Sinovac mainly focusses on vaccine business. Can you tell us simply how is the vaccine approval process in China like?

In the PRC, the China SFDA regulates and supervises biopharmaceutical products under the Pharmaceutical Administration Law, the Implementing Regulations on Pharmaceutical Administration Law, the Administration of Preclinical Laboratory Tests and Animal Tests.

Preclinical tests include in-vitro laboratory evaluation of the product candidate, as well as in-vivo animal studies to assess the potential safety and efficacy of the product candidate. Preclinical tests must be conducted in compliance with Good Laboratory Practice for Non-clinical Tests of Pharmaceuticals, or GLP. With respect to vaccines, the preclinical tests should also comply with Technical Guidance for Preclinical Tests on Prophylactic Vaccines and, in the case of SARS, the Technical Requirements on Preclinical Tests of Inactivated Vaccines against SARS promulgated by the China SFDA that strictly control the registration, procurement, manipulation and tests of SARS strains. We must submit the results of the preclinical tests, together with manufacturing information, analytical data and the sample of product candidate to the provincial SFDA as part of an investigational new drug application, or IND, which must be approved before we may commence human clinical trials. We cannot assure that submission of an IND will result in the China SFDA allowing human clinical trials to began, or that, once begin, issues will not arise that result in the suspension or termination of such human clinical trials.

Human Clinical Trial
Clinical trials involve the administration of the product candidate to healthy volunteers or vaccinees under the supervision of principal investigators, who are generally physicians or an independent third party not employed by us or under our control. Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. In Phase I, the initial introduction of the drug into human subjects, the
drug is usually tested for safety (or adverse effects), dosage tolerance, and pharmacologic action. Phase II usually involves studies in a limited vaccinee population to evaluate preliminarily the efficacy of the drug for specific, targeted conditions; to determine dosage tolerance and appropriate dosage and to identify possible adverse effects and safety risks. Phase III trials generally further evaluate clinical efficacy and test further for safety within an expanded vaccinee population. Clinical trials have to be conducted in compliance with the Good Clinical Trial Practice of Pharmaceuticals, or GCP. With respect to vaccines, we also have to comply with the China SFDA’s Requirements on Application for Clinical Trial of New Propylactic Biological Products. The sample vaccine products must be inspected by the China Medicine and Biological Products Examination Institute before they may be used in the clinical trials. We or the China SFDA may suspend clinical trials at any time on various grounds, including a finding that subjects are being exposed to an unacceptable health risk.

After three phases of human clinical trials, we will submit to the provincial level SFDA a report containing the results of the preclinical and clinical studies, together with other detailed information, including information on the manufacture and composition of the product candidate, to apply for a new drug certificate. For vaccines, we have to comply with the China SFDA’s Guidelines for Clinical Trial Report on Vaccines. In the meantime, we will submit raw materials of the product candidate to the China Medicine and Biological Products Examination Institute.

**GMP Certificate**
Before receiving a new drug certificate and production permit, we will need to submit to the China SFDA an application for a Good Manufacturing Practice Certificate, or GMP Certificate. A GMP Certificate is used to approve the manufacturing equipment, process and workshop used in producing a particular drug. The China SFDA has issued GMP standards for pharmaceutical manufacturers to minimize the risks arising out of the production process of drugs that will not be identified or eliminated through testing the final products. The application for a GMP Certificate should be approved or rejected within six months from the application date.

A GMP Certificate is valid for five years. However, prior to October 2005, a GMP certificate for a drug is valid for only one year except for drugs approved before the GMP practice was implemented by the China SFDA in 2005. The manufacturers should apply for a reassessment of their one-year term GMP Certificate no later than three month prior to the expiration of such GMP Certificates and, if approved, would receive a five-year GMP Certificate subject to reassessment by the relevant authority. According
Pre-clinical trial results submission to SFDA

Clinical Trial Approval

Conducting three phases of clinical trials

Clinical trial results submitted to SFDA

GMP Application

Production of three lots of products submitted to SFDA

New Drug Certification

GMP Certification

Production License

Batch Approval
to the current practice, we received a five-year GMP Certificate directly and should apply for a renewal of our GMP Certificate no later than six months prior to the expiration of our GMP Certificate.

**New Drug Certificate**
The provincial level SFDA will conduct a preliminary examination of our application for a new drug certificate. Once it decides to accept our application based upon such preliminary examination, the provincial level SFDA will, within five days, conduct an on-site examination on our production facilities and draw samples from three consecutive batches of our products. A medicine inspection institute designated by the provincial level SFDA will inspect the selected samples and later submit its inspection report to the China SFDA. At the same time, the provincial level SFDA will submit its opinion and examination report on our product candidates, together with our application materials to the China SFDA. If the China SFDA is satisfied with the examination results, it will issue a new drug certificate to us.

