U.S. – China JCCT Pharmaceuticals and Medical Devices Subgroup Meeting Summary

March 28 and 29, 2006, Beijing

Participants: See attachment.

Meeting Agenda:

I. OPENING CEREMONY
II. COMBINATION PRODUCTS
III. PHARMACEUTICAL TASK FORCE MEETING
   1) ELECTRONIC LABELING
   2) DATA EXCLUSIVITY/PATENT LINKAGE
   3) GENERICS
   4) EXCIPIENTS
   5) PHARMACEUTICAL TASK FORCE WORK PLAN
IV. MEDICAL DEVICES TASK FORCE MEETING
   1) DUPLICATION OF TESTING AND INSPECTION PROCEDURES
   2) STATUS OF ADVERSE EVENT REPORTING REGULATIONS
   3) DRAFT REGULATIONS ON MEDICAL DEVICE RECALLS
   4) DISCUSSION OF WORK PLAN ACTIVITIES
   5) STATUS OF IVD REGULATIONS
   6) FUTURE AREAS OF U.S. - CHINA COOPERATION
V. CLOSING PLENARY

I. OPENING CEREMONY

Mr. Wenzuo Chang (SFDA, Director General, International Cooperation Department) - Opening remarks. Welcomed the U.S. delegation. Introduced the SFDA staff and the participants from the Chinese pharmaceutical associations.

Ms. Lusheng Hui (SFDA, Deputy Commissioner) – Welcomed the U.S. and Chinese delegations. Congratulated all involved on the achievements of JCCT, which promoted the collaboration and benefited the citizens of both countries. JCCT has served as a dialogue and a platform to protect regulatory system, and enhance the trade between the U.S. and China.

Mr. Jeffrey Gren (DOC) – Expressed sincere appreciation to SFDA for hosting the Subgroup, and noted that ten years working together is a significant event. Introduced the U.S. delegation members. Mr. Gren covered three topics during his presentation – Subgroup accomplishments, the regulatory difference between medical devices and pharmaceuticals, and future Subgroup challenges.

A. Subgroup Accomplishments:
   - Ten years of working together with mutual cooperation is a significant achievement. U.S. - SFDA established close working relationship and have collaborated in many activities.
   - The U.S. and China have cooperatively organized several training programs including medical devices GMP, Quality Systems, In Vitro Diagnostics (IVD), medical device Good Manufacturing Practice, pharmaceutical Good Clinical Practice, Patent Linkage, and Data Exclusivity. These training seminars have resulted in a greater understanding on the part of SFDA regulators, increased communication, and improvements in the quality of China's regulatory medical devices and pharmaceutical systems.
   - The discussion and exchange of information during the many Subgroup and Task Force meetings have also led to regulatory modifications in many areas leading to a more streamlined regulatory review process, and procedures to insure safe medical products for Chinese citizens.

B. Differences Between Medical Devices and Pharmaceuticals
   - Medical devices have a relatively recent regulatory history and the products are very diverse. Also, most medical device manufacturers are mid to small size.
   - Pharmaceuticals have a long regulatory history and most companies are large multi-national firms.
   - Medical devices are based upon mechanical, electrical, and material engineering, and are designed to perform specific functions.
   - In the case of pharmaceuticals, products are developed through the process of trial selection and many products are in development, but very few ever make it to market.
   - In most cases the user of a medical device needs to be trained, and medical device innovation is rapid. The product life cycle for advanced medical devices is short, often less than 18 months.
   - For pharmaceuticals the products has a long life cycle. Pharmaceuticals are absorbs (metabolized) in the body, while medical devices are no absorbed in the body. Training is required to prescribe drugs.
   - Counterfeit products are a problem for both medical devices and pharmaceuticals, but the problem of counterfeit medicines is much more severe.
   - There are regulatory concerns with reuse of single use medical devices, and used medical devices, which is not the case for pharmaceuticals.

C. Future Vision:
   - Changes are happening dramatically in China, and China is one of the fastest growing markets for medical devices and pharmaceuticals in the world.
   - China is also a major manufacturer of medical devices and pharmaceuticals. By the 20-year Subgroup anniversary, China will be one of the world's largest markets for medical devices and pharmaceuticals, and will also be one of the world's largest producers for both of these industries. For example, experts predict that by 2020 China will be the second largest global market for medical devices.

- Currently 40 percent of global APIs (Active Pharmaceutical Ingredients) are produced in India and China, by 2020 experts predict that 80 percent of APIs will be produced in India and China.
- With growing global dominance in medical device and pharmaceuticals comes greater global responsibility.
- I would like to outline some goals for the Subgroup and China's global position in relation to this challenge.
- I believe that the Subgroup will become even more important in that the U.S. and China will be world leaders in medical devices and pharmaceuticals.
- A future challenge for U.S. and China to cooperate on is stopping the spread of counterfeit medicines. I hope that the US and China will become global leaders to overcome this problem.
- It is also important for China to continue to participate in global forums on pharmaceuticals and medical device – Global Harmonization Task Force for medical devices and the International Conference for Harmonization for pharmaceuticals.
- Since the start of the Subgroup in 1996 China has made great progress in modifying its medical devices and pharmaceutical regulatory systems based upon international practice.
- However, I expect that during the next ten years we will see an even more dramatic change as China becomes one of the major regulatory systems in the world and a major center for medical device and pharmaceutical manufacturing and innovation.
- As China becomes on of the world's major pharmaceutical manufactures, we expect China will place more emphasis in important issues, such as IP, data exclusivity, and counterfeit medicines.

D. Conclusion:

- I am personally looking forward to continuing to work with China on achieving the goals I have cited, in my role with the Subgroup.
- I am looking forward to the year 2016 and I sincerely hope to participate in the 20-year Subgroup anniversary.

