Cross-Border Life Sciences Collaborations in China – Part 2

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Presented by Lester Ross, Kenneth Zhou and Belinda Juran

Belinda: Welcome to part two of our discussion on Cross-Border Life Sciences Collaborations in China. I'm Belinda Juran, a partner in our life sciences technology transfer practice here at WilmerHale, and I'm based in Boston. I'm joined again with my partner Les Ross and Kenneth Zhou, who are based in our Beijing office.

I'll now briefly introduce our speakers, Lester Ross is a partner in our Beijing office in our corporate practice, focusing on mergers and acquisitions and regulatory matters. Lester represents both foreign and local firms in his practice, and one of the things he does among many is advising foreign companies on competition law and regulatory compliance in China. Les has held several leadership positions in the American business and legal communities in China.

We're joined by our partner Kenneth Zhou, who is also based in Beijing, and is a member of our corporate practice. His practice focuses on again, as with Les, a number of different areas including M&A, anti-trust regulatory matters, international dispute resolution, and foreign direct investment in China. Kenneth has advised foreign companies with respect to their strategic expansion in China. Kenneth is the former general counsel of the American Chamber of Commerce in China.

I'm Belinda Juran, a partner in our Boston office and I co-chair both our Life Sciences Group and our Technology Transactions and Licensing Group. With that, I'm going to turn it over to Kenneth to start today's presentation.

Kenneth: Thank you, Belinda. Today, we're going to cover part 2 of this presentation and we're starting with page 20 of the slide deck: Reform of Registration Procedure for Imported Drugs. We understand we have not yet completed page 19, but we will discuss relevant examples in the next few pages of the slide deck.

Reform of the registration procedure for imported drugs. China has been starting a reform with respect to the overall drug approval systems in the past few years. One of the most notable

decisions or opinions or policies issued by the former CFDA. Why we call former CFDA? Because, as probably a lot of you are already familiar with, China has just completed a sort of internal organization of all the central level ministries, departments, state council, committees. The CDFA is now called SDA, the State and Drug Administration, which is under the super ministry called the Ministry of Market Regulation.

Former CFDA and now SDA, they perform pretty much the same sort of responsibilities. Former CFDA in October 2017 last year promulgated these decisions with respect to certain registration procedures for imported drugs. This decision, of course, is a *decision*, so it's not that detailed. It is supposed to be a guideline; the detailed implementing set of policies will gradually come up. But if we look at this decision there are a few important changes.

First, is with respect to clinical trial development. Previously imported drug must await completion of phase two and phase three clinical study or receive marketing authorization outside China before beginning an international multicenter trial in China. Under the decision this requirement, for the first time has been eliminated, which we think will reduce significantly the development delays for many foreign companies. Except for biological products for preventive use which is governed separately by separate regulations, the decision has opened a phase one trial to global development, which means that for foreign applicants for new chemical drugs and new therapeutic biological products can conduct a full clinical development plan inside China, in parallel with global development program.

In terms of the clinical trial procedures, the decision has also set out a, compared to the past, a more simplified and a more straightforward process. Previously imported drug manufacturers, it's the foreign use of companies applying to conduct in international multicenter trial in China were required to submit three applications during the process.

The first one is the Multinational Clinical Trial (MNCT) application to request a global phase two and a phase three trials in China. Second, after the drug has been approved and the certificate of pharmaceutical product is available from the U.S. or EU, or any other jurisdictions outside China, the foreign manufacturers will have to submit an application to SDA, that's the State Drug Administration, to request a clinical trial waiver. Which really means exemption from the need to conduct additional local trials.

The third application is the New Drug Registration application which is really sort of an application to CFDA or SDA for approval of marketing authorization, MA. Now under the decisions, this process has been simplified under the decisions for clinical trial applicants or NDA which is the New Drug Registration application.

For imported new chemical drugs and innovative biological products, in general there's no need for the second application, which is the application to SDA to request a clinical trial waiver, which basically allows the applicant for an imported drug to apply directly for marketing authorization upon

completion of its international multicenter test in China, before the product has been approved in its home jurisdiction.

