subcategories under each heading.[14] Classification depends on the

10 Article 8 of the DAL.

11 Article 39 of the DAL.

12 The Provisions for Drug Registration (2007), http://eng.sfda.gov.cn/WS03/CL0768/61645.html.

13 Notice on the Plan for New Registration Categories for Chemically Synthesized Drugs (CFDA No. 51 2016).

14 Appendix 3 of the PDR.

drug's marketing approval status in China and abroad, source material, composition and other factors. The subcategories are not mutually exclusive, which can lead to confusion and duplicative requirements.

As explained below, certain types of drugs may be subject to separate and heightened requirements and require additional special permissions. An example of this would be drugs that the CFDA classifies as 'narcotic drugs' and 'psychotropic drugs,' which are discussed in the subsections below.

Devices

The RSAMD define 'medical devices' broadly as:

> *Medical devices means the instruments, equipment, appliances, in vitro diagnostic reagents and calibrators, materials and other similar or related articles directly or indirectly used with human bodies, including the computing software required. Their effectiveness is primarily achieved by physical or other similar means and not by pharmacological, immunological or metabolic means, although it may be assisted in its function by such means, the purpose of which is to achieve the following objectives:*
> *(1) diagnosis, prevention, monitoring, treatment or mitigation of diseases;*
> *(2) diagnosis, monitoring, treatment or mitigation of injuries or the functional compensation thereof;*
> *(3) inspection, replacement, adjustment or support of the physical structures or physiological processes;*
> *(4) life support or sustaining;*
> *(5) pregnancy control; and*
> *(6) provision of information for medical or diagnostic purposes by inspecting the samples of human bodies.*[15]

The RSAMD classify medical devices into three classes:

> *Class I medical devices means medical devices with low risks, and those for which safety and effectiveness can be ensured through routine administration; Class II medical devices means medical devices with moderate risks, which must be strictly controlled and administered to ensure their safety and effectiveness; Class III medical devices means medical devices with relatively high risks, which must be strictly controlled and administered through special measures to ensure their safety and effectiveness.*[16]

As with drugs, the CFDA and its relevant divisions have significant discretion to determine what constitutes a medical device and what class it fits into. Applicants for a device registration may make their own determination as to classification and then submit their

15 Article 76 of the RSAMD. This is an edited version of the translation that appears on www.chinalawinfo.com.

16 Article 76 of the RSAMD.

application to the CFDA or they can treat their device as a Class III and ask the CFDA to make adjustments.[17] The CFDA oversees an electronic portal that permits applications for a predetermination of device classification.

The CFDA maintains and periodically updates a classification catalogue showing its medical device classification decisions. By reference to this catalogue, along with general classification rules, the applicant can make its own determination as to classification. In 2016, the CFDA released a proposal for an amended catalogue with considerably more information, including product descriptions and intended uses.[18] Soon thereafter the CFDA convened a conference of experts on the amendment, and announced that it was accelerating the revision process. It is possible, therefore, that the revision could be finalised in 2017. Because classification determines data requirements for registration, it is often important to determine the class before starting trials or filing for an exemption.

As with drugs, the RSAMD and the Administrative Measures on Medical Device Registration, classify a medical device either as a domestic device or as an imported device, depending on whether the finished device is manufactured inside or outside China. If it is an imported device, the CFDA reviews and approves a registration application for Class II and Class III devices. Class I imported devices go through a notification system, which the CFDA also administers. For domestic devices, the review and the reviewing authority depend on the classification. Class I device manufacturers must notify municipal authorities before marketing their products. A provincial level FDA approves Class II medical device registration applications; and the CFDA reviews and approves Class III medical device registration applications.[19] The Measures on the Registration of In Vitro Diagnostic Reagents, which were also amended in 2014, set out a similar classification and registration scheme for IVDs.

Combination products

The CFDA issued a notice in 2009 to govern its review of drug and device combination products.[20] If the primary mode of action of a product is medicinal, the CDE will review it as a drug, or lead a joint and parallel review by both the CDE and the CMDE. If the primary mode of action of a product is not medicinal, the CMDE will review it as a device, or lead a joint and parallel review by the CMDE and CDE. One example of a product that the CFDA may treat as a combination product is a tissue-engineered product, which may be considered a medical device that may also have to meet certain requirements particular to the development of a biological product.[21]

Absent extenuating circumstances (e.g., substantial clinical need), the CFDA will not approve a combination product that is imported into China, if the product as a whole has not received any approval from the exporting country, or if the drug component of the product has not been approved in China or in the exporting country.

17 Article 16 of the RSAMD.

18 CFDA Notice Soliciting Comments on the Classification Catalogue for Medical Devices (CFDA 30 September 2016).

19 Article 5 of the Measures on Medical Device Registration.

20 Notice Concerning Registration of Drug and Device Combination Products (2009).

21 CFDA Notice on Tissue Engineered Medical Products and Related Application Requirements (CFDA 2007).

iv Non-clinical studies

Non-clinical studies for drugs must comply with the CFDA Drug Good Laboratory Practice Regulations,[22] which for the most part follow similar good laboratory practice (GLP) requirements in other countries. Non-clinical studies for drugs must be conducted by institutions that have been certified by the CFDA to perform such studies to be accepted as part of a drug registration application. The CFDA also accredits laboratories that conduct pretrial testing for Class II and III devices.

v Clinical trials

Drugs

Before a clinical trial can be initiated in China, the sponsor must submit a clinical trial application (CTA) to the CFDA, and the CFDA must approve it and issue a clinical trial permit. Although reform in this area is ongoing, the CFDA's review of a CTA can take about one year or more; an expedited review is potentially available for drugs that fit under the new drug pathway and those that are intended to treat certain illness or patient populations (e.g., children or the elderly) that the State Council or the CFDA consider to be clinically in demand. Priority review may also be possible for drugs that are in simultaneous development in the European Union and the United States. The CFDA is continually working to reduce this timeline for approval.[23] As discussed below, the CFDA has recently adopted a filing system for bioequivalence studies for generic drugs that is less onerous than the CTA process.

The CFDA requires that investigational drugs be manufactured at GMP facilities and comply with GMP standards. It also requires that government-certified laboratories conduct quality testing to confirm conformity with the quality standards.[24] The sponsor must also seek review and approval of the clinical trial by a qualified ethics committee, and if the institution has one, also by a clinical trial management committee for each clinical trial site; a process that can take more than a few weeks.

Clinical trials can be conducted only at institutions that have been inspected and certified by the CFDA for that type of clinical investigation. Clinical trials in China are also governed by pharmaceutical GCP regulations,[25] which largely follow similar GCP regulations in other countries. The GCP regulations and the PDR set out sponsor and investigator obligations, including for serious adverse events. The CFDA, or ethics committee, can hold or terminate a study for safety reasons.

Once a clinical trial protocol is approved by the CFDA, the information associated with it (including the protocol) can be difficult to amend, even for small changes. Although the agency is proposing to change current practice, its regulations still do not include a clear procedure for protocol amendments. This shortcoming has led to applicants having to file an entirely new CTA when making changes to their approved CTA.

22 Good Laboratory Practice Regulations (2003), www.sfda.gov.cn/WS01/CL0053/24472.html.

23 See, e.g., Proposed Opinion Regarding Implementation of Priority Evaluation and Approval for Reduction of the Drug Registration Application Backlog (CFDA 2015).

24 Articles 35 and 36 of the PDR. Also see the CFDA clinical trial flow chart: http://eng.sfda.gov.cn/WS03/CL0769/61658.html.

25 Pharmaceutical Good Clinical Practice Regulations (2003), www.sfda.gov.cn/WS01/CL0053/24473.html.

For investigational arms of clinical trials, in some cases the PDR specify the following minimum numbers of study subjects, and the trial must have sufficient statistical power.[26] The CFDA began to revise the application requirements for chemically synthesised drugs in 2016, with new data and application requirements.[27]

	Phase I	*Phase II*	*Phase III*	*Phase IV*
Therapeutic biologic	20	100	300	Not specified
Preventive vaccine	20	300	500	Not specified

Because under most circumstances, China's drug regulations require approval of the drug abroad prior to submitting the CTA, many foreign manufacturers choose to apply for a multiregional clinical trial, instead of the standard local trial. Under the PDR, a multiregional clinical trial (MRCT) application does not require approval abroad, but instead only requires that the development has entered Phase II elsewhere.[28] Once the MRCT is complete, the applicant can apply for a waiver to the standard local trial requirement and subsequently submit its application.

In 2013, the CFDA changed its policy as to when it would accept the waiver application. This change significantly lengthened the MRCT pathway, although it still remains viable. Specifically, the CFDA revised its policy in late 2013 to require that an application to waive the local trial requirement be submitted and approved separately before the applicant may submit the final licensing application. The CFDA has been considering reform of this policy to reduce unnecessary delays. Also, China has increasingly embraced the idea of MRCTs by adopting special guidance on these types of trials in early 2015, and policies are now being proposed to encourage domestic drug manufacturers to participate in these trials.[29]

Devices

Clinical data are used to establish safety and efficacy of medical devices that are registered for marketing in China.[30] In general, manufacturers must submit clinical trial data to register Class II and Class III medical devices (including *in vitro* diagnostics).[31] No clinical trial is required for Class I devices.[32]

The revised 2014 RSAMD broadened the exemptions from clinical trials for certain devices and for IVDs. The exemptions for devices include: (1) devices for which there is an identical type of device on the market with a well-established safety record following many years of clinical use; (2) devices that can be evaluated effectively through non-clinical data;

26 Appendixes 2 and 3 of the PDR.

27 New Chemical Drug Registration Category Application Material Requirements (Trial Implementation) (CFDA No. 80 May 4, 2016).

