Study on Metrics and Distribution Mechanisms; Pharma Innovation for Low-Income Populations

A Report (D2.1)¹ for

Chinese Academy of
Science and Technology for Development

November 2009

¹ The research leading to these results has received funding from the European Community’s Seventh Framework Programme under grant agreement 217665. This report has been reviewed and accepted by the Innova-P2 project partners
Contents

Chapter 1: Overview of Global Burden of Disease Measurements
I. Basics of Measures of Global Burden of Disease (GBD)
II. Application of Measures of GBD
III. Evaluation of Measures of Global Burden of Disease

Chapter 2: Stress calculation report for a typical disease among low income populations in China
I. Study contents and methods
II. Calculation process and result of chronic Hepatitis B disease burden
III. Discussion and suggestions

Chapter 3: Reform of the Chinese Medical Health System and the Medical Intellectual Property System
I. Reform of the Chinese Medical Health System
II. Reform of the Chinese Medical Intellectual Property System

Chapter 4: Basic Considerations of Supporting the Innovation of Drugs for Low-Income Populations

References
Chapter 1:

Overview of Global Burden of Disease Measurements

Before the 1980s, the evaluation indexes applied for disease burden were mainly conventional indexes such as morbidity, mortality and ranking of death causes. With the medical mode changing, such conventional indexes have increasingly failed to meet the requirements of the modern medical mode. This is mainly because conventional indexes considered only the biological outcome of diseases, but not the comprehensive effect of different indexes and it is hard to compare these directly between different countries and regions. From 1988 the Harvard School of Public Health and the World Health Organization, with the support of the World Bank, and jointly with over 100 experts from all over the world, spent more than five years exploring the Disability Adjusted Life Year (DALY), as a measurement to quantify all the losses of healthy life lost. This was then eventually applied to the analysis of GBD. In the 1993 World Development Report, the World Bank initially put forward the concept of the Global Burden of Disease (GBD), and used this concept to study the strategies of different countries, especially the developing and middle-income countries, in controlling the priority of diseases and defining the basic health service package. Disease burden is substantially a kind of community diagnosis approach to studying the disease and health status of a particular community. Using such an approach to study the disease burden of different countries and carry out comparative studies becomes the study of GBD. In this paper, by concentrating on the measures of the Global Burden of Disease as introduced and developed by Murray and Lopez, we review the measures of the Global Burden of Disease.

I. Basics of Measures of Global Burden of Disease (GBD)

The Disability Adjusted Life Year (DALY) refers to all the life years lost from the first incidence of illness or disease until death, including the years of life lost (YLLs) and the years lived with disability (YLDs). The DALY for a particular group is achieved by comprehensively calculating the YLLs and YLDs of the group and then carrying out a weighted adjustment with the age-based relative value (age-weighing) and time-based relative value (discount rate) of life years. DALY is a kind of negative comprehensive measurement index for health status, life quality (mainly referring to disability) adjustment and life loss. What it reflects is YLL by disease or YLL recovered by interference. One DALY indicates one YLL.

1. Basic Formula of DALY

DALY is a comprehensive index combining YLL and YLD. To calculate the YLLs using the “Western” Family-model Life Table No. 26, the life expectancy at birth is
taken as 82.5 years for a female and 80.0 years for a male, \( cx^\alpha e^{\beta x} \) as the age weighing function and the index function \( e^{-\gamma(x-a)} \) as the discount rate. The duration of each disease is weighted by the disability weighting of 0~1 so as to convert it into YLLs. Calculation method of the DALY of a given disease is follows:

\[
\text{DALY} = \text{YLLs} + \text{YLDs}
\]

YLL refers to DALY loss caused by death from disease; YLD refers to DALY loss caused by deformity.

Calculation method of YLLs and YLDs:

\[
x = a + \int Dcxe^{-\beta x}e^{-\gamma(x-a)}dx = a
\]

Whereas:

D: disability weighting (D=0~1, D=1 when died)

a: age when disease or death happens

L: life loss caused by disability course or early death

\( \gamma \): discount rate (=0.03 in GBOD analysis)

\( \beta \): age-weighting coefficient (=0.04 in GBOD analysis)

K: age-weighting modulation factor (0~1)

C: a constant (=0.1658 in GBOD analysis)

According to the severity of temporary disability or permanent deformity, deformity and disability can be classified into six types with different weighted values (see Table 1). 0 represents fully healthy, 1 represents death and the weighted value ranges from 0 to 1. In case of any temporary or permanent disability caused by disease, the remaining expected life years shall be multiplied with the disability weight for conversion.
Table 1: Classification and Weighted Values of Disability

<table>
<thead>
<tr>
<th>Disability Level</th>
<th>Weighted Value of Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>At least one of the following activities is limited: entertainment, education, generation and employment</td>
</tr>
<tr>
<td>2</td>
<td>One of the following activities is mostly limited: entertainment, education, generation and employment</td>
</tr>
<tr>
<td>3</td>
<td>Two or more of the following activities are limited: entertainment, education, generation and employment</td>
</tr>
<tr>
<td>4</td>
<td>All the following activities are mostly limited: entertainment, education, generation and employment</td>
</tr>
<tr>
<td>5</td>
<td>Instruments are required for daily life such as cooking, shopping and undertaking housework</td>
</tr>
<tr>
<td>6</td>
<td>Assistance of others is required for daily life such as cooking, personal sanitation and self-relief</td>
</tr>
</tbody>
</table>

In the Global Burden of Disease in 1990: Summary Results, Sensitivity Analyses and Future Directions, Murray and Lopez conducted the sensitivity analyses on the measurement of GBD.

The discount rate (r) used in calculating ranges from 0% to 10%, with a changing gradient of 2.5%. To determine the sensitivity of results to the use of non-equalized age weights, a new parameter shall be introduced. The following formula is used to substitute the simple index age-weighing function in the original DALY formula:

\[ KCxe^{-rk} + (1 - K) \]

In the formula, K is a constant of age-weighing. When K =1, the age-weighing function is the same with DALYs, but when K = 0, the age weights are equal.

The entire GBD is calculated by cause, age, gender, country and region. At the discount rate of 0%, 2.5%, 5%, 7.5% and 10%, calculation is conducted under each discount condition with a K value respectively of 0, 0.25, 0.5, 0.75 and 1. Out of 1.25 million charts and tables generated thereof, only a few are selected herein for discussion and analysis. In the following discussion, stress will be placed on the qualitative impact of variable r and K value on the final result.

Changes of R and K value show almost no impact on the difference between different genders of the total DALYs. At the global level, the male proportion ranges from 51% to 52% and only from 52% to 59% even at FSE with maximum difference. Although showing an extremely small impact on the difference of total GDLs between male and female, the change of discount rate actually has an impact on the distribution of the total DALYs by ages. No matter what K value is, increasing the discount rate will reduce the proportion of age groups ranging from 0 to 4 years and from 5 to 14 years in the total GBD, while the proportion increases for the adult groups (45-59 years) and the elder group (more than 60 years). In changing the age group at the age of 15-44 years, the change of discount rate shows an extremely small impact on the
proportion of the total DALYs. The impact of changing from equalized to non-equalized age weight by increasing the K value from 0 to 1 on the age distribution of total DALYs is much smaller and even more complex. When the discount rate reaches 5%, the non-equalized age weight can reduce the burden in the age range of less than 45 years. In comparing the value of DALYs obtained using the original formula under the condition of r=3% and K=1 with the value obtained using the “classic” version of equalized age weight at the discount rate, the total DALYs by age show a limited difference, because certain impacts with the discount rate of 3% are set off by the non-equalized age weight. At a high discount rate, incremental K value increases the impact of discount rate on the age distribution.

