# The State of Clinical Trials: China 2011

*The growing medical needs of China's large and diverse population will continue to drive novel drug development within China and an increasing number of both global and domestic clinical trials being performed here.*

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## Background

With 1.3 billion people, China represents significant opportunity for both multinational and domestic drug companies. As of 2011, China has become the second largest pharmaceutical market worldwide, and is expected to continue its rapid growth to overtake the US as the largest market by 2020 (IMS Health, 2011; ChinaBio, 2010). This rapid growth can be attributed to the increasing demand within China, driven by factors such as the rapidly aging population and increasing incidence of chronic diseases. By 2050, the average age in China will be approximately 45 compared to the 2011 average age of approximately 35. This is part of an overall aging trend by the China population (Figure 1), creating an increasing demand for pharmaceuticals. This is also related to the increasing incidence of chronic diseases. Annually, 80% of all disease deaths in China are a result of chronic diseases such as cardiovascular disease, stroke and cancer (曹元水, 2010).

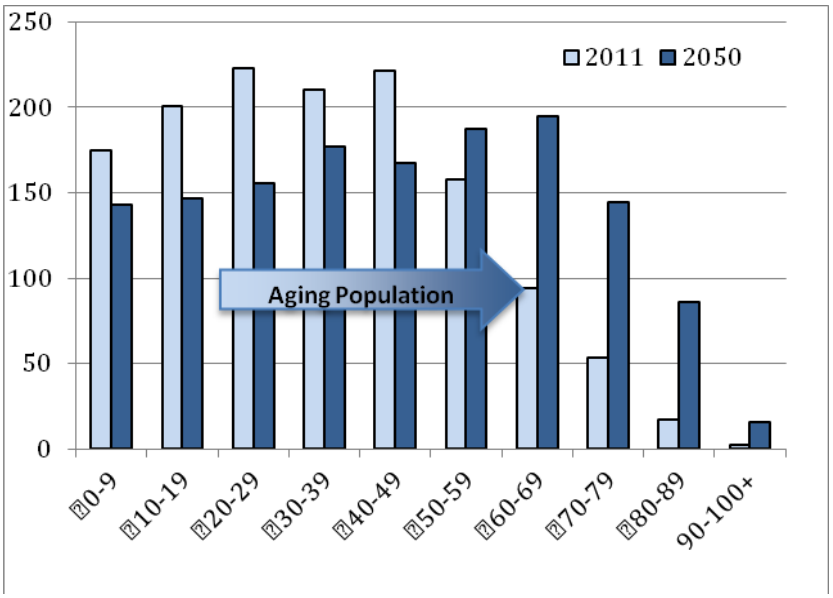


**Figure 1. China's Aging Population** *(Source: Wolfram Alpha, ChinaBio)*

Furthermore, ChinaBio's research has shown that over the next 15 years, the elderly population will have 14 million new cases of diabetes mellitus, 31 million new cases of cardiovascular disease, and 8 million new cases of stroke (ChinaBio, 2010). These numbers are anticipated to rise as the population ages and China continues its rapid development, becoming more susceptible to the same chronic lifestyle diseases (such as diabetes and cardiovascular disease) as western countries. Additionally, China still suffers from several infectious diseases not typically seen in developed countries. Infectious diseases such as viral hepatitis, tuberculosis and typhoid fever still account for over 1% of all deaths from disease (China Ministry of Health, 2010). This unique combination of diseases of both developing and developed countries creates a China-specific demand that helps drive the development of China's pharmaceutical industry.

## Pharmaceutical Development in China

While historically China's pharmaceutical industry has focused on the generics market, China's current demand has shifted its focus towards novel drug development. As the pharmaceutical industry seeks to meet the healthcare needs of China's population through increased pharmaceutical development, there are a growing number of clinical trials being performed within China. In 2009, over a thousand clinical trial

protocol applications were approved by the SFDA (Table 1) (Dr. Li JinJu, 2010). A significant number of these had international applications as part of multinational trials, demonstrating China's increasing ability to develop drugs for both the Chinese and global markets.

**Table 1. 2009 SFDA Clinical Trial Protocol Approvals** *(Source: SFDA, APEC)*

| | Local Application | | | International Application | Total |
|---|---|---|---|---|---|
| | Small Molecule | TCM | Biologic | | |
| New compound or formula | 267 | 91 | / | 171 | 529 |
| Others | 391 | 10 | 26 | 149 | 576 |
| Total | 658 | 101 | 26 | 320 | 1105 |

A further demonstration of the increasing number of China clinical trials can be seen in the growing number of multinational company (MNC) sponsored clinical trials in China. Prior to 2003, there were less than 20 MNC-sponsored clinical trials initiated per year. However, in 2003 several government agencies were combined to form the State Food and Drug Administration (SFDA). While this resulted in a temporary decrease in the number of initiated clinical trials as new regulatory measures were established, the rapid increase from 2004 to 2006 is evidence of how the improved regulations increased the attractiveness of the pharmaceutical Industry in China. The rapid increase has since slowed due to the overall decrease in R&D spending by large MNCs. This has resulted in fewer MNC-initiated multinational trials with branches in China, as can be seen by the decrease in global trials from 2008-2010 (Figure 2). However, the continued growth of domestic clinical trials during this period indicates the robust interest by MNCs in developing products for China's pharmaceutical market. Overall the number of MNC-sponsored clinical trials being performed in China quintupled from just 24 trials initiated in 2004 to 129 trials initiated in 2010.