28 Article 44 of the PDR.

29 See Guidance on Drug International Multicenter Clinical Trials (For Trial Implementation) (CFDA 2015); Notice to Seek Comments on the Policies to Expedite the Reduction of Drug Registration Application Backlog (CFDA 2015).

30 Article 17 of the RSAMD.

31 Article 17 of the RSAMD.

32 Article 17 of the RSAMD.

and (3) devices that can be evaluated through pre-existing data on the same types of devices.[33] To further define these categories, the CFDA issued multiple catalogues of exempt devices,[34] the latest having been issued in September 2016,[35] and guidance on how to determine whether a device falls under one of these broad exemptions. Exemptions similar to (1) and (2) also exist under the revised IVD regulations.[36]

Clinical trials of Class II and most Class III medical devices do not require CFDA approval. However, the CFDA has issued a catalogue of a subclass of high-risk Class III devices for which pre-approval of the clinical trial is required.

All trials for both medical devices and IVDs must take place at hospitals and other healthcare institutions that the CFDA has accredited to conduct device trials.[37] The system of accreditation is still developing.[38] While no pre-approval from the CFDA is required (unless the device is designated as a high-risk Class III device), all medical device clinical trials must be approved by the institution's ethics committee and notified to the provincial-level government where the clinical trial sponsor is located. The CFDA issued procedures to implement this provincial notification requirement in July 2015.[39] In addition, under the revised RSAMD, device trials must comply with medical device GCPs. The CFDA issued new GCPs for medical device trials to support registration with the CFDA.[40] These GCPs added to the provisions on informed consent (including those on consent from children and others who lack the capacity to consent), requirements for agreements between sponsors and the site, and the coordination of multisite trials.

Human genetic resources

Foreign companies that sponsor clinical trials in China and collect human biospecimens must apply for approval to do so jointly with the Chinese clinical trial site (i.e., the hospital) from the Office of Human Genetic Resource Management within the Ministry of Science and Technology. This approval can also cover the exportation of the biospecimens and the data associated with them. This approval is required regardless of whether the foreign company is conducting genetic tests and covers any sample that contains human DNA.[41]

vi Named-patient and compassionate use procedures

China has not promulgated regulations or formally established any regularly accessible mechanism to allow named-patient or compassionate use of a drug or medical device

33 Id.

34 Notice on Issuing the Catalogue of Class II Medical Devices that are Exempted from Conducting Clinical Trials (2014), available at www.cfda.gov.cn/WS01/CL0087/105224.html; Notice on Issuing the Catalogue of Class III Medical Devices that are Exempted from Conducting Clinical Trials (2014), available at www.cfda.gov.cn/WS01/CL0087/105225.html.

35 Notice Second Batch of Medical Devices Exempt from Clinical Trials (CFDA No. 135 2016).

36 Articles 18 to 20 of the Measures on the Registration of In Vitro Diagnostic Reagents (2014).

37 Article 18 of the RSAMD.

38 Measures for the Accreditation of Medical Device Clinical Trial Institutions (draft for public comment), available at www.cfda.gov.cn/WS01/CL0779/110987.html.

39 Article 18 of the RSAMD.

40 Good Clinical Practices for Medical Device Clinical Trials (CFDA No. 25 2016).

41 Tentative Measures on the Management of Human Genetic Resources (1998).

outside clinical trials and prior to marketing authorisation. The CFDA permits limited drug compounding or medical device manufacture by hospitals for use on their own patients, sometimes without having to receive CFDA clinical trial approval or marketing authorisation.[42] In addition, Chinese drug regulations provide for the importation of unapproved drugs to satisfy urgent clinical needs and are needed in the case of national emergencies. The urgent clinical need standard is a high one that is difficult for individual patients to meet, but may be used somewhat more commonly when the drug is necessary to treat a specific group of patients to prevent the spread of serious contagious disease.[43]

vii Pre-market clearance

Drugs

CFDA review and approval is required for the domestic production or importation of drugs. The PDR provide five types of drug registration applications: (1) new drug; (2) generic drug; (3) imported drug; (4) supplemental applications; and (5) re-registration.[44] With the exception of (4) and (5), the type of application depends on where the finished dosage form of the drug is manufactured. If manufactured and finished outside of China, the drug is considered an imported drug, and an imported drug application must be submitted to obtain an imported drug licence.

If the drug is manufactured inside China, the drug is considered a domestic drug, and either a new drug application or a generic drug application must be submitted to obtain the drug manufacturing licence. The new MAH Pilot allows the applicant to obtain a product licence without a manufacturing licence. A new proposal for an amendment to the PDR would simplify this system and provide for different types of registration applications (e.g., clinical trial, marketing, supplement) without making a distinction between imported and domestic drugs. However, it is not clear whether that proposal, which did not have an accompanying explanation, would eliminate other distinctions between imported and domestically manufactured drugs, such as those related to regulatory exclusivity and priority review status.

Imported drug application

Under most circumstances, before submitting an application for an import licence the drug must have been approved for marketing in the country where the manufacturer has its principal place of business or where the drug is manufactured. The foreign manufacturer holding the relevant approval for the foreign regulatory health authority must be the applicant before the CFDA and, under most circumstances, will be required to present a certificate of pharmaceutical product to show marketing abroad. Under recent reform proposals, the CFDA has proposed to treat imported drugs approved abroad as falling under the category of generic drugs,[45] because of a recent policy decision (discussed below) for new drugs to be defined as new to the world, and not merely new to China.

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42 Article 25 of the DAL; Article 10 of the Regulations for the Supervision and Administration of Medical Devices.

43 Article 37 of the DALIR.

44 Article 11 of the Provisions for Drug Registration (2007).

45 Notice Regarding the Solicitation of Opinions regarding the Marketing Authorization Holder System Pilot Plan and the Chemical Drug Registration Category Reform Plan (CFDA 2015).

If the drug for import is not yet approved abroad, the CFDA is given the discretion to approve it, if the application provides adequate data to establish safety and efficacy, and there is clinical need for the drug in China.

In addition, the foreign manufacturer must submit drug samples from three batches to be tested by the National Institute of Food and Drug Control (NIFDC) for conformity with product specifications and quality standards. The manufacturer must also appoint a local entity in China to act as the agent for the imported drug registration.[46] The CDE reviews the application data for safety and efficacy. Generally, if safety and efficacy are established through a trial, and the NIFDC drug sample testing results are satisfactory, the CFDA will approve the application and issue an imported drug licence.

New drug application

As noted, for chemically synthesised drugs, a new drug is now considered to be one that is new to the world in the ways specified in registration Categories 1 and 2 described in subsection iii, *supra*. For a new drug application, the CDE assesses safety and efficacy. If established, it will order a pre-approval GMP inspection, during which drug samples will also be taken, and sent for testing by the NIFDC to check conformity with product specifications and quality standards. If the pre-approval GMP inspection and NIFDC testing are satisfactory, the CFDA will approve the application and issue a drug approval number, provided the manufacturer has already obtained a drug manufacturing facility permit.

The CFDA has now implemented the MAH Pilot for drugs manufactured in China. The MAH Pilot began in 2015 and will last until 2018, and is being implemented in 10 provinces (including Beijing and Shanghai). Under the Pilot, individuals of Chinese citizenship, research institutions and holders of drug manufacturing licences would be permitted to hold a licence for a product and have important rights and responsibilities over the final product, including the rights to sell, distribute and receive profits from the drug. However, those individuals or entities could contract out the manufacturing without holding the facility licence.[47] Although on a limited scale, the MAH Pilot permits smaller research and development entities to hold product licences without developing costly facilities that they cannot afford.

Generic drug application

With the exception of originator drugs manufactured abroad, drugs that are not new to the world are generic drugs and go through an abbreviated process through which they establish therapeutic and quality equivalence to a reference product marketed in China or abroad. Equivalence is established either through a bioequivalence study or an *in vitro* study, if the drug qualifies for an exemption. In other cases, the applicant may have to conduct an efficacy study. In most cases, the reference product will be an originator product, but the CFDA will also permit an 'internationally recognised' generic product to serve as a reference product.[48]

Generics on the market that are on the Essential Drug List (2012 version) for reimbursement in healthcare institutions and in solid oral forms must demonstrate equivalence

46 Articles 84 to 95 of the PDR.

47 Id. Notice for Issuing the Plan for the MAH Pilot (State Council General Office No. 41 2016).

48 Opinion on Developing Therapeutic and Quality Equivalence Evaluation for Generic Drugs (State Council General Office No. 8 2016).

by the end of 2018. All other fixed oral dosage form generics can freely determine when they will demonstrate equivalence, but the first generic manufacturer to seek such approval will get three years of exclusivity during which equivalence applications for other generics of the same type will not be accepted.[49]

The CFDA has been developing and implementing a new set of guidelines for demonstrating bioequivalence. Under this new system, bioequivalence studies may begin after the applicant has notified the CFDA through an electronic platform.[50] The CDE review of a generic drug application proceeds in parallel with manufacturing site inspection and collection of drug samples by the provincial FDA, as well as drug quality testing by the NIFDC. If results are satisfactory, the CFDA will approve the application and issue a drug approval number to the applicant, which should have already obtained a drug manufacturing facility permit, unless it is part of the MAH Pilot.[51]

The pathway for biosimilars is somewhat different. That is to say, biologics for which there is an existing standard may be brought on the market. However, the PDR require that all biologics go through the application pathway for new drugs, and do not provide for a separate biosimilar category.[52] But the application requirements may still be different depending on the subcategory of biologics. For example, biologics for which there is a pre-existing national standard typically only need to conduct Phase III studies in China and for others Phase I may be waived.[53]

In 2015, the CDE finalised a guidance document on biosimilars, intended to strengthen the methods for research and development of similar biologic products and their stepwise characterisation and comparison to reference originator products, including a quality comparison, and non-clinical and clinical evaluations. The new guidance also includes some provisions on labelling and pharmacovigilance.[54] The way that this guidance is intended to interact with existing law and regulation governing the approval process for all biologics is still not entirely clear.