As the composition of causes for the burden of different age groups differs, changing the discount rate and age weight not only will change the overall age distribution of DALYs, but will also change the relevant importance of premature death and deformity and different causes. The burden proportion caused by deformity ranges from 25% to 45%; when the discount rate is 0 and the age weight is equalized, the proportion caused by deformity is the lowest; when the discount rate is 10% and the age weight is non-equalized, the proportion is the highest. Similar to the age distribution of the total DALYs, the change of discount rate shows much greater impact than the change of K value. In fact, K value shows a slight qualitative impact according to the level of discount rate.

In *Quantifying the Burden of Disease: the Technical Basis for Disability-adjusted Life Years* (1994), a new approach was put forward to determine the burden of disease, which has provided important technical support for DALY.

The report put forward a time-based determination approach, which has provided a simple and intuitive determination method, with time as the determination unit, for the life years with disability and life years lost at premature death and revised the previous concept of YLL.

In order to test the impact of the changing r and K value on causes, in each country or region as well as worldwide, one needs to calculate the total DALYs of each cause, using different r and K value pairs, and then carry out the linear regression for each result as compared to the original result. The squared value of r in the linear regression analysis can be used to determine the similarity between the specific result of cause and the GBD result. Under this circumstance, the squared value of r is the standard to determine what difference actually exists between difference results of the burden of disease, using a new assumption to extract from original data for re-calculation. Since the total of Groups I, II and III has increased greatly the squared value of r in the linear regression analysis, such values are excluded. When the squared value of r is 1.0, it indicates an excellent pairing between the two; when the squared value of r is 0.0, it indicates that there is no correlation between the two groups of evaluation and analysis. At a global level, the squared value of r ranges from 0.84 when r=10%, K=0 to 0.99 when r=2.5%, K=1. When the value of r is not equal to zero, the result due to the incremental K value is even closer to the original
study analysis, but, when the discount rate is zero, the impact of incremental K value is just the opposite.

Two extreme values (the “classic” approach with r=0 and K=0 and the “development economic” approach with r=10% and K=1) can be compared with each other. The GBD result of the “development economic” assumption (with the squared value of r being 0.91) is closer to the “classic assumption” (with the squared value of r being 0.98) and the results of the two extreme values are surprisingly similar. The overall impact of the changing r and K value is almost due to the impact on the transformation of the age distribution and thus the balance between Group I and Group II is changed. Upon completion of the same linear regression within each group, the analytical result of the squared value of r obtained ranges from 0.97 to 1.0 for Group I, from 0.94 to 0.98 for Group II and from 0.99 to 1.0 for Group III.

According to the summary analytical result of the sensitivity testing analysis, the following conclusions are obtained. First, discount shows an extremely important impact on the evaluation and analysis of the total DALYs distribution by ages. Second, the non-equalized age weight shows less impact as compared to the remarkable impact of discount rate and such impact is often contrary to the time impact. Third, discount rate and age weight shows less overall impact on the calculation of the disease burden resulting from special causes. Thus, we may conclude as follows: the quantitative analytical result of disease burden depends on the specific assumption of time and the age weight used to a great extent. Although we have not given a detailed testing analysis in this study, we have conducted the testing analysis on the results arising from the changes in the specific values of deformity weight. As a whole, the impact of such changes on the overall result exists but is rather limited.

According to the summary analytical result of the sensitivity testing analysis, the following conclusions are obtained:

1. Discount shows an extremely important impact on the evaluation and analysis of the total DALYs distribution by ages.
2. Non-equalized age weight shows less impact as compared to the remarkable impact of discount rate and such impact is often contrary to the time impact.
3. Discount rate and age weight shows less overall impact on the calculation of the disease burden resulting from special causes.

From the above, the following conclusion is obtained: the quantitative analytical result of disease burden depends on the specific assumption of time and the age weight used to a great extent. As a whole, the impact on the result arising from the changes in the specific values of deformity weight exists but is rather limited.
II. Application of Measures of GBD

In its 1993 *World Development Report: Investment on Health*, the World Bank measured the GBD by applying DALY as a unit. This was the first study that carried out the comprehensive evaluation on premature death and deformity caused by various diseases for different groups in the world, which has successfully estimated the global disease mode in 1990 and forecast the global burden of disease by 2020.

The report of the *Healthy Life Expectancy for 191 Countries in 1991* is a typical case of applying the DALY approach.

For 191 countries, from the uncertainty distribution of Healthy Life Expectancy (HLE), the report extracts an observation value of HLE, HLE value to conduct the regression of X value (health expenses or total life expectancy for each person). This process is repeated 1,000 times to sample non-alternatively, for each country, from the distribution of HLE. Each time, one group of new HLE is operated for regression of X value to obtain the 1,000 times of estimated value of the regression slope used to estimate its 90% reliability.

Since mortality is of great significance to the proportion of the total burden of disease (YLD/5 YLLs less due to mortality), the report evaluates the YLDs by using the YLDs/YLLs by cause of mortality and national YLLs by cause of death and average health expenditures per person, as estimated for the region by gender and age. The report evaluates the national YLDs, by using the regional estimate of YLD proportion of 1,000 groups by age and gender, along with the national group distribution. Then, such YLDs are used to evaluate the unknown incidence of YLDS without age-weighing by age, gender and cause of disease.

The total of YLDs for all reasons will lead to an overestimated incidence of deformity, due to the co-existing disease between different states. The calculation output is as follows:

With its average HLE of 74.5 years at birth in 1999, Japan led the international standard. In 1999, Japanese HLE was 77.2 years for women and 71.9 years for men. After Japan are Australia and France and then some industrialized countries in West Europe. Canada ranked 12th, with the uncertainty ranging from 8 to 14. USA ranked 24th (70.0 years, with the uncertainty ranging from 22 to 27). Vietnam and Thailand have even lower HLE, while Burma is far behind other Southeast Asian countries in terms of HLE.

The HLE for Russian females is 66.4 years, which is 3 years lower than the average level for Europe, and only 56.1 years for males, which is 7 years lower than the average level for Europe. This is the widest gender difference in the world, indicating that the mortality for male adults in Russia increased sharply in the early 1990s. Other former Soviet countries also observed the same rate.

The ten countries with the lowest healthy life expectancy are in Sub-Saharan Africa,
where AIDS is most prevalent. In the countries of Southern Africa, life expectancy is reduced by 15~20 years as compared to AIDS free population. In other African countries, the life expectancy is lost by 5 ~ 10 years due to AIDS.

As a whole, in 1999, global life expectancy at birth was 64.5 years, being 6 years more than that over the last two decades. The global healthy life expectancy at birth was 56.8 years, being lower than the total life expectancy (77 years). The global healthy life expectancy for female was 57.8 years, being higher than that for the male (55.8 years).