Mr. Wenzuo Chang (SFDA) – The JCCT Subgroup has resulted in significant dialogue and cooperation between China and the U.S. This annual meeting is of particular importance because it is just prior to Chairman Hu's visit to the U.S. and because it is the 10th anniversary. For the past 10 years, based on equality and open dialogue, we achieved great improvement and promoted trade and investment. This group made significant contribution. Dialogue, cooperation and win-win was the theme of this group, and will be the goal in the future. I want to address two issues during my remarks:

1) Review: We established this JCCT Subgroup by signing a memorandum in 1996. In 1998, the memorandum was revised when the SFDA was formed. We worked together to strengthen the regulatory system on pharmaceuticals and medical device, reduced and eliminated the regulatory and trade barriers. We organized many trainings on GMP, GCP, data exclusivity and so on. The U.S. side made significant contributions. Both sides make active feedback for each other's concerns.

2) Future Vision and Continued Cooperation:

- China will continue to be compliant with the agreed up on terms and procedures to work.
- Within the framework of the JCCT Subgroup we will continue to discuss issues of concern for both countries.
- China will maintain international rules and regulations.
- The Subgroup should provide more input on solving various issues and provide safer medical products to citizens of both countries, and make contributions to the friendship between the U.S. and China.

Thanks to DOC and SFDA, and particularly Mr. Gren for the contributions to the JCCT Subgroup.

II. COMBINATION PRODUCT

Note: Medical Devices and Pharmaceuticals Task Forces joined for this session

John Stigi (FDA, Center for Device and Radiological Health) – Made the presentation on combination products, its definition, application and review processes.

Definition of combination product: 21 CFR 3.2 (e) (summarized below)

- Two or more regulated components combined or mixed in some ways as a single entity
- Two or more single/separate products packaged together.
- A product packaged separately but intended for use only with an approved individually specified product, where both are required to activate the intended use.

Combination product review can involve offices for drug, device and biologics. There is no independent office to handle the review, nor a unique application form. Combination product is handled within the existing FDA regulatory framework. .

In 2002, the FDA established the Office of Combination Products. The responsibility of the office includes: 1) has the final word on which center will be the lead review center, 2) resolves issues if the review takes too long, 3) provides technical supports to other centers, 4) develops policies regarding combination products, 5) reports to Congress on the implementation of the policies on combination products.

PMOA (Primary Mode Of Action) definition was published on 8/25/05 and effective on 11/23/05: the single mode of action that provides the most important therapeutic action, or the action that provides the most important overall therapeutic effect. PMOA dictates which division will be the lead division for reviewing the application and is charged with reconciling different requirements that may exist under the individual divisions, such as GMP, number of clinical trials, user fees, labeling, and so on. The firm can request for designation (RFD), and should make the request early in the product development process, which allows the firm to work with the correct center in the FDA early on. Firm

should recommend which center should be the lead reviewer. If the FDA does not respond within 60 days, then the firm's recommendation will be in effect. RFD should be brief in length (<15 pages). PMOA definition is very new. The FDA will take any opportunity to clarify or revise the rules. The FDA encourages industry to give feedback on any confusion or question.

III. Pharmaceutical Task Force Meeting – Following the lunch break, the Subgroup attendees split into the two Task Forces – Medical Devices and Pharmaceuticals.

Opening Session

The Pharmaceutical Task Force was Co-chaired by Mr. Zhang Wei, Director General, Drug Registration Department, SFDA. Other SFDA participants included:

- Ms. Xie Xiaoyu, Deputy Director General, Drug Registration Department
- Mr. Feng Guoping, Counsel, Drug Registration Department
- Ms. Ding Jianhua, Division Director, Division of Chemical Drugs, Drug Registration Department
- Dr. Yin Hongzhang, Division Director, Division of Biologics, Drug Registration Department
- Mr. Xie Shichang, Division Director, Division of TCMs, Drug Registration Department
- Mr. Liu Jingqi, Consultant, Division of Biologics, Drug Registration Department
- Mr. Sun Lei, Deputy Division Director, Division of Drug Supervision and Inspection, Market Compliance Department
- Ms. Zhang Yanli, Principle Staff Member, Division of Chemical Drugs, Drug Registration Department
- Ms. Zhang Qi, Principle Staff Member, Division of Regulations, Policy and Regulations Department
- Dr. Lin Changyuan, Principle Staff Member, Division of Regulations, Policy and Regulations Department
- Mr. Wang Xiangyu, Senior Staff Member, Division of Cooperation, International Cooperation Department
- Mr. Wang Jiawei, Program Officer, International Cooperation Department
- Ms. Dong Jiangping, Director of Information Department, Center for Drug Evaluation

The U.S. Co-chair was Mr. Jeffrey Gren, Director, Office of Health and Consumer Goods, U.S. Department of Commerce. The U.S. delegation included:

- Chris Costigan – Director, Corporate Affairs – Asia, Pfizer, PhRMA
- John Farah– Vice President for Exports – Cephalon Inc., BIO
- John Hu – U.S. Pharmacopeia
- Peter Scheuer, Director, Research and Development based Pharmaceutical Association in China (RDPAC)
- Cheryl Xu, PhRMA
- Cathy Yang, Senior Manager, Drug Regulatory and Medical Affairs, RDPAC
- Ling Ye, Manager, Hospira, Inc, Generics Pharmaceutical Association, GPhA

- Alexa Smith, Colorcon, Inc., International Pharmaceutical Excipients Council (IPEC)
- Richard Craig – Commercial Officer, U.S. Embassy
- Ms. Shuyu Sun – Commercial Officer, U.S. Embassy

The Pharmaceuticals Task Force focused on these issues:
1) Electronic Labeling with SPL Technology
2) Data Exclusivity and Patent Linkage
3) Generics
4) Proposed SFDA Regulations on Excipients
4) Discussion of Work Plan Activities
6) Future areas of U.S. - China Cooperation

A. ELECTRONIC LABELING with SPL Technology - Prof. Zheng, Qiang (Center for Pharmaceutical Information and Engineering Research, Peking University) – Professor Zheng made a presentation on the new structured product labeling (SPL) technology. This technology facilitates electronic labeling storage, transfer, and accessibility. The U.S. FDA has recently adopted SPL as means to manage its electronic labeling database. SFDA staff expressed interest in learning more about this new technology and there were several questions asked by SFDA staff.

