

## China’s Regulatory Review on New Drugs and Oncology Market

June 20, 2016

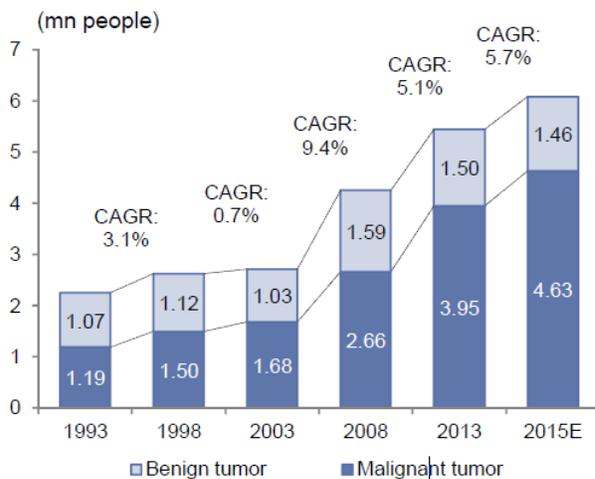
[Lan Huang, Ph.D.](#) & [Richard A. Brand, M.B.A.](#) | BeyondSpring Pharmaceuticals

China poses new and unique compliance challenges for pharmaceutical companies that are aiming to work in the country. The Chinese government has been proactive in approving new, safe pharmaceuticals quickly, as well as in protecting its population. There is a dire need for oncology pharmaceuticals, especially for lung cancer, as it is the most prevalent type in China, according to China’s 2015 cancer statistics report. There are many factors concerning China’s regulatory review on new drugs and the oncology market to understand when entering this market.

Factors that are associated with cancer in China include an aging population, sustained environmental pollution and unhealthy lifestyle/dietary habits. Cigarette smoking in particular continued to be prevalent long after the habit subsided in the U.S.

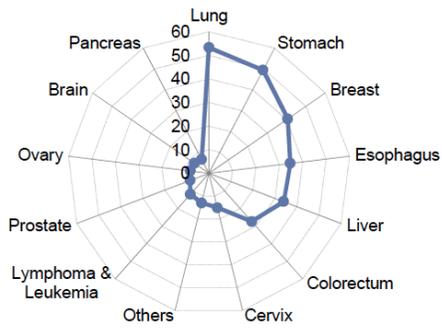
**Figure 1: Rising tumor prevalence**

Prevalence trend of cancers in China anti-cancer drug categories



Source: National Health and Family Planning Commission (NHFPC).

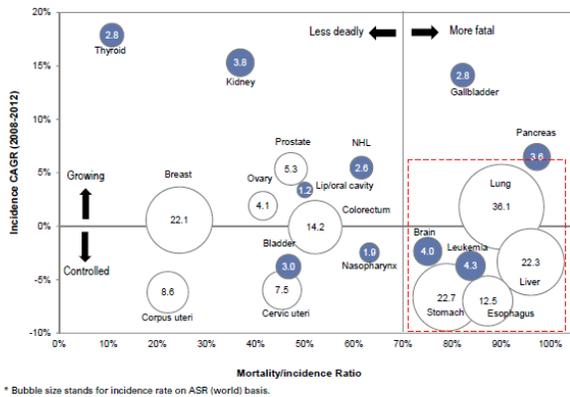
**Figure 2: China incidences by sites in China, 2015**



Source: Cancer Statistics in China, 2015.

### Figure 3: Lung cancer is the most prevalent cancer in China

Mapping of major types of cancers in China by incidence growth rate, mortality/incidence ratio



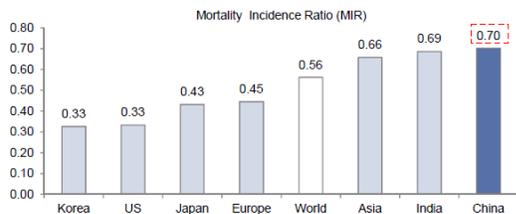
\* Bubble size stands for incidence rate on ASR (world) basis.

Source: CLOBOCCAN 2008, 2012.

### China experiences higher mortality

The bar chart below presents the mortality/incidence ratio (MIR) to measure the fatality of cancers in various parts of the world. In 2015, China's MIR was 0.70 compared to 0.58 for the world's average. The MIR in the U.S. Europe, Japan and Korea were lower.

Exhibit 56: Undertreated China has higher mortality/incidence ratio



Source: IACR GLOBCCAN.