In 1999, the HLE at birth ranged from 37 years for African males to 70 years for women in the West European countries. This difference is almost double the HLE between groups in the major regions of the world. The HLE and the total life expectancy is DLE (Disability Life Expectancy). The proportion of DLE in the total life expectancy at birth is 18.9% in Africa and 8.8% in Europe. At birth, there is a close correlation between the total life expectancy and HLE in different countries.

In most regions of the world, the HLE for females is higher than for males. Such gender differences usually increase due to the increase of average life expectancy. In the world, Russia shows the biggest difference of HLE by gender: the HLE is 66.4 years for females and only 56.1 years for males. The most common explanation is that Russian males observe a high incidence of excessive drinking, which results in a high incidence of accidents, violence and angiocardiopathy. From 1987 to 1994, the danger of premature death increased by 70% for Russian males. But since 1994, the life expectancy for males has increased, as is also the case with other former Soviet countries.

### III. Evaluation of Measures of Global Burden of Disease

DALY has taken into full account the burden due to death and disability caused by disease and also such factors as age and time in calculation. As compared to the previous indexes, it has more completely reflected the burden of disease on groups, not only providing a tool for the World Bank to study the burden of disease, but also academically developing the methodology of evaluating the burden of disease and improving the ability of elevating and comparing the burden of disease in different regions. Thus, it is currently the best index used in the world to evaluate the burden of disease.

In application of DALY, some problems have also been observed for further studies, such as the quality of data for calculation of DALY, subjective or conceptual problems reflected in age, deformity weighing and discount rate and effectiveness and use of DALY.

DALY has been criticized mainly in two aspects: one is doubt about the objectiveness of the index, viewing the discount rate, age weight and disability grade introduced for
DALY as only representing the views of the researchers and the experts of the World Bank, and not necessarily representing the actual conditions of the regions analyzed. The other is the technical defect with the index. DALY selects the highest life expectancy of the world as the estimated value of the life expectancy at birth, naturally resulting in the overestimation of the burden of disease for the countries with lower life expectancy. The calculation of DALY requires high-quality health information and thus the index cannot be used for those countries with a shortage of health information. Actually, most of the developing countries lack the information required for application of DALY.

DALY is calculated on the basis of various data of group level such morbidity, mortality and average course of disease and cannot be applied to individuals and cannot evaluate the individual burden of disease or YLL in following up a case by regular visits. The study of the factors relating to the burden of disease through DALY is essentially to use the method of sectional ecological epidemiology, with which various uncertain factors can hardly be regulated. Do different social groups (especially different economic groups) have different healthy life years (HeaLY) by quantity?

In measuring the burden of disease with DALY, certain consideration is given to the mental and social function loss caused by disease, but the objects harmed by disease are still limited to the groups of patients. Actually, disease will also cause a burden to other groups than the group of patients, such as families and society, which are not included in the scope of GBD. The reason for the burden of disease is a complex system, involving various factors, including, in addition to the physiological factor, also the income, education background, employment, behavior and environmental factors (such as smoking, sports activities, food and drink and health care). To comprehensively evaluate the burden of diseases, it is necessary to analyze systematically the multi-layer burden caused by disease to individuals, families and society and integrate the biological, psychological and social indexes to extend the measurement and evaluation of the burden of disease to the whole social system so as to evaluate the impact of disease on the whole society.

In view of the evaluation method for the burden of disease, DALY analyzes and evaluates the burden of one disease in a unitary state, but various chronic disease have a long course of disease, while the development of such diseases will experience several health states, in each of which the medical measures and burden of disease differ. In this regard, in studying the burden of such diseases, we may consider using the Markov Model to analyze the burden of disease in different states.

According to some of the experts, DALY index needs to be reconsidered in terms of age weighing, disability weight, discount rate, etc. In terms of age weighing, it is necessary to pay attention to the contribution of the elders to culture and economy, especially the elder society. In terms of disability weight, consideration should be given to the impact of difference of life state and gender of groups in different regions.
In measuring the global burden of disease with the index of DALY, original data is a relatively prominent problem. Firstly, the data of mortality and morbidity for the developing countries is relatively weak and is uncertain. Secondly, it is hard to estimate the health demands of groups that have not been satisfied, but the burden of such diseases show an impact and such factors have been considered in calculation with DALY. Thirdly, YLD observes overestimation as well as under-estimation. The under-estimation includes the negligence of some diseases and paroxysmal deformity, while the overestimation includes the problem of complicating diseases. For instance, DALY evaluates the disability weight separately for each type of disease. When one person suffers from two or more diseases, it may overestimate the burden of disease [14]. This problem is especially common among the middle-aged and elder groups. Finally, aggregation of disease impacts on the calculation of the burden of disease as well which will result in difficulties in assessing priorities.

Chapter 2:

Stress calculation report for a typical disease among low income populations in China

I. Study contents and methods

The object of this study is to calculate the disease stress of atypical disease among low income populations in China and provide a scientific basis for the evaluation of the “Health Impact Fund”.

1.1 Study contents

1.1.1 An example of a typical disease among low income populations (disadvantaged groups) of China is selected to learn the basic information of the disease. Chronic hepatitis B is selected in this study as the preferred typical disease for the evaluation of the “Health Impact Fund” in China.

1.1.2 Screen and argumentation of basic therapeutic drugs and their efficacy on chronic hepatitis B. Nucleoside analogs is selected in this study as the specific drug for therapeutic application.

1.1.3 Confirmation of the method for disease burden calculation and performance of calculation. International disease burden calculation method (DALYs) and health efficacy evaluation index (quality adjusted life years, QALYs) were selected in this study.

1.1.4 On the base of the calculation result, the two main methods for disease stress calculation, DALY and QALY, were systematically evaluated.
1.2 Study methods

1.2.1 Quantitative methods: Life quality investigation of hepatitis B patients

Aim of investigation: To obtain health-improved life quality efficacy value for the calculation of QALY.

Contents of investigation: Internationally accepted SF-36 scale and CLDQ scale were selected to measure the health effectiveness values of patient group and control group.

Selection of investigation samples: Chronic hepatitis B patients in the department of infectious diseases in a Grade III Class A hospital were selected for the study of case comparison. There were 100 chronic hepatitis B patients treated with nucleoside analogs in the case group and 100 chronic hepatitis B patients without nucleoside analogs treatment in the control group. The total number of subjects was 200.

1.2.2 Qualitative methods: Investigation by expert consultation

Contents of investigation: Selection of therapeutic drugs for diseases; selection criteria for the subjects of questionnaire; determination criterion for therapeutic effects of drugs; effective rate of drug treatment; disease conversion, and methodology.

Global officially published hygiene technical evaluations were taken advantage of to preliminarily determine the possibility of state transition. The domestic famous experts of hepatic diseases were also invited to consult about the state transition possibility of documents collection. Experts were inquired by questionnaire if they agree with each transition possibility, otherwise, they were asked to put forward appropriate index values. After two rounds of expert consulting, every expert was prone to agree with each transition possibility. Middle value was set as the basal value for Markov model analysis.

Investigation method: Experts interview; discussion groups on specific topics.