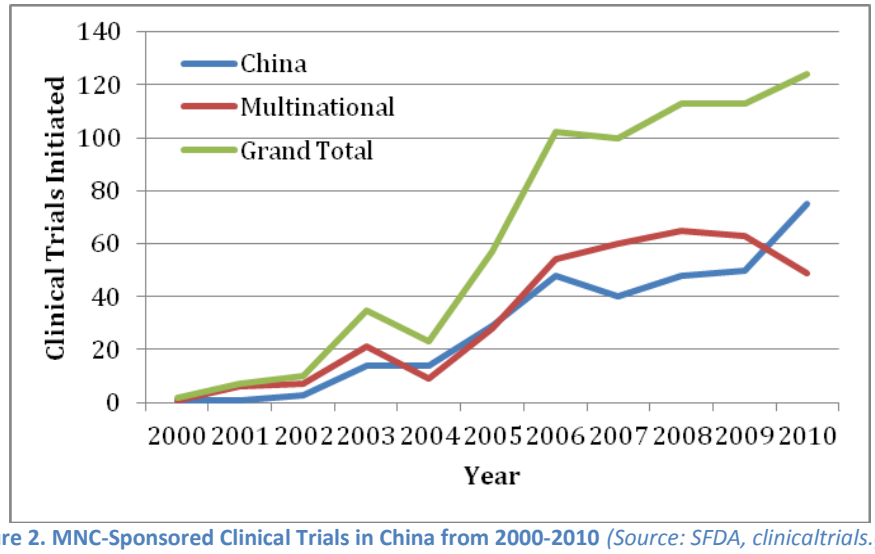


**Figure 2. MNC-Sponsored Clinical Trials in China from 2000-2010** *(Source: SFDA, clinicaltrials.gov)*

The increased interest in developing pharmaceuticals for the China market has led to the establishment of a large number of certified clinical trial institutions. There are over 320 certified institutions ranging from state-run hospitals to specialized clinics. They are distributed widely throughout 31 different provinces,

although many are located near known life science clusters such as Beijing and Shanghai (Figure 3). The number of certified institutions allows for easy access to China's large patient population while ensuring quality through strict oversight and regulation by the SFDA.

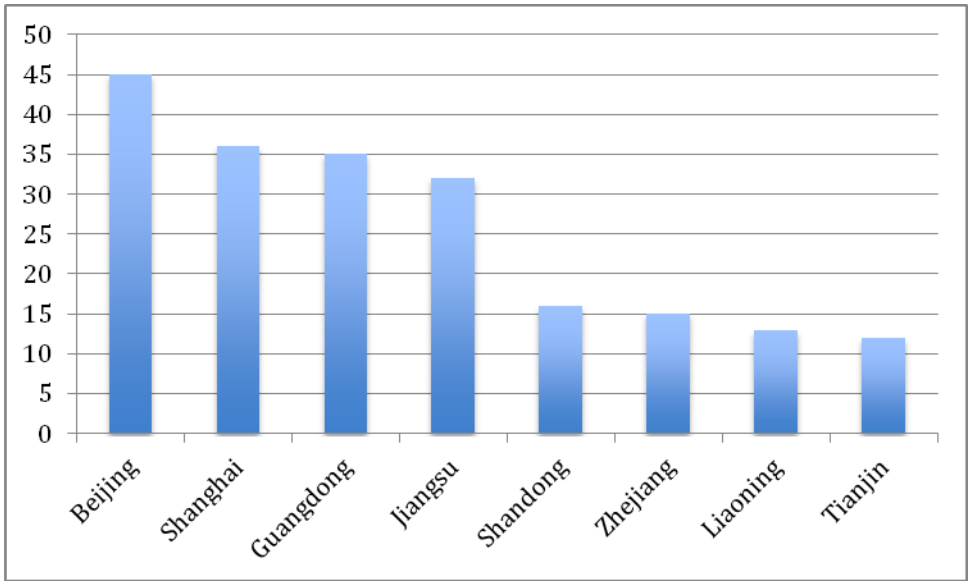


**Figure 3. Certified Clinical Trial Institutions by Province** *(Source: SFDA, ChinaBio)*

Pharmaceutical developers also benefit from the relatively low cost of clinical trials in China. Since clinical trials account for roughly half the cost of drug development, China's lower cost encourages drug development within China (Dimasi 2007). This cost efficiency is, in part, due to the ease of patient recruitment in China. Difficulties in patient recruitment are the most frequently cited cause for delay in western country clinical trials. In fact, over 86% of US clinical trials experienced an average delay of 366 days as a result of difficulties with patient recruitment (Haiyan Yang, 2008; Centerwatch, 2008). Since delays in clinical trial initiation can cost upwards of $35,000/day, this represents a significant and costly bottleneck for pharmaceutical development (Haiyan Yang, 2008; ProModel). By contrast, patient enrollment time in China can be reduced by as much as 30% compared to western countries (PriceWaterhouseCoopers; Boston Consulting Group, 2008).