Approval timelines

In 2015, the CFDA began examining what had become a huge application backlog for both drugs and devices. The Agency has tens of thousands of applications pending, with thousands more being filed each year. The State Council and the CFDA have committed to significantly reducing this backlog by 2018. The CDE's last annual report, released on 3 March 2016, indicated that the drug backlog had been reduced from approximately

49 Notice on Several Matters Related to the State Council General Office's Option on Demonstrating Therapeutic and Quality Equivalence of Generic Drugs (CFDA No. 106 26 May 2016).

50 Provisions on Chemical Drug Bioequivalence Study Notifications (CFDA 2016).

51 Chapter 5 of the PDR.

52 Article 12 of the PDR.

53 Appendix 3 of the PDR.

54 Draft Guidance on the Research and Development and Technical Evaluation of Similar Biotherapeutic Products, available at www.cde.org.cn/zdyz.do?method=largePage&id=212.

22,000 to 17,000 applications, which is a reduction of around 22 per cent.[55] The CFDA has also committed to increasing the speed of the reviews and criteria for review and approval by adding review personnel and creating review guidelines.

With these new reforms still in progress, the total time for review, site inspection, drug sample testing, and final approval of an imported drug licence, a new drug application or a generic drug application is in flux, but it can still take one to two years. Most of this time continues to be occupied by the CDE review process. The PDR provide for 150 business days for CDE review of new or imported drug applications, and 160 business days for CDE review of generic drug applications. In practice, CDE review often takes longer. If the CDE needs additional information, it can issue a request to the applicant, and the review clock stops. The applicant will have four months to provide the additional information, and the CDE will have an additional 40 days to review the additional information. Requests for additional information are common in all applications, and also sometimes repeated, although the CDE is required to avoid repeated requests. Reviewers may meet with the applicant upon request but may not do so unless the drug is new to the world or has an improvement that is new to the world.

Priority review is available for certain drugs that treat serious or life-threatening conditions, including new drugs for treatment of HIV, cancer or orphan diseases, and new drugs that treat unmet medical needs. The CFDA has recently introduced new priority categories, including drugs that treat diseases prevalent among children and the elderly, that are on national scientific research plans, foreign innovative drugs that transfer manufacturing to China, and drugs that are being developed simultaneously in the US and Europe.[56] Priority status facilitates applications by permitting the applicant better access to CDE reviewers for their marketing applications and in some cases for questions about their clinical trials. Publicly available information suggests that the fast-track mechanism has, in fact, shortened review times. Past practice indicates that priority status can improve timelines reducing them down to nine months, and even six in some rare instances.

Re-registration application

The registration for an imported or domestic drug is valid for five years. Six months prior to expiry of the registration, the applicant must submit a re-registration application to the CFDA if it is an imported drug or to the PFDA if it is a domestic drug. Re-registration applications generally do not require new clinical data, though data from the required Phase IV study may be a condition of renewal. The CFDA or PFDA must complete the review and either approve or deny the application within six months of accepting the filing. If the re-registration application is not approved, drugs manufactured after expiry of the existing marketing or manufacturing authorisation may not be marketed in China.[57] On 29 December 2016, the CFDA released a proposal to transfer the decision-making power

55 Annual Report of the CDE (3 March 2016).

56 Notice on Several Questions of Policy Related to Drug Registration Evaluation and Approval (CFDA 2015).

57 Chapter 9 of the PDR.

over re-registration applications for imported drugs to the CDE. If adopted, it is assumed that this approach would reduce the delays encountered when the CDE transfers the application to the CFDA to make a final decision following the CDE's technical review.[58]

Supplemental drug application

Certain post-approval changes to a drug, whether imported or domestic, require CFDA approval of a supplemental drug application. The applicant must be the company that holds the existing marketing or manufacturing authorisation. While major post-approval changes require the CFDA or PFDA review and approval, some minor changes can be notified to the agency and implemented without review and approval.[59] The proposal described above related to re-registration of imported drugs would also transfer final approval over supplemental applications for both imported and domestic drugs to the CDE to reduce delays.

Devices

Some form of pre-market review and approval is required for domestic production or importation of all three classes of medical devices. Domestic and imported Class I devices must be notified to either the municipal food and drug regulatory authority where the manufacturer is located or the CFDA if manufactured abroad, before being placed on the market. Once the applicant submits the notification, the authorities will make an 'on-the-spot' determination to issue a notification certificate, provided that the materials are complete.

As noted above, domestically manufactured Class II devices must be reviewed and approved by a PFDA. Class III medical devices, as well as Class II and III imported medical devices, must be approved at CFDA level. For imported devices, the applicant must appoint a regulatory agent in China. For all Class II and III devices, government-certified laboratories first verify conformity with the device's 'technical requirements', which the applicant must formulate in advance, and applicable standards through testing. This testing is often referred to as registration testing or type testing. For Class I devices, the applicant may submit its own internal test results.

The statutory time frame for agency decisions on the different types of devices depends on the class of the device and type of technical review required. For Class I devices, either the municipal FDA or the CFDA (if an imported device) will make an immediate determination of the completeness of materials and, if complete, accept the notification.[60] In the case of a Class II or III device, the relevant agency will make a determination as to whether the application is complete and appropriately filed (e.g., the agency has jurisdiction). Within three days of acceptance of the application, the materials are sent on to a technical review institution, which under normal circumstances has 60 days to complete its review. If outside expert help is required or the institution decides that it needs to conduct an inspection of the applicant's quality management systems, then the time may be extended beyond the 60 days. Similarly, the technical review institution may make a one-time request for any

58 Decision on Adjusting the Procedures Related to Part of the Examination and Approval of Certain Administrative Matters.

59 Chapter 8 of the PDR.

60 Notice on Several Matters Related to Class I Medical Device Notification (2014), available at www.cfda.gov.cn/WS01/CL0087/100816.html.

supplementary materials required. It then has another 60 days from the time of receipt of those materials to make its decision. Once the technical review is complete, the CFDA has 20 days to make a decision.

In reality, applicants may experience significant delays waiting for certain stages of this process to begin, although the CFDA is applying similar measures to those described above for drugs to combat these delays for devices and the existing device application backlog.[61] The CFDA already gives priority to innovative devices (described below) and, in 2016, as part of its effort to reduce delays and focus its resources on key areas, it issued new procedures on priority review for devices associated with national scientific initiatives, those with orphan indications, those that treat children or the elderly and other devices that serve urgent clinical needs.[62] Those accepted to these pathways get priority access to CMDE reviewers to regarding the design of their application.

After approval, a medical device registration certificate is issued by the appropriate level of FDA, and the certificate is valid for five years. Six months prior to the expiration of the five-year period, the manufacturer must submit a medical device re-registration application. If the renewal application is not approved by the time that the licence expires, then the application will be deemed approved.

Changes to certain elements of the registration require amendments or updates. The type of amendment and the length of review depends on whether it is a 'licensing matter' or a 'registration matter'. Licensing matters include the non-proprietary product name, its model, its specifications, its structure, its composition, its scope of use (indications), its technical requirements and the foreign site of a manufacturer. Registration matters include the name of the applicant, the name of the agent and their addresses. In the case of a domestic manufacturer, the address of the manufacturing site is also a registration item. For registration items, the original licensing agency will issue a revised licence in 10 working days. Licensing items require another technical review before a modified registration certificate will be issued.[63]

viii Regulatory incentives

Chinese regulation is designed in some respects to encourage innovation and development and manufacturing of products in China for which there is particular clinical need and value through expedited pre-market approval pathways. In contrast, post-approval regulatory incentives are very weak and their implementation is incomplete. China has established a system of patent protection for drugs and devices. There is some limited regulatory data protection for a new chemical entity, although these data protection are difficult to enforce in practice, and China has a kind of *de facto* market exclusivity implemented through a new-drug monitoring period (described below) for a drug that has not been manufactured in China or is locally manufactured in China.

61 Articles 33 to 36 of the Measures on the Registration of Medical Devices.

62 Procedures on Priority Review and Approval for Medical Devices (CFDA No. 168 2016).

63 Articles 49 to 53 of the Measures on the Registration of Medical Devices.

Drugs

Patent protection

China gives 20 years of patent protection. It does not give patent term extension to compensate for CFDA's drug registration review and approval time. An applicant is required to provide information on patent status in China as part of its drug registration application. If there are relevant third-party patents in force, the applicant must make a declaration of non-infringement, which the CFDA will publish.[64] In practice, however, the CFDA has not implemented these provisions rigorously, and there is no true patent linkage system in China. Non-infringement declarations do not automatically trigger the requirement that the applicant notify the patent owner, nor can an originator manufacturer apply to stay the CFDA's approval decision if they discover an infringing application. If the drug is covered by third-party patent rights and the applicant is not able to file a non-infringement declaration, the applicant can file the application two years prior to the patent expiration, and the CFDA can review the application and, if approvable, grant the approval upon expiry of the patent.[65] In a recent proposal to amend the PDR, the CFDA proposed to further reduce this protection, asking applicants to make the determination on their own and offering no regulatory pathway to stop approval of the generic. Under this amendment, applicants would resort to the Patent Law to resolve any disputes.

