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REGULATION

FACING UP TO CHINA'S VICISSITUDES

BY TAMRA SAMI, SENIOR EDITOR

Faced with an additional two- to four-year delay for drug launches in China due to a new government interpretation of regulations governing multiregional clinical trials, global companies may want to consider partnering with domestic companies earlier in development.

Multinational pharma companies (MNCs) increasingly have been using multiregional clinical trials (MRCTs) to accelerate the lengthy drug approval process in China. Many sponsors now include Chinese patients in global Phase III trials rather than running a China-specific trial following U.S. or EU approval.

But earlier this year, **China FDA** surprised industry by changing its long-standing interpretation of the MRCT pathway, indicating to some sponsors that an additional clinical trial application (CTA) would be required prior to submission of an NDA or BLA. The new interpretation, which was not published, altered a policy that had been in place since 2002.

As widely interpreted by many MNCs and legal specialists, the path to market now will take three applications and three approvals, compared with two applications and two approvals under prior practice (see "China Registration Process for Imported Small Molecules," page 12).

As a result, many imported compounds progressing toward approval via the MRCT pathway have been derailed, and companies can expect launches to be delayed an additional two to four years, according to a report from McKinsey & Co. released at the BioCentury China Healthcare Summit in November.

More than 30 applications reportedly have been affected by the new policy interpretation. According to McKinsey,

WANT TO GET INTO CHINA FASTER?

Dan Zhang, CEO of CRO **Fountain Medical Development Ltd.**, suggests four steps multinational companies can take to get their approved products on the market in China in one to two years. The approach takes advantage of the ability of domestic Chinese companies to reference approvals by the U.S. **FDA** and **EMA** to expedite **China FDA** approval. It also checks a regulatory box that requires domestic drugs sold in China be manufactured inside the country, thereby skipping the extra step of applying for an import drug license (IDL), which typically takes two years.

1. The multinational company transfers the technology to a Chinese partner that has local manufacturing capability.

2. The Chinese partner submits an sNDA to China FDA.

3. The provincial FDA conducts an on-site inspection for GMP manufacturing. The Chinese partner demonstrates consistency of API, excipients, packaging, quality control and manufacturing processes.

4. CFDA grants marketing approval and the final GMP certificate. The process is applicable to both chemical drugs and biologics.

— TAMRA SAMI

examples include **Boehringer Ingelheim GmbH**'s Gilotrif afatinib for head and neck cancer; **GlaxoSmithKline plc**'s respiratory drug Breo fluticasone; **Johnson & Johnson**'s Invokana canagliflozin for Type II diabetes; **Roche**'s breast cancer drug Perjeta pertuzumab; and **Pfizer Inc.**'s Inlyta axitinib for kidney cancer.

The changing landscape could encourage more cross-border partnerships between multinationals and leading domestic companies.

NEW GUIDANCE

In late November, CFDA released draft guidance that clarifies how to include China in MRCTs, but the agency was silent on the industry's biggest question: Is an additional clinical trial application required after completing a multinational study?

Although a procedural question, it is an important one to sponsors, given China's lengthy approval process for INDs, which can take 10-22 months according to a white paper jointly issued by the **R&D-based Pharmaceutical Association Committee** (RDPAC) in China and the U.S. **Biotechnology Industry Organization**.

"The guidance does not clarify the ambiguity in the [Drug Registration Regulation] as to how an MRCT should proceed to a new drug application or biologics application," Ropes & Gray Partner Katherine Wang wrote in a recent note to clients. The draft guidance is also "silent on whether a separate IND application is still required if the MRCT data meets all the substantive requirements to be accepted for the NDA or BLA review in China."

The draft guidance does help to clarify uncertainties in other areas.

"Prior to this regulation, there was a crackdown on what CFDA considered 'fake' international multicenter trials in that some of the multinational sponsors would create an international multicenter trial that would include China and Taiwan and a few other Asian countries for Chinese patients, but then the results were not used in their U.S. **FDA** and European filings," said Helen Chen, L.E.K. Consulting partner and co-head of the firm's China practice in Shanghai.

"This is because China patient enrollment takes a long time, so including China in U.S. and European trials for registration would delay U.S. and European approvals, still the key gating countries," she added.

Global companies also increasingly sought regulatory waivers to avoid conducting a required local trial, asserting the Chinese data from MRCTs supported approval.

CFDA granted waivers for "a few of the cancer trials for registration, and then many companies started using this approach and started considering this the standard without realizing that this was the exception," said Chen.

As waivers became more common, domestic companies complained to CFDA, claiming waivers were an unfair shortcut for multinationals.

CLARITY?

In the draft guidance, CFDA encourages sponsors to use MRCTs for unmet medical needs in China and for serious life-threatening diseases. The agency also recommends that sponsors consider additional pivotal studies in China or regional studies with Chinese patients.

"The guideline talks about the substantive criteria and the conditions under which data from multicenter regional studies would be able to

ENSURING CORRUPTION-FREE TRIALS

Companies conducting clinical trials in China now face an additional layer of scrutiny at the hospital level that may further delay drug approvals.