An added benefit for patient recruitment is the large treatment-naïve population in China. As recently as 2003, over 75% of the population did not have any medical insurance (China Ministry of Health, 2010). These patients are more likely to enroll in order to obtain quality healthcare treatment, further lowering costs for pharmaceutical developers in China. Once recruited, patients in China have increased retention rates due to the strong relationship between patient and healthcare provider (Haiyan Yang, 2008). Patients are often more compliant with study protocols and are less likely to withdraw, resulting in a low attrition rate that aids pharmaceutical development.

In addition to a large treatment-naïve patient population, China also has a diverse disease burden containing high incidences of diseases from both developing and developed countries. This results in a high patient density for many disease conditions, further decreasing the difficulty of patient recruitment for specific diseases (Table 2).

**Table 2. Percentage of Main Diseases of Inpatients in Hospitals in 2009**
*(Source: China Health Statistical Digest 2010)*

| Urban | | Rural | |
|---|---|---|---|
| Disease | % | Disease | % |
| Diseases of the Respiratory System | 13.04% | Diseases of the Respiratory System | 17.54% |
| Diseases of the Digestive System | 11.09% | Pregnancy, Childbirth & the Puerperium | 15.12% |
| Pregnancy, Childbirth & the Puerperium | 10.02% | Injury, Poisoning & External Causes | 14.01% |
| Injury, Poisoning & External Causes | 9.36% | Diseases of the Digestive System | 12.26% |
| Diseases of the Genitourinary System | 6.40% | Cerebrovascular Disease | 5.70% |
| Cerebrovascular Disease | 5.50% | Diseases of the Genitourinary System | 4.68% |
| Malignant Neoplasms | 5.01% | Certain Infectious & Parasitic Diseases | 4.09% |
| Ischemic Heart Disease | 3.79% | Ischemic Heart Disease | 3.25% |
| Endocrine, Nutritional, & Metabolic Diseases | 3.58% | Disease Originating in the Perinatal Period | 2.50% |
| Certain Infectious & Parasitic Diseases | 3.08% | Malignant Neoplasms | 2.36% |
| Total | 70.87% | Total | 81.51% |

**Table 3. Mortality of Top 10 Major Diseases in 2009**
*(Source: China Health Statistical Digest 2010, ChinaBio)*

| Cause | Deaths | % |
|---|---|---|
| Malignant Neoplasms | 2,176,599 | 25.50% |
| Cerebrovascular | 1,869,442 | 21.91% |
| Heart Disease | 1,605,850 | 18.82% |
| Diseases of the Respiratory System | 1,106,459 | 12.97% |
| Injury & Poisoning | 601,276 | 7.05% |
| Diseases of the Digestive System | 206,828 | 2.42% |
| Endocrine, Nutritional & Metabolic Diseases | 206,623 | 2.42% |
| Disease of the Genitourinary System | 9,7114 | 1.14% |
| Infectious Disease | 9,0799 | 1.06% |
| Disease of the Nervous System | 7,9060 | 0.93% |
| Total | 8,040,052 | 94.21% |

China's diverse disease burden results in a large unmet medical need that drives its pharmaceutical industry to develop therapeutics specifically addressing the medical problems of the Chinese population (Table 3). Unlike other major pharmaceutical industries, there is an emphasis on developing therapeutics for oncology and infectious diseases, accounting for 31% and 21% respectively of clinical trials from 2004-2010 (Figure 4). While infectious diseases account for only a relatively small number of deaths per year, this is often not reflective of the incidence rate as many of the most prevalent infectious diseases in China result in death as a result of other complications. A prime example of this is the high incidence of hepatitis infection, with over 1.4 million reported cases but only 1,000 reported deaths in 2009 (China Ministry of Health, 2010). Since hepatitis frequently results in further complications such as liver cancer (the second highest cause of cancer mortality in China (China Ministry of Health, 2010)), deaths as a result of hepatitis are generally underreported. The focus of pharmaceutical developers on infectious diseases such as viral hepatitis demonstrates that, while international applications for Chinese drugs are increasing, developers in China are primarily focused on developing drugs for China. The many benefits to performing clinical trials in China only serve to increase the attractiveness of the China market.