**Production Permit**
Simultaneously with the application of a new drug certificate, we also apply to the provincial level SFDA for a production license to manufacture the new drug to be approved by the China SFDA. The production license application will be examined with a similar two-stage procedure as with the new drug certificate, first by the provincial level SFDA followed by the China SFDA. After the provincial level SFDA accepts the application, conducts the on-site examination and forms its opinion, the provincial level SFDA will transfer the file to the China SFDA. When the China SFDA decides to issue the new drug certificate, it will further examine whether the applicant holds a License for Pharmaceutical Production and whether the applicant has proper production facilities. With the criteria met, the China SFDA will issue the production permit together with the new drug certificate. The production permit is valid for a term of five years and must be renewed before its expiration. During the renewal process, our production facilities will be re-evaluated by the appropriate governmental authorities and must comply with the then effective standards and regulations.

Under certain circumstances, for instance, where drugs are developed to prevent or cure such epidemics such as SARS, the China SFDA provides for an accelerated proceeding for its review of the new drug certificate application and production permit application relating to such drugs.

The China SFDA will specify a monitoring period ranging from three to five years when approving the first production permit for most new drugs. During this monitoring period, the manufacturers holding the new drug certificates have to report regularly to the provincial level SFDA, among others, the production process, efficacy, stability and side effects of the new drugs involved. During the same period, the China SFDA will not accept any new application for approval of the same drug involved. However if a third party has filed an application for the same drug and obtained the clinical trial permit before the monitoring period commences, the third party may still obtain a new drug certificate and production permit for the same drug.

We are not required, in most cases, to conduct clinical trials prior to commencing the manufacture of pharmaceutical products for which there are published state pharmaceutical standards on safety and effectiveness, although we have to apply for a production permit from the China SFDA.

We cannot commence the manufacture of a new drug unless and until we have obtained a GMP certificate, valid new drug certificate and production permit.

**Batch Approval**
Our vaccine products cannot be distributed in the market before they are approved for sale by relevant
medicine inspection institute. We have to apply for examination and/or inspection of each batch of our products by the relevant inspection institute. For each batch of products, we will provide the inspection institute with samples together with manufacturing records, internal inspection records and other quality control documents. The inspection institute will review the documents and inspect the samples and issue a batch approval within approximately two months, if our manufacture procedures and quality of the products are ascertained to have met the standards as approved by the China SFDA. With the batch approval, we may distribute the approved batch of vaccines to the market.

How well are your products (Healive, Bilive, Anflu) doing? Which is the best seller?
There are three products on the market, Healive® - the first Inactivated Hepatitis A vaccine in China; Bilive®-Hepatitis A & B combined vaccine and Anflu®- Split Influenza Vaccine.

Healive® was launched into market in 2002. In the past, most inactivated Hepatitis A vaccines in China were imported from other countries. Through National the Ninth Five-year scientific and technological project on medicines, we successfully developed the first proprietary inactivated Hepatitis A vaccine in China and industrialized and commercialized the vaccine, which is widely introduced and used throughout China till today. The clinical research data shows the seroconversive rate of the subjects inoculated with the vaccines for full vaccination schedule is 100% and the safety, immunogenicity, the clinical result and the quality of the vaccine is comparable to the imported inactivated Hepatitis A vaccines. Currently, Healive® is being sold in 27 provinces and cities in China. In 2006, 2.6 million doses were sold in China, which generated in the sales revenue of RMB 100 million. Now, Healive® is the most widely used inactivated Hepatitis A vaccine in China.

Bilive® was launched in 2005, which is used to enhance immunogenicity. As the supplement of Hepatitis A vaccine and Hepatitis B vaccine, the demanding quantity is not very large.

Sinovac launched Anflu® in autumn of 2006 and the key purpose is to introduce the new product to our customers.

Who are your main customers for each of these products?
In China, the disease control system includes provincial CDC, municipal CDC, county CDC and inoculation clinic. Sinovac’s vaccines are distributed through different CDC systems in China. Based on the principle of disease control that companies provide the high-quality vaccines to the disease control system, which keep the subjects away
from infectious diseases through vaccination, Sinovac sells all the vaccine products only to provincial, municipal and county CDCs. The provincial CDCs and municipal CDCs are responsible for purchasing the vaccines and then distributing to subordinate CDC and inoculation clinics, which regulates the execution of vaccination, and also ensures the quality, proper management of vaccines, supervision and instant disposal in case of adverse effects.

