US-China Joint Commission on Commerce and Trade
Medical Device and Pharmaceutical Subgroup
Pharmaceutical Task Force
April 11-12, 2005
Washington, DC

Overview

The U.S. - China Joint Commission on Commerce and Trade (JCCT) Medical Devices and Pharmaceuticals Subgroup meeting was held in Washington, D.C. on April 11-12, 2005. The Subgroup opened with a plenary session that included all participants on both the Medical Device and Pharmaceutical Task Forces. Each of the Task Forces then pursued separate tracks until a joint discussion on In Vitro Diagnostics (IVDs) and the U.S.- China Health Care Forum reunited them.

Brief self introductory presentations were made by the trade organizations present during the Pharmaceutical Task Force. In attendance were Biotechnology Industry Association (BIO), Consumer Healthcare Products Association (CHPA), Generics Pharmaceutical Association (GPhA), Pharmaceutical Research and Manufacturers of America (PhRMA), Plasma Protein Therapeutics Association (PPTA), Pharmaceutical Security Institute (PSI), U.S. Pharmacopoeia (USP), Regulatory Affairs Professionals Society (RAPS).

The meeting concluded with a joint plenary session in conjunction with the Medical Device Task Force and the signing of a new Work Plan. The next Pharmaceutical Task Force meeting will be in August 2005, in Beijing.

Opening Plenary Session

Deputy Under Secretary Timothy Hauser opened the Subgroup with remarks welcoming the Chinese State Food and Drug Administration delegation and expressing Commerce's appreciation to U.S. industry associations for their participation. Joseph Bogosian, Deputy Assistant Secretary for Manufacturing, who is the U.S. Co-chair of the Subgroup, noted the Subgroup's ambitious agenda, and emphasized the importance of these face to face meetings. DAS Bogosian also discussed the recent ITA reorganization, and how it would benefit the Subgroup. He also emphasized that the Subgroup meeting was an excellent opportunity to learn about changes in the regulatory environments in both countries, to discuss regulatory issues, and to work towards a better understanding of issues.

Pharmaceutical Task Force Meeting

The Pharmaceucal Task Force was Co-Chaired by Mr. Zhang Zhijun, Deputy Director General, Department of Drug Safety and Inspection, and Mr. Jeffrey Gren, Director of the Office of Health and Consumer Good at U.S. Department of Commerce. The Pharmaceutical Task Force focused on four issues:

1) Regulation of Clinical Trials
2) Local Analytical Testing Requirements

3) Regulation of bulk active pharmaceutical ingredients (APIs)
4) Data Exclusivity

Pharmaceutical Task Force Opening Comments

Mr. Gren began the Pharmaceutical Task Force meeting with his opening comments. He greeted the delegation warmly. He expressed regret that Mr. Chang Wenzuo was not able to lead the delegation this year, but extended a special welcome to Madam Zhao Li Li, Deputy Director of SFDA's Department of International Cooperation, who has stepped in to fulfill that role.

Mr. Gren pointed out that 2006 will mark the 10th year of this JCCT Subgroup. He noted that the pursuit of the best healthcare for the citizens of both countries has remained the steadfast guiding principle of this JCCT Subgroup.

Madam Zhao then spoke for the Chinese delegation in expressing their thanks to DoC for the preparation necessary in hosting this event and also for its continuing help to bridge SFDA and U.S. FDA. Continued information exchange with U.S. FDA is a high priority to SFDA.

SFDA Presentation of Current Pharmaceutical Industry Status and Upcoming SFDA Regulatory Priorities

There has been much development in the pharmaceutical industry recently. China is now the second largest active pharmaceutical ingredient (API) exporter. But investments are still limited and quality systems are not yet adequately sophisticated so the potential is far from realized. Nevertheless the multi national corporations (MNCs) have 630 active joint pharmaceutical ventures with China and total sales reached $364 Billion RMB (US $44 Billion) last year.

SFDA will work to align GMP provisions with those of international practice. Emphasis will be shifted from random to regular inspections. Other areas SFDA will devote resources to strengthening are the approvals process, safeguards to ensure drug safety, and means to protect the population from counterfeit drugs. SFDA will also broaden its focus to include not only pre-market surveillance, but also post-marketing surveillance. In addition, there are two other main tasks before SFDA. The agency will aim to strengthen regulatory activities in the rural areas and to increase vigilance over drug advertising.

It is SFDA's goal to strengthen China's drug regulatory framework to encourage not only foreign investment but also to support domestic companies' entry into international markets.