Investigation objects: Twenty experts in different fields such as clinical pharmaceutics, drug development, clinical medical treatment, epidemiology, hygiene economics, public health etc were invited in two groups on specific topics for discussion.

1.2.3 Calculation method for the disease burden

At present, the main disease burden calculation methods include Disability Adjusted DALY and QALY.
1.3. Typical disease and the selection of its therapeutic drugs

1.3.1 Disease and the selection rationale and principle of its therapeutic drugs

- Incidence and prevalence of the disease
- Severity of disease and its overall influence on the people, health and society
- Disease intervention
- Type and characteristics of therapeutic drugs for disease
- Cost and efficacy of therapeutic drugs

1.3.2 Disease selection

1. Hepatitis B is one of the most common infectious diseases. The number of patients or carriers is estimated to be 40-50 million people. Based on the statistics by China Ministry of Health, the incidence of hepatitis B has been on the top of the list among infectious diseases for many years and is still increasing. The incidence of chronic hepatitis B in China is 0.108% as demonstrated in statistics of infectious disease incidences in the mandatory report for class A and B infectious diseases issued by Ministry of Health in 2007.

2. If the treatment of chronic hepatitis B is not undertaken in time or is inappropriate, it will convert to hepatic cirrhosis and liver cancer, which seriously influences the people’s life quality and causes a huge economic burden to the country. The mortality is as high as 0.034% for the residents of big, small and medium-sized cities as reported by Ministry of Health in 2007, which ranked first in the list of mortalities of infectious diseases in China.

3. The incidence and mortality of chronic hepatitis B are so high that they are closely related to the current situation of the country and the characteristics of the infection of chronic hepatitis B. First of all, as a developing country, China has a large population with high distribution density. The medical service levels are limited in some areas. It brings difficulty to the control and prevention of infectious diseases in China. Secondly, the onset characteristics of chronic hepatitis B include wide routes of transmission, slow onset, incurable course of disease, expensive medical cost, and furthermore most of the patients have no symptoms. It further increases the possibility of infection from chronic hepatitis B among poor population in China’s countryside. The onset mechanism of chronic hepatitis B has not been fully explained, and it cannot be completely cured by current medical and scientific technology. Therefore, the most ideal therapeutic effects at present are the continuous negative conversion of hepatitis B DNA, serological conversion between e-antigen and e-antibody, and normal liver function.
1.3.3 Selection of therapeutic drugs for hepatitis B

The specific therapeutic drugs for chronic hepatitis B mainly include interferon and nucleoside analogs. In recent years, nucleoside analogs have drawn more and more attention as the effective therapeutic drug for chronic hepatitis B. Compared with the previous widely used interferon, nucleoside analogs especially suit the treatment of chronic hepatitis B patients in China. Its advantages are manifested by following aspects:

1. Nucleoside analogs interfere with the nucleotide metabolism of hepatitis B virus, inhibit the replication of the virus, and directly act on the virus itself, while the action mechanism of interferon is to promote the anti-virus immunity of the body. In comparison, the therapeutic efficacy of interferon is relatively low, especially for decompensation hepatic disease patients; for instance, it has no improving effects on patients with hepatic cirrhosis or chronic hepatitis accompanied by significantly increased bilirubin.

2. The administration of interferon needs injection. The storage of the drug needs refrigeration. It is not convenient for drug administration and the adverse effects are strong. However, the delivery of nucleoside analogs is through oral administration once a day with little adverse effect, which is relatively more convenient.

3. Interferon is expensive, and is not on China’s national list of essential drugs issued in 2009. Most of the common interferon is made domestically. One treatment course is usually 0.5~1 year. With 50~80 Yuan per vial, the cost for one treatment course is estimated to be about 9000~12000 Yuan. There are several dose specifications of long lasting interferon, all of which are imported. One treatment course is usually 0.5~1 year. With 1000~1500 Yuan per vial, the cost for one treatment course is estimated to be about 9000~12000 Yuan.

4. There are various oral nucleoside analogs. Zidovudine, Lamivudine, and Stavudine were specified in the national essential drug list in 2009. One treatment course of Lamivudine (Heptodin) takes at least 2~2.5 years. The price is about 17 Yuan per tablet. The cost for one treatment course is about 6000 Yuan. However, Lamivudine is seldom used alone in clinics due to its drug resistance effect and is usually combined with other drugs of the same category. One treatment course for Entecavir takes at least 2~2.5 years. The price is about 38 Yuan per tablet. The cost for one treatment course is about 13000 Yuan. One treatment course of Tibifuding is usually 2~2.5 year. The price is about 24 Yuan per tablet. The cost for one treatment course is about 8600 Yuan.

5. Therefore chronic hepatitis B is selected as the research disease in this study. The common drug for hepatitis B, a kind of nucleoside analogs, Entecavir is selected as the target drug for investigation to compare and discuss the calculation methods for disease burden.
II. Calculation process and result of chronic Hepatitis B disease burden

2.1 DALY

DALY is the overall measurement of the healthy life years cost by death and disability from disease and is the overall estimation of the life quantity and quality using time as unit. It includes the loss of healthy life years cost by early death and the loss of healthy life years under disability conditions caused by disease. One DALY represents the loss of one healthy life year.

DALY (recommended by WHO) is used as an index for the measurement of the disease burden of hepatitis B virus infected patients. It comprehensively measures the burdens which are brought to individuals and countries by chronic disease caused by hepatitis B virus infection, and provides references for the establishment of disease prevention strategies.

2.1.1 Process of the measurement

- Source of the data
  The number of disease onset and death in different gender and age groups in China from 2005 to 2007 is obtained from direct network reporting system and “Health Statistics Yearbook”.

- Selection of the DALY disability weight
  When calculating DALY, the calculation of the age, gender and disability weight of chronic hepatitis B is referred to the measurement in 1996 described in “The Global Burden of Disease” published by WHO. The criterion is currently the main basis for the international calculation of disease burden.

  The disability weight of hepatitis B:

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Disability Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>0~4 years old</td>
<td>0.170</td>
</tr>
<tr>
<td>5~14 years old</td>
<td>0.181</td>
</tr>
<tr>
<td>15~44 years old</td>
<td>0.209</td>
</tr>
<tr>
<td>45~59 years old</td>
<td>0.212</td>
</tr>
<tr>
<td>60~</td>
<td>0.212</td>
</tr>
</tbody>
</table>

- Calculation tools for DALY
  EXCEL and SASS9.13 are used to complete the data process and calculation.
2.1.2 Results of the calculation

1. The incidence and mortality of hepatitis B in China from 2005 to 2007

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence (1/100 thousand)</th>
<th>Mortality (1/100 thousand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>84.44</td>
<td>0.070</td>
</tr>
<tr>
<td>2006</td>
<td>94.18</td>
<td>0.077</td>
</tr>
<tr>
<td>2007</td>
<td>98.38</td>
<td>0.065</td>
</tr>
</tbody>
</table>

As indicated in the above table, the incidence of hepatitis B in China increased during 2005 to 2007, with the highest value at 2006 and a little decrease in 2007.