Data protection

Pursuant to its obligation under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and other related bilateral commitments, China offers six-year regulatory data protection to new chemical entities. This protection is formally provided in Article 20 of the PDR and Article 35 of the DALIR. Within six years of approval, the CFDA is not allowed to approve another application (usually a generic drug application) that includes or refers to the innovator's data unless the innovator has authorised such use, or the innovator data have been publicly disclosed.

In practice, this provision is difficult to implement because the term 'new chemical entity' is not defined, and the CFDA has not issued procedures surrounding various aspects of this protection. As such, companies have not experienced a true benefit from this protection. Innovator companies have continued to express concerns about the operation of the data protection provisions, including whether the CFDA approves generic drug applications prior to the expiration of the data protection period. The CFDA has promised to include a definition of a new chemical entity in amendments to drug legislation or regulations. However, in its final plan for restructuring the chemical drug registration categories, the CFDA did not include a definition for a new chemical entity for purposes of regulatory data protection. In its 2016 proposal to revise the PDR, the CFDA removed provisions on regulatory data protection altogether, making the future of such protection uncertain.

Marketing exclusivity

China does not have true regulatory marketing exclusivity. Article 66 of the PDR provides that the CFDA has the discretion to set a 'new-drug monitoring period' of up to five years, when it approves the manufacturing of a domestic drug that is first in its class. The monitoring

64 Article 17 of the Provisions on Drug Registration.

65 Articles 18 to 19 of the PDR.

period is not available for imported drugs and, under the revised chemical drug registration categories, the monitoring period only applies to innovative new drugs and improved new drugs, which means it only applies if the drug (or its innovation) is new to the world. The monitoring period does not apply to generic drugs. During the monitoring period, the drug is under enhanced adverse event monitoring requirements, and the CFDA is not allowed to approve the clinical trial, manufacturing, or importation of another domestic or imported drug in the same class for the same indication. If, however, the approved domestic drug is not manufactured within two years of approval, the CFDA can approve another domestic or imported drug application. The monitoring period does not provide complete exclusivity, however, because if the CFDA has approved the CTAs of other applicants for the same drug, those applications may proceed to registration.

Devices

The regulations for the registration of medical devices do not require patent certification or contain provisions on data or market exclusivity. The revised RSAMD expressly state that any patent disputes will be handled under the relevant laws (i.e., the Patent Law).[66] There are procedures for expedited review and approval of medical devices where there is a public health emergency and the same kind of device is not marketed in China, or is marketed but is in short supply. Medical devices undergoing expedited procedures also benefit from assistance from the CFDA during development and registration.[67]

The CFDA has also created an expedited pathway for review of applications for 'innovative devices'. To qualify as an innovative device:

a the patent for the technology must be held in China;
b the primary work on the product's design and use mechanisms must have been the first of its kind in China;
c its safety or functionality must be a fundamental improvement over comparable technology;
d it must be leading technology internationally; and
e the device must have clear clinical value.

In addition, well-controlled preliminary research must be completed and there must be a basic product model. The data must be complete and traceable.[68] The innovative device pathway does not entitle applicants to marketing exclusivity, however. It provides the applicant with priority in terms of access to communication with the CFDA regarding its application and the ability to hold a licence without a manufacturing facility. As noted above, the CFDA has recently released procedures on additional priority pathways, which are based on more on clinical needs and not other IP-related criteria.

66 Article 48 of the RSAMD.

67 Articles 4 to 5 of the Procedures for Emergency Review and Approval of Medical Devices (2009).

68 Article 2 of Procedures on the Examination of Innovative Medical Devices (Trial Implementation) (2014), available at www.sda.gov.cn/WS01/CL1237/96654.html.

ix Post-approval controls

Adverse events

Drug and medical device manufacturers are obligated to establish systems to report and analyse adverse events and product complaints, and meet any conditions imposed as part of the product approval.[69] In 2011, the CFDA issued detailed regulations on adverse reaction and event reporting for drugs and devices. The Measures on the Administration of Adverse Drug Reaction Reporting and Monitoring (2011) require FDAs at national, provincial and municipal levels to set up adverse event collection systems, and imposes reporting and monitoring obligations on not only the drug manufacturer, but also drug distributors and healthcare organisations. Specific reporting time frames and follow-up actions are set out for handling individual cases, clusters of cases, periodic accumulative reporting, enhanced monitoring and imported drug reporting.[70]

For medical devices, the CFDA promulgated the Measures on the Administration of Medical Device Adverse Event Monitoring and Re-evaluation (Interim), and issued Guidance on the Monitoring of Medical Device Adverse Event (Interim) to impose detailed adverse event reporting obligations on device manufacturers, distributors and user facilities. The system and requirements are similar but not identical to those for drugs.

In late 2015 and then again in late 2016, China released a revised version of the Measures on the Administration of Medical Device Adverse Event Monitoring and Re-evaluation for public comment. That draft introduced a more concrete role for technical monitoring institutions; modifications to the timelines for manufacturers, distributors and healthcare institutions to report on and evaluate adverse events both on an individual and periodic basis; a clearer definition of a serious adverse event; and more concrete requirements and guidelines for targeted monitoring of certain devices and device re-evaluation.[71]

The CFDA has the authority to order mandatory recalls of drugs and medical devices because of serious adverse reactions or other safety issues.[72] Manufacturers and distributors also have different obligations, in varying circumstances, to cooperate with, report on or implement recalls. For example, for medical devices, the manufacturer is required to conduct an investigation and evaluation of adverse event and other safety-related information to determine whether they reveal a 'defect' (i.e., an unreasonable risk of bodily harm under normal conditions of use) with the device. A defect obligates the manufacturer to recall the device. The manufacturer must also classify the recall into one of three classes, the first class

69 See, e.g., Articles 41 to 44; 67 to 68; and 121 of the PDR, and Article 169 for drugs, and Article 48 of the RSAMD (requires manufacturer to establish device AE reporting system, and tracking system on Class III devices).

70 The Measures on the Administration of Adverse Drug Reaction Reporting and Monitoring (2011), Chapters 2 to 6.

71 Notice Soliciting Comments on the Revised Draft of Administrative Measures on Monitoring Medical Device Adverse Events and Re-Evaluation (CFDA/NHFPC 2015); Notice Soliciting Comments on the Revised Draft of Administrative Measures on Monitoring Medical Device Adverse Events and Re-Evaluation (State Council OLA 2016).

72 The Measures on the Administration of Drug Recalls were promulgated in 2007, and the Measures on the Administration of Medical Device Recalls (Interim) were promulgated in 2011.

being the highest risk and the third being the lowest. If a manufacturer does not conduct a recall voluntarily, then the CFDA may order one. The manufacturer must report on the progress of the recall and its final results.

Transfer of licences

Transfer of licences is more difficult to achieve in China than in, for example, the United States. Part of the reason is that CFDA regulations give extremely limited guidance on this issue and regulatory changes have created further uncertainty. Another reason is because of the connection between the product permission and the manufacturing facility permissions.

Although the marketing authorisation holder system described above may ultimately change this, for domestically manufactured drugs, the licences are issued to the specific manufacturer, for the specific manufacturing site and for the manufacturing of the particular drug. In other words, the Chinese system is a combination of manufacturing authorisation and marketing authorisation. As a result, any transfer will typically trigger a review and approval process, where the qualifications of the transferee will be carefully examined. The supplemental application will be denied if the transferee does not meet the relevant requirements, such as having qualified personnel necessary to comply with applicable GMP requirements. There are two licences involved: the drug manufacturing facility licence, which is issued to the manufacturing site and requires renewal every five years, and the drug manufacturing licence and the corresponding drug registration certificate and approval number, which require renewal every five years. The second licence can only be issued to an entity that has the first licence.

For drugs, transfer of licences in China would probably need to involve the transfer of the ownership of the manufacturing facility, and this is usually done via an equity acquisition of the holder of the two licences. In fact, the CFDA regulations have specifically prohibited any 'purchase and sale, rental, or other loan of the licences', and engaging in those activities could trigger revocation of the relevant licence.

Regarding devices, these issues are somewhat different. The CFDA has permitted the Class II and Class III device product licences to transfer between entities using an application to amend the name of the applicant on the licence. For Class I devices, the new applicant would likely submit a new filing, which could be accomplished relatively quickly. The applicant may have to make other changes to items on the licence, such as the registration agent and the manufacturing site, depending on the details of the deal. These procedures are not laid out in the regulations but are an internal procedure that the CFDA and its provincial counterparts follow.[73]

There are more specific provisions on the transfer of device manufacturing licences. Under the revisions to the Device Manufacturing Regulations, the manufacturing licence travels with the entity. If the entity survives a merger or split, then the licence need only be modified. If the original entity is dissolved, then the licence will not be transferred and any new entity must apply for a new licence.[74]

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73 Articles 49 to 50 of the Measures on Medical Device Registration; Article 15 of the Measures for the Supervision and Administration of Medical Device Manufacturing. For imported devices, a change of a manufacturing address abroad is a more complex process that requires the submission of more information and a longer timeline.