This simplified procedure, of course, the decision itself do not have a lot of details, but the expectation in the market is this simplified procedure is expected to shorten the approval time, the approval process by at least one year. Whether this is going to be true or not—we will see.

The next decisions also set out a more simplified process or requirements for evidence documents, that the notable points are the decisions eliminate the requirement that an imported drug be approved outside China before China grants marketing authorization, in case of an imported new chemical drug or innovative therapeutic biological products. This is very important because it can certainly sort of shorten the entire marketing authorization application time and the process.

For an imported drug in which IMCT has already been conducted in China the applicant may directly apply for marketing approval with the SDA, the State Drug Administration, after the multicenter trial has been completed. This also gives a lot of manufacturers the flexibility to go ahead and to file an application for marketing approval without going through a lot unnecessary sort of steps in between.

The next one is the shortened review and approval timeline for imported drugs as a whole. We have collected some data, the data shows that 19 imported cancer drugs were approved in 2017, up from 7 approvals in 2014. Generally speaking, in terms of the volume of approvals, it has been going up.

In addition to the volume, the average approval time for imported cancer drugs has been, in general, cut from 420 days to 111 days. The average time for approval for cancer drug clinical trials has been cut from more than 240 days to 114 days. But again here, we talk about the imported cancer drug which is something that the Chinese government encourages import.

The overall time frame for these type of drugs (cancer drugs), are in general now subject to a sort of a shortened approval time period. Which does not necessarily mean that the overall approval time for other imported drugs is shortened at the same time. But at least this decision is a good sign, which shows that the government (the former CFDA, or SDA) is taking steps to implement the reform in order to have the imported drugs—especially those which China needs badly—to go through a faster, more transparent and straightforward approval process in China.

Here's an example: it's basically a recent example with respect to a product, from Merck. This drug, the vaccine, HPV vaccine, SDA only took nine days to approve. This is the first time in China the government approved an imported drug so quickly. The legal basis or the process of this expedited approval is sort of set out in another regulation of policy promulgated by the government earlier.

If we look back at slide 19, the government, promulgated this innovation opinion. This innovation opinion was promulgated in October 2017. And this opinion, including a lot of things in terms of the steps, the direction the government is trying to take in order to sort of reform the overall regulatory landscape with respect to pharmaceuticals.

But among all these points there are a few points which are very important. We have mentioned some of those last time. These points include the drugs that offer new solutions for treating life-threatening diseases or address critical unmet medical needs may be eligible for conditional approval. What does conditional approval mean? Conditional approval means, before completion of phase three confirmatory trials. So long as early and mid-stage study of data indicates their efficacy, and predicts their clinical value, the marketing authorization application could be approved on conditional basis.

This is very important because the foreign manufacturers they don't have to wait until the completion of phase three, before they submit the marketing authorization application for approval, which can apparently shorten the time. But on the other hand, if we look at the conditions it's very clear, it says "the conditional approval applied to new solutions for treating life-threatening disease or address critical unmet medical needs."

In other words, it's not all kinds of drug applications will be subject to this accelerated marketing approval process. There are limited categories of drugs can sort of receive this special treatment. Companies receiving conditional approvals must develop a risk management plan and initiate confirmatory post-approval study as per the requirements in the conditional approval. In other words, the government, in the conditional approvals reply, they will set out the detailed conditions, which the applicant will have to comply with, after the approval is granted. Similar approval process will be given to treatment for rare diseases, etc. And under the condition that post-approval commitment study is required.

If we go back to slide 22, here Merck is the first product which received this expedited approval and approved in such a short period of time. There are a lot of details on this page with respect why the reasoning from the Chinese government. It's because this fast-track approval process, the government realized the urgent demand for this vaccine to prevent cervical cancer which is a very serious common disease in China.