2. Composition of hepatitis B in China from 2005 to 2007

DALY of hepatitis B is mainly composed of YLD from 2005 to 2007, the weight of which is 93.88%, 93.61 and 94.61, respectively (see figure 6). The characteristics of the high mutilation incidence and low mortality of hepatitis B has seriously affected the people’s life quality.
3. DALY intensity of hepatitis B in different age groups

Table 3: DALY intensity of hepatitis B in different age groups

<table>
<thead>
<tr>
<th>Age</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DALY intensity (person year) (person year/thousand)</td>
<td>DALY intensity (person year) (person year/thousand)</td>
<td>DALY intensity (person year) (person year/thousand)</td>
</tr>
<tr>
<td>0~</td>
<td>68.80</td>
<td>135.27</td>
<td>102.06</td>
</tr>
<tr>
<td>5~</td>
<td>1253.03</td>
<td>1341.32</td>
<td>941.03</td>
</tr>
<tr>
<td>15~</td>
<td>21843.29</td>
<td>24439.15</td>
<td>23987.36</td>
</tr>
<tr>
<td>30~</td>
<td>27520.53</td>
<td>31226.84</td>
<td>30201.32</td>
</tr>
<tr>
<td>45~</td>
<td>15011.65</td>
<td>17107.58</td>
<td>17151.73</td>
</tr>
<tr>
<td>60~</td>
<td>3437.59</td>
<td>3824.02</td>
<td>4195.45</td>
</tr>
<tr>
<td>70~</td>
<td>1173.93</td>
<td>1251.47</td>
<td>1473.26</td>
</tr>
<tr>
<td>80~</td>
<td>150.87</td>
<td>142.27</td>
<td>186.35</td>
</tr>
</tbody>
</table>

- During the 3 years, the loss of healthy life in 30~ age group is the biggest. Then it is 15~ age group. These two age groups are the high risk groups. The social factors include: High living pressure leads to decrease of resistance and increased chance of infection. Strengthening the disease control to these two age groups has realistic significance to reduce the disease burden brought by hepatitis B.
- The DALY intensity in 45~, 60~ and 70~ age groups increases year after year.
- The DALY intensity in 0~ and 5~ age groups increased year after year from 2005 to 2006, but decreased a little in 2007.

4. DALY comparison of hepatitis B between genders

Generally, DALY is higher for men than for women. During 2005 to 2007, the DALY
of men was highest in 2006 and dropped a little in 2007, while DALY of women has been increasing year after year.

Table 4: DALY comparison of hepatitis B between genders

<table>
<thead>
<tr>
<th>Year</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DALY</td>
<td>DALY intensity</td>
<td></td>
<td>DALY</td>
<td>DALY intensity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(person year)</td>
<td>(person year/thousand)</td>
<td></td>
<td>(person year)</td>
<td>(person year/thousand)</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>50306.66</td>
<td>0.075</td>
<td></td>
<td>20153.04</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>55989.17</td>
<td>0.085</td>
<td></td>
<td>23478.73</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>53792.56</td>
<td>0.079</td>
<td></td>
<td>24266.01</td>
<td>0.038</td>
<td></td>
</tr>
</tbody>
</table>

2.2 QALY

2.2.1 Process of the measurement

1. The states are set according to the study objectives and the natural course of disease to determine the possible existing interconversion and recycle period.

In the Markov state transition model, time unit is of fixed length. One time unit represents one stage. One year is set for each new stage in this study. Since the disease progression of chronic hepatitis B is very slow, a 40-year old chronic hepatitis B patient, whose ALT basal value was >2*ULN (upper limit of the normal value), was set as basis with the endpoint of cycle period >99% to mimic the disease progression of hepatitis B patients treated with Entecavir and placebo, respectively.

It is assumed by the Markov model that all the state transitions occur at the same time, while the transitions occur step by step within one stage with the average time for transition taking about half the length of the Markov cycle period. The assumption of the Markov model may lead to the overestimation of the expected existence in absorbing state and underestimation of the expected existence in non-absorbing state. Therefore:

2. Determination of the transition possibility among different states

Complete random blind controlled experiments for the treatment of chronic hepatitis B by Entecavir, and hygiene economics analysis documents were retrieved from the electronic databases of CNKI and Pubmed. The published guidelines (common understanding) in China, Asian and Pacific area, Europe, and United States and Global officially published hygiene technical evaluations were also referred to, in order to preliminarily determine the possibility of state transition. The domestic famous experts of hepatic diseases were also invited to consult about the state
transition possibility of documents collection. Experts were inquired by questionnaire if they agree with each transition possibility, otherwise, they were asked to put forward appropriate index values. After two rounds of expert consulting, every expert was prone to agree with each transition possibility. Middle value was set as the basal value for Markov model analysis. The basal value for mortality referred to the statistics of age, population and mortality throughout the country issued by National Statistics Department to calculate all the death reasons and mortality for all age groups.

Table 5: Basal value of state transition possibility and mortality in Markov model

<table>
<thead>
<tr>
<th>From:</th>
<th>To:</th>
<th>Year transition possibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative conversion (HBeAg-)</td>
<td>Chronic hepatitis B</td>
<td>Placebo 15.00% Entecavir 21.00%</td>
</tr>
<tr>
<td></td>
<td>Compensated hepatic cirrhosis</td>
<td>1.00%</td>
</tr>
<tr>
<td></td>
<td>Liver cancer</td>
<td>0.47%</td>
</tr>
<tr>
<td>Chronic hepatitis B (HBeAg+)</td>
<td>Negative conversion</td>
<td>9.00%</td>
</tr>
<tr>
<td></td>
<td>Compensated hepatic cirrhosis</td>
<td>2.10%</td>
</tr>
<tr>
<td></td>
<td>Decompensated hepatic cirrhosis</td>
<td>0.67%</td>
</tr>
<tr>
<td></td>
<td>Liver cancer</td>
<td>0.28%</td>
</tr>
<tr>
<td>Compensated hepatic cirrhosis</td>
<td>Decompensated hepatic cirrhosis</td>
<td>7.40%</td>
</tr>
<tr>
<td></td>
<td>Liver cancer</td>
<td>0.82%</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>7.41%</td>
</tr>
<tr>
<td>Decompensated hepatic cirrhosis</td>
<td>Liver cancer</td>
<td>2.50%</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>32.50%</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Death</td>
<td>64.70%</td>
</tr>
</tbody>
</table>

3. Determination of effectiveness value and cost

a. Estimation of health effectiveness value

The Markov state effectiveness possibilities of chronic hepatitis B were estimated on the basis of collection of study materials at home and abroad and combining part of the results of qualitative study.
### Table 6: Life quality score of different states

<table>
<thead>
<tr>
<th>State</th>
<th>Life quality score (effectiveness value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis B</td>
<td>0.95(0.9~0.95)</td>
</tr>
<tr>
<td>Compensated hepatic cirrhosis</td>
<td>0.9(0.8~0.92)</td>
</tr>
<tr>
<td>Decompensated hepatic cirrhosis</td>
<td>0.54(0.5~0.65)</td>
</tr>
<tr>
<td>Hepatocyte hepatic carcinoma</td>
<td>0.5(0.3~0.5)</td>
</tr>
</tbody>
</table>

#### b. Calculation method for cost

According to the documentary records average annual direct medical costs are, , , 12,649 Yuan for chronic hepatitis B, 22868 Yuan for compensated hepatic cirrhosis, 21,327 Yuan for decompensated hepatic cirrhosis, and 18498 Yuan for liver cancer, under common treatment.