Issues of Interest

Regulation of Clinical Trials and Local Analytical Testing Requirements

Mr. Gren opened by summarizing the issue: that requirements for market approval in China often necessitate duplicative efforts that do not take advantage of the current and future direction of pharmaceutical product development and international practice.

He pointed specifically to the need for China to align its domestic Good Clinical Practice (GCP) regulations with those of ICH GCP guidance documents and international practice. Without clinical trial requirements in compliance with international practice, U.S. companies encounter substantial barriers to market entry, since these differential standards are likely to result in the need for locally conducted studies. These studies can be costly, can delay market entry (often as much as two to three years), and can be scientifically unfounded.

Furthermore, the requirements for Clinical Trials Authorization (CTA) are comparable to data requirements for New Drug Approval (NDA) in other major markets. In effect, companies must often wait for completion of development for completion of development programs elsewhere for data in order to begin trials in China, thus duplicating efforts and having to apply for approval much later than in other markets. Similarly, agency review and response times also account for the significant delay to market.

Another contributor to the delay to market is the requirement for full analytical testing. At the investigational, pre-marketing, and post-marketing stages, the product is submitted for government laboratory testing, under specifications that may be based on methodology used in china, rather than that developed and validated by the sponsor. Although this testing may be intended to guarantee product quality, practices for quality assurance have moved beyond repetitive batch testing with the introduction of finished product testing to ensure Good Manufacturing practice (GMP) compliance. Acceptance of a common standard would be key to removing these types of costly, duplicative requirements.

SFDA Response:
In response, the Chinese delegation agreed that they have heard much feedback from industry on these issues. They stressed that both imported and domestic drugs are subjected to the same requirements. For background purposes they clarified their classification system for drug applications:

> Class I : Never marketed internationally
> Class II: Marketed in foreign markets but not in China – Chinese legal requirements dictate that limited samples trial data be submitted. Trials similar to those for local drugs need to be conducted
> Class III: Already marketed in China – if sponsor can provide complete dossier then there's no need for clinical trial

They acknowledge that there have been complaints that some of the trials required are not scientifically based and/or are redundant. SFDA reminded all that its mission is to enforce the laws and uphold testing requirements; much of its actions need to be evaluated from all points of view.

SFDA also acknowledged that generic drugs that are not marketed in China but are already marketed in international markets face some difficulties.

In addressing Mr. Gren's concerns regarding the need for GCP alignment, Mr. Bai Huiliang first stated that trials must be conducted in Chinese SFDA certified facilities in accordance with Chinese law. He then went on to explain that there are 13 chapters devoted to GCP regulations (30 Articles, approximately), most of which are in compliance with international regulations. There are 185 certified clinical sites that are carefully monitored. During GCP certification, SFDA pays careful attention to management and quality control. During GCP implementation, there are specific requirements for the protocol and for investigators who conduct the trial. To ensure the safety of subjects, there is an ethics committee to provide guidance. This ethics committee is independent and provides feedback such as "agree" or "disagree with comments," etc.
SFDA carries out regular and random inspections and levies heavy penalties when deficiencies are found.

Despite improvements, SFDA acknowledged that shortcomings remain: 1) Understanding of GCP principles is limited in some places, 2) Ethics requirements are not fully understood, 3) Implementation of GCP is sometimes impaired. Thus, SFDA hopes to have more frequent dialogs with U.S. FDA on GCP implementation.

Open Discussion:
Mike Garvin, PhRMA
Mr. Garvin commended SFDA on their efforts on GCP. The two primary issues for PhRMA, however, remain regulation of clinical trials (review times, transparency, etc.) and local analytical testing requirements. A suitable environment for innovative R&D in China presents enormous growth potential. PhRMA wants to work closely with SFDA and U.S. FDA to support China's participants in the Global Clinical Trials Network.

Ms. Ling Ye, Hospira
Ms. Ye referred back to SFDA's comments earlier on generics. Why do generics face such difficult barriers when they have already been shown to be safe and effective?

SFDA responded that drugs that have never been marketed in China are regarded as "new drugs" regardless of whether they are innovative or generic. "New drugs" are divided into the following three categories:

1) Innovative – never marketed in China
2) Generics – reference drugs never marketed in China (so regarded as new drug). Preparation of these dossiers could encounter more difficulties
3) Generics – reference drugs marketed in China

David Lepay, U.S. FDA
Mr. Lepay clarified that FDA accepts data from international trials as basis for approval for new drugs. There is no requirement that a clinical trial must be conducted in U.S., but these studies must meet the follow criteria. FDA must be able to:

1) Inspect the trial sites
2) Ensure that the trials were conducted in an ethical manner

3) Ensure that the trials are applicable to U.S. population (for example, through bridging studies).