B. DATA EXCLUSIVITY (DE) and PATENT LINKAGE (PL)

Mr. Gren (DOC) – DE and PL are very important areas of our interest. Proper protection of DE and PL will create research and innovation environment in China and enhance the investment and collaboration between the two countries.

Mr. Mark Cohen (USPTO, Beijing Attaché) – Many times, in the JCCT we have raised issues on DE and patent linkage by U.S. companies, but SFDA has rightfully asked for examples. There is also a need for transparency on how the process for DE actually works under SFDA's system and procedure such that we no longer engage in abstract discussions on the issue of DE.

Ms. Minna Moezie (USPTO) – Minna thanked the JCCT subgroup for the opportunity to discuss DE and patent linkage with specific reference to consideration of patent rights in the drug approval process. This meeting presents an opportunity to learn more about the system, as it exists for the process of DE and patent linkage to overcome confusion on the U.S. side as to how these are managed by SFDA. Could the Chinese delegation respond to the questions relating to their DE system sent to them in advance of this meeting? We can take these one by one.

1) We understand that Article 35 of the implementing regulations provides for DE for NCEs (New Chemical Entity). The question we have is "What qualifies a drug as an NCE under Article 35?" Currently, there is confusion for the U.S. industry on this definition.

2) What is the legal or regulatory framework for establishing requirement of generic companies to seek approval for their generic versions of the innovator products?
3) What is the policy on DE for products approved prior to December 1, 2002, when new policy on Drug Registration took effect?
4) We are unclear on the scope of DE; does it apply to biological products, as it does to chemical products?
5) What is the procedure for obtaining Data Protection – is it automatic or is there an application required by the innovator?
6) Who enforces the DE protection and by what measures?
7) For future discussions and consistency of these discussions, which Department of SFDA will be responsible? Can the official of this Department participate regularly in the JCCT discussions on this important topic?
8) Who is designated contact on matters of DE if there is such a contact available at this time?

SFDA Response– For most of the current SFDA participants present, this is their first time here at this forum and they need to understand how the practice is administered in the U.S. Although Article 35 sets forth the principles, there are not sufficient specific requirements set forth in Chinese law or procedures. Meanwhile, the Chinese already pay attention to DE and patent exclusivity, which will be considered when drafting new policies. In China, the local legal system cannot permit strict copying of the procedures as used in the U.S. Especially with reference to patent linkage where courts, the patent office, and other agencies have not established the policy for enforcing. SFDA is trying to communicate with Courts and the State Intellectual Property Office (SIPO) to understand how all three units can cooperate. Recently, the Chinese patent law has been revised. Last week, a specific forum was established with foreign experts to participate for better understanding of the related issues. SFDA also wishes to take the opportunity of this Subgroup to learn about the issues and US practices.

Mr. Mark Cohen – Noted that Mr. Zhang's answer demonstrates the need to have better definition in the laws, since laws, not people, define the practice of DE and patent linkage. China's recent focusing on innovation is very germane to its growth and China's dealings with the U.S. system.

Minna Moezie – Under TRIPS, Article 39, these are not specifically called NCE protection in the U.S. We call this new drug protection. Data relating to new chemical products is given five years protection if it applies to a drug product that has no active moiety previously approved by FDA in any other drug product. This means that, in U.S., if a drug contains any approved active moiety, it will not be eligible for five-year protection. In other jurisdictions, if a drug contains at least one new active moiety, then the drug would be eligible for DE. The active moiety is the molecule or ion that is responsible for the therapeutic action excluding the appended portions. For example, in morphine freebase and morphine hydrochloride the active moiety is morphine and all the other salts or adducts are considered equivalent active moieties.

Dossier requirements for generic applications. Under U.S. rules, in a generic application with same dosage form as the originator, FDA cannot require the generic manufacturer to provide more data than bio-equivalency data. Hence, a complete clinical trial showing safety and efficacy cannot be required by FDA. In the U.S. procedures, this is considered an abbreviated NDA (ANDA).

The scope of exclusivity provisions of Hatch Waxman Act clearly applies to small chemical entities, meaning that for small organic molecules, the period of non-reliance is five years, which cannot be relied upon by generic applicants. In the U.S., there is no system for showing equivalency of biological products. The FDA has determined that an ANDA process for biologicals would result in the approval of unsafe products. The consequence is that for every new biological applicant in the U.S., an entire clinical efficacy and safety package is required.

As part of NDA approval, the originator must request DE as part of its NDA application.

For NCE/DE protection, FDA is not permitted to accept a generic application for a product with the same active moiety during the five year DE period.

Mr. Zhang of SFDA, asked his staff to explain SFDA procedures.

SFDA Response– In any new applications for approval, the data is collected by the applicant (pre-clinical, toxicity, safety, clinical) that is audited by Provincial SFDA office receiving the application.

For generic products, SFDA adopted ICH guidelines with bioequivalency study requirements. A combination of several small molecules requires, for example, new clinical trials. Therefore, Mr. Ding asserted that by requiring each of the items from a new applicant, this ensures the exclusivity of each applicant. He expressed hope that in the future, more information would be exchanged. Other authorities responsible for DE and IPR must become more responsible. Over the past several years, SFDA has been put in a very difficult position just by the point of IPR and DE.