Tariff reduction and other market liberalization measures for imported anti-cancer drugs, again we're talking about anti-cancer drugs, not other drugs. These tariff reductions including this decision from the Standing Committee of the State Council, which is China's cabinet, to reduce tariffs on imported anti-cancer drugs starting from May 1st this year, the 5% to 6% import tariff for anti-cancer drugs and specialized specific drugs.

Typically in addition to tariff there's another sort of standard 17% of value added tax (VAT). But now for these type of drugs, the 17% import VAT, will also be substantially reduced.

The Medical Insurance Department of the Ministry of Human Resources and the Social Security has also initiated work plans for the negotiation of reimbursement of anti-cancer drugs that were not covered by medical insurance. These are the other things that are related to this innovation or reform recently.

This next slide is a summary table with respect to the marketing authorization approval process, which is self-explanatory. It lists out the approval time frame for the government approvals. There could be a lot of delays because this is based on government regulations. This include the government administrative licensing period or feedback time under relevant regulations which does not take into consideration with respect to, for example, technical evaluation. This could take a long time and does not necessarily take into consideration that, the coming back and forth, the communication between the manufacturer and the government authority. But this chart is helpful with respect to sort of laying out the general time frame and the general approval steps.

The next slide talks about the encouragement of development and the production of generic drugs. This is something perhaps more important for Chinese domestic manufacturers, not necessarily sort of very important to the audience today. But if you're interested you can take a look in terms of what are the steps that the government is taking in terms of sort of encouraging more generic drugs.

The intellectual property rights are very important especially for drug innovators. The Chinese government, in the past have promulgated a lot of regulations, but the enforcement really lacks. In recent years the government is trying to strengthen the enforcement. With respect to drug innovators, the government promulgated this innovation opinion which we have talked about before. This innovation opinion is really sort of a policy document, it lays out the general sort of guidelines, the direction, where the government is going to go in the future. But it does not necessarily have the details.

Also, CFDA has promulgated this circular 55 which we have briefly discussed in part 1 last time. But again, a very important part of this regulations talks about how to strengthen intellectual property protection for drug innovators which is very relevant to us. The first one is the year drug patent linkage. The current regulations, basically the practice is they're not really sort of clearly provide whether the innovators of patent holders of the underlying drug can bring a patent infringement action in court against generic manufacturers' pre-market infringement.

Generic manufacturers can file a drug registration application with the SDA within two years before the expiration of such drug patent, which basically makes it impractical for innovators, patent holders, to initiate such patent lawsuits under the current legal regime. That's clearly the shortcoming of the current legal regime. The innovation opinions and the circular five, they made significant progress at least on a general, sort of a high-level policy level with respect to the patent linkage system.

These regulations outline the patent linkage system for the first time, in the past we did not have that in China. For example, innovators can bring infringement actions before the SDA's grant of marketing approval for the generic products in the first place. Patent linkage is also provided between pharmaceutical regulatory approvals and patent infringement.

Third, the patent linkage system will also provide greater stability in patent enforcement for both innovators and the generics in China by showing innovators their innovation is amply protected. Of course, that's the intention of the policy document. With respect to its implementation, we still need to wait and see. But at least these policies they set out, at this sort of high level, a general sort of direction in terms of where the Chinese government is going to go with respect to IP protection.

Under Circular 55 which compared to the innovation opinions, Circular 55 has a little bit more details in this connection. The details include upon the filing of an application for drug registration, the applicant must submit a statement stating that the relevant patent rights of which the applicant is aware. If the applicant seeks to challenge a patent the applicant is to declare non-infringement of the relevant patent and notify the patent owner within 20 days of filing.

There are still issues which remain unclear. For example, the patent law, Circular 55 and the innovation opinions, they set out a strengthened IP protection regime for drug, innovators. But the patent law, which is really a high-level law, are still lax in this connection.

There's a question as to how to reconcile, the innovation opinions and the Circular 55 on one hand, and the patent law on the other hand. The patent law needs to be amended to provide the marketing approval applications for generic drug products covered by innovator's patent may constitute infringement. It is unclear in terms of which court will have jurisdiction over these matters.

