

# Conducting Strategic Clinical Trials in China

**FACILITATOR:** Now I'd like to introduce Dr. Jim Wei, who currently serves as director of clinical pharmacology at Medpace. Medpace is a mid-sized CRO. Medpace actually has an exhibit here in the exhibit area. So be sure and stop by and see Dr. Wei and some of his colleagues at Medpace. His responsibilities are to help sponsors in their early phase drug development programs including study design, data analysis, data interpretation, and regulatory strategies for IND and NDA submissions. Dr. Wei is a frequently invited speaker for international conferences. I understand you spend a lot of time going back and forth between China and the United States. At this point, he's working diligently with a number of regulatory agencies and committees in China to help develop their drug development processes there. Prior to joining Medpace, he was a senior reviewer for the office of clinical pharmacology for the FDA for almost 10 years and received an outstanding service award in 2005. He received his PhD in pharmaceutical sciences at Idaho State University in 1995 and his medical degree in '83. Thank you. And we look forward to your presentation.

**DR. JIM WEI:** Today I just want to share my experience and knowledge about the conduct of clinical trials in China. As mentioned in the introduction, prior to joining Medpace over two years ago, I worked at FDA. After joining Medpace, I have made extensive trips to China and participated in many clinical trial-related activities, including China SFDA training program, bringing and organizing former FDA officials to the China SFDA. Today I would like to share my experience with you all.

The general topic covered here is to describe what is the current status for regulatory environment in China and what are the clinical facilities to conduct clinical trials in China? What's the difference between US and China and also what is the recent outcome regarding US FDA site inspection in China. Also, we'll describe the disadvantages and the advantages to do that in China. And finally, I would like to de-

scribe the strategy to conduct the clinical trials — planning, training, and monitoring are very essential.

Why China? People always say that. Why China? First of all, it's the economic downturn time and now I think it's become a very essential time for improving cost-effective areas. That's why a lot of global companies are now setting up specifically for their out-

sourcing resource in China instead of outsourcing offices across China, to help develop the program. By doing that, they cut the cost significantly. In general, the conduct of clinical trials is about half of the cost compared to US.

Secondly, is the huge population in China. That is a big reward for enrollment. The population is so large and also the clinical centers in China are very concentrated. Two thousand beds per hospital is very common in all the major cities. This is the reward. In going there, the enrollment would be a lot more rapid and easier compared to the sites here. And thirdly, the huge market in China and with the economy continuing to advance, the marketing share for their drug is significantly increasing in the last 5 to 10 years and continues to grow. This is going to be, or can be, a huge profit for drug developers.

I want to describe a little bit here what are the processes and differences between US FDA and the China SFDA. In US FDA, we know that all the drug submis-

sions and IND NDA are relayed to the particular division. Administrative review is conducted in the division office level at FDA and the technical review is finished by clinical division. And also, the initial filing review is completed by a review team within the division. However, compared to China, the structure is very different.

First of all, administrative review is handled by the department of drug registration which is a different center under SFDA. The technical review is finished by center for drug evaluation which is that review center equivalent to CDER at FDA. Then the final review is handled by a third center called the center



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Jim Wei is the Clinical Pharmacology Director at Medpace and has extensive experience in the clinical trial regulatory aspects of early phase cardio-metabolic studies.

For more information on Dr. Wei, see page 4.

for filing. Therefore, there is a lot of administrative time overlap so the work is not as efficient as here in the US.

In general, the China SFDA — their regulatory perspective — has had significant improvement in the last five years. They are adopting more and more ICH and FDA guidance. And previously, they usually modify and combine their own standard. They develop their own China SFDA guidance. Now, they recognize with their inexperience in the particular drug regulation, that their own regulation guideline becomes impractical, particularly when they are dealing with the more global companies. The China SFDA is adopting more and more ICH guidance.

Previously, the China SFDA usually did not accept pre-IND meetings and consultations. Now they do. This is a big improvement for regulatory environment. The sponsor definitely can talk to SFDA and ask the questions, ask the strategies, and ask for agreement. China SFDA usually is very close-the-door. They do not participate in any public domain, public conference. Now they are actively involved in the international conferences such as the DIA meetings, AAPS, and many regional workshops. They are continuing to build up in-house expertise review teams such as the statistician review team. They established it last year in 2009, and also they are continuing to make efforts increasing the staffing in the review team and trying to shorten the regulatory review timeline. They are also implementing good review practice as US FDA often practices. They now have a more science-based approach to handle the review applications. They try to be open and fair and correct for every application. With China SFDA, now sponsors have more training workshops inside China to promote ICH, GMP, GLP, and GCP guidelines and also respect your therapeutic guidelines. In 2009, China SFDA CDE conducted 12 workshops to train the domestic investigators, CROs, and other staff in China.