## China Regulatory Review Process

The China FDA grants accelerated review under its Category 1 and 1.1 [programs](#) to drugs that meet three criteria:

- The company that submits the drug for review must be a domestic company in China
- The drug must also be manufactured in China
- Finally, the drug must be an innovative drug

Also helpful in expediting review are drugs that have received the Innovative Drug Award and drugs from scientists who've received the "1,000 Innovators Award" from the Chinese President. Recipients of the "1,000 Innovators Award" include professionals in many disciplines and industries. Only a few of the recipients are in the pharmaceutical discipline; therefore, it is an exclusive honor to receive this award.

Since Phase III clinical trials enroll large numbers of patients, the Chinese government seeks to protect its population from drug candidates that have not shown efficacy. To initiate a Phase III trial a drug must receive a Phase III CTA (Clinical Trial Agreement) from the cFDA. These are only granted to drugs meeting the cFDA's criteria for both safety and efficacy. In contrast, a drug must only have demonstrated safety to obtain the equivalent Investigation New Drug ([IND](#)) application from the U.S. FDA. Demonstrating efficacy is the objective of the Phase III trial in the U.S.

After the Phase III trial, obtaining an NDA ([New Drug Application](#)) from the China FDA can be achieved by demonstrating non-inferiority in the primary endpoint and superiority in a secondary endpoint(s). Superiority to other approved drugs must be demonstrated in the primary endpoint in order to obtain an NDA from the U.S. FDA. Therefore, China's FDA could approve oncology drugs that are based on non-inferiority, rather than superiority. [Betta Pharma](#) received cFDA NDA approval of Icotinib with non-inferiority in efficacy with IRESSA, but better safety. According to The Wall Street Journal, for one thing, in China, a drug doesn't have to [prove superiority over existing drugs](#), which is a major hurdle in the U.S., where 90 percent of candidates get dropped in the clinical process.

Those innovative oncology drugs developed by Chinese domestic companies that obtained a Phase III CTA have all subsequently received an NDA. Thus, receiving the cFDA's CTA to launch a Phase III clinical trial is critical.

For drugs that are administered intravenously and have been manufactured in the West through Phase II trials, when beginning to manufacture in China, one only needs to show chemical equivalence of the Chinese manufactured output compared to the Western product.

## The China Oncology Market – Challenges and Trends

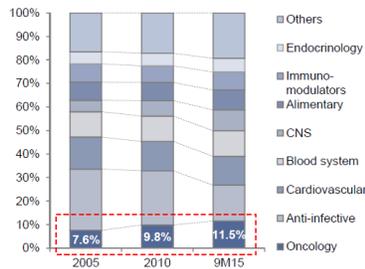
The oncology market in China is evolving, as the Chinese oncology pharmaceutical market remains predominantly a cash pay market, meaning when an individual is diagnosed, that patient and the family pay for the treatment.

The Chinese national government introduced an insurance program, which allows potential reimbursement for treatment. Pharmaceuticals priced at one-half of their U.S. price and approved by the [China FDA](#) can be eligible for reimbursement under the national plan. Beta Pharma plans to be the first to qualify for national insurance. Some provinces' programs approve pharmaceuticals for reimbursement if priced at 70 percent of their U.S. price and approved by the cFDA.

Cancer care has not yet become as decentralized as it is in the U.S. The great majority of patients throughout China go to centers in Beijing, Shanghai or Guangzhou for treatment. These major centers are headed by physicians who've trained in the West.

**Figure 5: Anti-cancer drug: 11.5% of China market in '15**

**Exhibit 40: Anti-cancer drug: 11.5% of China market in '15**  
China drug market by category (2005-2015)



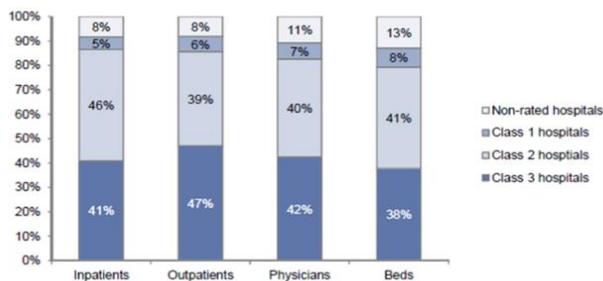
Source: PDB database

### Implications of concentrated cancer care

Over 80 percent of China's physicians are with its Class 2/3 hospitals, the higher end. These hospitals have 79 percent of the beds. Of all in-patients in China, 87 percent go to Class 2/3 hospitals.

