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Is more really less in China's new drug approvals?

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Pharmaceutical industry insiders hearing of the huge numbers of new drugs being approved in China lately – including some billed as truly innovative – might understandably wonder if China's global pharma competition is about to be shrunk like its textile industry competitors from the southern USA to southern Africa's Lesotho.

After all, in 2003, China became the world's first nation to approve a gene therapy, Gendicine, an adenovirus vector *TP53* gene construct for treatment of squamous cell carcinoma of the head and neck and now in trials for a wider range of cancers [1]. Within days, the Chinese company that developed the drug, Shenzhen SiBiono GeneTech Company, posted on its website its intention to 'become the world's leading gene therapy pharmaceutical company'.

The following year, some 10,011 new drug applications (NDAs) flooded into the State Food and Drug Administration (SFDA), in Beijing, and the vast majority were approved, according to Bill Liang, Managing Director of China Healthcare Consulting, a company in Los Angeles, CA, that provides business support services to foreign pharmaceutical and medical companies doing business in China (B. Liang, personal communication). In comparison, only 136 NDAs were approved by the US FDA during 2004.

Add to that apparent imbalance in activity Beijing's announcement last year of massive new increases in government funding of biotech for the next five years, and a New York Times revelation that China appears on the brink of approving the world's first oncolytic virus therapy for cancer [2], and it's not difficult to imagine that China will soon begin – or already has begun – to outpace the USA in new drug development.

However, as is often the case in both science and business, a closer look below surface appearances reveals a more complex and a more interesting reality.

Raw NDA numbers don't tell the story

Relying on raw numbers of NDAs filed or approved in the USA and China to compare the two nations' creative pharmaceutical or biotech output would be misleading, noted Liang, because an NDA might be required in either nation for new uses of drugs already available. Yet that plays out in very different ways in the USA and China.

In China, an NDA is filed for every drug to be introduced into the Chinese pharmacopoeia – typically imports – and for every new way of using any drug already in use, as well as for genuinely newly created drugs. And China is now in the process of registering, through NDAs, every drug now in use there not previously registered, including the huge numbers of herbal and nature-based medicines that are part of traditional Chinese medicine. Nothing comparable is happening in the USA, hence there are far fewer NDAs filed yearly with the US FDA. So, a far greater percentage of NDA approvals in the USA are for genuinely new drugs, compared with the percentage of genuinely new drugs approved in China (Figure 1).

In both nations, only a compound not previously approved for marketing as a drug anywhere in the world is considered to be a true new drug, called a new chemical entity (NCE) in China, and a new molecular entity (NME) in the USA.

'Of the 10,011 NDAs submitted to China's SFDA last year, none were for truly new drugs, that is, new chemical entities – NCEs', said Liang. 'The NDAs submitted to SFDA in 2004 included over 8500 applications for changes in dosage, route of administration or other new uses of drugs that were already within the Chinese pharmacopoeia, and some 1500-plus others were applications to register newly imported drugs', noted Liang.

The Chinese NDA numbers reflect only applications, as SFDA typically does not publicly identify new drugs approved, Liang said, 'blockbuster drugs like Gendicine are notable exceptions, so we can know there were virtually no really new drugs among those approved last year. If there had been, SFDA would make sure everyone heard about it', he added.

In comparison with the 1000s of NDAs filed in China last year, but virtual absence of NCEs among them, only 119 NDAs were approved by the US FDA in 2004, but those included 36 true new drugs, which the FDA calls NMEs (www.fda.gov/bbs/topics/ANSWERS/2005/ANS01346.html) (Figure 1).

NDA approval times in the USA and China

The US FDA divides review of NDAs into two classes: priority drug review, for those drugs meant to treat a life-threatening condition for

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which there is no acceptable treatment, and review of all others, which are referred to as standard drug reviews.

Among the 119 NDAs approved by FDA in 2004, 29 were approved after priority reviews with a median completion time of six months, and 90 others were approved after standard reviews with a median length of 12.9 months. Among the 36 true 'new drugs' (either NMEs or new biologics), 21 got priority reviews averaging six months, and 15 receiving the longer standard reviews, averaging 24 months.

In 2003, 72 NDAs were approved by the US FDA. Of those, 14 received priority reviews with a median length of 7.7 months, and 58 others received standard reviews with a median time of 15 months. Among the total NDAs approved in 2003, 21 were NMEs, with nine approved after priority reviews lasting a median of 6.7 months and 12 were approved after standard reviews lasting a median of 23 months.