Again, in terms of IP protection for innovators, improved drug data exclusivity. China at this point and its current legal regime, the drug data exclusivity is not something that has a lot of details under the current Chinese legal regime. However, the innovation opinions provide more details with respect to data exclusivity. For example, the opinions provide that drug registration applicants are entitled to data exclusivity when fighting drug registration applications with the government.

The data will be restricted to clinical trial data and other data developed by applicants of innovative drugs for rare disease, etc. Applicants for generic drugs that succeeded in patent challenges. The data protection scope is much more broadened compared to what was provided under a previous regulation, the regulations for implementation of the drug administration law, under which only a developer of a new drug containing a new chemical entity is entitled to drug exclusivity. Also, on this page, it lists the time period with respect to drug exclusivity.

China also has this sort of Chinese version of the "Orange Book," which is the catalog of marketed drugs in China. This is specifically mentioned in Circular 55. The purpose is to encourage research and development and innovation of new drugs. We have a lot of details on this slide, but I would

like to mention a few points which are more important. Now each approved drug will be classified as an innovative drug, improved new drug or generic drug that has passed review for equivalency and quality and efficacy.

Besides scientific information on the drug's use and the market approval holder's information, the record may also include such IP information as lists of relevant patents and the data protection and the drug monitoring period. In other words, this Circular 55 gives a sort of a direction in terms of how detailed and the scope with respect to this catalog of marketed drugs in China.

The next slide talks about the Market Authorization Holder Program. The important thing here is since 2016, an initiative by the Chinese government known as the Market Authorization Holder, MAH Program, has been piloted in 10 provinces, with a goal of reforming the licensing process for drugs. This MAH initiative requires a Chinese company, which also sort of including foreign investor enterprises in China. At this point this program does not apply to foreign drug manufacturers, but we thought it's useful to have the information here for the sake of completeness.

With that, I will pass this to Les. Les will continue the presentation starting from cross-border transfer of clinical data.

Lester: Thank you, Kenneth. Let me just mention something first on slide 30 which is relevant, which is for a foreign licensor of a drug. You want to be sure in the license agreement that the actual producer of the drug in China is going to be the Market Authorization Holder, the MAH, or that you're comfortable with whomever the MAH is authorizing to do the manufacturing. Essentially the outsourcing of manufacturing is an important innovation in China, because it accelerates the commercialization of research results, and avoids the burden of establishing separate manufacturing facilities, meeting GMP requirements, even for companies or colleges and universities when they produce a single drug or two. But nevertheless, in terms of a licensing agreement it's very important that you be aware of that.

Before we turn to slide 31, let me also bring to your attention one more item, which is just today, the American Chamber of Commerce in China, both Kenneth and I are active in that, launched its annual whitepaper and the annual whitepaper which is available on the AmCham website includes a lengthy chapter entitled "Healthcare Services, Pharmaceuticals and Medical Devices." There's a bit of overlap to what we're talking about here, but it's primarily directed to the concerns that companies that are involved in those three segments of the industry here in China, that is healthcare, pharma, and medical devices have with respect to government policies, while at the same time recognizing the improvements, some of which we are covering in greater detail here today. I'll leave that with you as something that you may want to consult going forward.

Slide 31 addresses a very important concept of cross-border transfer of clinical data. China has imposed a number of restrictions on data transmission, here we're talking about clinical data, but there's also an even more recent restriction on the cross-border transfer of scientific data. These

constitute some serious issues with respect to the burden placed both on research and monitoring of clinical trials, and subsequently on the performance of drugs when it enters the market.

This is driven largely by national security concerns, although to some extent it's also driven by the important desire to protect personal privacy. But that means that the principal driver, unlike say in Europe, is not personal privacy with respect to the GDPR which took effect just last Friday, but rather the Cyberspace Administration of China. And as you can see on slide 31 the key document is the cybersecurity law and that follows with a whole series of documents, which haven't in most cases taken effect yet, but are beginning to. These include both regulations, and standards, and requirements, for security assessments with respect to data.