**Figure 6: class 2/3 hospitals captured 80% of flows and cancer patients**

**Exhibit 54: Class 2/3 hospitals captured 80%+ of flows and cancer patients**

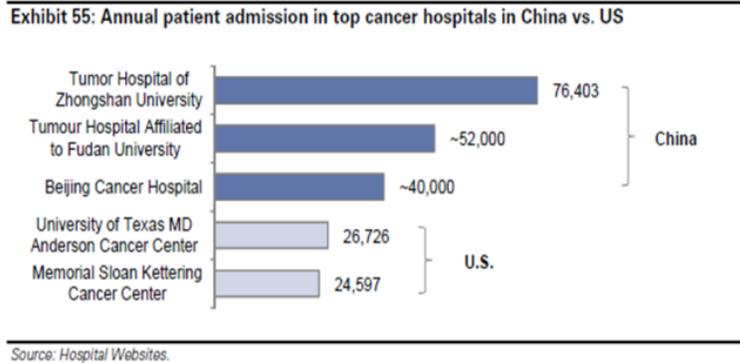


Source: National Health and Family Planning Commission

This concentration can make it easier for pharmaceutical companies to enroll patients in Phase III clinical trials and access patients for marketing after regulatory approval.

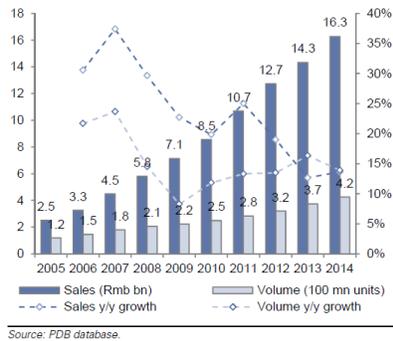
Patient admissions in the top cancer specialty hospitals in China compared to the U.S. demonstrates part of the picture that cancer care is more centralized in China. In 2013/2014, the leading cancer hospitals in China each admitted 40,000 to 76,000 patients annually. The U.S. comparables admitted around 25,000.

**Figure 7: Annual patient admission in top cancer hospitals in China vs. US**



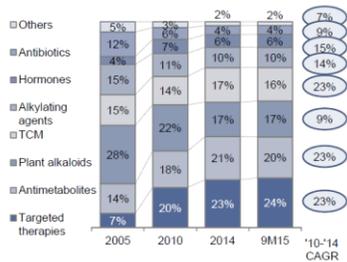
**Figure 8: Anti-cancer drugs sales/vol +14% yoy in**

China anti-cancer drugs market (same hospital 2005-2014)



**Figure 9: “Therapy upgrade”**

Market share shift of major anti-cancer



Source: FDB database

## Factors influencing healthcare in China

Healthcare has improved in China as physicians such as Dr. Yan Sun returned after training at [M.D. Anderson Cancer Center](#) to improve China's healthcare infrastructure. Healthcare also became more of a national priority as the country developed and other needs were increasingly met.

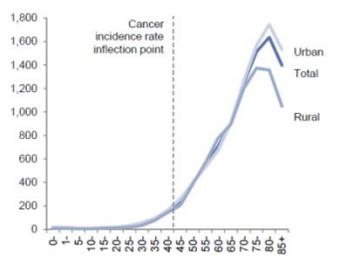
Rising disposable income has had an impact on healthcare in China. Also recently a few domestic innovative target drugs have been approved and are available at lower prices.

## Cancer incidence rates and China's aging population

Approximately 97 percent of China's total cancer patients are over 40 years old. For people over the age of 65, those living in urban areas show an incidence rate that's notably higher than their rural counterparts. If this continues to hold true, then we can forecast the country's cancer incidence rate to rise with continued urbanization of the Chinese population.