The cost of Entecavir is 12,324 Yuan per year, calculated according to the drug bid price in Heilongjiang Province in 2008. Since the current study only considers Entecavir or placebo treatment for chronic hepatitis B, the medical cost in the Entecavir group is the common medical cost (12,649 Yuan) for chronic hepatitis B, plus the annual cost of Entecavir (14,600 Yuan), while the costs for the other two disease states are equal. 5% discounts were taken for all the medical costs in the future.

### Table 7: Annual average direct medical costs for chronic hepatitis B-related diseases

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>Entecavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis B</td>
<td>12649</td>
<td>24973</td>
</tr>
<tr>
<td>Compensated hepatic cirrhosis</td>
<td>22868</td>
<td>22868</td>
</tr>
<tr>
<td>Decompensated hepatic cirrhosis</td>
<td>21327</td>
<td>21327</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>18498</td>
<td>18498</td>
</tr>
</tbody>
</table>

#### 4. Determination principle for the optimal therapeutic regimen

The lower the cost-effectiveness ratio, the better it is. The baseline therapeutic regimen is good, when the incremental cost-effectiveness ratio, incremental net
currency benefit, and incremental net health benefit are negative.

5. Statistics method: TreeAge Pro 2009 was used to set the Markov model for simulation analysis.

2.2.2 Results of the calculation

After one year’s use of Entecavir, the expected life time for chronic hepatitis B patients is 26.32 years with an average annual medical cost of 5351 Yuan. Compared with the placebo, extended life time per capita is 0.14 year for Entecavir treatment. Increased medical cost (incremental cost-effectiveness) for one year’s extension of life time is 9814 Yuan. Considering the life quality score of the chronic hepatitis B related state, 0.15 QALY is extended per capita. Increased medical cost (incremental cost-effectiveness) for one year’s extension of life time is 9160 Yuan.

Table 8: Cost-effectiveness analysis of chronic hepatitis B

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Life medical cost (C, Yuan)</th>
<th>Expected life time (LYs)</th>
<th>C/LY or △ C/ △ LY</th>
<th>Quality adjusted life year (QALYs)</th>
<th>C/QALY or △ C/ △ QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entecavir one year</td>
<td>140837</td>
<td>26.32</td>
<td>5351</td>
<td>24.85</td>
<td>5667</td>
</tr>
<tr>
<td>Placebo</td>
<td>139463</td>
<td>26.18</td>
<td>5327</td>
<td>24.70</td>
<td>5646</td>
</tr>
<tr>
<td>One year Entecavir treatment compared with placebo</td>
<td>1374</td>
<td>0.14</td>
<td>9814</td>
<td>0.15</td>
<td>9160</td>
</tr>
</tbody>
</table>

Because this study mainly focuses on the exploration of methodology at the current stage, one year’s Entecavir treatment is specified in the Markov model. The mimic of practical therapeutic regimen will be carried out in the following work.

III. Discussion and suggestions

3.1 Discussion

3.1.1 Loss of healthy life years for hepatitis B

It is demonstrated in this study that from 2005 to 2007, the incidence of hepatitis B in China increased year after year although the rate of increase is declining. The
incidence increased by 97.4/100,000 from 2005 to 2006, while the number is 42.0/100,000 thousand from 2006 to 2007. Mortality and DALY intensity increased year after year from 2005 to 2006 and decreased a little in 2007. After analysis of the reason for the trend, China began to pay more efforts to the prevention of hepatitis B. It not only focused on strengthening the immunization of new-borns, but also expanded immunization of the population aged under 15 years, which effectively lowered the incidence of hepatitis B and reduced mortality. The composition of DALY loss for hepatitis B is mainly YLD within 3 years, which indicates that the disease has the characteristics of a low case-fatality rate and a high mutilation rate. The diseases with these characteristics usually have long disease course and low life quality. The DALY loss of men in the hepatitis B infected population in China is higher than (twice that) of women. Therefore, men are the population with the highest risk, to which more efforts should be paid in hepatitis B prevention and control. When taking corresponding measurements, hygiene administrations should strengthen health education among male risk groups to improve the healthy life years of male hepatitis B patients. The working and study pressure in 30~ and 15~ age groups is relatively higher than in other age groups in China. They are often in a stress condition, which may lead to a decrease of resistance to infectious diseases and increased chance of infection. If the loss of healthy life among these two age groups can be effectively controlled, it will have important significance to reduce the hepatitis B disease burden of the whole society.

3.1.2 Economic evaluation of hepatitis B treatment by nucleoside analog, Entecavir

The efficacy of treatment for chronic hepatitis B by Entecavir has been confirmed; it can rapidly decrease the HBV-DNA titer, increase ALT normal conversion rate, and significantly improve liver inflammatory necrosis and fibrosis. Also, due to its low rate of drug resistance, it can be used as the first-line drug for current chronic hepatitis B treatment. Based on the clinical trial and related documentary materials, as well as expert interview and onsite investigation data, the Markov model was employed to analyze the cost effectiveness of Entecavir treatment for chronic hepatitis B. The results indicate that, compared with placebo, the medical cost is below 10000 Yuan for Entecavir to extend one year of life. Although there is still no local threshold standard for the evaluation of cost-effectiveness, according to the most conservative reference index, the per capita gross domestic product was above 15000 Yuan in 2006. We have reason to believe that it is more cost-effective to treat chronic hepatitis B with Entecavir, which can keep patients from the psychological and financial burden of lifelong therapy.

Since there is not enough basic data domestically, this study did not directly compare cost-effectiveness between Entecavir and other treatments for chronic hepatitis B like a-interferon, but instead confirmed that Entecavir is more cost-effective than placebo. This study calculated the lifelong medical cost of chronic hepatitis B based on the reported direct medical cost. It only increased medical cost for chronic hepatitis B
when using Entecavir. However, the fact that the use of Entecavir may reduce the use of other drugs was not considered. Therefore, the result may underestimate the cost-effectiveness of Entecavir.

For the convenience of data collection and Markov model analysis, some restrictive conditions were set in the study. For instance, the negative conversion rate of HBeAg equals to natural negative conversion rate after withdrawal of Entecavir; the recurrence rates after negative conversion of chronic hepatitis B patients treated with Entecavir and placebo were the same; the progression of the recurrent patients who had undergone HBeAg negative conversion equaled to that of patients who had not undergone HBeAg negative conversion. All of these conditions may influence the results.

3.1.3 The application of Disability Adjusted Life Year (DALYs)

So far, DALY is the most comprehensive index for the evaluation of harm to people by diseases. The harm that diseases do to human health includes early death and disability (transient disability and permanent deformity). The common character of the two aspects is to reduce the healthy life time of humans. Taking into consideration the overall situation of incidence and death, as well as the weight of disease harm, weight of age, and discount rate, and considering the effects of disease-caused results such as death, disability (loss of living and working capability), DALY calculates the loss of healthy life time caused by each disease in one area, and objectively, scientifically, and comprehensively evaluates the harm by various diseases. DALY is the important index to make up health policy and distribute health resources.