What is the difference from the regulatory perspective, China SFDA versus US FDA? You have to understand that China SFDA is used to focus and handle the generic drugs rather than new drug applications. And the US FDA's major focus is on the new drug applications. China SFDA is used to focusing on the import of drug and the domestic development in very small scope; and the US FDA is handling all of the IND/NDAs. China SFDA usually is relying on more existing data, more on clinical trial experience and the data. US FDA is focused on the independent,

the new data collected from the new clinical trials. There are many focus differences. China SFDA are more focused on manufacturing. They approve drugs — they don't call it marketing authorization, they call it approval of manufacturing for the drug. The processing is different. There is quite a big difference when we go to China as to the kind of clinical trials; we need to understand the scope of the regulatory environment there.

The drug classification in China is very different from what we are dealing with in the US FDA. They have six classes for the drug applications and the new class one was a new medical entity and the class three is a new molecular approved in foreign countries but China. The requirements in China are very unique. They are not indication-specific. All the guidelines apply to all drug applications. For example, if you conduct the new molecular entity it requires the phase I study, the minimum is 20 to 30 subjects. Single dose and multiple doses are

same. These are the minimum requirements. For phase III, is 300 subject minimum requirements for every new drug application. This is the kind of regulation that is very different from US FDA. They are still pretty much inherited that they have groups which they only handle the generic drug or new drug. However, the rule's still there so therefore when we come to the clinical trials, this is the minimum requirement still there. You have to meet their standard.

This is just for the timeline when we try to organize the clinical trials, help prepare the clinical trials in China. For the center for review or for the filing, it takes 30 days. But that 30 days is not the US FDA 30-day "no news good news". Their 30-day is 30 business days. That means 1-1/2 months for the filing plus for review 90 business days, and then finally for the drug registration, it takes another 30 days. The total time for the review of a protocol takes 7-1/2 months. However, if there is additional data or information requested in general, in a realistic, it takes about 9 to 12 months to have approval for the clinical trial protocol. This is a chart for the organization in SFDA/CDE and where they handle the clinical applications for the protocol and new drug applications. Office one and office two mainly focus on the traditional Chinese medicine and the rest of the three offices handle the western medicines. The structure is very similar to the US FDA structure across this organization.

China SFDA now is more open and they more often invite US FDA officers and also colleagues to have

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training to their staff. In June 2009, SFDA invited FDA Alumni Association to conduct a science-based review process in training workshop and three former FDA officer directors, Dr. Goldenberg, Dr. DeLap, and Dr. Houn, and three others including myself went there to give a one-day workshop. And that workshop was very well received and all the review staff were required to attend such workshop. This was a picture taken before the workshop with CDE officials. In the center is Dr. Li. He is center director for CDE in China. Such activities significantly boost the China SFDA's capacity and awareness and the global regulatory environment, so they are willing to take more steps to train their staff and adopt more ICH US FDA guidance. This is a very good start and this year we will do it again. Conduct another workshop to have their SFDA internal training.

In China, in the facilities that conduct the clinical trials, there was an increase in learning. And from the historical perspective, the China drug development to support the global development started with manufacturing. The GMP facilities provide a lot of drug substance for a lot of global companies as they are suppliers. Now, they are moving to the pre-clinical service CROs, and FDA in the last year, 2009, inspected three pre-clinical CROs and also they inspected one bioanalytical laboratory in China. All this pre-clinical inspection went well and they accepted all.

In the US, the sponsor can choose individual investigator sites. In China, the hospital is the only place to conduct clinical trials. And this hospital must be credential certified, GCP certified by China SFDA. When you go to a clinical trials for the hospital site selection, you have to ask if this hospital is certified by China SFDA. In China so far, they have 430 hospitals certified GCP clinical trial sites. Twenty centers actually focus on oncology drug development and there are 115 Phase I units. Most of the sites are very small, 8 to 24 beds. But now, I think last year, there are two Phase I units. The bed size increased to 72 beds per unit. With over 30,000 clinical investigators in China across the country, now the government invests in what is called the drug development platforms across the regions. In every major city, there are clinical development platforms which are organized clinical centers, investigators, ethical committees. All are ready to take global trials.