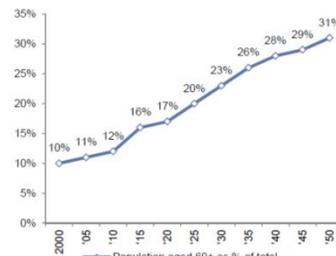
**Figure 10: Population aged 60+ on the rise**

Exhibit 48: Cancer incidence in China by age and location



Source: Cancer Statistics in China, 2015

Exhibit 49: Population aged 60+ on the rise



Source: Population Division of United Nations

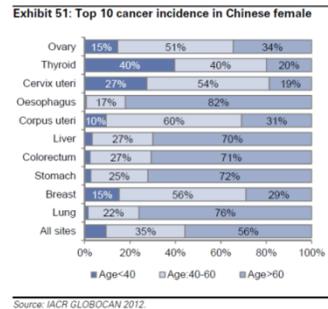
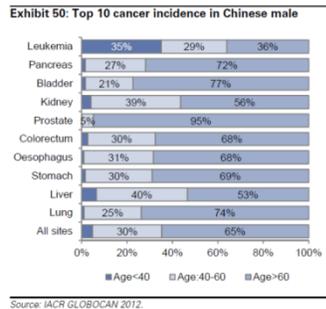
By 2030, China's population over the age of 60 is forecast to rise to 342 million. By 2050, the number of elderly people in China will increase to 440 million, 31 percent of the total population by 2050. In 2010, China's elderly were 12 percent of the population, according to Cancer Statistics in China, 2015.

## Types of cancers and their incidence among different age groups

As in the population at large, most cancer types afflict males in China who are over 40 years old. The exception is leukemia. Chinese males under 40 account for 35 percent of those with leukemia.

**Figure 11: Top 10 Cancer incidence in Chinese male incidence in Chinese female**

**Figure 12: Top 10 cancer**



Women aged 40-60 have a higher incidence of some female specific cancers (i.e., breast cancer, corpus uteri cancer, cervix cancer and ovary cancers) compared to the older population.

**Pollution as increased factor for cancer**

Air pollution in China cities is significantly worse than Tokyo, London or New York. According to recent data from the [Global Burden of Disease Project](#), air pollution is caused 3.2 million deaths in 2010. Particulate matter is a carcinogen according to the [International Agency for Research on Cancer](#).

**Other causes**

Other causes of cancer (i.e., reports of “cancer villages” in China) are referenced in “Attributable Causes of Cancer in China”. Chronic infection and tobacco smoking are major causes (Figure 14).

**Figure 13: Air pollution in China in 2014**

Exhibit 52: Air pollution in China in 2014

City	Average PM 2.5 Density
<b>China cities</b>	
Xingtai	131.4
Baoding	127.2
Shandong	122.6
Shijiazhuang	122.6
Handan	114.2
Hengshui	107.6
Dezhou	106.0
Liaocheng	99.8
Langfang	99.3
Tangshan	98.4
Aiyang	94.8
Zibo	93.4
Lahwu	93.4
Yichang	92.1
Linyi	91.9
Beijing	83.2
<b>Average</b>	<b>104.9</b>
<b>Other notable cities</b>	
Tokyo	15.8
London	15.3
New York	11.2
<b>Average</b>	<b>14.1</b>

Source: Bloomberg, Greenpeace East Asia, King's College London, Tokyo Metropolitan Research Institute for Environmental Protection, U.S. Environmental Protection Agency

Figure 14: Major causes of cancer Global vs. China

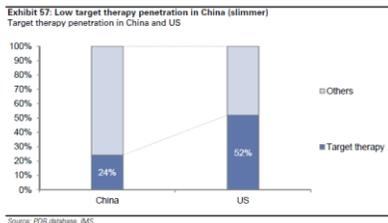
Global	
Major causes of cancer	% of cancer caused
<b>Behavioral and dietary risks</b>	
High body mass index	~13%
Low fruit and vegetable intake	
Lack of physical activity	
Alcohol use	
Tobacco use	20% of global cancer, 70% of global lung cancer
<b>Viral infections</b>	20%
<b>Others</b>	47%
China	
Chronic infection	29%
Tobacco smoking	23%

Source: WHO, Cancer Statistics 2015

In 2014 in China, the penetration rate for target therapy drugs was 24 percent. In contrast, the rate in the U.S. was 52 percent (see the bar chart below).

In China, seven of the top 20 oncology drugs are target therapy drugs. In the U.S., target therapy drugs are 16 of the top 20.

Figure 15: Low target therapy penetration in China



### Target therapy penetration in China and US

The difference between cancer drug offerings in China and the U.S. can be addressed through innovative drugs receiving faster approval in China. This is an objective of the government.