Although DALY is a comprehensive evaluation index, there still exists debate in the application of DALY to calculate disease burden. Attention should be paid to the following aspects:

1. The application of DALY largely relies on the available materials of anthropology and epidemics. It is difficult for most developing countries to obtain the complete information to calculate DALYs. They have to estimate the health condition of the countries or regions, extrapolating from local materials or using materials from WHO and other countries. The conditions of economics, health, culture and races are different for different countries. Therefore, efforts should be paid to make the materials of gender, age, death registration and population as complete and reliable as possible. The material obtained should be classified according to the disease classification method of the GBD.

2. DALY does not measure all damages to health from disease, and therefore does not reflect all the conditions related to the patient’s loss of capability. This is because DALY does not consider individual health satisfaction, but instead estimates the patient’s burden according to the degree of disease, and demonstrates that the life of invalids is inferior to healthy persons due to their suffering. Where there is disability, there is DALY value. The larger the degree of disability and the longer the time, the bigger the DALY value is. In addition, DALY does not involve the burden to family, friends and society
caused by diseases.

3. Social or interpersonal complexities are not taken into account by age weighting. For instance, in the family a child may be considered more important than its parents, even though they create the wealth. Social benefits might lay particular stress on the young and the old. The standard in developed countries is applied for the expected life time, which might overestimate the loss of life time on the aggregate level. In addition, it is also biased for DALYs, in the calculation of which the loss of 1 year of life for 10 persons equals the loss of 10 years for 1 person.

4. The cost-effectiveness ratio (cost saved by each DALY) estimated according to DALYs neglects benefits other than the prevention of early death and disability (for instance it does not take into account the increased chances of individual education and employment). When considering potential economic or social effectiveness, this kind of DALY estimation still needs improvement.

3.1.4 Application of quality adjusted life year (QALYs)

The aim of government health care expenditure is to create health and to bring “long life and good life” to everybody. “Long life” represents the “quantity of life”, while “good life” emphasizes the “quality of life”. The theory of QALY is the combination of the two aspects. Due to the new conception and easy calculation of QALY, the practical applications of the measurement are constantly increasing. At present, the measurement of “quality” and “quantity” of life by QALY is mostly applied to the assessment of new medical services and drug economics, which is a very important measuring index regarding the distribution of resources in health economics and decisions regarding the individual selection of appropriate medical services.

The key point for QALY calculation is how to measure effectiveness. Common effectiveness measurements include direct measurement and indirect measurement; direct measurements includes the rating scale method, standard gaming methods and time-trade-off. The rating scale method is the most straightforward with strong operability, but its result is only the rating classification of various health conditions. It is difficult to compare among different patients. Life quality weight estimated by standard gaming methods has a strong theoretical basis but weak operability and no calibration method. Life quality weight measured by time-trade off is part of the healthy life year with strong operability. Life quality scale is developed by indirect measurements in the form of a survey table, which can conveniently and practically describe the life quality of individuals. At present, scholars have not agreed on the optimal scale method for QALY. Due to the involvement of subjective value factors, even with the improvement of measurement technology, the estimation of bias-subjective effectiveness value still faces challenges. Therefore, more value consensuses need to be obtained to reach a common agreement.

3.2 Suggestions

Health resources in China are limited within such a large population. The application
of economic analysis methods for medical interventions (drugs) during the development of health policies can greatly improve the availability of health resources, which is worthy of vigorous popularization and creative studies. Although there are scholars going deep into the field at present, it is only through the promotion of relevant policies, that the economic evaluation of medical interventions (drugs) can obtain greater development in China. In the field of the economic evaluation of medical interventions (drugs), a set of standard measurement tools and methods with detailed standard procedures, which is suitable for global use, and especially by developing countries, is needed. In the development of this, the following aspects should be considered:

3.2.1 Quality evaluation scales related to health and health effectiveness parameters
Cost-effectiveness analysis can uniformly quantify life quality, which is in favor of comparisons among different diseases and different therapeutic regimens. The measurement of effectiveness value is in favor of the judgment of health condition and variation of different individuals and in favor of the individual evidence-based decision and overall distribution of limited resources. The effectiveness value of health condition has been put forward for more than 30 years internationally, but it has not been widely recognized and applied domestically in China. Apart from the differences in cultural background, economic conditions, and religious belief, both complex measurements and non-evaluated life quality scales in Western countries are difficult to apply to the domestic Chinese investigation.

3.2.2 Age weight, time discount, gender insensitivity
Discount, age weight and disability grade have been introduced into the DALY index for the measurement of disease burden. DALY selects the global highest expected life time as the estimated value of life expectancy at birth, the result of which will exaggerate the disease burden in those countries of lower expected life time. Age weight aims at the life value of different age brackets. There are many debates as to whether it should be regarded as equal from the angle of human rights, or if more weight should be given to the young and middle-aged from the angle of social contribution,. Which one is more reasonable and more acceptable by most people, remains to be further investigated.

3.2.3 How to give attention to both efficiency and justice
The case for a disease burden measurement index is based on the premise that the resources for health are limited, while the requirement for therapy and health care is potentially unlimited. Therefore, it leads to the tense relation between available resources and patients’ requirements. If “effective” and “cost effective” standards are set as the basis for the distribution of health resources, then the risk of injustice is possibly hidden. Efficiency has always been a major concern, while justice and other
problems it brings have seldom been noticed. Then the problem is triggered about the basis for social effectiveness and life value. Therefore, the need is to form a standard measurement which can be widely accepted by academia, which is simple and easy to do.

3.2.4 The obtaining of basic data

A lot of data in several aspects such as death, disease and health services are needed in the calculation of disease burden and economic evaluation. The most difficult part of the study is also the obtaining of basic data. The key point in the data analysis in China is not that there is no data but whether the data is usable. There are a lot of statistical methods to obtain stable parameters for analysis. However, most of these methods need raw data for calculation. Therefore, the optimal way to solve the problem of a lack of analytical data is to reinforce data sharing.

Chapter 3:

Reform of the Chinese Medical Health System and the Medical Intellectual Property System

I. Reform of the Chinese Medical Health System

The Chinese medical health industry has developed fast in recent years as a result of government reforms. But China has many special conditions: a vast population; a low per capita income; an unbalanced development of urban, rural and regional medical health industries; irrational resource distribution; weak rural and community medical health services; an imperfect medical security system; a nonstandard drug production circulation order; imperfect hospital management systems and operating mechanisms; insufficient governmental health input; rapid increase of drug expenses, and too heavy personal burdens.

In March 2009, the Central Committee of the Communist Party of China and the State Council released the Opinion on Deepening Medical Health System Reform (hereafter referred to as “the Opinion”).