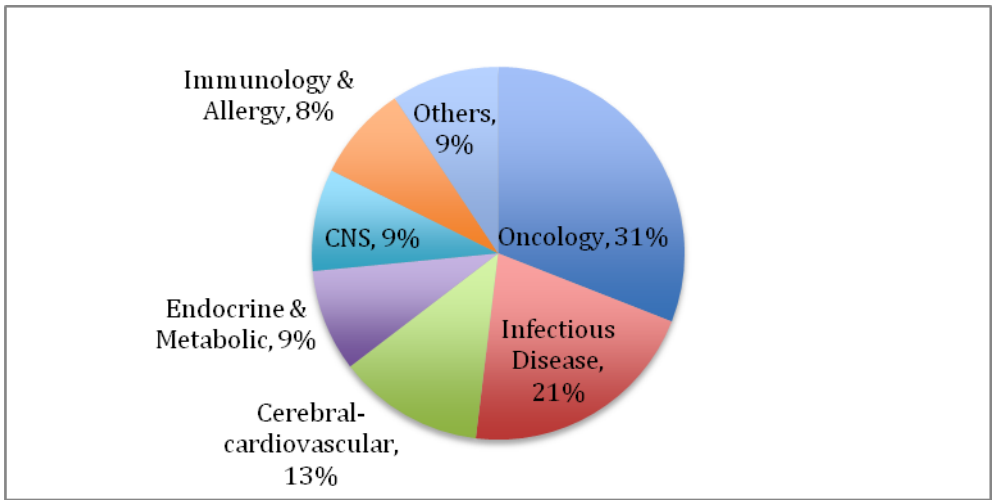


**Figure 4. Clinical Trials by Therapeutic Area from 2004-2010** *(Source: ChinaBio)*

The large number of highly talented people available to support development within China further increases the attractiveness of performing clinical trials in China. In recent years, there have been an increasing number of life science industry professionals returning to China from Western countries (Figure 5). Over 450,000 high value professionals returned from 2004-2010, with over a quarter of them returning in 2010. These professionals bring with them considerable experience in the pharmaceutical industry, often taking leading roles upon their return. Additionally, there is an increasing trend of developing talent domestically. In 2009, there were over 10,000 new life science students enrolled in domestic colleges and over 2,500 graduates, an increase of 5.8% from the previous year.

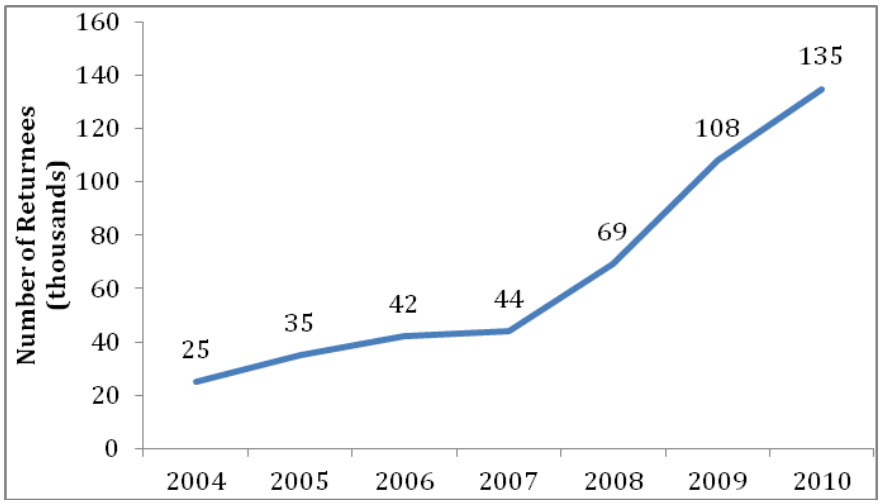


**Figure 5. Life Science Returnee Trend** *(Source: ChinaBio)*

## Regulatory Environment

Prior to 1985, China had no legislation requiring premarket testing for new drug products. Instead, approval was easy to obtain from any provincial department of health. However, as the need for stricter drug regulation became apparent, the Drug Administrative Law was passed with the aim of establishing a clear regulatory pathway for premarket testing, approval and quality control of pharmaceuticals. Since then, China has continued to improve its regulatory controls for the pharmaceutical industry, establishing the current standards in 2006.

The current standards set by the SFDA have strict requirements for the development, marketing and production of new drugs. Investigational New Drug (IND) applications have a similar structure to those in other countries and include both preclinical and toxicity trials. China's requirements for preclinical trials typically take 1-3 years to complete with several companies opting to outsource, using specialized preclinical contract research organization (CRO) companies. Preclinical CRO companies typically perform in vitro and in vivo animal trials to demonstrate proof of concept for IND submission, as well as create disease models for future development.

China's preclinical trials timeline is typical based on international good laboratory practice standards. However, China is unique in that there are especially rigorous requirements for toxicity trials. These trials add anywhere from one to six months to the preclinical development timeline. Typically a minimum length of six months is required for novel Class 1 molecules, especially those intended for chronic disease indications. Other molecules may only require a toxicity trial of one month, depending on the therapeutic classification.

In addition to preclinical and toxicity data, IND applications must also include the proposed clinical trial protocol, investigator information, and manufacturing information, all of which must be certified and/or inspected by the SFDA prior to approval. Unfortunately the large amount of information to be reviewed can result in longer processing times (Figure 6). Unlike the US FDA, there is no 30-day implicit acceptance for IND applications. Instead, each application must receive a formal response from the SFDA. This process can take up to two years depending on the application, after which it is generally considered denied. Typically the SFDA returns an official response within eight months. However, there is a special procedure for novel molecules targeting therapeutic areas designated by the SFDA as a priority for innovative drug development. Applications made using this procedure generally receive a response in five months.