**Panfl u™ (pandemic influenza)**
- Targeting pandemic influenza virus (H5N1)
- Co-developed by Sinovac and China CDC
- Virus strain is delivered by NIBSC, influenza network laboratory of WHO
- Phase I clinical trial approved by China SFDA on November 22, 2005
- Phase I results published in The Lancet on September 7, 2006 and showed good immunogenicity
- Phase II clinical trial commenced in May, 2007
  - Tolerance, safety, and immunogenicity will be tested
  - To determine the dosage and inoculation schedule

**Recent Excerpts from The Lancet**
“… In a previous trial published by The Lancet, scientists found that 30 micrograms of a vaccine containing part of the H5N1 virus given in two doses with an adjuvant, an additive that can increase effectiveness, produced a good immune response in humans. In the latest trial, Chinese researchers tested the effectiveness of a vaccine that contains a modified version of the whole H5N1 virus plus adjuvant. Vaccines made of whole viruses are known to trigger greater immune responses but are also known to produce more side-effects…” (Press release by The Lancet, 7, September 2006)

**Japanese Encephalitis Vaccine**
- Mosquito-born virus that infects the central nervous system in human beings and animals
  - Humans, especially children, are susceptible to JE virus
  - Significant unmet need in Southeast Asia and Western Pacific
- Improved technology for large scale production
- Prepare application for Phase I clinical trial

**SARS Vaccine**
- Independently developed by Chinese scientists
- Received authorization from the China SFDA in January 2004 to conduct the Phase I clinical trial
- On 5 December 2004, the PRC Ministry of Science and Technology, the Ministry of Health and the China SFDA jointly announced Phase I results
  - No adverse reactions and demonstrated safety
- Intend to resume process required to obtain regulatory if virus re-emerges
- Completed Phase I clinical trial
What was your profit for the last financial year?
In 2006, Sinovac incurred a loss, but net loss decreased by 86.4% to $696,000 in 2006 from $5,111,000 in 2005.

Tell us about the vaccine for SARS. At what Phase of development is it at now? How long more can it be commercialised? Now that the SARS period is over, how are you going to market this product? To whom are you targeting?
Phase I clinical trial of SARS vaccine has been completed. Since there are no more cases, the entire three phases of clinical trial could not be completed without outbreaks. Currently, the project is suspended.

Tell us about the avian flu vaccine that Sinovac is working on. At what stage of development is it at now? Who are your target customers And which countries are they from?
The China State Food and Drug Administration (SFDA) recently granted Sinovac approval to commence the Phase II clinical trial of Panflu (TM), a human use vaccine against the H5N1 strain of pandemic influenza virus. Panflu was jointly developed with China CDC.

Two types of the H5N1 vaccine were approved by the SFDA to commence clinical trials. The first type is the H5N1 whole viron inactivated vaccine for which the Phase I clinical trial was completed in 2006. The Phase Ib and II clinical trials for the H5N1 whole viron inactivated vaccine will be conducted to further test the tolerance, safety, and immunogenicity and to determine the dosage and inoculation schedule. During the Phase Ib and II trials, the age groups of the participants will be enlarged by adding youths and the elderly. The second type of vaccine is the H5N1 split viron vaccine, for which the Phase I and II clinical trials will be conducted continuously. The
trials will focus on the vaccine’s tolerance, safety, and immunogenicity. It is anticipated that the Phase II clinical trials will commence simultaneously for the two types of vaccines in order to determine the vaccination dosage and inoculation schedule for drafting the registration standards and specifications for the vaccine.

Sinovac commenced development of Panflu in February 2004 as part of the global united battle to fight pandemic influenza. In June 2006, the results of phase I clinical trial were revealed and showed good immunogenicity and safety. On 7, September 2006, the results were published in The Lancet, a global renowned medical periodical, that provided worldwide recognition for the Phase I clinical trial results of the pandemic influenza vaccine (H5N1) developed by Chinese scientists.

Sinovac has received an invitation from WHO to participate in the campaign to solve the issue with access to pandemic flu vaccine by developing countries. We are willing and able to help our country and many other countries in this public health issue.

What is the routine vaccination program for China’s citizens? With its huge population, vaccination is difficult. However, it is indeed important. What kind of vaccination program would you like to see the Chinese Ministry of Health implement?

In China, five kinds of vaccines including BCG, HBV, DPT, MV and OPV are provided free of charge for Chinese children by the government. The provincial government, the government of self-governed districts and municipalities directly controlled by the central government may increase some vaccines to the vaccination schedule. For example, the government of provinces in southern China also provide JE vaccines or Meningococcus A vaccines for citizens.