Its aim: Realize the goal that everybody should enjoy a basic medical health service; solve the most urgent problems for the benefit of the greatest number of people; adhere to the public benefit nature of public medical health; insist on the policy of prevention orientation, village focus and traditional Chinese and western medicine combination; coordinate basic medical health service levels with socio-economic
development and fully promote the role of Traditional Medicines Sector.
Overall goal: Establish and improve the basic medical health system covering urban and rural residents, provide the masses with a safe, effective, convenient and cheap medical health service. By 2011, the per capita fee for basic public health service to be not less than 20 RMB.
In order to solve the rural medical health service problem of lower per capita income, this Opinion proposes the following measures:

1. Vigorously develop the rural medical health service system. Further improve the rural medical health service network with the backbone of a county hospital and the basis of a town health center and a village clinic. Establish a more perfect medical health service system at grass-roots level within 3 years.
2. Overall, implement a new rural cooperative medical system, gradually improve governmental subsidy, properly increase peasant payment, improve security ability; improve the urban and rural medical aid system, subsidize difficult populations and their unaffordable medical expenses, solidify the bottom line of medical security. Explore and establish a basic medical security management system of urban and rural integration.
3. In the medical health service at grass-roots level, vigorously popularize suitable TCM techniques. Promote the inheritance and innovation of TCM through the policies of supporting TCM development.
4. In developing areas, strengthen the development of the medical health industry in poverty-stricken minority areas.

Proposal of this Opinion: Establish a national basic drug system, and improve the drug storage system. Reform of drug pricing mechanism. Rationally adjust the range of governmental pricing, and encourage enterprise's autonomous innovation through price leverage, and promote the production and use of national basic drugs. Gradually implement a drug economic appraisal system before introducing the fixed price for new drugs and patent drugs. Regard medical health technological innovation as the focus of national technological development, accelerate the implementation of major medical projects, encourage autonomous innovation, strengthen research on the prevention and treatment technique of serious diseases and the key technology of new drug research, and strive for new breakthroughs in basic medical, application, high-tech, TCM and combined Chinese and Western medicine research.
In November 2009, the State Development and Reformation Commission, the Ministry of Health, and the Ministry of Human Resources and Social Security jointly released the Opinion on Reforming the Pricing Mechanism for Drug and Medical Services. Basic principles: not only encourage research and innovation but also use basic drug and suitable technology; encourage enterprises and medical organizations in improving the ability and impetus of innovation; research and develop new products and new technologies; protect and support TCM development; improve the overall competitive power of the pharmaceutical industry; jointly consider economic development level, basic medical security level and mass affordability; encourage the
use of basic drug and suitable technology; relieve mass burden for exaggerated drug expenses. Allow a higher profit margin within a rational time limit for drugs of higher innovation degree, and promote enterprises in developing innovative drugs.

II. Reform of the Chinese Medical Intellectual Property System

In 2008, the State Council released the *Outline for State Intellectual Property Strategy*. This outline proposes to promote the creation and use of intellectual property, strengthen its protection, and prevent its abuse. This outline also proposes the following two special tasks directly related to TCM protection:

1. Improve the protection, development and utilization system of hereditary resources; prevent its loss and disorderly utilization; manage the relationship between protection, development and utilization; establish rational mechanisms for its acquisition and benefit sharing, and guarantee informed consent rights for its providers.

2. Establish and improve the protection system of traditional knowledge. Support its arrangement and inheritance; promote its development; improve the management, protection, utilization and coordination mechanisms of traditional medical intellectual property, and strengthen the protection, development and utilization of traditional processes.

In 2008, China revised Patent Law for the third time, with the following main adjustment of medical health:

1. Implement compulsory licenses for drugs with patent right for the purpose of public health. As specified in Clause 50 of the new Patent Law, and for the purpose of public health, for drugs with patent rights, the patent administrative department of the State Council can compulsorily permit their export to countries and regions in accordance with relevant international treaties joined by the People’s Republic of China. This regulation reflects international consensus on limiting drug patents to safeguard public interests.

2. Disclose patent information for hereditary resource utilization. As specified in Clause 26 of the new Patent Law, based on the invention and creation completed through hereditary resource, the applicant shall state its direct and original source in the application document; and otherwise shall state reason. This regulation benefits the protection and utilization of hereditary resources (such as TCM).
Chapter 4:

Basic Considerations of Supporting the Innovation of Drugs for Low-Income Populations

Globally, disease is significantly related to income level. For example, of 20 million tuberculosis patients globally, 95% exist in developing countries. Due to generally higher R&D cost and higher price of drugs, low-income populations in developing countries often do not treat diseases through drugs which then causes higher rate of illness-induced death. In recent years, many developing countries have faced serious public health crises due to global diseases (such as AIDS and avian flu). Since 2003, some developing countries began to compulsorily license the patent for AIDS drugs through the TRIPS agreement. In 2005, some countries compulsorily licensed the patent for avian flu drugs. In 2007, Thailand compulsorily licensed the patent for a cardiovascular disease drug. Even some developed countries begin to adopt compulsory drug licenses. For example, during 2005~2007, Italy compulsorily licensed 3 drugs.

Compulsory drug license guarantees human health rights, but conflicts with the current intellectual property system. Thus, drug developers cannot make profits from their intellectual property, and do not develop drugs for low-income populations any more. Therefore, drugs influencing the health of the majority of people are ignored. As an important issue, the reform of the international intellectual property system should establish a mechanism to both allow drug developers to make profits through intellectual property protection and facilitate low-income populations obtaining necessary drugs.

The Health Impact Fund provides a mechanism of choice. Drug developers as part of this fund will sell drugs at cost prices to low-income populations. In some lower-income countries, acceptable drug price may be even lower than production costs, and the governments can subsidize sales prices. Thus, this fund may face the following problems:

1. The lower return than average market profit rate may be unattractive for drug developers. Otherwise, the government cannot bear such subsidy.
2. Some least-developed countries may enjoy the greatest benefit. However, if the fund is paying according to the degree of health impact, there might be difficulties in raising the right amount.
3. At present, most drug intellectual properties are reserved by drug developers of developed countries. However, this fund mainly sources funds from developing countries, to mainly support the R&D of drug developers in developed countries. Thus, developing countries will face an increasing gap from developed countries in their drug R&D ability. Therefore, this fund may
not properly solve the problems of drug supply in developing countries.

In China, there are 40 million poor people (mostly in rural areas). Through reform and development over many years, China has gradually formed a medical health security system to solve drug problems for low-income populations through the following mechanisms (as discussed in detail above):

1. Establish a medical health service system for low-income populations;
2. Establish a new rural cooperative medical system;
3. Establish national basic drug system. China has set a new category of national basic drugs, and makes the price of basic drugs acceptable for low-income population;
4. Encourage Chinese enterprises for R&D and innovation; protect and support TCM development; encourage the use of basic drugs, and encourage suitable technology.

The development of traditional drugs (especially the improvement of its R&D ability in developing countries) may become a main route to reducing drug prices for low-income populations and solving the public health crisis in developing countries. The Chinese population accounts for 1/4 of global population. To solve the medical health problem for Chinese low-income populations is the greatest Chinese contribution to global public health crisis. The Chinese will also further utilize the advantages of traditional drugs to freely provide medical aid for developing countries. Developing countries should be organized to cooperate in the R&D of traditional drugs through the subsidy of international organizations and developed countries.
References


Han Bai. Important function of anti-virus therapy in the chronic hepatitis B treatment [J]. World Chinese Journal of Digestology, 2008, 16 (1), 5-9


[19] Tai DI, Chen CH, Chang TT, et al. Eight year nationwide survival analysis in


[28] Larry Lacey, Xianzhong Lu, Alison Tan. Economic evaluation of anti-virus therapy to HBeAg negative chronic hepatitis B in China.