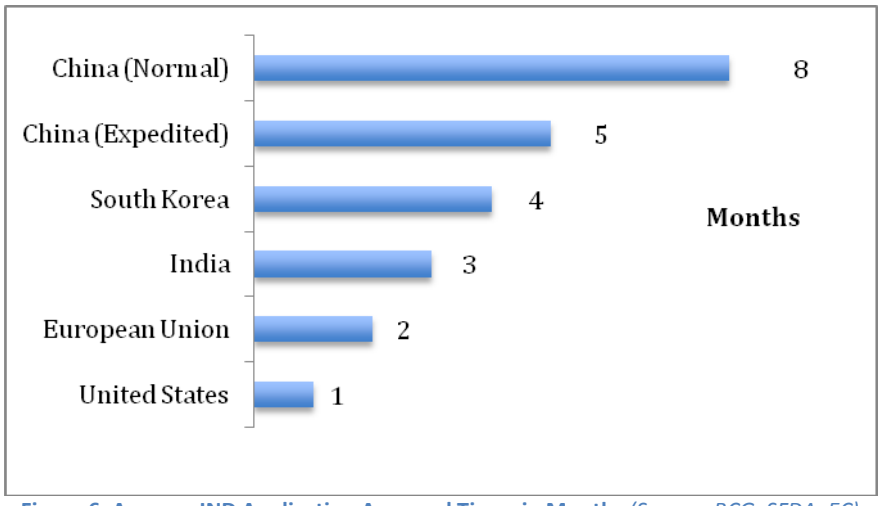


**Figure 6. Average IND Application Approval Times in Months** *(Source: BCG, SFDA, EC)*

Once IND approval is granted, the pharmaceutical developer may begin a clinical trial while remaining closely monitored by the SFDA to ensure compliance with both the protocol guidelines and clinical trial regulations. Each successive clinical trial phase requires a new submission of both the current clinical trial data and a proposed protocol for the next phase of the clinical trial. However, processing times for these approvals are generally shorter, resulting in an average duration of approximately five years to complete all clinical trial phases.

Unlike the US FDA, the SFDA typically does not publicize its responses to clinical trial phase protocol applications. This lack of transparency and the flexibility in clinical trial duration makes it almost impossible to accurately judge the failure rate of drug candidates once they are in clinical trials. New Drug Applications (NDAs) can be submitted when all clinical trial phases are completed. The SFDA does not routinely publish data on new drug approval times, making it difficult to compare NDA processing times to those in other countries. Typically, the SFDA takes even longer to process NDA submissions (1-2 years) due to the increased amount of data provided and the potential harm that could come from a mistaken approval. The SFDA will frequently bring in experts to provide input on the scientific validity of the data, as well as request more data from the applicant, before returning a formal decision.

## Looking Forward

### *Increasing Demand*

China's pharmaceutical market will continue to rapidly expand in the upcoming years due to the steadily increasing demand of China's population. While much of the growth is due to the rapidly aging population and increasing incidence of chronic diseases, future growth will also be driven by an increase in healthcare access through an increase in healthcare spending and the increasing average income of the population.

Healthcare spending is a priority for the Chinese government, whose plan is to increase healthcare expenditures 12-15% per year to 2.1 trillion RMB (325B USD) in 2013 (Morgan Stanley, 2009). A large part of this is to fund implementation of the New Cooperative Medical System (NCMS), which aims to increase the number of people with healthcare insurance. As of 2008, over 80% of the population has some type of medical insurance, with 68% of the total population covered by the NCMS (China Health Statistical Digest 2010).

Access to healthcare has also been improved by the increasing average annual household income in China (Figure 7). The per capital annual income for the average household has increased 11% for urban households and 10% for rural households over the past decade, without correcting for inflation. However, living expenditure as a percent of income fell from almost 53% in 2000 to below 49% in 2009, resulting in an overall increase in disposable income for the average household.