SFDA is responsible under Chinese law only for quality, safety and efficacy; however, other agencies are responsible for enforcement of IPR and DE. No patent linkage has been established under Chinese patent law. If SFDA tried to suspend or stop an applicant based on patent infringement, SFDA is at risk of being taken to court by applicants since Chinese law does not authorize SFDA to act as DE and IPR policeman. Such disputes must be directed to the courts, not by SFDA. If either the court or the Chinese patent office determines that IPR or DE is violated, then and only then can SFDA suspend a marketing authorization.

Mark Cohen – Without skipping too far ahead to linkage, the multinationals have been advised of the Chinese system, but also recognize the value of even a de-minimus linkage administered by SFDA. USPTO has had extensive conversations with SIPO and we are

aware that National IP Strategy Office of China is revising the patent laws with foreign encouragement to include strong patent linkage provisions.

Just last week, Jung Fa Guang in meeting with Mark Cohen expressed interest in how to strengthen the law. Any movement towards commercialization may be considered a civil infringement to a patent holder. We are seeking either statutory regulation or definition of circumstances where an approval by SFDA would be considered patent infringement in and of itself. It also seems that it is in China's interest to have companies seeking to market a product on notice that their activities might be considered infringement and hence, uneconomical for such companies to progress their applications and pre-commercial obligations without adequate notification of their potentially infringing acts. The earlier one knows, the better for all concerned to make economical innovation and healthcare and avoid the problems thrown at SFDA's doorstep in the absence of adequate DE and linkage.

Returning to the matter of DE, many U.S. companies raise concerns about DE and lack of current transparency and their data packages protected in accordance with China's laws and regulations. Mr. Cohen wanted to know if the complaints were well founded or not. Some companies illustrate that at the same time, or shortly before their own marketing approval, up to 60 generics were approved using the originator's own clinical data (reliance of generics on innovator's data) whether under AP, patent or accelerated review by SFDA. There is a concern that under current SFDA regulations, class 3 (generic) applicants are able to secure rapid approval during the period of review of the originator's application with the likelihood of reliance upon the originator's data.

SFDA Response- SFDA was somewhat dumbfounded and believed that there must be a misunderstanding, stating it is not possible for up to 60 generics to have obtained approvals before the originator's application is approved. If the classification is the same, both the imported and domestic must follow the same regulations.

Cheryl Xu – This is not a misunderstanding, but the experience of innovator firms in the Chinese market.

Mark Cohen – Mark indicated that he is collecting information, which is confidential at this point, but either he, or preferably, the originator companies themselves, may disclose the circumstances in the future. Such frank disclosures would illustrate the need for clear rules and procedures to make quite transparent the process and internal procedures of SFDA.

Peter Scheuer – I am happy to hear that new SFDA leadership is willing to hear about the circumstances and understand the issues raised by lack of linkage and frailty of reliance upon originator data jeopardizes innovation in China. RDPAC and the foreign industry are quite interested in establishing a dialogue to reveal solutions to a heretofore, challenging situation for originators coming to the Chinese market with innovative substances. In the past, companies were told that a) they didn't file for DE, or b) that DE was automatic, or c) that biologics were included or not included in provisions for DE.

We are interested in constructive conversations with identified, responsible parties within SFDA.

SFDA Response- SFDA expressed concerns of the past SFDA leadership, particularly in regards to registration and that now, there is opportunity for fresh dialogue, understanding and working relationship.

SFDA Response– Ownership of rights to data or patents is not the purview of SFDA. In China, civil ownerships are authorized by the patent office or the trademark office. Any disputes are settled by the courts. SFDA and applicants have only an administrative role; ownership rights are not suitably determined by SFDA. The best way is for articles to be put in the Chinese patent law to endow SFDA with administrative authority to arrest/suspend an application.

Mark Cohen – About a year ago, Elaine Wu (USPTO) visited with Chinese officials in order to discuss where legal reform may be necessary to ensure a robust patent linkage system. We are aware of the unique features of the Chinese legal system but also acknowledge that between 60,000 – 100,000 cases are determined at an administrative level that are uniquely available in China which are not permissible in the US. For example, the Chinese patent office is able to punish infringers where USPTO is unable to administer justice or enforce intellectual property rights.

Peter Scheuer - Acknowledge that there is a limited group of stakeholders having to do with pharmaceutical IPR and DE. Maybe five inclusive of SDFA, SIPO, courts, others such that if RDPAC and USPTO able to participate in a meaningful discussion with all the stakeholders, there is a greater chance of clarity for all concerned as to how to achieve satisfactory results for all concerned.

SFDA Response- From previous experience preparing for an International (Rome) Congress on IPR, the Patent office and TM office acknowledged a scarcity of cases for such infringement of IPR in the pharmaceutical industry except some counterfeit TMs.

SFDA Response – We need concrete examples of problems encountered.

SFDA Response– We need to understand what the exact differences are in our regulations. For example, which part of our rules is not good enough? What needs to be revised or added?

Mr. Cohen suggested some topics to work on in the near future:

- DE and PL
- Patent terms evaluation and inspection
- Civil enforcement
- Anti counterfeiting

Mr. Gren (DOC) – Let's develop some action items for near future. With Mr. Cohen here in Beijing, and RDPAC, we can start to work with SFDA right way, and need not to wait until the next Task Force meeting.

SFDA agreed with Mr. Gren's suggestion, and that following the meeting SFDA staff would begin working with Mark Cohen**.**

C. SUBGROUP WORKPLAN– PHARMACEUTICAL ACTIVITIES

Mr. Gren from DOC outlined the proposed the pharmaceutical activities on the proposed Work Plan (the workplan was provided in advance to SFDA and was included in each participant's folder.)

SFDA had two questions regarding the work plan. 1) The target audience for the GCP training should be inspectors or investigators? 2) For the GCP training with an ethics focus, whether classroom or on site training will be more effective?

Mr. Gren (DOC) said that we want to know what you want so that we can get the right trainers. Then, get funding from the appropriate sources, industry and/or government.