As part of the government's crackdown on corruption, **China FDA**, along with the **National Health and Family Planning Commission** and the **Traditional Chinese Medicine Administration**, in mid-October issued a regulation that requires prior review of trials by Chinese medical institutions to ensure doctors do not sidestep ethics rules.

The regulation requires medical institutions to establish a Clinical Research Management Commission (CRMC) to review and approve clinical trials after the studies already have been scrutinized by an ethics committee, according to the law firm Sidley Austin.

The CRMC must inform the local health authority that the research does not violate any laws or ethics, that the clinical investigator has no conflict of interest, that no commercial bribery is involved, that the research infringes no intellectual property rights and that the product has no quality defects or safety risks that cannot be adequately controlled, according to a note to clients written by the firm's China life sciences leader, Chen Yang.

"The regulation will have a significant impact on clinical research activities in China," Yang wrote. "It covers some previously unregulated clinical research by medical institutions; it also adds an extra layer of approval at the hospital level to those drug and medical device studies sponsored by manufacturers, which are already subject to CFDA approval."

Yang told *BioCentury* it is unclear how the regulation will work with existing CFDA regulations for clinical trial sponsors.

"The primary purpose of the rule is to increase hospitals' oversight of clinical studies and avoid potential risks of bribery," Ropes & Gray Partner Katherine Wang told *BioCentury*. "I anticipate that the approval practice can vary from one hospital to another, and would recommend that sponsors work closely with hospitals to minimize potential delays."

The CRMC also will ensure that study payments are made to the hospital, not individual physicians, and that sponsors do not influence prescribing decisions, said Wang.

Each government agency issues regulations from its own perspective, she noted. "CFDA requires clinical trial authorization to make sure patients are protected, and the health authority wants to issue its own requirements to make sure there is no corruption."

— TAMRA SAMI

be used as a replacement for local study data for registration purposes," Wang told BioCentury.

According to Wang's note, the draft guidance requires MRCT sponsors to submit the same dossiers to CFDA that are submitted to regulatory authorities in developed countries: "A uniform protocol must be observed to rule out inconsistencies of evaluation methods among cross-regional sites and investigators."

Sponsors also must evaluate the entire MRCT data set and conduct a trending analysis of Asian and Chinese subjects. Chinese subjects must be representative of the relevant patient population in China and sponsors must determine whether the sample size of Chinese patients is sufficient to demonstrate safety and efficacy.

CFDA may also inspect all study sites, including off-shore sites.

"The purpose of this guideline is to spell out consistently what the requirements are, and what the expectations are, so that companies have a clear standard to follow," Wang told BioCentury.

"Overall, I think it's a very good signal," she added. "But the fundamental question that the industry is worried about is whether the change in CFDA's position would delay the time to market of their new products."

According to Wang, even if a multinational sponsor can waive a local registration study by completely referencing the MRCT data, "they now need to line up for the clinical trial approval again to get the waiver."

Although MNCs remain "agitated" over the additional procedural step, Wang told BioCentury the guidance provides "a good opportunity for the industry to have an official channel with CFDA, influencing the shape of the guideline, or trying to influence the thoughts of CFDA on multicenter studies in a more constructive way."

Public comments on the draft are due Dec. 22.

STRATEGIES FOR MOVING FORWARD

The need to introduce new drugs is particularly urgent given increased pricing pressure on mature products, which account for 70-80% of sales in China for the average multinational, according to McKinsey.

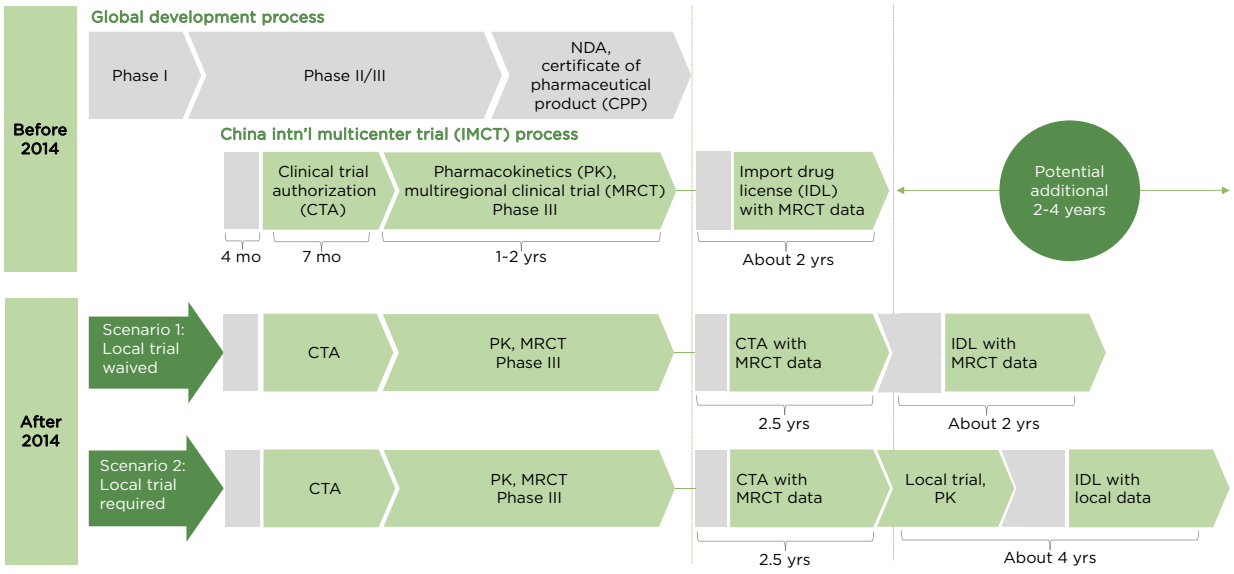
Companies should review their China strategy to determine how best to get through the approval process and make up for revenue shortfalls from delayed marketing authorizations, said L.E.K.'s Chen.