74 Article 18 of the Medical Device Manufacturing Regulations (CFDA 2014).

Note that for imported drugs and medical devices, there is no manufacturing licence. Accordingly, it is easier to transfer the imported drug or device licence as long as the transferee meets the requirements of a new applicant or licence holder for the China imported drug or device licence (e.g., it must be a manufacturer that holds the foreign marketing authorisation that provided the basis for the CFDA to grant the China licence).

Suspension or revocation of approvals

The CFDA can suspend or terminate a clinical trial, or suspend or revoke a marketing authorisation if there are serious product safety issues, or if the manufacturer fails to comply with associated regulatory requirements. In comparison with many other regulatory schemes, the CFDA has many more grounds to suspend or revoke an approval. First, the marketing authorisation needs to be renewed periodically every five years for drugs and devices. Every year, the CFDA decides not to renew many products, based on various grounds set out under the law. The PDR, for example, provides in Article 126 that:

> *In any of the following circumstances, a drug shall not be re-registered [if]:*
> *(1) the application for re-registration is not made prior to the expiry date;*
> *(2) the relevant requirements set by the State Food and Drug Administration when approved for marketing are not met;*
> *(3) the Phase IV clinical trial is not completed as required;*
> *(4) the adverse drug reaction monitoring is not conducted in accordance with regulations;*
> *(5) there are uncertain therapeutic efficacy, serious adverse reaction or other factors harmful to human health upon re-evaluation by the State Food and Drug Administration;*
> *(6) the drug approval documents shall be withdrawn in accordance with the provisions of the Drug Administration Law;*
> *(7) the production conditions prescribed in the Drug Administration Law are not met;*
> *(8) the obligation of observation period is not fulfilled in accordance with regulations; or*
> *(9) there are other circumstances not in conformity with relevant regulations.*

For devices, a renewal will not be granted if: (1) the filing of the application is not timely; (2) compulsory standards for the medical device have been revised and the device fails to meet the new standards; and (3) specific conditions related to medical devices needed for treating rare disease or for public health emergencies are not met.[75]

Second, there are multiple types of non-compliance that can trigger licence suspension or revocation in China. For example, the DAL provides for the revocation of drug approval licences on various grounds, including:

a if there is production or sale of counterfeit or substandard drugs;[76]
b if there is non-compliance with customs rules for imported drugs;[77] or
c where the labels do not meet applicable requirements.[78]

75 Article 55 of the RSAMD.
76 Articles 74 and 75 of the DAL.
77 Article 81 of the DAL.
78 Article 86 of the DAL.

The RSAMD provide for the re-evaluation and potential revocation of medical device licences when:

a new developments in science and technology raise questions about the safety and effectiveness of the device;

b adverse event reporting raises questions about the safety and effectiveness; and

c any other circumstances that the CFDA determines warrant a re-evaluation.[79]

The revised RSAMD provide that obtaining a licence via fraudulent or corrupt means is grounds for revocation of the licence.[80] Other activities that constitute impermissible marketing of devices or marketing of devices known to be unsafe or not in compliance with standards may result in fines, seizures, disgorgement, and, in certain circumstances, blacklisting from the industry.

x Manufacturing controls

Drug and Class II and III device manufacturing facilities located in China must hold a manufacturing licence, and be certified as compliant with drug or device Good Manufacturing Practices. Class I device facilities submit a notification to local food and drug regulatory authorities.

For drugs, any proposed establishment of a facility must be approved by government agencies responsible for economic planning, and by the PFDA for potential ability to meet GMP requirements. Upon completion of the facility construction, the facilities must pass GMP inspection and receive a GMP certificate before they can be issued a drug or medical device manufacturing licence. Product sample testing by government labs is required as a part of the review and approval of clinical trial and marketing authorisation processing, and pre-approval inspections are required, all designed to ensure GMP compliance.

All device enterprises must comply with quality management rules (i.e., GMP and other medical device standards). Class II and Class III device facilities must be verified as device GMP-compliant before a local authority will issue a manufacturing licence. This requires a compliance inspection.[81] If any manufacturer is found to be non-compliant with rules, and does not correct the violation, it can be fined or shut down.[82]

Contract manufacturers must be similarly GMP-compliant, and hold the requisite manufacturing licence. Under some circumstances, in which the CFDA has determined that the products present heightened risk, such as in the case of implantable devices, biologics, psychotropic drugs or narcotic drugs, the agency will not permit contract manufacturing.[83]

79 Article 51 of the RSAMD.

80 Article 64 of the RSAMD.

81 Article 10 of the Measures for the Supervision and Administration of Medical Device Manufacturing.

82 Article 67 of the RSAMD; Article 67 of the Measures on the Supervision and Administration of Medical Devices.

83 Article 12 of the Regulations on Drug Contract Manufacturing (2014).

xi Advertising and promotion

Drugs

Advertising

The CFDA must pre-approve all drug advertising and prohibits any direct-to-consumer advertising of prescription drugs. The term 'advertising' is broadly defined under the general Advertisement Law and can include any published media that directly or indirectly introduces the product (or service). As a result of amendments to the Advertisement Law in 2015, the legislature has made it more prominent that the definition of advertisement will include websites, mass emails, and postings on microblogs and other social media sites.[84] Article 3 of the Detailed Rules on Implementation of Administration of Advertisements – which was issued in 2004 but remains effective – also contains a generally phrased list of the various media and promotional activities as examples, including product samples. Therefore, there is ample authority on which agencies can enforce against sponsors. Promotion or advertising of a drug prior to CFDA approval is prohibited, although some strictly limited scientific exchange may be permissible.

The drug-specific advertisement requirements and prohibitions are provided in a number of Chinese laws and regulations, including the Measures for Review of Drug Advertisement (Advertisement Measures) and the Standards for Drug Advertisement Review and Release (Advertisement Standards), both of which were promulgated jointly by the CFDA and the SAIC in 2007. The SAIC began revising the Drug Advertisement Standards in 2015, but the draft that it issued did not propose to make substantial changes to the basic features of the system.[85] The CFDA issued a proposal to revise its procedures for approving drug, device and health food advertisements in late 2016, but it has not yet finalised that rule. As the Advertising Law sets many of the limits on substantive content, the CFDA's rule was primarily procedural.

The provincial FDA where the advertiser is located must review and approve all drug advertisement materials. Article 4 of the Advertisement Measures provides that advertisements of prescription drugs can only run in CFDA-approved medical journals (currently, the CFDA has approved about 557 such journals). The prohibition on consumer advertising of prescription-only drugs also prevents many indirect advertising activities, such as sending journals or reprints to the public, or any other means of advertising to the public.

Upon approval, drug advertisements are given an approval number, which appears on the advertisements. Advertisement approval is valid for one year only and no change is allowed to an approved advertisement. Upon the approval's expiry, or if any change is needed to an approved and unexpired advertisement piece, a new advertisement application must be filed and new advertisement approval obtained. The CFDA has posted on its website all advertisements that have been approved and those against which there has been enforcement.

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84 Draft for Comment of the Interim Measures on Supervision of Internet Advertising (2015). To date, these measures do not appear to have been finalised. Under the Advertisement Law of China (2015), which applies to all advertising, including drug or device advertising, the term advertisement is defined in Article 2 as 'any commercial advertisement, which a commodity or service provider bears the costs for, through certain media or forms, directly or indirectly introducing their commodities being sold or services being provided'.

85 Drug Advertisement Examination Standards Draft for Comment (SAIC 2105).

The penalties for unapproved changes to an approved advertisement include immediate revocation of the advertisement approval, and rejection of any advertisement application for the subject drug for one year. Heavier penalties would apply in the event that an illegal advertisement expands the scope of the indications or primary therapeutic function, exaggerates efficacy or seriously deceives and misleads consumers. Such heavier penalties include the provincial FDA suspending the sale of the subject drug within the province that has jurisdiction, and ordering the drug company to run corrections regarding the advertising concerned.

Promotion

The term 'promotion' is not defined under Chinese law. Any activity related to a drug is promotional, if the intent is promotional, as that term is commonly understood (i.e., where it is intended to further the acceptance and sale of the drug). This includes a broad array of product launch activities and associated materials. As noted above, scientific information exchange, including exchange of off-label information, can be viewed as non-promotional when conducted appropriately, because the intent is to advance science and medicine through the exchange of scientific information between medical professionals, rather than to further the acceptance or sale of a drug.

China prohibits advertising or promotion outside the content of the approved label or package insert ('off-label promotion'). The prohibition against off-label advertising is set out in Article 6 of the Advertisement Standards:

> *The advertisement content relating to the indications or the primary therapeutic functions must be consistent with the drug instructions approved by the CFDA, must not expand or maliciously conceal, and must not contain any theories, viewpoints, or similar contents that are outside the drug instructions.*

The Regulations on Administration of Drug Product Instructions and Labels require that: 'drug instructions and labels shall be approved by the CFDA, the labels must be based on the drug instructions, and the contents of the labels shall not exceed the scope of product instructions, and shall not contain wording or symbols that imply therapeutic effectiveness, misleading use, or inappropriate promotion'. The Drug Administration Law of China also prohibits off-label promotion through other means, such as labelling materials, including the spoken words and written or video materials used by sale representatives in promotional discussions with physicians.