SFDA Response: Considering our responsibility, we would like the training to target inspectors. For the ethics committee inspection, we want to have on site inspection to learn by hand-on experience how the U.S. inspectors to inspect ethics committees in the U.S.

Mr. Gren (DOC): If SFDA has funding to travel to the U.S., I don't think there is a problem to conduct the training in the U.S. I will have to confirm with U.S. FDA that there is no problem to have non-U.S. personnel to visit the sites. Mr. Gren solicited the U.S. delegations input.

Ms. Ling Ye (GPhA) – Hospira will be glad to host SFDA's visit, tour of facilities and the R&D centers.

John Farah (Cephlon) – Cephlon will also be glad to host, given the understanding of SFDA's purpose of the visit.

Next there was discussion about the next Pharmaceutical Task Force Meeting. Mr. Gren suggested Beijing during late August. SFDA said that they were very busy and could only afford a one-day meeting. Mr. Gren responded that one day was no problem since the Task Force meetings generally only last one day. SFDA staff asked if a half-day OTC (Over the Counter) drug roundtable could be part of the Task force meeting. Mr. Gren agreed to this and asked what SFDA would like covered. SFDA said that wish to learn more about how OTC drugs are regulated, and the process of converting patented drugs to OTC status. Mr. Gren explained that once he returns to Washington he would work with U.S. FDA, the Consumer Healthcare Products Association, and PhRMA to begin organizing this roundtable.

Agreement was reached that the August Task Force agenda would include discussion on a possible SFDA's visit to the U.S. related to counterfeit medicines and how APIs are handled in the U.S.

SFDA also expressed interest in a vaccine regulation roundtable; however, SFDA needs more time to discuss internally. It was agreed this would also be discussed during the August Task Force meeting.

D. GENERICS

Ms. Ling Ye (GPhA) – We have talked about issues regarding requirements for generic drug applications during the past two meetings. I would like to ask some questions as a representative of the generic industry to clarify certain some confusion or inconsistency.

1) What are the clinical trail requirements in China for generic drug applications? What are the specific requirements for different dosage forms (oral, injectable, emulsions, large molecules)?
2) When is a bioequivalence study required? Will it be required for injectable dosage? If require, it is for the purpose of comparison with the innovator product or with the native population? What, if any, animal toxicity studies are required for generics?
3) What is the procedure for SFDA submission and review for products produced at a forging company's Chinese manufacturing site? Is it the same as for products produced at a foreign company's non-Chinese site or a Chinese company's international site? Or an OEM product manufactured by a Chinese company for a foreign company?
4) What is SFDA's definition for biogenerics?
5) What is the clinical trial requirements for biogenerics?
6) Is bio equivalency study required for biogenerics?
7) Will the time frame for the review process be the same for generics and biogenerics? If not, what causes the difference?

SFDA Response – These are very detailed technical questions. Next time we should bring only questions on policies to JCCT. Detailed questions can be answered through the consulting forum that SFDA holds twice every month. Regarding the animal toxicity, the applicant or the researcher should know better than I what animal toxicity studies are needed. API manufacturing process dictates the toxicity study requirements.

SFDA regards generic drugs are those of the same dosage, formulation, strength, and so on. There is no need for clinical trials for generics in general. The requirement for different dosage forms are as follows:

Solid dosage:	need B.E. (bio equivalency)
Emulsion:	need B.E.
Large molecule:	need B.E.
Injectable with single API:	no need for clinical trial

As for the required scale for BE studies, we currently require at least 100 pairs. However, it really should be considered on a scientific basis. What number is statistically meaningful? In the future, we may remove the requirements of the minimum numbers. It has to be scientifically sounds.

Regarding where and the manufacturer that produces the drug, only the site makes a difference:

Made outside China: considered import
Made inside China: considered domestic

Technically there is no difference, administratively, import needs to state the approval status by the originating country.

Biologics always need clinical trials.

SFDA does not have a definition for biogenerics. All biogenerics require clinical trial. As for BE study, we monitor international requirements and keep a close eye on it. Currently, we cannot replace clinical trials with BE studies. We watch EU's development for BE on recombinant hormones. There are some possibility for BE to replace clinical trial. We may consider accept BE to replace clinical trial, when the BE methods are correct and mature.

The time requirement for review of biogenerics is the same as for other generic drugs.

E. EXCIPIENTS

Mr. Gren (DOC) – This is an important issue for our group to address. We understand that China is in the process of developing more stringent requirements for excepients than is the case in the U.S., Europe and other developed countries. If China implements these more stringent regulations there may be consequences, such as excepient producers may not export their products to China may decide against producing excipients in China.

Ms. Alexa Smith (IPEC Americas) – Ms. Smith made the presentation on behalf of the IPEC (International Pharmaceutical Excipients Council) and industry coalitions with the comments on SFDA's Proposed Pharmaceutical Excipient Regulations: The China Import Drug Excipient Application requirements.

Mr. John Hu (USP) – John Hu made a presentation on USP requirements on excipients and the excipients verification programs.

Ms. Cathy Yang (RDPAC) – RDPAC represents seven global pharmaceutical companies in China. Ms. Yang asked SFDA the following questions: What impact the new excipient requirements will have? How will the new requirements affect the review time for applications that have already been submitted?

SFDA Response– Topic on excipients has been discussed during last week's meeting with RDPAC and IPEC. This discussion is on the developments of our regulations. The discussion will help us to make a better decision. We believe we should base our decision on facts. U.S. members provided many materials on excipients regulations. We will study them and learn from them. We will take these into consideration and make our regulations according to Chinese situations.

Ms. Ling Ye (GPhA) – Will the new excipients regulation be in effect this year?

SFDA Response – No effective date has been announced. The proposed new regulation are only proposed and not in effect. Currently SFDA is still using the existing regulations for excepients.

Mr. Jeffrey Gren (US DOC) – We understand that SFDA has begun to implement the more stringent excepient regulations.