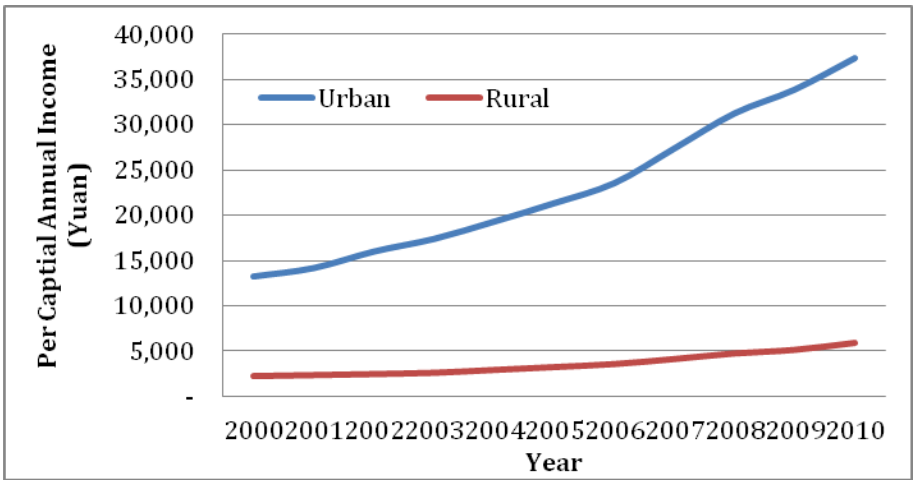


**Figure 7. China Annual Household Income** *(Source: ChinaBio, China Statistical Yearbook 2010)*

Furthermore, the urban population in China is forecasted to have a growing middle class, with more than 100 million people joining China's middle class every five years (Figure 8) (Houdard, 2011). These factors demonstrate the increasing ability of the Chinese population to afford quality healthcare, driving a demand for drug development within China.

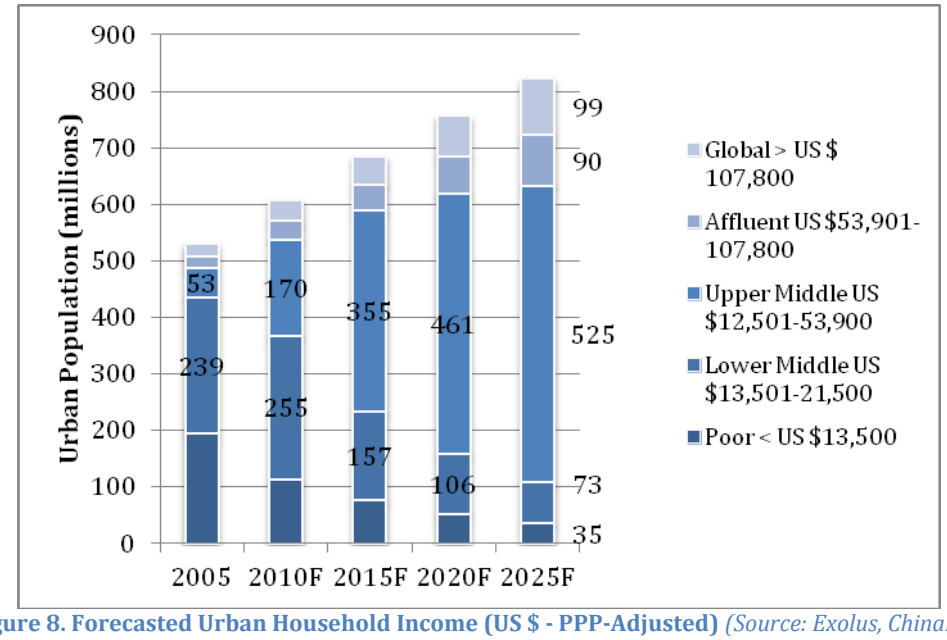


**Figure 8. Forecasted Urban Household Income (US $ - PPP-Adjusted)** *(Source: Exolus, ChinaBio)*

***Increasing Pharmaceutical Development***

The increased demand for and access to healthcare continues to drive the growth of the pharmaceutical industry. As a result, the pharmaceutical industry has increased drug development as it seeks to capitalize on

these market trends. Evidence of increased drug development exists in the industry's expenditure on R&D, which has increased over 23% since 2001 (Ministry of Science and Technology, 2010). As the demand for quality healthcare continues to grow, ChinaBio has forecasted that R&D spending will continue to grow to over 7B USD in 2015 (Figure 9).