Devices

Device advertisements also currently require pre-approval. Regulation of advertising and promotion of medical devices are somewhat similar to those for drugs as described above. The rules for advertising and promotion of medical devices are set out in several regulations, such as the RSAMD, the Measures on the Examination of Medical Device Advertisements (2009) and the Standards on the Examination and Release of Medical Device Advertisements (2009), which, like the drug standards, are now also under revision as a result of the 2015 amendments to the Advertisement Law.[86]

86 Draft Standards on the Examination of Medical Device Advertisements (SAIC 2015).

xii Distributors and wholesalers

China requires a licence for a company to engage in the retail or wholesale distribution of drugs that are manufactured by other companies. No such distribution licence is required for a drug manufacturer to distribute the drugs that it manufactures for itself, provided it has obtained a CFDA drug registration and approval number. Similar to licensing of drug manufacturing facilities, the distributor must meet: the economic planning requirements (for a retail distributor or pharmacy, e.g., factors include the number of residents for the area to be served, the public transportation available to the residents and actual local demand); and the ability to meet quality requirements, as evidenced by the passing of a good supply practice (GSP) inspection and receipt of a GSP certificate. Distribution of drugs via the internet is also restricted and requires the CFDA's permission.

A similar system of device distribution licences also exists for Class III medical devices, unless the manufacturer is distributing its own devices from its facility. Distributors of Class II devices no longer need a licence, but those distributors must submit a notification to their local municipal governments. In either case, the entity must certify that it has appropriate premises, storage conditions and quality management systems and personnel for its scope of operation.[87] The CFDA also finalised GSPs for devices in December of 2014, which became effective as of their release date.[88]

xiii Prescription status

The CFDA classifies drugs as prescription drugs or over-the-counter (OTC) drugs, and requires the CFDA's review and pre-approval for both. For the purposes of distribution and sale, the CFDA further classifies OTC drugs into Type A or B, where Type A drugs can be sold only by pharmacies or distributors that have received drug wholesale or retail distribution licences, and Type B drugs can be sold at most retail places, such as convenience or grocery stores if approved by provincial governments. The National Health and Family Planning Commission regulates prescribing behaviour for physicians, including a requirement that physicians use the non-proprietary names of drugs. The CFDA has not set up prescription or non-prescription classifications for medical devices.

xiv Imports and exports

Imported drugs or medical devices for marketing in China must be pre-approved by the CFDA and fully comply with the applicable regulations by the CFDA and the Chinese customs before they can be imported into China for distribution and sale. Additional requirements, such as special import or export permits, are required for narcotic or psychotropic substances.[89]

87 Articles 29 to 31 of the RSAMD.

88 Article 66 of Medical Device Good Supply Practices, available at www.cfda.gov.cn/WS01/CL0087/110920.html.

89 Article 45 of the DAL.

Drugs that are imported for processing and re-export do not require CFDA pre-approval. Only provincial FDA notification is required for such products provided they will not be sold or used in China.[90] Additional testing at the border may be required.[91]

The CFDA generally does not impose the same requirements for export of drugs or devices and relies instead on the regulatory oversight of the country where the drug will be exported. Manufacturers of exported drugs and certain devices must still obtain a manufacturing licence and comply with good manufacturing practices and standards. There are exceptions for nine types of drug[92] and two types of device,[93] which the CFDA has placed into the catalogue of drugs and devices subject to full CFDA supervision.[94] In addition, special export permits are required for the export of some narcotics or psychotropic substances. In most cases, drug and device manufacturers must also submit a filing to their local government prior to export.[95] Certificates of free sale for foreign import authorities may be available from provincial governments, provided that the China manufacturer meets the relevant requirements.

xv Controlled substances

China exercises heightened control over narcotics and psychotropics. The State Council promulgated the Rules on the Administration of Narcotics and Psychotropics in 2005, and the CFDA, the Ministry of Public Security, and the Ministry of Health recently jointly issued the revised Catalogue of Narcotics (2013) and the revised Catalogue of Psychotropics (2013). Special heightened control is exercised by multiple government agencies over the growing of plants where narcotics or psychotropics are extracted, and the clinical trial, manufacturing, transportation and distribution of narcotics and psychotropics. For example, government agencies set the total amount of narcotics and psychotropics needed annually, while the CFDA then sets the annual production plan based on the current supply and stockpile, and the CFDA and the department of agriculture together set the annual growing plan. Special permits are given only to limited entities to study, produce and distribute narcotics and psychotropics.

xvi Enforcement

Enforcement against violations of drug or medical device requirements is undertaken by the FDAs at national, provincial and lower local levels, with cooperation from other government agencies such as the SAIC, NHFPC, and the public security bureau (China's police force)

90 Regulations on the Administration of Drug Processing for Export (2003).

91 Administrative Measures for the Inspection and Supervision of Imported Medical Devices (2007).

92 Gentamicin, atorvastatin, sildenafil, oseltamivir, cefoperazone, glycerine, heparin, artemisinin and traditional Chinese medicine in finished dosage form and indicated for erectile enhancement.

93 Glucose-testing strips and condoms.

94 Notice on Implementing Catalogue Administration on certain drugs and devices for export (2008), available at www.sfda.gov.cn/WS01/CL0245/33456.html.

95 Article 3 of the Administrative Regulations on Filings for Contract Manufactured Drugs for Foreign Enterprises (2005); Article 70 Administrative Measures on the Manufacturing of Medical Devices (2014).

at all levels of government. Routine and for-cause inspections are the primary means of detecting actual or suspected violations, and complaints from competitors are often the triggers for the for-cause inspections. The CFDA has also adopted comprehensive regulations on unannounced inspections for drug and device manufacturers.

The focus of inspections can include many compliance requirements and activities, such as those targeting GxPs (GLP, GCP, GMP, GSP), data integrity, conflicts of interest, bribery, violative advertisement and off-label promotion. The penalties include revocation of licences and certificates, which can be imposed (see Section II.vii, *supra*) on post-approval controls in many more situations than in the US. Other penalties include administrative fines, seizures of product, disgorgement of profits and blacklisting of companies and individuals. Monetary penalties tend to be lower than in the US. Criminal liability can be imposed for many violations, and disbarment from engaging in drug or device work is possible. Production or distribution of counterfeit medicines as defined by the DAL may be subject to life in prison or the death penalty if the violation causes death or especially serious harm.[96]

Recently, the CFDA has been requiring manufacturers, distributors and clinical trial sponsors to conduct self-evaluations into GxP compliance and report on the results to the CFDA. For example, in mid-2016, all holders of device distribution licences were required to take stock of compliance with device distribution regulations and GSP over a two-year period and report back to the CFDA on any non-compliances and plans for remediation. Failure to comply risked the holder's distribution licence.[97] The CFDA has required similar self-evaluation for drug clinical trials and certain device manufacturers.

III PRICING AND REIMBURSEMENT

China has recently begun to reform its system for drug pricing. Specifically, it has abolished the 'maximum retail price' for drugs, and is now implementing a plan to permit those prices to be set more by the market and by reimbursement standards negotiated more openly by stakeholders. Specifically, for drugs that are reimbursed on China's state insurance plans (discussed below) the price will be determined by reimbursement rates. For patented drugs produced exclusively by one manufacturer, the price will be set through transparent negotiations between the manufacturer, government and healthcare industry representatives. Prices will still be set or guided by the government for certain types of drugs, such as narcotic drugs and psychotropic drugs. For all other drugs, however, the prices may be freely set by the manufacturers, provided that they accurately reflect costs.[98]

Most insurance is through state plans. The government operates three basic insurance programmes: one for urban employees, one for urban non-state-employed residents and one for rural residents, covering nearly 90 per cent of the nation's population. Covered drugs for the urban plans are included in the National Reimbursement Drug List (NRDL), with a total of 2,151 drugs in its most recent version, which the government is considering revising in 2017. The covered drugs for the rural plan may vary by province.

96 Article 141 of the Criminal Code of the People's Republic of China.

97 Notice on Regulating Distribution Activities in Medical Device Circulation (CFDA 112 7 June 2016).

98 Circular Concerning Opinions on Advancing the Drug Pricing Reform (National Development and Reform Commission 2015).

The NRDL is categorised into A and B lists. Drugs on List A are the National Essential Drug List, and are fully reimbursable in any province. Drugs on List B are only partially reimbursable under various insurance schemes at the provincial level. Pricing for the drugs on the NRDL are determined by government agencies based on various factors, including cost of production, clinical need, and supply and demand. The pricing and coverage decisions are taken primarily by the NDRC and its local counterparts (the pricing bureau), as well as the Ministry of Human Resources and Social Security. Drug manufacturers and distributors are required to report various production costs and sales information to the government agencies, and based on such information, the government agencies decide on the prices by applying complex formulae.

By contrast, the commercial insurance sector is very small, but the government is trying to expand it.[99] For example, in the past three years the government has been trying to promote critical disease insurance for individuals that have exceeded their coverage level under the state plans. Individuals with qualifying diseases that obtained critical disease coverage would be eligible for 50 per cent reimbursement under those plans. The government has encouraged the commercial insurance sector to play a strong role in providing this type of coverage.[100]

A pricing system also exists for medical devices, but its features may differ depending on the locality. In some localities, the government will set a maximum retail price for devices. The manufacturer reports information about its costs to the government and is then permitted a certain mark-up that is set by the government.