SFDA Response – The new regulations are not in effect. We will examine if any SFDA provincial offices are starting to use the draft regulations, since they are no supposed to be used.

IV. Medical Devices Task Force

Opening Session
The Medical Device Task Force was Co-chaired by Mr. Zhang Zhijun, Director General, Medical Device Department, SFDA. Other SFDA participants included:

- Mr. Chang Yongheng, Assistant Counsel, SFDA Department of Medical Devices
- Dr. Zhang Gaotong, Principle Staff Member, Division of Regulations, Policy and Regulations Department
- Ms. Wang Xiaoye, Principle Staff Member, Division of Cooperation, Department of International Cooperation
- Mr. Zhang Lu, Program Officer, Division of Cooperation, Department of International Cooperation
- Mr. Chang Wenzuo – Director General Int'l Cooperation Dept.(only for part of 1st day)
- Mr. Xu Qiang – CAMDI
- Mr. Li Dongling - CAMDI

The U.S. Co-chair was Mr. Jay Biggs, Senior Analyst, Office of Health and Consumer Goods, U.S. Department of Commerce. The U.S. delegation included:

- Ms. Nancy Travis – Associate VP, Global Strategy and Analysis (Asia), AdvaMed
- John Meakem – National Electrical Manufacturers Association
- Carolyn Albertson – Director Global Government Affairs, Abbott *
- Fred Halverson – Vice President, Corporate Regulatory Strategy, Medtronic *
- Bryan Schneider – Manager, Global Regulatory Affairs, Digene Corporation *
- Lindsay Tao – Johnson & Johnson, Representing AmCham

- Richard Craig – Commercial Officer, U.S. Embassy
- Ms. Shuyu Sun – Commercial Officer, U.S. Embassy

* Representing AdvaMed

The Medical Device Task Force focused on six issues:
1) Duplication of Testing and Inspection Procedures
2) Status of Adverse Event Reporting Regulations
3) Draft Regulations on Medical Device Recalls
4) Discussion of Work Plan Activities
5) Status of IVD regulations
6) Future areas of U.S. - China Cooperation

Duplication of Testing and Inspection Procedures

The U.S. Co-chair Mr. Biggs, mentioned that the Department of Commerce has raised this issue with China's Ministry of Commerce as part of the JCCT Plenary discussions, and noted that the JCCT Plenary meeting was scheduled to take place on April 11 in Washington, D.C.. Mr. Biggs asked whether the Ministry of Commerce had been in contact with SFDA on this issue. Director General Zhang Zhijun responded that elevating this issue to the JCCT Plenary had sped up and enhanced communication between SFDA and AQSIQ on this issue. DG Zhang also indicated that SFDA was eager to see this issue resolved, and noted that while there were still procedural and technical issues to be worked out, SFDA hoped to work these out in meetings with AQSIQ following our Subgroup meeting.

Status of Adverse Event Reporting Regulations
Mr. Biggs noted that during past Medical Device Task Forces, the U.S. side had emphasized the importance of having an adverse event system that clearly places final responsibility for evaluating adverse events with the central government, and that manufacturers play an important role in analyzing adverse events. The U.S. delegation asked for an update on the status of the Adverse Events Reporting regulations, and whether or not a reporting pilot program was still being carried out.

DG Zhang indicated that this was one of the Medical Device Division's priorities for the coming year. Currently the Policy and Regulation department was evaluating the draft regulations, and they had been in consultation with Ministry of Health on this issue, since hospitals were involved in reporting adverse events. DG Zhang also indicated that they were also looking at how adverse events were handled by other countries.

When asked whether or not there would be further opportunities for industry to comment on drafts of this regulation, DG Zhang said that SFDA still welcomes industry input, and indicated that SFDA hopes to have these regulations promulgated by the end of 2006.

The AmCham representative noted that AmCham had previously sent letters to SFDA noting that the proposed reporting timeframes were very short for companies to find the

root causes of adverse events. DG Zhang responded that in the current draft, the reporting timeframes were 24 hours for death, and 10 days for serious events. DG Zhang noted that this issue was still under discussion by SFDA.

The U.S. delegation asked for an update on SFDA's thinking regarding to whom manufacturers should report adverse events. SFDA responded that hospitals will report to Adverse Event monitors at the local level, make the preliminary decision on whether to report to Provincial level Adverse Event Monitoring Centers (AEMC). If it is more serious, the report will also go to the national center that will then make the final analysis. The manufacturer is to report to the local AEMC and, if it is a serious event, also to the national AEMC. Both industry and manufacturer will conduct investigation into the cause of the event. Manufacturer will make follow up reports to the AEMC. Both industry and government need to take an active role in this system. The local AEMC is responsible for handling the event. Before the government makes a final decision, they will listen to feedback from manufacturer, review and analyze industry's report. But the government makes the final decision. Mr. Chang Yongheng noted that the preliminary report should be made by the company, to either provincial or national level officials, and then both SFDA and the manufacturers needed to actively investigate the event further. SFDA made a distinction between initial adverse event reports, and follow up analysis, stating that while initial reports of potential adverse events needed to be reported within the timeframe established, more in depth analysis by manufacturers could be provided later.

Given the importance of an effective adverse events reporting system, both sides agreed to holding a post market surveillance workshop in September 2006 that would cover adverse event reporting, and medical device recalls. This event was included in the Subgroup Work Plan.

Draft Regulations on Medical Device Recalls

The U.S. delegation emphasized that, similar to adverse events, deciding whether to recall a medical device, or take other remedial action, is a very important decision with major impact. The U.S. delegation suggested that recall decisions be centralized and that manufacturers be given an official role in the decision-making process. In response to a question about the status of these regulations, SFDA stated that this was one of the Medical Device Division's priorities for the coming year. SFDA has collected similar regulations from other countries, and has started drafting these regulations.