The most important thing is to recognize that anybody who operates a computer network in China, as well as the providers of services to such networks, is regarded as a network operator, and bears certain burdens with respect to compliance. Now those burdens are not as extensive as those for a critical infrastructure operator, and so far there are no foreign investment companies that qualify or appear to qualify as critical information infrastructure operators. That's because of restrictions on foreign investment. And in any event network operators still have substantial obligations in this regard.

On slide 32, you can see that the burdens that apply with respect to cross-border transfer of clinical data there's definitions of personal information. In addition, there's also a separate category of data that is important data. This includes data related to national security, economic development, and social and public interest, societal and public interest, which are very broad categories. Because in China national security includes health security, economic development, etc., could be construed to constitute information on a chronic disease that affects large numbers of people in China, or an epidemic, disease, or something else like that.

The burden on network operators is pretty substantial, and that obviously applies to producers of drugs, manufacturers of drugs in China, but to the extent that one is a licensor and without a presence in China, but nevertheless wants to monitor and ultimately bears responsibility for clinical trials, it means that any information that comes forward has to first obtain the privacy consent from the individual. And in addition to that, be essentially anonymized before it's transferred.

Network operators in certain circumstances may have to obtain a security assessment, and that includes thresholds based on the number of individuals, perhaps that's unlikely to be achieved, or a large database. There are also issues again with respect to population health, data with respect to personal information and important data and otherwise outbound data transfers that are deemed to impact national security or public interest.

Again, there will be no approval unless there is the consent of the owner or the person with the information, or if it may jeopardize personal interest, or otherwise go back to, as we indicated before, the national security and public interest. In any event, this imposes a substantial

compliance burden. I also mentioned that scientific data is involved under a separate set of regulations which we did not cover here. Review our client alert on this subject.

This, in our view, constitutes a significant impediment to cross-border research on pharmaceuticals, medical devices, and the like, as well as broader subjects with respect to science, even as China decries restrictions on access by Chinese companies and individuals to research institutes, and Silicon Valley and the like in the United States. So that's important to recognize as well.

Slide 34 addresses the flip side of the increased market access associated with innovative drugs that the government has introduced and that Kenneth covered just a few minutes ago. The government having to face a higher burden in terms of the pricing of drugs, has introduced over the last three years new procedures to govern the pricing of drugs. Previously drug manufacturers, distributors, and ultimately the hospitals will all allow to mark up the price of drugs before it reached, of course, the individual, the patient, etc.

Well, what's happened is the government has expanded the insurance system, which of course, means that more people are covered. The government is also allowing (at least in terms of cancer, and one would expect other innovative drugs over time) more expensive drugs to enter the market. In order to keep the prices down, the government has established a relatively transparent negotiating mechanism for the determination of prices under which standards are set, then the government determines which drugs are to be included in the formulary.

Ultimately there is a national reimbursement drug list, and an additional round of negotiations at the hospital level or the pharmacy level. Most people still buy their prescription drugs at the hospital level. The government has cut out the intermediate distributor level so that there really are only two invoices along the way.

In this way the government has tried to cut out the possibility for markups increase in the price of drugs before they are delivered. In addition, it's important to recognize for a number of innovative drugs produced by foreign providers in particular, many of them are going to be more widely available through foreign-invested hospitals. Right now, there are about 60 foreign-invested hospitals and other institutions that have been approved here by the government.

But those institutions are not eligible for the government insurance reimbursement project. The price of the drug to the patient is somewhat higher, and that's a significant concern for again the foreign business community, American business community here in China, that's addressed in the AmCham chapter that I mentioned before, the whitepaper chapter.

Again, the government has also, as Kenneth referenced before, encouraged the introduction of generics here in China. This is covered in slide 35 in part. While the government is providing stronger protection for patented drugs, at the same time, the government is also encouraging off-patent drugs to be marketed once drugs are off-patent, and with some greater flexibility for the

pricing of generic drugs under the assumption that there'll be more competition in place. In addition, to encourage the faster marketing of generic drugs to reduce the pricing advantage that the patented drug producer enjoys.