"What is changing are some of the business models," she said. "For example, some of the smaller companies that thought they might be ready to enter China on their own will partner out their products instead."

A domestic company could help to optimize a foreign company's regulatory strategy by bypassing the lengthier MRCT pathway in favor of China trials. In many cases, domestic companies also can access CFDA's accelerated approval pathway, nicknamed the Green Channel.

CHINA REGISTRATION PROCESS FOR IMPORTED SMALL MOLECULES

The new CFDA policy interpretation on multiregional clinical trials (MRCTs) could add two to four years to regulatory reviews for small molecules by potentially requiring companies to "stand in line" for a second clinical trial authorization (CTA) and review of the MRCT data before submitting an NDA, and risk being required to conduct a local clinical trial. All this would be added to the existing step of obtaining an import drug license (IDL). The timeline for biologics is longer due to additional sample testing and a requirement to run Phase I-III trials. *Source: McKinsey & Co.*



"Like everything in China, you have to carefully look at the benefits and costs," said Franck Le Deu, who heads McKinsey's Greater China healthcare practice in Shanghai. Multinationals would give up a lot of control if they partner out their assets, he added, and while the local industry is becoming more innovative, it is still quite nascent.

Also, it is not yet clear how early in the asset's development cycle is ideal for partnering with a local company, said Debra Yu, managing director of Labrador Advisors, a China advisory firm.

What is clear is that the quality of local companies is improving quickly, which Yu and Le Deu said should fuel cross-border partnerships to accelerate China development.

One example is the Shanghai start-up **Zai Laboratory Inc.**, which recently in-licensed two preclinical respiratory compounds from **Sanofi**. Partnering with a domestic company prior to Phase III would simplify the China development process for multinationals, according to Samantha Du, Zai's founder and CEO.

"For some drugs, especially biologics, multinationals could consider parallel development in China," she said. This includes "licensing to a China company or jointly developing in China."

Drugs targeting large unmet needs in China, such as cancer, HBV or rheumatoid arthritis, may be particularly well suited for this approach, Du suggested.

Multinationals could even cut the time to market to one to two years by partnering with domestic companies that have manufacturing capacity, said **Fountain Medical Development Ltd.** CEO Dan Zhang. If a product is already approved outside China, the MNC would transfer the technology to a Chinese partner to run local trials and avoid the additional applications for a drug import license (see "Want to Get into China Faster?," page 10).

"If multinational companies want to remain competitive, they need to consider a more China-specific strategy instead of just positioning China as a lucrative commercial market," advised Ropes & Gray's Wang, who is based in Shanghai. "They need to think of more creative ways about how they develop products in China to time the process more efficiently and competitively."

McKinsey's Le Deu remains optimistic about China's R&D potential, noting a change in perspective is what's needed.

"Fundamentally, there needs to be a change in paradigm in the way people are thinking about the challenges," he said. "For example, stop thinking multinationals versus locals, or quality innovation versus cheap generics. Instead, recognize that the agenda of multinationals and leading local companies is increasingly overlapping."

Local companies are also facing limitations in the efforts to access innovation, Le Deu noted. These local players could be engaged by global companies and together they could more effectively engage regulators to help build a more rewarding innovation ecosystem. bc

COMPANIES AND INSTITUTIONS MENTIONED

Biotechnology Industry Organization (BIO), Washington, D.C.
Boehringer Ingelheim GmbH, Ingelheim, Germany
China Food and Drug Administration (CFDA), Beijing, China
European Medicines Agency (EMA), London, U.K.
Fountain Medical Development Ltd., Beijing, China
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
National Health and Family Planning Commission, Beijing, China
Pfizer Inc. (NYSE:PFE), New York, N.Y.
R&D-based Pharmaceutical Association Committee (RDPAC), Beijing, China
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Traditional Chinese Medicine Administration, Beijing, China
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Zai Laboratory Inc., Shanghai, China

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BIOCENTURY PUBLICATIONS, INC.

NEWSROOM
pressreleases@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589
CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589
WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922
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