As with drugs, coverage by the national plans and reimbursement rates for medical devices are set by a combination of central and local government agencies. Medical institutions (i.e., hospitals and clinics) acquire devices through restricted procurement processes.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Administrative and judicial remedies are available in China to appeal agency decisions and redress illegal government practices. Administrative regulations are rarely challenged in the courts for alleged defects in the underlying authority or rule-making procedures because China's Administrative Litigation Law prohibits 'abstract' challenges of this sort to the validity of administrative rules. Most efforts to formally challenge the CFDA focus on challenging concrete CFDA administrative decisions instead. Processes are available for both administrative reconsideration and judicial review of administrative decisions, but it may be difficult to win controversial cases in court in the absence of a clear violation by the agency of laws, regulations or its own rules. Statistics from China's Office of Legislative Affairs show that in 2013, the CFDA was involved in a total of 150 administrative reconsideration cases, and only one administrative lawsuit was brought against the agency.[101]

99 Several Opinions on Accelerating the Development of the Modern Insurance Service Industry (State Council 2014).

100 Opinions on the Full Implementation of the Critical Disease Insurance Program for Urban and Rural Residents (State Council 2015).

101 2013 National Administrative Reconsideration and Administrative Litigation Statistics and Data Table, available at www.chinalaw.gov.cn/article/jggz/fztjxx/201403/20140300395412.shtml.

i Administrative reconsideration

When an applicant is not satisfied with a government agency's decision, the applicant may file an administrative reconsideration request for review by either the government agency itself or its supervising ministry or department within 60 days.[102] To file an administrative reconsideration request challenging a CFDA decision, the applicant must have legal standing to do so. The complaint must name the respondent and the specific decision the applicant is challenging.[103] Permissible grounds for reconsideration are:

a the agency's fact finding on major issues is incorrect and evidence is inadequate to support the decision made;
b the law was erroneously applied;
c the agency violated relevant statutory procedures;
d the agency exceeded its authority or abused its power; or
e the decision was obviously inappropriate.

A special division in the CFDA, the Administrative Reconsideration Office (ARO), is responsible for handling administrative reconsideration requests to challenge decisions made by the CFDA itself or its local offices. For complex cases and cases involving a challenge to underlying laws or regulations, the Administrative Reconsideration Committee (ARC), which consists of the Commissioner and Deputy Commissioners of the CFDA and ranks higher than the ARO, will hear the case.

The ARO or ARC will examine the request and decide within five days if it meets the requirements for reconsideration.[104] If so, it will be accepted for review and the ARO or ARC is obliged to render a decision within 60 days. If the situation is complicated, the time for review may be extended by a maximum of 30 days. The ARO or ARC may affirm the administrative decision, or overturn it and remand the matter to the government agency with instructions to take either a specific or an alternative administrative act. The decisions of the ARO and ARC are legally effective upon the signature of the head of the CFDA.[105] The applicant can appeal the decision of the ARO or ARC to the State Council, whose decision is final, without the availability of judicial review.

ii Judicial lawsuit

If an applicant decides not to appeal the ARO or ARC's decision to the State Council, it may bring a judicial lawsuit in the People's Court against the ARO within 15 days after the time limit for reconsideration expires.[106] If the People's Court finds that any of the following conditions are met, then the administrative act must be annulled or partially annulled, or the defendant must be ordered to take another alternative administrative act:

a the major evidence was inadequate;
b the administrative agency erroneously applied the law or regulations;

102 Administrative Reconsideration Law (1999).
103 Administrative Reconsideration Measures of the CFDA (2013).
104 Article 17 of the Administrative Reconsideration Law; see also Article 48 of the Regulations on the Implementation of the Administrative Reconsideration Law (2007).
105 Article 20 of the Administrative Reconsideration Measures of the CFDA.
106 Article 38 of the Administrative Litigation Law (2014).

c the administrative act violated legal procedures;
d the administrative act exceeded authority; or
e administrative power was abused.[107]

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

China has enacted laws and regulations to prohibit bribery, kickbacks or other inappropriate financial relationships or sponsorship. The DAL contains these provisions and penalties for violations could include revocation of the drug or medical device approvals, civil fines and criminal penalties. In addition, the SAIC administers regulations against commercial bribery. Bribery cases may also be handled through the criminal justice system. Scrutiny of these activities has grown substantially in the past two years since the government launched anti-bribery investigations of foreign drug manufacturers.

The fallout from those investigations has resulted in much more significant scrutiny of the relationships between drug companies and healthcare providers by regulators in China. The NHFPC issued a policy of 'Nine Prohibitions' (or bad acts in the healthcare system) that would be the focus of government scrutiny and enforcement resources, as well as blacklisting rules meant to curb ethical abuses in the healthcare sector. The Nine Prohibitions include:

a no linkage between healthcare provider incomes and profits from drug sales or medical services;
b no rebates for prescribing medicine or referrals for services or drugs;
c no overcharging of patients;
d no accepting illegal donations;
e no illegal advertisements or promotion of drugs, devices, food or other products by medical institutions or healthcare providers;
f no collation of statistics for commercial purposes or personal gain by healthcare providers;
g no private buying or selling of drugs, devices or other equipment by healthcare providers;
h no acceptance of kickbacks or commissions from healthcare companies or engagement in entertainment activities provided by those companies; and
i no solicitation or acceptance of financial benefits from patients.[108]

In late 2013, nine agencies, including the NHFPC and CFDA, issued a joint opinion (a blueprint of sorts) intended to create higher standards for ethical conduct by physicians and

107 Article 54 of the Administrative Litigation Law; see also Article 6 of the Provisions of the Supreme People's Court on Several Issues Concerning the Hearing of Administrative Cases of International Trade (2002). Similar interpretations can be found in Provisions of the Supreme People's Court on Several Issues Concerning the Application of Laws in the Hearing of Anti-Dumping Administrative Cases (2002) and Provisions of the Supreme People's Court on Several Issues Concerning the Application of Laws in the Hearing of Countervailing Administrative Cases (2002).

108 Notice on Improving the Medical Health-Care Workstyle and Establishing the Nine Prohibitions.

other hospital personnel in their dealings with the drug industry. The opinion also mentioned higher standards for safety for medical devices but singled out corruption associated with drugs as the primary target.

Scrutiny in this area continues to be very significant and regulatory reform is continuing. In late 2014, the NHFPC issued measures on clinical research projects at medical and other health institutions, which, among other things, called for stronger clinical research and ethics committee management of these projects, and guidelines for financial management intended to prohibit payments directly to investigators.[109]

In order to further control improper incentives given by the drug industry to Chinese hospitals, in 2015, the NHFPC released regulations further circumscribing donations to healthcare institutions, emphasising that all such donations must have an acceptable charitable purpose and that charities (all donations must flow through approved charities) must conduct a thorough review of the donor and the plan for the donation itself.[110] Anti-corruption investigations and physician kickbacks continue to be significant issues in China.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Compensation can rely on provisions specifically on drugs and devices in the Tort Law, and perhaps on provisions in other laws, such as the Consumer Protection Law, the Product Quality Law and the Regulations on Medical Disputes. The Regulations are currently under revision. Compensation is available when the product is defective or not made according to compulsory national standards. Drugs or medical devices can still cause injuries in the absence of product defects or medical malpractice, but no special strict liability has been set up for compensation under such circumstances.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

China's Anti-Monopoly Law (AML) took effect on 1 August 2008 and enforcement has become increasingly prominent in the healthcare industry in the past four years. Three enforcement agencies are responsible for enforcing the law: the Anti-Monopoly Bureau of the Ministry of Commerce (Mofcom), the Anti-Monopoly and Anti-Unfair Competition Enforcement Bureau of the SAIC and the Price Supervision and Anti-Monopoly Bureau of the NDRC.

Mofcom reviews 'concentration' – defined as a merger, an acquisition of assets or equity that confers control over another company, or an acquisition of a decisive influence over another company through contract or other means. The NDRC and SAIC handle price-related and non-price-related violations, respectively, in connection with monopoly agreements and abuse of dominance.

109 Administrative Measures on the Development of Clinical Research Projects at Medical Health Institutions (NHFPC 2014).

110 Administrative Measures on Accepting Donations for Public Welfare by Healthcare Entities (for Trial Implementation) (NHFPC 2015).

All three agencies have bought enforcement actions against companies in the life sciences sector. Mofcom imposed conditions on two transactions involving life sciences companies: *Pfizer/Wyeth* (2009) and *Novartis/Alcon* (2010). In the *Pfizer/Wyeth* case, Mofcom conditioned its clearance on Pfizer's commitment to spin off, under the supervision of a trustee, its swine mycoplasma pneumonia business, including tangible assets and intellectual property rights necessary to compete. Novartis, rather than facing a structural remedy like Pfizer, was barred from selling its Infectoflam product or similar opthalmological anti-infective products in China and required to terminate within 12 months a distribution agreement it had with Hydron (the largest contact lens distributor in China) regarding Novartis's contact lens-care products, as a condition for the approval of its acquisition of Alcon. Hydron had been appointed as the sole distributor for Novartis in China since 2008 and Mofcom was concerned that, post-transaction, the distribution agreement could lead to coordination in prices, quantity and sales regions between Novartis and Hydron.