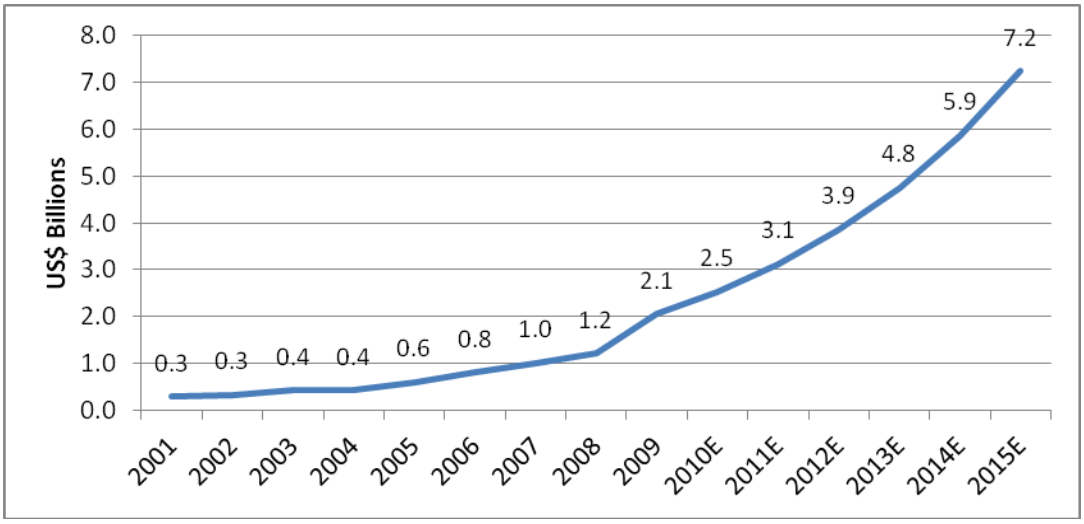


**Figure 9. Industry R&D Expenditure Forecast** *(Source: ChinaBio, China S&T Statistical Yearbook 2010)*

In addition to the growing industry expenditure on R&D, the Chinese government has made the development of the biotechnology sector a priority in their 12th five-year plan by dedicating 3.1B USD to its continued development (Richard Daverman, 2011). This is in addition to the 162 government programs and initiatives worth over 100M RMB that ChinaBio has identified as supporting drug development, emphasizing the government's commitment to the development of targeted therapeutics for the China market and further driving drug development in China.

The increased industry and government expenditure on R&D has already resulted in the development of novel therapeutics, with a total of 3,200 novel molecule patents published since 2000 (Figure 10). While not all will qualify for the special IND application for innovative drugs, this increasing focus on developing novel drugs for the China market is evidence of growing drug development within China.

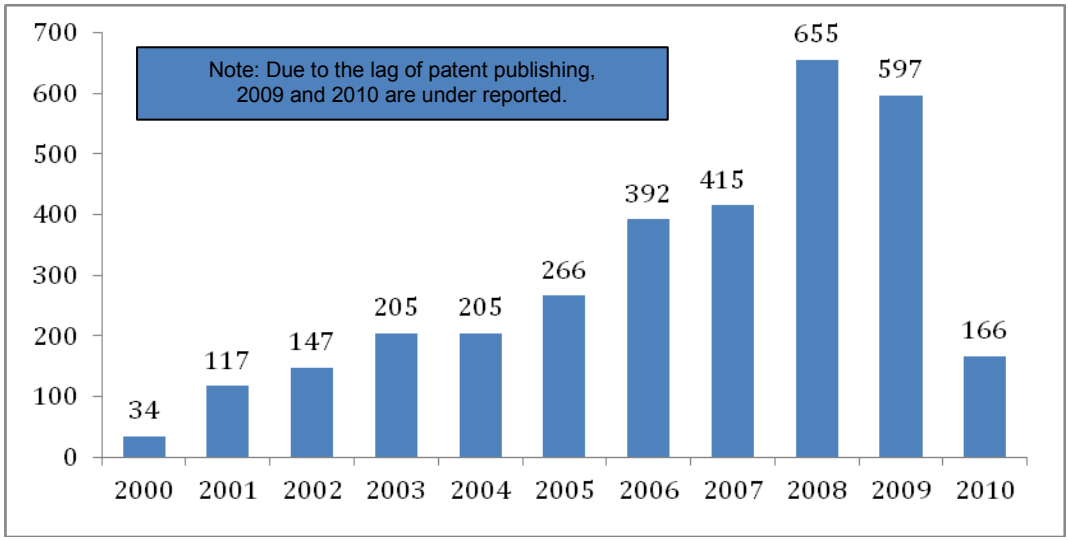


**Figure 10. Novel Molecule Patents from 2000-2010** *(Source: ChinaBio)*

In the past, one of the benefits of drug development in China was the relatively low cost of performing clinical trials. However, as China's pharmaceutical industry continues to develop, these costs are anticipated to rise. Increased access to healthcare not only increases demand for effective therapeutics, it also reduces the population of treatment-aïve patients, increasing difficulty of patient recruitment for clinical trials. However, the majority of insurance holders in China are covered by the NCMS, which currently only provides minimal coverage for its enrollees. So while the reduced number of treatment-naïve patients will result in an increase in delays, patient recruitment will likely remain quicker and more efficient than recruitment in western countries.

Additionally, as China's government continues to work to ensure that the entire Chinese population has access to healthcare, there will be an increasing number of registered doctors and hospitals (Figure 11). As more of hospitals are built, there will likely be an increase in the number of certified clinical trial institutions In China. This will allow access to a wider range of patients, further supporting fast patient recruitment in China.