Up to last year, US FDA conducted eight clinical site inspections. This inspection is a result. It came out with a very similar finding to US sites which was, "no

significant error or misconduct there." You can see that this is a list I copied from an FDA clinical investigative list site. You can see that the latest is March of last year. A clinical site inspection—all the deficiencies here are all minor findings; therefore, the clinical sites in China are capable to conduct GCP standard and reinforce it by US FDA or EMEA.

What advantage is there to conduct clinical trials? As I mentioned, there is improved regulatory environment, larger patient populations, national levels, the medical specialty organization society strongly support such GCP trials in China and develop all the many local cooperative groups, supporting groups there, and the Chinese are involved in many global trials. Many investigators actually are quite experienced. The global and the local CRO exist there and are fully equipped to already help with clinical trials. The GCP guideline and training program is readily available across the country in the medical centers and the cost is definitely an advantage for R&D—the development has a low travel cost, low monitoring, project management fees. All these costs are significantly lower compared to US.

Of course, there are some shortcomings to conduct the clinical trials. One of them is ethnic difference in the standard of dose in the clinical trials have to apply to US population. The Chinese patients are often taking alternative medicines concurrently. The China SFDA has a problem with placebos. It depends on the clinical trial design; certain clinical trials may not pass at their ethical committee. The Chinese GCP guideline is something slightly different from US practice. In China, we have to imagine that approval of a clinical protocol takes about 7-1/2 months and you have to get written certification for your protocol approval. That's not like in the US, "no news is good news". In China, you have to hear the written news.

Here, I want to share some of the data. What is China drug market? You can see that in the last 15 years, the China marketing share for the drug significantly increased. But this year, they're expecting China to become number five drug market across the world. This is quite a big advance and the market is continuing to grow. We can see that all the global companies existed in China. You can look at global growth. It's a single digit. However, this global company in China growth is all two digits. Look at a very dramatic contrast. But also I have to mention here, the China domestic pharmaceutical companies grow in a very rapid pace. In the last 5-10 years, the an-

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nual growth is 36%. We cannot ignore the local domestic pharmaceutical companies.

This is just fact sheets describing the China domestic pharmaceutical companies and the revenue that can widely range from 10 million to 1 billion USD for their market. And they have a lot of cash flow these days. Most of it is generated by their own profit and also China now has a lot of other areas. They are shifting a lot of bonds to support pharmaceutical R&D and clinical development. A lot of foreign venture capitals there and also the government funding; for example, in 2008, a government grant for 6.6 billion Chinese money was invested in the pharmaceutical industry. That money is free for any company, for domestic companies, private or state run companies. And the Chinese government plans the next five years to continue to issue the government grant of 12 billion Chinese money to the pharmaceutical industry. Now that type of investment in China is visible. We can see it. A lot of companies receive such free grants for their drug development program.

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In China, the pharmaceutical industry has their own in-house drug development pipeline and now it's becoming more and more visible. The Chinese invented a new molecule entity in the various therapeutic areas. But also the Chinese pharmaceutical companies are increasing their interest in acquiring new drug candidates from foreign companies now. The Chinese pharmaceutical companies are increasing interest in co-developing with the foreign pharmaceutical companies for their drug candidates in China market.

This is my last slide. I just want to summarize what I just mentioned today. My message here is that in China, the regulatory environment is significantly improved and China can conduct good GCP standard clinical trials everywhere. However, training and close monitoring is essential for your successful clinical trials over there. And also one message I want to say here is the China domestic pharmaceutical companies are increasing their interest in acquiring drug candidates from foreign companies and increasing interest in co-developing drug candidates in China market with foreign pharmaceutical firms. I'm going to stop my time here and thank you for your attention. Thank you.

**FACILITATOR:** Are there any questions for Dr. Wei? Dr. Wei, could you comment on the different therapeutic areas that may be of most interest in the hospitals in China? Because I saw that cancer was ob-

viously of interest – the anti-cancer drugs – in about 20 of the hospitals. But obviously there are very many more hospitals and they are much larger than the hospitals here. So I was curious as to what the therapeutic areas might be.

**DR. WEI:** Yes, many hospitals have respective therapeutic centers like diabetes treatment centers, hypertension clinical centers, coronary disease and heart disease centers. And some diseases when in China are called for treatment to oncology hospitals.

Some of the oncology hospitals are huge. All the oncology patients are sent to the cancer centers. Their center may be 500 beds. It's a huge center for oncology. And that type of hospital across all the major cities all across the country in different regions. Therefore, if you conduct a specific clinical indication for your drug candidate, it's easier I think compared to here. You can directly target certain hospitals and the certain medical centers for their

strength in the particular therapeutic area. I think in that comparison, the enrollment is much easier and rapid compared to the US and the western societies.

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