In 2002, 78 NDAs were approved by the US FDA. Of those, 11 received priority reviews with a median length of 19.1 months, and 67 others received standard reviews with a median time of 15.3 months. Among the total NDAs approved in 2002, 17 were NMEs, with seven approved after priority reviews lasting a median of 16.3 months and 10 were approved after standard reviews lasting a median of 15.9 months.

In 2001, 66 NDAs were approved by the FDA, with 10 getting priority reviews averaging six months, and 56 getting standard reviews averaging 14 months. The FDA approved 24 true new drugs that year, with seven approved after priority reviews averaging six months, and 17 approved after standard reviews averaging 19 months.

In 2000, 98 NDAs were approved by the FDA, with 20 getting priority reviews averaging six months, and 78 approved after standard reviews averaging 12 months. Of those approvals, 27 were NMEs and nine were approved in priority reviews lasting a median of six months while the other 18 were approved in standard reviews averaging 19.9 months.

Because China's SFDA does not routinely publish data on new drug approval times, statistical comparisons are difficult to make. However, for registration of drugs already in the Chinese pharmacopoeia not requiring a clinical trial, approval time usually ranges between one year and 18 months, Liang commented. For an NDA involving only a new use or dose of a drug, which typically require brief, confirming clinical trials, three years from the time of filing for clinical trials to approval is typical, said Liang. The approval time for a true new drug is likely to be much longer, he noted, ranging between six and eight years or even longer from initial application through approval.

Drug approval processes in China and the USA

China's drug review and approval processes are closely modeled on the US agencies and procedures. In both nations, three phases of clinical trials generally precede any request for approval of a truly new drug.

In the USA, an NDA is formally submitted to the FDA for approval of a new drug. The application includes data on the chemical makeup of the drug, its manufacture, and animal and human trial data. The Center for Drug Evaluation and Research reviews the drug, recommending to the FDA approval or denial.

For foreign companies seeking NDA approval in China, the path to drug approval is similar to USA procedures. But for Chinese companies, the path to SFDA approval must begin at the provincial branch of the SFDA, which then passes on its recommendation to the SFDA in Beijing. In either case, if an NDA is only for a