SFDA clarified that recalls would be based on information provided regarding Adverse Events. Recalls would also be reported to the Adverse Event Monitoring Centers by manufacturers. The Monitoring Center would issue a report after they draw conclusions about the adverse event report, send their opinion to the Medical Device Department of SFDA who would then decide if a recall was necessary. There was also discussion about the definitions and distinctions between active recalls, voluntary recalls done by the manufacturer, and passive recalls that are mandated by the government when the manufacturer has been reluctant to take a product off the market.

The U.S. delegation initiated an in depth discussion on how medical device recall are handled in the U.S., including the use of "Dear Doctor" letters. The U.S. delegation emphasized that in most cases, the manufacturers provide doctors with information on the problem, and allow doctors to make the final decision on what are the appropriate steps to take to best protect the patient. In response to questions from the Chinese Medical Device Industry Association (CAMDI), the U.S. delegation clarified that these letters are seen by the FDA. It was decided that this would be a topic that could be better addressed as part of the Workshop on Post Market Surveillance, when there would be more time for an in depth discussion on both the U.S. recall system, and the details of SFDA's recall regulations.

Discussion of Work Plan Activities

Both Co-chairs agreed that the Medical Device Task Force would hold an IVD Workshop in Beijing, during the Summer 2006. SFDA asked the U.S. delegation to provide a draft agenda, and to suggest concrete dates. Both sides also agreed to hold a Medical Device Post Market Surveillance workshop, which would focus on international best practices in adverse event reporting and medical device recalls. This workshop would be held in September 2006, along with a Medical Devices Task Force meeting.

The location(s) for these events was not specified. The U.S. delegation indicated that they would like to arrange these activities to coincide with the Asian Harmonization Workshop that will take place in Seoul, South Korea sometime during September. SFDA requested that, if possible, these events not take place in late September. SFDA also made the point that under the Subgroup's Terms of Reference, it was not necessary to meet every year between full Subgroup meetings.

Status of IVD regulations

Mr. Biggs began by expressing his thanks to SFDA for participating in the IVD Roundtable in November 2005. The U.S. side was very impressed with the depth of knowledge and interest demonstrated by SFDA staff involved in this event. SFDA also expressed satisfaction with this event, and mentioned that they hoped the IVD workshop in 2006 would be around the same size.

SFDA provided an update on the status of the IVD regulations, noting that if there are no changes to the draft version of the regulation (i.e. blood screening products will still be regulated as pharmaceuticals) then the new regulations will be published soon, but if it is decided to revisit the blood screening issue, the final draft could take a while.

The U.S. delegation asked whether or not there would be a grace period allowed whereby products currently on the market may remain on the market under the current regulations, perhaps until they are up for re-registration. SFDA responded that the new regulations would have some articles on transition period, and that for products that still have valid registrations, they can still be marketed. However, if a product's registration has expired, then the products must be registered under their new classification (many of which will now be regulated as medical devices).

The U.S. delegation also asked about whether it would be possible to expedite the registration of tumor markers (many of which have been under review for as long as two years), or to provide registration extensions for assays whose licenses are nearing their expiration date. SFDA responded that for products that are already have licenses, it is hard to continue the process. SFDA suggested that if a company was eager to get a license, then it might be faster to apply for re-registration as a drug, even though this would be more complicated than applying as a device. SFDA reiterated their concerns that without a finished regulation, it would be difficult to make these types of changes without a legal or legislative back up.

The U.S. delegation raised concerns that documentation requirements for IVD products were almost all the same, despite having three risk classes. The U.S. delegation pointed out that in the U.S., lower risk classifications have lesser documentation requirements. It was pointed out that the U.S. FDA focuses more of its resources on the 4 percent of Class III high-risk products than it does on the 96 percent of the low and medium risk products. SFDA agreed with this principle, although they were unsure of whether China's market faced the same product risk ratios.

SFDA pointed out that the draft IVD regulation provided a significant level of detail for clinical trials and testing of Class III products and imports, while Class I and II products were exempt from testing. SFDA noted that they put all new medical devices in Class III, and now they are in the process of trying to re-classify these. The U.S. delegation noted that GHTF has draft guidance documents that provide guidance on IVD classification. SFDA responded that they were closely following the GHTF, and they are now considering how to classify products and integrate this into one procedure. SFDA's current regulations regarding classification may be considered interim and next year they will make the relevant adjustments

The U.S. delegation also asked about IVD test systems. Industry representatives made the point that would like to be able to register reagent products as a "system," i.e., the system consists of calibrators, controls, and reagents, as well as the accessory reagents, which is the practice in the US and Canada. SFDA responded that they understood the logic of this approach, but given their current system (which divides IVDs into medical devices or pharmaceuticals), it would be very difficult to test products as a single system. SFDA indicated that this is something that they would re-consider in the future.

Industry also asked about product change reporting, noting that it would be more effective if manufacturers were able to report only "significant change," as they do in the U.S. SFDA agreed that in theory this made sense, but in reality it is hard for reviewers and local officials charged with post market surveillance to determine whether or not changes are "significant." The IVD portion of the discussion was concluded with both sides agreeing to an additional JCCT Workshop on IVDs to be held during the Summer of 2006 in Beijing. The U.S. delegation promised to provide an initial draft agenda, and possible dates.

<u>Future areas of U.S. - China Cooperation</u>

Increased Use of Quality Systems
In response to a question about how to expedite China's utilization of quality systems, SFDA responded that they were actively promoting greater use of QS, and that this was one of the key tasks for the Medical Device Division. By the end of the year, SFDA hopes to release general provisions on SFDA's quality systems requirements. However, a guidance on how to implement or establish a QS probably could not be in this year's work plan. SFDA emphasized the importance, and difficulty of, making Chinese companies comfortable with quality systems.