Since 2013, the NDRC has stepped up its enforcement of the AML, particularly in the area of pricing of pharmaceutical drugs and medical devices. The agency conducted surveys on the pricing and marketing practices of over 100 pharmaceutical and medical device firms in 2016, and has formally initiated investigations against a number of multinational and domestic firms in the sector. In some respects, these pricing investigations were overshadowed by commercial bribery cases in the healthcare sector.[111]

In 2013, a Shanghai High Court ruled in favour of a plaintiff in the first successful private suit under the AML for vertical price-fixing. The case, which involved Johnson & Johnson's device business for surgical sutures in China, related to a distribution contract setting minimum resale prices, also known as resale price maintenance (RPM). The court found that the plaintiff had carried its burden of showing that the defendant's conduct created a vertical restraint that had an anticompetitive effect. The court analysed: (1) whether there was sufficient competition between manufacturers in the market; (2) whether the defendant exercised market dominance; (3) the defendant's motives in entering into the distribution agreement; and (4) whether the anticompetitive effects of the conduct outweighed any negative effects on fair competition. The court awarded approximately US$85,000 in lost profits as a result of its finding of these violations.[112]

In 2016, the NDRC is continuing to pursue pharmaceutical and medical device firms for vertical anticompetitive agreements (e.g., RPM). In December 2016, the NDRC fined Medtronic (Shanghai) Management Ltd, the China subsidiary of Medtronic, US$17.3 million for engaging in RPM and other vertical restraints.[113] The NDRC stated in its decision that Medtronic deployed a multilayer distribution system in China and, through distribution agreements, email notifications and oral discussions, Medtronic restricted the resale prices of its distributors at all levels, despite the fact that these distributors are independent market players

111 Benjamin Shobert and Damjam P. DeNoble, 'Understanding China's Antimonopoly Investigations', *China Business Review*, 30 March 2014, available at www.chinabusinessreview.com/understanding-chinas-antimonopoly-investigations/.

112 Chunfai Lui & Stephenson Harwood, 'A Landmark Court Ruling in China: Resale Price Maintenance As Examined in the Johnson & Johnson Case', *CPI Antitrust Chronicle*, available at www.competitionpolicyinternational.com/file/view/7010.

113 See 'The NDRC's Administrative Penalty Decision [2016] No. 8,' available at www.ndrc.gov.cn/fzgggz/jgjdyfld/fjgld/201612/t20161209_829717.html.

rather than Medtronic's affiliated entities. It also restricted the bidding prices of its distributors and prohibited them from selling to customers outside of the allocated geographic markets or from selling competitors' products. According to the NDRC, such vertical restraints, including RPM, harmed both intra-brand and inter-brand competition in the relevant markets. The NDRC thus considered that such conduct violated Article 14(1) and (2) of the AML and does not qualify for exemptions set forth under Article 15. The monetary penalty accounts for 4 per cent of Medtronic's sales of the relevant products in 2015.

In addition to RPM investigations, the agency also investigated horizontal anticompetitive agreements (i.e., cartels under Article 13 of the AML) in 2016. In January 2016 and July 2016, the NDRC fined eight Chinese companies approximately US$1 million for two cartels involving API and tablets of allopurinol, a medication used to decrease high blood uric acid levels,[114] and estazolam, a basic drug treating insomnia,[115] respectively. According to the NDRC, the companies engaged in price-fixing and allocating geographic markets for the sales of their products, and were considered as violating Article 13 of the AML.

The SAIC, the agency focusing on non-price related AML violations, also actively pursued enforcement in 2016. In December 2016, a local branch of the SAIC fined a domestic API supplier for refusal to deal (i.e., refusal to supply downstream manufacturers of a drug treating clavus with the necessary API that it has been supplying continuously for the past few years).[116] The company, Chongqing Southwest No. 2 Pharmaceutical Plant, is said to be the only remaining China-based manufacturer of phenol APIs, an essential raw material for the production of salicylic acid and phenol plasters. In 2014, the company appointed an exclusive agent and stopped supplying other drug manufacturers with the API for 23 months. Chongqing AIC thus considered that the company abused its dominant position by refusing to deal with its customers without justification. The company's illegal gains in the amount of approximately US$70,000 was confiscated and a punitive penalty of approximately US$2,500 was imposed.

The pharmaceutical/medical devices sector in China is becoming increasingly sophisticated, not only because it is a highly regulated industry, but also because the government is working hard to curb rising medical costs, reduce the burden on the health insurance system and eliminate corruption. Against that background, the sector has become one of the top enforcement priorities of the government agencies. As the sales to hospitals involve a public procurement and bid process, legal compliance is further complicated by the intersection with bid rigging and anti-bribery rules, and the role of the SAIC and other agencies. It appears to be a growing trend that companies seek antitrust, anti-corruption and unfair competition advice in order to better adapt to China's evolving regulatory environment as all three antitrust law enforcement agencies in China continue to step up their efforts in the sector in 2017.

114 See 'The NDRC's Administrative Penalty Decision [2016] No. 1-4,' available at http://jjs.ndrc.gov.cn/fjgld/201602/t20160202_774107.html.

115 See 'The NDRC's Administrative Penalty Decision [2016] No. 5-7,' available at http://jjs.ndrc.gov.cn/fjgld/201607/t20160727_812579.html.

116 See 'The Chongqing Municipal AIC's Administrative Penalty Decision [2016] No. 15,' available at www.saic.gov.cn/zwgk/gggs/jzzf/cfjd/201612/t20161213_173318.html.

ii Transactional issues

Government approval is a key issue to bear in mind for any M&A or joint venture deals in China. Depending on the nature of the target company and the deal structure, different types of approvals may be required. For example, an acquisition of an onshore Chinese target company will require approvals from a number of government agencies including the Ministry of Commerce (or their local counterparts) and the NDRC. In addition, if structured as an asset acquisition of a Chinese pharmaceutical business, additional approval from the CFDA is required for the relevant operating permits to be reissued (such as the drug manufacturing licence or the drug distribution licence, as the case may be).

Joint ventures are commonly used for Western life sciences companies seeking to enter the Chinese market. Approval by the Ministry of Commerce or one of its local counterparts is required for setting up joint ventures. In addition, if the joint venture wishes to engage in business activities requiring special licences, such licences must be obtained before the relevant activities may be included in the joint venture's business scope. By way of background, a corporate entity in China is only permitted to conduct business activities listed in its business scope on its business licence issued by the government authority. This is particularly relevant for companies in the life sciences space because many activities in this space require specific licences, such as a drug manufacture licence or drug distribution licence. In recent years, the Chinese government has limited the issuance of new drug distribution licences by significantly raising the threshold requirements, making them very difficult to obtain.

Apart from mergers and acquisitions and joint ventures, complex life sciences transactions commonly seen in the US and Europe, such as licensing and collaboration arrangements, have been rare in China. This is owing to the fact that China's life sciences industry has traditionally been dominated by generic players and there are few innovative assets in China. This is now beginning to change; fostered by government policies encouraging innovations in biotech, increasing numbers of innovative biotech companies have sprung up in China. At the same time, more Chinese generic companies seek to grow into the innovative side of the business by partnering with Western companies. As a result, the number of licensing and collaboration deals has increased markedly in the past few years.

VIII CURRENT DEVELOPMENTS

China has been revising its framework statutes for drugs, devices, food and cosmetics for the past three years. Following the revision of the RSAMD, the revision of the implementing regulations related to devices continued throughout 2016 with new regulations or proposals on classification, device naming and inspections, as well as proposed regulation in areas such as advertising and adverse events. The CFDA will most likely finalise its substantial revision to the device classification catalogue in 2017, and work to streamline review and approval processes to reduce the application backlog and wait times for devices that fill critical needs.

In the drug space, the CFDA will likely continue to reduce application wait times and streamline approval processes. It will also continue to refine and develop the projects on reference products for generic small molecule drugs and the MAH Pilot.

The larger questions are the timing of revisions to the DAL and PDR. As discussed herein, the CFDA released a substantial amendment to the PDR in July 2016 that included a more uniform approach to clinical applications and marketing applications. It remains unclear as to whether the CFDA will finalise the PDR revision prior to the revision of the DAL and, if so, when. It is unlikely that the DAL will be finalised in 2017, although it is

possible that a draft could emerge. The CFDA may also want to let its pilot projects play out before finalising the DAL and PDR. For example, the MAH Pilot does not end until 2018, and its results, while promising thus far, will still be emerging at that time.

On the issue of enforcement, GxPs will likely remain an important area for both drugs and devices. As noted in Section II.xv, *supra*, the CFDA has conducted several investigations into GxP compliance, and it is possible that it will focus on additional areas. The CFDA is likely to continue to promote enforcement of its new medical device GCPs and it may finalise its new drug GCPs in 2017.

It is expected that China will to reform its drug and device pricing and reimbursement system. The reforms of the pricing system that began two years ago are supposed to involve a more open and transparent mechanism, involving more stakeholders, for determining reimbursement rates. These rules are still taking shape.

Appendix 1

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Shaoyu Chen is a partner at Covington & Burling LLP, based in the Beijing and Shanghai offices, and is the managing director of the firm's China food and drug practice. Mr Chen has 15 years of experience in food and drug law, including serving as assistant chief counsel at the US Food and Drug Administration Office of Chief Counsel, as senior counsel at California-based Amgen Inc, and as chief compliance counsel for GE Healthcare China. Mr Chen represents pharmaceutical, biotechnology, medical device, food, dietary supplement, and cosmetic companies in matters involving the China CFDA, the US FDA and other government agencies; he assists clients on legal and regulatory issues related to CFDA and FDA oversight, including those pertaining to pre-clinical research, clinical trial, marketing approval, advertising and promotion, manufacturing GMP, drug safety, and import and export. Mr Chen also advises companies on other legal matters, such as those related to collaboration, anti-unfair competition and general corporate affairs and business conduct. Mr Chen received his undergraduate degree from Peking University, and his Juris Doctor from the University of Nebraska, where he served as executive editor of the *Nebraska Law Review* and graduated with distinction.

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