Mr. Lepay said the U.S. system has worked well for the last 25 years. Where it has not worked the FDA is trying to revaluate and finalize changes to tighten the system. The changes propose to:

1) Link U.S. acceptance requirements to international acceptance requirements, e.g. U.S. GCP guidance documents to ICH GCP guidance documents. FDA is working with three groups that are also aligning their standards to ICH efforts: WHO, ISSO, and PAHO. Goal is to get consistency – same standards for trials throughout the world.
2) Require new documentation to ensure that GCP was followed
3) Ensure the right of inspection – site as well as documentations that support GCP, etc.

Mr. Lepay continued his presentation and spoke of the two levels of GCP training that are effective:

1) Educational exchanges directed at investigators who will conduct the trials
2) Educational exchanges directed at regulators to increase understanding of how FDA inspects and trains inspectors. Dialogs between regulators are important, since the regulators in turn teach others. Consistency reduces waste and duplication.

Mike Garvin, PhRMA
Mr. Garvin is also the coordinator of PhRMA's ICH efforts. ICH created the Global Cooperation Group to develop regulatory training programs for economics with developing regulatory systems. He encouraged the Chinese SFDA to participate in the APEC Life Sciences Innovation Forum (APEC LSIF) to further their GCP efforts.

SFDA Response to David Lepay on GCP comments
In response, SFDA made three points:

1) China pays close attention to ICH developments and takes part in meetings, even though they are not members. Many technical guidelines in China now follow ICH. China is actively moving in the same direction as ICH.
2) Like U.S. FDA, SFDA also considers clinical results from trials conducted elsewhere in the world when they are applicable. It must be noted though that China does not have enough manpower to conduct foreign trial inspections.
3) SFDA proposed that China's investigators and regulators need to be trained in methods to implement GCP and in protocol design.

Local Analytical Testing Requirements

SFDA responded to Mr. Gren's comments on local analytical testing requirements by stating that SFDA is driven by two incentives: 1) To make sure that quality control standards are met in all phases of drug development, and 2) To make sure that the products can be postmarketing tested adequately. Thus, it is important to have consistent testing standards that meet China's needs from the beginning. SFDA agrees with moving from lots inspection to a quality systems approach, but noted that the agency is shorthanded and cannot send inspectors.

Bulk Chemicals

Mr. Gren framed the issue. China ranks among the highest in importance internationally as a supplier of bulk active pharmaceutical ingredients and intermediates to pharmaceutical manufacturers. SFDA regulates the manufacture of bulk chemicals that have medical use by requiring that any chemical substance used to produce legitimate drugs be granted an "Approval Number" by the SFDA. Nevertheless, there have been unauthorized sales of bulk material whose only use is for the manufacture of patent-protected medicine.

These unauthorized APIs in turn could be sold to drug counterfeiters who endanger public health by using these API-like materials without caring for the assurances that come with SFDA regulation of safety and current Good Manufacturing Practice (cGMP).

Industry makes several recommendations to SFDA in addressing issues related to bulk active pharmaceuticals ingredients:

1) SFDA could support modifications to regulatory framework to ensure that production and trading of a medication's active ingredient in bulk form fall under the same regulations governing production and trading of pharmaceuticals.

2) SFDA could take steps to increase its confidence that API substances already registered are indeed used by their manufacturers to make pharmaceutical finished products or that they are sold to other drug companies licensed by SFDA to manufacture finished pharmaceutical products. For example, SFDA could impose record-keeping requirements, mandating that each approved API manufacturer keep a complete and reliable record on the kinds of approved API substances it produces as well as the identity of the purchasers, taking special care to document purchasers' SFDA licenses.

3) SFDA could also, with support from high-level Government, establish and lead an inter-ministerial task force to combat the manufacture and sale of APIs as chemical products for illegal use.

4) SFDA could support the modification of the Criminal Law and Criminal Procedure to ensure that violations of the existing laws and the regulations be subject to more vigorous criminal prosecution.

Mr. Gren emphasized that counterfeit drug enforcement is a global issue and solutions will require global cooperation.

SFDA Response:
SFDA responded by saying there are 1,000 manufacturers of API for chemical uses, all working in compliance of Chinese GMP regulations. "Their products are legitimate." In accordance with WHO pre-sale certification is required for export. There exists an information exchange mechanism whereby purchasers can check for licensing.