Figure 16: Targeted therapy dominates US but underpenetrated in China

# Top 20 anti-cancer drugs in US and China

**Exhibit 58: Targeted therapy dominates US but underpenetrated in China**  
Top 20 anti-cancer drugs in US and China

US			China			
#	Brand name	Generic name	Approval year	#	Generic name	Approval year
1	Rituxan	Rituximab	1997	1	Paclitaxel	1992
2	Avastin	Bevacizumab	2004	2	Docetaxel	1996
3	Herceptin	Trastuzumab	1998	3	Pemetrexed	2004
4	Gleevec	Imatinib	2001	4	Rituximab	1997
5	Alimta	Pemetrexed	2004	5	Oxaliplatin	2002
6	Zyliga	Abiraterone	2011	6	TGO	1999
7	Sprycel	Dasatinib	2006	7	Trastuzumab	1998
8	Imbruvica	Ibrutinib	2013	8	Capecitabine	1998
9	Afinitor	Everolimus	2009	9	Kanglaite	1995
10	Xtandi	Enzalutamide	2012	10	Imatinib	2001
11	Perjeta	Pertuzumab	2012	11	Gemcitabine	1996
12	Opdivo	Nivolumab	2014	12	Temozolomide	1999
13	Ibrance	Palbociclib	2015	13	Ubenimex	1987
14	Treanda	Bendamustine	2008	14	Irinotecan	1996
15	Velcade	Bortezomib	2003	15	Aidi	2002
16	Abraxane	Paclitaxel	2005	16	Letrozole	1997
17	Tasigna	Nilotinib	2007	17	Erlotinib	1999
18	Yervoy	Ipilimumab	2011	18	Gefitinib	2003
19	Erlbitux	Cetuximab	2004	19	Bevacizumab	2004
20	Tarceva	Erlotinib	2004	20	Ranibizumab	2006

\* Blue highlights stand for target therapy.

Source: PDB database, IMS.

**Figure 17: More target therapy drugs among top anti-cancer drugs in China**

## Top 20 anti-cancer drugs in China (2005-2015)

**Exhibit 59: More target therapy drugs among top anti-cancer drugs in China**  
Top 20 anti-cancer drugs in China (2005-2015)

#	Row Labels	2005	#	Row Labels	2010	#	Row Labels	9M15
1	Paclitaxel	13.1%	1	Docetaxel	10.5%	1	Paclitaxel	8.3%
2	Oxaliplatin	9.7%	2	Paclitaxel	9.3%	2	Docetaxel	5.8%
3	Docetaxel	8.7%	3	Oxaliplatin	6.8%	3	Pemetrexed	5.6%
4	Gemcitabine	6.2%	4	Capecitabine	5.1%	4	Rituximab	4.4%
5	Epirubicin	5.4%	5	Gemcitabine	4.3%	5	Oxaliplatin	4.3%
6	Kanglaite	4.6%	6	Rituximab	3.9%	6	TGO	4.2%
7	Pirarubicin	3.9%	7	Pemetrexed	3.2%	7	Trastuzumab	3.7%
8	Vinorelbine	3.5%	8	Epirubicin	2.8%	8	Capecitabine	3.6%
9	Aidi	3.4%	9	Trastuzumab	2.7%	9	Kanglaite	3.4%
10	Capecitabine	3.3%	10	Gefitinib	2.7%	10	Imatinib	3.2%
11	Leucovorin	3.3%	11	Aidi	2.5%	11	Gemcitabine	2.8%
12	Rituximab	2.6%	12	Imatinib	2.0%	12	Temozolomide	2.2%
13	Carboplatin	1.3%	13	Irinotecan	2.0%	13	Ubenimex	2.0%
14	HCPT	1.3%	14	Cetuximab	1.9%	14	Irinotecan	2.0%
15	Irinotecan	1.3%	15	Letrozole	1.8%	15	Aidi	1.9%
16	Gefitinib	1.2%	16	Erlotinib	1.8%	16	Letrozole	1.9%
17	Ifofamide	1.2%	17	Anastrozole	1.8%	17	Epirubicin	1.8%
18	Cisplatin	1.1%	18	Sorafenib	1.7%	18	Gefitinib	1.7%
19	Daclizumab	1.1%	19	Compound Matrine	1.7%	19	Bevacizumab	1.7%
20	Ubenimex	1.0%	20	Pirarubicin	1.6%	20	Ranibizumab	1.7%

\* Light blue highlights point to plant alkaloids drugs. Grey highlights point to target therapy drugs.

Source: PDB database.

<http://www.pharmacompliancemonitor.com/chinas-regulatory-review-new-drugs-oncology-market/10881/>