The Chinese government issued several regulations and laws on the implementation of vaccination programs to regulate and control the vaccination, including the inoculation procedure, the requirements of inoculation rate, cold chain delivery, reporting of infectious diseases, effectiveness of vaccines, adverse event disposal responsibilities and so on.

In 2007, the state government pays much more attention to the control of infectious diseases and the vaccine inoculation. Premier Wen Jiabao pointed out in the government report that in 2007, the national vaccination schedule will be enlarged to include 15 infectious diseases (12 of the 15 diseases need to be prevented by vaccine inoculation from children) which could be effectively controlled by vaccine inoculation, including Hepatitis A. Epidemic cerebrospinal meningitis will also be included into the National Immunization Program. That is to say children will be inoculated with 11 kinds of vaccines to prevent 12 infectious diseases for free instead of 5 vaccines for 7 diseases. For the whole schedule, the government will increase the expenditure to RMB 2.8 billion.
To develop vaccines, there is the problem of finding the right adjuvant. Does Sinovac spend a lot of its efforts on finding the right adjuvant? What are some of the adjuvants that are used for its vaccinations?

We are using the Al adjuvant. But we realize that the adjuvant plays a significant role in our vaccine’s effect, therefore we are actively searching for a suitable new adjuvant.

You did Hepatitis A research for 20 years. Tell us about your background and how you embarked on this journey of vaccine business.

In the 1980s when the Hepatitis A outbreak incurred, Mr Weidong Yin worked in Tangshan City Hygiene and Anti-Epidemics Station. He saw with his own eyes in small villages that the children infected by Hepatitis A virus were in bed, but in the medicine-chest with him, there were only some simple medicines to ease the symptoms and a stethoscope. There was no way to control the epidemic. So Mr Yin decided to find the breakthrough for the development of the Hepatitis A vaccine.

In 1985, Mr Yin was assigned with the project of “purifying the HA virus from 2BS cells”. The isolated Hepatitis A virus was named TZ84 with a short reproducing cycle and a high capacity of antigen, which was perfectly suitable for the production of 2BS cells and can be used for the research of reagent and vaccines, and also verified to have reached international levels. In 1987, Mr Yin finished the research of “ELISA kit for Hepatitis A vaccines”, which explored a new way for diagnosing Hepatitis A.
But as a doctor, he may save thousands of patients’ lives in his life time, but if the vaccine can be developed, millions of people will be prevented from some diseases in one year’s time, or even one disease could be eliminated.

In the early 1990s, the vaccines produced by US companies entered the Chinese market. The family with a monthly income of RMB 300 would even pay RMB 400 to buy the imported Hepatitis A vaccines for their children. And families with much lower income could not afford. So Mr. Yin made up his mind to let all the Chinese use the vaccines produced in China at a lower price and high quality in the near future.

In 2000, the company completed the R&D of the first inactivated Hepatitis A vaccine in China. In 2001, Sinovac Biotech Co Ltd (Sinovac Beijing) was founded in ZhongGuanCun Science and Technology Park. In less than five years, the first proprietary Hepatitis A&B combined vaccine in China - Bilive was industrialized and launched into the market. In late 2004, Sinovac took the lead in completing the Phase I clinical trial on the inactivated SARS vaccine in the world. And Sinovac also completed the Phase I clinical trial for human use pandemic influenza vaccine (H5N1) and Phase II clinical trial has been approved by China SFDA.

We hope we could realize two objectives through our own efforts: to provide Chinese children with international quality vaccines and provide children in the world with international quality vaccines made in China.

What are some vaccines that you predict will be available in the future?
There will be new type of adjuvants and vaccines with new immune methods available in the future. HIV vaccine is expected by the whole world, but it is hard to predict when it could be successfully developed.

What are your views on DNA vaccine? Will it be workable?
DNA vaccine is a newly developed vaccine. The technology can be used as a foundation for the development of future vaccines and thus speed up the R&D process of vaccines. Compared with traditional vaccines, the DNA molecule is much more stable, which is easy for transportation and storage, but some issues need further research. Those are whether DNA vaccine, as an exogenous DNA, could intergrade or interrupt the normal function of DNA in host, whether these exogenous DNA could induce dissolution or immunification. With the development of technology and research, a DNA vaccine will bring huge benefit for human beings.

Currently, what kind of methods are Sinovac using for vaccine production?
Sinovac has used and established several technology platforms during the production process, which involves all aspects in vaccine production. We will select to use different platforms according to the types of vaccines and the future development of vaccines. For example, we use egg-culture to produce influenza vaccines and cell-based technology to produce Hepatitis A antigens.