Keep in mind also that the government favors international reference pricing to major international markets. It's not going to allow drugs to be priced exclusively on a high value in China, and instead will look to the United States, or leading jurisdictions in Europe, or in East Asia, and try to find a market where the price is lower and then use that as leverage against the foreign drug producer.

Slide 36 addresses the drug pricing procedure. The drug first has to be registered with SDA, then it has to be included on a reimbursement list to have volume. That's either the national reimbursement drug list or various provincial reimbursement drug lists. Off-patent drugs are handled differently, but in general, the procedure is intended to reduce the prices. The government argues in this regard that once you're on one of these lists you're going to make up in volume what you lose in terms of price.

Despite the improvements, there are still shortcomings in Chinese law with respect to the protection of patent rights. One of them includes a longstanding regulation, the Technology Import and Export Regulation, which we call TIER, that was actually promulgated just 1 day after China acceded to the WTO protocol on accession in 2001.

Basically, it restricts, among other things, the right of the original patent holder to regulate improvements of products, so improvements on the original patented drug or other technology. This is a particular regulation that's a subject of considerable concern. The government of the United States a couple of weeks ago in the list of eight demands presented to the Chinese government with respect to changes in Chinese trade and investment policy, included this among the issues. And it's certainly of concern also to governments in other jurisdictions.

There are also some shortcomings in China's patent law that are relevant. For example, one of the provisions in China's patent law unlike in the United States, says that "If a patent is jointly owned, unless the parties agree, one party alone without the consent of the other party can license the patent to another party." There is also a restriction on the assignment of a patent by a domestic party to a foreign party, as well as a restriction on the grant back of improvements by the Chinese party to the foreign party.

There are some significant improvements. To some extent it is possible to work through those protections in the licensing agreement, but it's also important to recognize how important the reputation of your Chinese licensee is. A reputable licensee is going to be far, far or less likely to resort to such stratagem than one that is not. Which means there has to be some significant effort to investigate your licensee before moving forward.

Slide 40 essentially summarizes the points that I've made before with respect to the government's efforts to control drug expenses, including the full implementation of the two-invoice system by the end of 2018. That is one manufacturer obviously, that manufacturer could, of course, be the licensee and one distributor. No more extensive change in the distribution process that results in the multiple markups.

Public hospitals are no longer entitled to the 15% markup, the effort of course, in this regard is to force them to charge for services, which historically has not been done. The 15% markup on drugs was intended essentially to cover the services they provided. But there is resistance among consumers, patients to pay for services. Hospitals are concerned that they may be less able to support their pharmacy departments going forward. That of course, may lead to patients buying more of their drugs, the prescription drugs in pharmacies outside hospitals. That is yet to be seen but that seems to be a likely consequence of this.

Then there's an implementation of a multi-tier treatment system from the end of 2015. What this means is the government looks to its tiered hospitals and wants to discourage people from going to the top tier hospitals and would prefer that they go to the lower tier hospitals. I know people were concerned about digital medicine essentially acting as a liaison both for standalone digital medicine practices and also for the higher tier hospitals assisting the lower tier hospitals by providing online therapeutic services to guide the practitioner at the lower tier hospital, and avoid the crunch at the top tier hospitals, which are historically and even today both quite overburdened and more expensive.

These are changes that are taking place here as we speak. Again, one of the changes that has also taken place is a greater openness to foreign healthcare institutions, to some extent foreign practitioners. But there's a lot more taking place in terms of China's financial markets with respect to the support for pharmaceutical production or pharmaceutical innovation.

As the Chinese companies are selected to the MSCI index, then we're going to see more foreign investment as well in the Chinese pharmaceutical industry, as well as medical devices and healthcare. We will stop here, and thank you, very much for listening.

Belinda: Great, thank you both and everyone for joining. If you have any additional questions, please feel free to reach out to Les, or Kenneth or me.

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