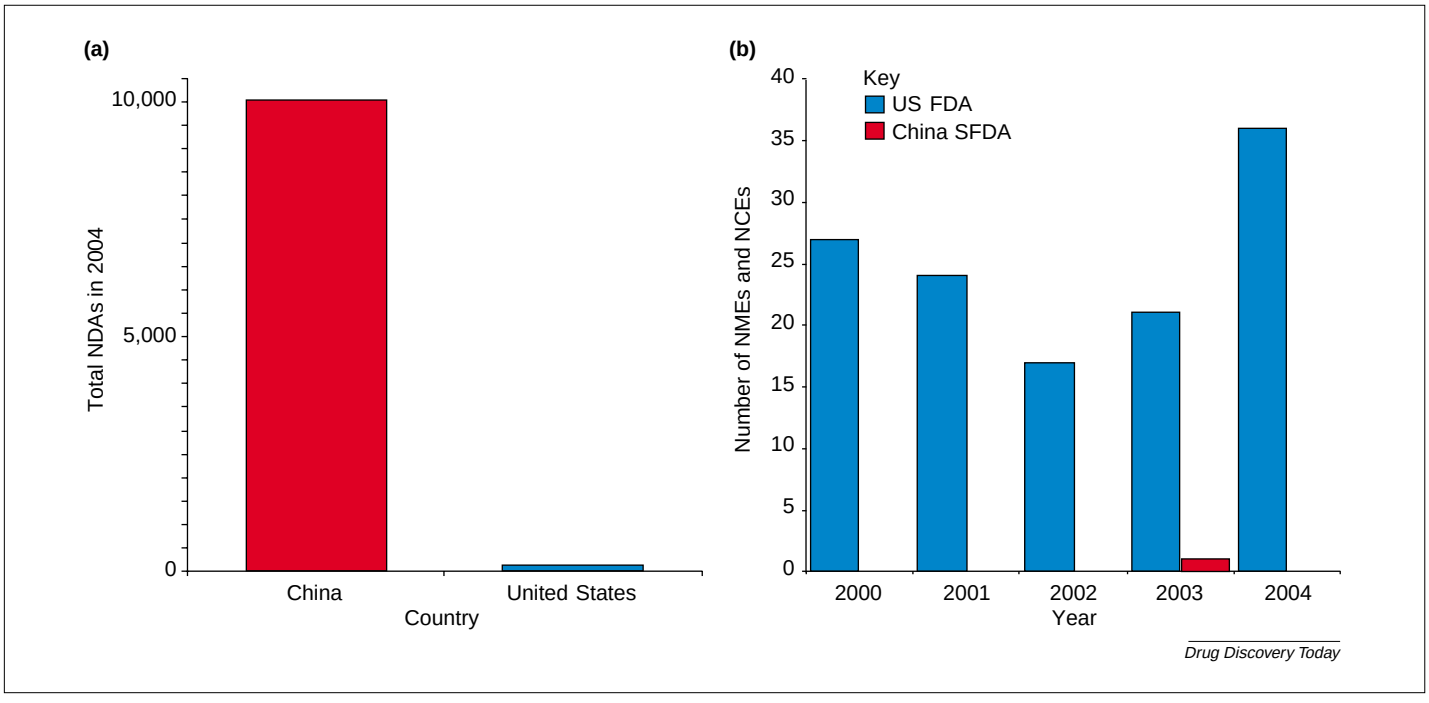

FIGURE 1

New drug applications in China and the USA. (a) Total NDAs approved 2004; **(b)** NMEs or NCEs approved 2000–2004.

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new use of a drug already in the Chinese pharmacopoeia, it might not require a clinical trial, said Liang. For drugs never before marketed in China but already approved in the USA, a small-scale clinical trial is usually required to validate the safety and efficacy data presented in the NDA documentation, said Liang.

But it is extremely rare to see a genuinely new drug – an NCE – created in China, because the industry there is simply not yet sufficiently mature at this point, he noted.

'In the US, you identify a new gene or molecule and realize it has clinical ramifications and start to work on that. That just doesn't happen yet in China', said Liang. 'We have not seen any Chinese company identify a new gene or molecule by themselves and then move on to clinical trials', he noted.

In comparison with the one blockbuster drug approved by China in recent years – the cancer drug Gendicine – 14 new cancer drugs have been approved by the US FDA in the years 2000–2004 [3]. Among those, there was a new monoclonal antibody in each of those five years and the molecular target drugs Gleevec (imatinib mesylate) in 2001, Iressa (gefitinib) in 2003, and Tarceva (erlotinib) in 2004.

Slant drilling into foreign pipelines?

Whereas true drug discovery has so far been rare in China, one variation on the drug discovery theme is not uncommon among Chinese companies, said Liang. 'Chinese biotech firms follow research literature and Phase II and Phase III trials in the US, Japan, and other nations very closely', said Liang.

If the molecular identity of a tested compound has been published and it is not patented in China, a company in China may legally duplicate it and file an NDA, according to Chiang Ling Li, a partner and intellectual property (IP) rights attorney in the Hong Kong office of the international law firm Baker and McKenzie (C.L. Li, personal communication). Then the Chinese company can begin its own studies of the drug, essentially 'slant drilling' into rich pipeline data to begin the race towards approval of the drug at a later stage of the game, closer to the finish line – approval and marketing of the drug – than the drug's original developer. 'There have been many SFDA approvals for drugs that are in Phase III trials in the US, Japan, and other countries', said Liang.

Access to foreign company data might have played a role in Beijing's approval of Gendicine. Therapeutic use of the gene encoding p53 was patented in the USA before 2003, and licensed to Introgen Therapeutics there, according to that company. China joined the World Trade Organization (WTO) in 2001, and the SFDA now requires NDAs to be accompanied by a signed statement that no patented work is being used without authorization.

In a new variation on an old theme, Shanghai Sunway Biotech – identified by the New York Times as likely to soon have the world's first oncolytic virus approved – recently offered and paid US$1 million to California's Onyx Pharmaceuticals, from which it earlier silently borrowed the medicine's basis. Sunway modified the drug, completed successful clinical trials in China and has promised Onyx Pharmaceuticals US$10 million more if it is brought to market in the USA [4].

With increasing pressure from other nations to refrain from questionable trade practices, China's biotech and pharmaceutical industries might someday be truly comparable with pharma in the USA and other nations that have more-mature drug development industries. But until that time, those seeking to meaningfully compare the output of the nascent Chinese pharmaceutical industry with those in other nations longer engaged in drug development will need to compare not just the quantity of NDAs filed and approved – when such numbers are published – but also will need to focus more on the source of innovation in the truly new drugs approved in the various nations engaged worldwide in drug development today.

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