Biocompatibility
The U.S. delegation raised questions about some of SFDA's evaluation centers requesting certain biocompatibility tests to be done locally, instead of accepting the ISO 10993 based test results submitted by manufacturers. The U.S. delegation asked whether this represented a policy shift by SFDA, or is this simply a matter of some of the evaluation centers not understanding the testing protocols of ISO 10993. The SFDA representative from the Medical Device Evaluation Center responded that the DOC 130 is still valid, and its is still possible to accept data and test results from manufacturers in developed market. However, the Medical Device Evaluation Center said that the problem was that some of the (DOC 130) submissions from developing nations were incomplete, unclear, or hard to translate.

The Medical Device Evaluation Center representative stated that requiring companies to re-do biocompatibility testing was ineffective, and that SFDA needed to strengthen internal standards in this area. The U.S. delegation offered to provide more information about the ISO 10993 standard, including whether or not there were any Chinese experts who had participated in the drafting of the standard.

Chinese Reduction in Hazardous Substances
The U.S. delegation briefed SFDA on the status of the Chinese Reduction in Hazardous Substances (RoHS) Regulations, including concerns about recent reports that the RoHS catalogue will be expanded to cover medical devices. In response to a question about what role SFDA will play in the process of developing China's RoHS catalogue, SFDA indicated that the Ministry of Information Industries and the State Environmental Protection Agency were the lead ministries for this issue, and SFDA would simply implement whatever was decided upon.

The U.S. delegation provided information about the EU Environmental Directorate drafting RoHS measures without consultations with other Directorates involved with medical devices, and how a similar approach in China could negatively affect the availability of medical devices in the Chinese market. The U.S. delegation also mentioned that the EU had exempted some medical devices from RoHS requirements, but that this might change. The Chinese Medical Device Industry Association (CAMDI) representative also asked about how the U.S. was addressing European RoHS issues. SFDA concluded this discussion by noting that, if needed, they would provide comments

into the Chinese RoHS process, but that they could not guarantee that their comments would be consistent with the U.S. delegation's suggestions.

Closing Comments
Mr. Biggs expressed his appreciation for the effort that SFDA put into organizing the Subgroup meeting, and noted that this Task Force meeting was very successful in advancing the U.S. Department of Commerce's healthcare agenda. These accomplishments included:

- Reaffirmed that SFDA still welcomes industry input on draft Adverse Event Reporting regulations, which SFDA hopes to have promulgated by the end of 2006. SFDA agreed to discuss these in further detail as part of a Post Market Surveillance Workshop in September 2006

- Learned that Medical Device Recall regulations are one of SFDA's priority issues for 2006, and that SFDA would like to learn more about the U.S. system as part of the Post-Market Surveillance Workshop.

- Received an update on the status of SFDA's regulations on IVD products. IVD regulations are going to be released sometime this summer. There will be additional review over the next year or so, and that this review would include re-classifying certain IVD products out of Class III. SFDA also indicated they are considering GHTF guidance on this subject.

- SFDA also indicated that in the future they would re-consider the possibility of testing and registering IVD assay calibrators, controls, reagents and instruments as well as accessory reagents as a whole system.

- Provided SFDA with information on potential concerns that medical device industry has with China's Reduction in Hazardous Substances regulations. The U.S. delegation agreed to provide additional information about the European RoHS regulations and the medical device exclusions.

- Clarified that SFDA still accepts biocompatibility test results based on ISO 10993, and the U.S. delegation agreed to provide additional information on how this standard is implemented in the U.S..

- Agreed to hold the next JCCT Medical Devices and Pharmaceuticals Subgroup April 2007 in Washington, D.C.

V. CLOSING PLENERY

Mr. Chang, Wenzuo appointed Mr. Zhang, Wei and Mr. Jay Biggs to deliver the closing remarks for the Pharmaceutical Task Force and Medical Device Task Force, respectively.

Mr. Zhang, Wei (SFDA) – Summarized the topics that were discussed during the two-day meeting. Both sides openly expressed opinions and understanding of the issues. We obtained certain agreements and mutual understanding, despite differences. The U.S. delegations experience and suggestions in the areas of generics, and excipients will be beneficial for China to establish its regulations and rules. SFDA has agreed to work with Mark Cohen of DOC's Patent and Trademark Office on data exclusivity and patent linkage.

Mr. Jay Biggs (DOC) – We shared common ground on several issues. Collaboration is on the right track. Chinese medical device associations' participation is very beneficial. Topics discussed include: adverse event reporting, recalls, IVD, biocompatibility, greater use of quality systems, and China's new Reduction in Hazardous Substances (RoHS) regulations. The Task Force agreed to hold workshops on post market surveillance (including Adverse Event Reporting and medical device recalls), and on IVD regulations.

Mr. Jeffrey Gren (DOC) – I am pleased with the achievements of the ten-year anniversary Subgroup meeting. We will start a second decade of work together. The next Subgroup meeting will be in Washington D.C. in April 2007. We also agreed to have a Pharmaceutical Task Force meeting in late August, and a Medical Device Task Force meeting in September. Although this year there will be Task Force meetings in between Subgroup meetings, Task Force meetings in between Subgroup meetings are optional and at the discretion of DOC and SFDA.

One of the strengths of this Subgroup is having industry participation in an open exchange of information. The new leadership from SFDA demonstrated cooperation, as has been the case in the past. Mr. Gren thanked SFDA for organizing this meeting and the ten-year anniversary celebration. Mr. Gren also thanked USFCS China for the great job coordination with SFDA, and Jay Biggs and Victoria Kao for their hard work. All of these efforts contributed to a highly successful meeting.

Mr. Wenzuo Chang (SFDA) – He was also very pleased with the meeting, and thought hat once again there was good cooperation and joint discussions. He thanked DOC and SFDA staff for their great effort.

Mr. Jeff Gren and Mr. Wenzuo Chang signed the Subgroup Work Plan. A copy of the signed Work Plan is attached.