Open Discussion:
Mr. Gren asked the delegation how bulk API is monitored to prevent its use in counterfeit drug production.

SFDA answered that they encourage manufacturers who buy to check for appropriate paperwork, and that it is the responsibility of the receiving countries to monitor the use of API exports to that country.

Mr. Gren then pointed out that sale of APIs to other countries where the bulk chemicals then end up in counterfeit products is a big problem. Mr. Gren added that global cooperation is the only way to control counterfeit drugs.

SFDA acknowledged that this is a confusing issue. It is required in other countries of manufacturers to have the Drug Master File (DMF) of the chemicals they use. In China they must obtain the appropriate SFDA documents. China's Article 48 stipulates that if bulk chemicals are used without SFDA licensing and proper documentation the finished products are considered counterfeits, even if they meet regulatory quality standards. The issue is manufacturers of other countries getting bulk material from chemical manufacturers. SFDA does not have jurisdiction – this is a trade issue, SFDA cannot stop exports. SFDA cannot track the APIs to see if they are used for legitimate use. Unless China says to other countries they can only import SFDA licensed bulk chemicals – SFDA has no jurisdiction.

There was consensus that further discussions will be beneficial.

<u>Data Exclusivity</u>
Mr. Gren framed the issue. In 2002 China adopted data exclusivity provisions as part of its WTO ascension. These provisions provide no less than six years of protection commencing from the date of marketing approval in China. Mr. Gren asked the SFDA delegation how this six year exclusivity is currently being implemented asked for recent developments addressing issues raised by industry.

SFDA said that without approval from the data holder SFDA will not license, since all data will need to be sourced. Furthermore, SFDA will not release data. SFDA emphasized that the same standards apply for all applications, whether foreign or domestic. The Chinese delegates then noted the difficulty associated with obtaining a working definition for new

chemical entity (NCE). They also raised concerns regarding the disclosure of data, e.g., if info is released through the media, such as internet, would that still be considered data disclosure?

SFDA asked for specific examples of data exclusivity infringement. Ms. Cathy Yang of RDPAC reminded the delegation of the data exclusivity workshop for SFDA regulators that occurred in February earlier this year. Specific case studies were analyzed then. Mr. Mike Garvin of PhRMA said that PhRMA had examples but would need prior consent from innovator companies before disclosure.

Mr. Gren proposed that a dedicated session with U.S., Chinese, EU regulators, as well as other multinational partners such as WTO, on these issues be considered. Mr. Garvin of PhRMA said PhRMA would support such effort. SFDA delegation also favorably entertained the idea, but added that developing countries should also be part of the conversation. SFDA emphasized that the commitments made during WTO ascension will be honored, but welcomed this opportunity to discuss case studies from which implementation principles can be derived.

Closing Plenary Session

The Subgroup closed with the Summaries of the Task Force discussions by the Task Force Co-chairs, and the signing of the Subgroup Work Plan for the coming year.
The signed Work Plan proposes the following activities (the detailed Work Plan is attached):

July 2005	In Vitro Diagnostics Roundtable
July 2005	JCCT Pharmaceuticals Good Clinical Practices Workshop
August 2005	JCCT Medical Devices Good Manufacturing Practice Workshop
August 2005	JCCT Medical Devices Task Force Meeting
August 2005	JCCT Pharmaceutical Task Force Meeting
Fall 2005	U.S. – China Standards and Conformity Workshop
Spring 2006	JCCT Medical Devices and Pharmaceuticals Subgroup Meeting and Medical Device and Pharmaceutical Task Force Meetings (Beijing)

After the signing, DAS Bogosian thanked participants for the time and energy put into Task Force discussions, and noted that real progress made on many of the issues discussed. As this was his first Medical Devices and Pharmaceuticals Subgroup that he had chaired, he noticed the bond of friendship between participants in the Subgroup, and stated his hope that these bonds will continue to grow stronger as the Subgroup participants continue working together on the issues.

Assistant Secretary for Manufacturing and Services Albert Frink brought the Subgroup meeting to a close by introducing his new position as the A/S for Manufacturing and Services and his intended goals. He also stated that this Subgroup exemplifies a successful way two countries can work together to increasing market access and opportunities for growth in the health industries between our two countries, and that he was pleased that this Subgroup in particular has been so active and successful.

Accomplishments
This Pharmaceutical Task Force meeting was very successful in advancing Department of Commerce's healthcare agenda. Accomplishments include:

- Engaging SFDA in in depth discussion on China's progress toward aligning its Good Clinical Practices (GCP) methodologies with those accepted internationally. Clarified training needs of the Chinese SFDA regulators in furthering that goal and laid groundwork for a GCP workshop (July 13 –15 in Beijing) as next step in addressing that need.