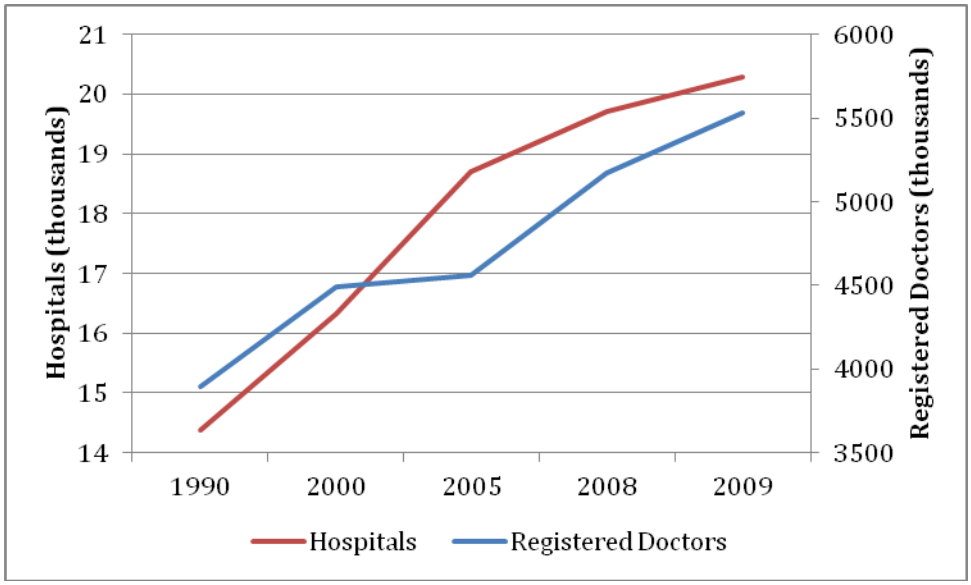


**Figure 11. Hospitals and Registered Doctors in China from 1990-2009** *(China Health Statistical Digest 2010)*

***Regulatory Environment***

China will continue to increase the quality of drug R&D, manufacturing and commercialization as the SFDA works to enforce high regulatory standards within China. As the SFDA gains experience monitoring the pharmaceutical industry, China's pharmaceutical industry will benefit from an improved international reputation for quality therapeutics.

Furthermore, as China becomes more experienced at drug development, there will be a growing number of Class 1 novel drug IND applications. Current Class 1 novel drug IND approvals are already driving an increasing number of clinical trials in China with over 40 IND approvals in 2010 (Figure 12). With 19 applications already approved in the first half of 2011 and an additional 53 applications currently being processed, ChinaBio anticipates that the number of Class 1 novel drugs in clinical trials will continue to increase.

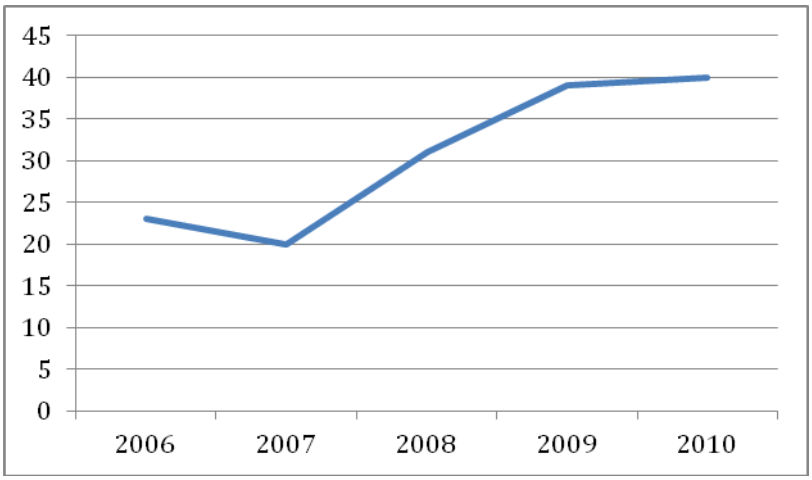


**Figure 12. Class 1 IND Approvals from 2006-2010** *(Source: ChinaBio)*

This increase in the number of drugs in clinical trials in China will ultimately lead to an increase in the number of NDA submissions. From 2006-2010, there were 29 Class 1 NDA submissions to the SFDA, resulting in 12 approvals and 1 rejection, with 16 applications still in process (ChinaBio). Due to the relatively recent evolution of China's regulatory environment, the number of approved NDAs is not reflective of the current drug development environment, as no IND applications approved under the current regulations has yet had a NDA approved by the SFDA. This is partially due to the time needed to complete all clinical trial phases and partially to the current long processing times of the SFDA. However, as more drugs with INDs approved under the current regulation are developed, ChinaBio anticipates there will be an increase number of NDA submissions.

As the number of IND and NDA submissions continues to increase, the SFDA will gain more experience with managing the regulatory process. This will result in a decrease in the processing time for applications, resulting in a faster application return to developers. This will ultimately reduce the overall time of drug development and further supporting novel drug development in China.

## Conclusion

The medical needs of China's large and diverse population will continue to drive novel drug development within China as the growth of its pharmaceutical industry quickly outpaces that of the rest of the world. This growth has led to an increasing number of clinical trials performed in China, supported by many factors beyond China's medical need, such as an increased availability of talent, funding and technology. Additionally, as the SFDA continues to improve and regulate the quality of clinical trials performed in China, domestically developed pharmaceuticals will have increasingly global applications, driving China to become the #1 pharmaceutical market in the future.

*ChinaBio® LLC helps Western companies bring novel assets to China by analyzing the market opportunity and competitive landscape, developing clinical strategies, identifying partners, establishing corporate entities and negotiating and managing contracts. Companies with pre-clinical, clinical and approved products are potential candidates to leverage China's resources and capabilities. For more information, please contact us.*

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