- Obtaining SFDA's view on current status of the Chinese pharmaceutical industry and a preview of SFDA's upcoming regulatory priorities.

- Ascertaining the need and soliciting support for further talks dedicated to appropriate regulation of bulk active pharmaceutical ingredients (APIs) and implementation of data exclusivity provisions. These issues are to be viewed on a global scale, requiring input from Chinese, EU, developing world, and U.S. regulators, as well as multinational partners such as WTO.

- Engaging SFDA in a discussion about U.S. FDA regulation of In Vitro Diagnostics products and why the U.S. approach would be beneficial for Chinese companies as well as Chinese regulators.

Next Steps

- Generate interest and support among appropriate Chinese, EU, developing world and U.S. regulators, as well as multinational partners such as WTO, for talks focused on appropriate regulation of APIs, with an eye toward minimizing drug counterfeiting incidence. Implementation of data exclusivity provisions is another area of focus that will need international input. Will work with PhRMA to solicit industry input and specific examples of data exclusivity infringement to be used as case studies for discussions.

- Implement plans for pharmaceutical Good Clinical Practice (GCP) workshop, to be staged in Beijing from July 13-15, 2005. The objective of this workshop is to facilitate China in aligning its GCP methods with those accepted internationally.

Pharmaceutical Task Force Participants

Chinese State Food and Drug Administration
Mr. Bai Huiliang, Director General, Department of Drug Safety and Inspection
Ms. Zhao Lili, Deputy Director General, Department of International Cooperation
Mr. Zhang Zhijun, Deputy Director General, Department of Drug Registration
Mr. Wang Zhexiong, Deputy counselor, Department of Drug Safety and Inspection
Mr. Yin Hongzhang, Division Director, Division of Biologics, Department of Drug Registration
Mr. Wang Xiangyu, Program Officer, Interpreter, Department of International Cooperation

U.S. Government:

U.S. Department of Commerce:
Timothy Hauser, Deputy Undersecretary for International Trade
Albert Frink, Assistant Secretary for Manufacturing and Services
Joseph Bogosian, Deputy Assistant Secretary for Manufacturing
Jeffrey Gren, Director, Manufacturing and Services/Office of Health and Consumer Goods
Cheryl McQueen, Director, Market Access and Compliance/Office of China Economic Area
Kristie Mikus, Pharmaceuticals and Biotechnology International Trade Specialist, Manufacturing and Services/Offices of Health and Consumer Goods
Victoria Kao, Pharmaceuticals and Biotechnology International Trade Specialist, Manufacturing and Services/Offices of Health and Consumer Goods
Emily Arakaki, Biotechnology International Trade Specialist, Manufacturing and Services/Offices of Health and Consumer Goods
Jennifer May, Trade Policy Analyst, Market Access and Compliance/Office of China Economic Area
Elaine Wu, Attorney-Advisor, U.S. Patent and Trademark Office (was scheduled to attend, but a last minute conflict developed)

U.S. Food and Drug Administration:
David Lepay, Director of Good Clinical Practice Programs, Office of the Commissioner

U.S. Pharmaceutical and Biotechnology Industry:
Mike Garvin, Pharmaceutical Research and Manufacturers of America (PhRMA)
John Fowler, Chief Business Officer, U.S. Pharmacopoeia (USP)
John Hu, Vice President International – China, U.S. Pharmacopoeia (USP)
Nancy Blum, Director, Global Assistance Initiatives, U.S. Pharmacopoeia (USP)
Kathleen Jaeger, President, Generics Pharmaceutical Association (GPhA)
Christine Simmon, VP, Public Affairs & Development, Generic Pharmaceutical Association (GPhA)
Marvin Samson, Teva USA, Representing GPhA
Ling Me, Hospira Inc., Representing GPhA
Lila Feisee, Director for Intellectual Property, Biotechnology Industry Association (BIO)
Sara Radcliffe, Director for Science and Regulatory Affairs, Biotechnology Industry Association (BIO)
Tom Kubic, Pharmaceutical Security Institute (PSI)
David Spangler, VP – International, Consumer Healthcare Products Association (CHPA)
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Cathy Yang, Senior Manager, Drug Regulatory and Medical Affairs, Research and Development based Pharmaceutical Association in China (RDPAC)
Sherry Keramidas, Executive Director, Regulatory Affairs Professionals Society (RAPS)