

THE CHINESE BIOLOGICS DRUG MARKET: demand and execution

In the past decade, China's drug market has been expanding in double-digit percentages. This has brought about a huge increase in local drug makers and has lured multinational pharmaceutical companies to develop, manufacture and commercialise their drug products in China. The regulatory and cultural obstacles that foreign companies encounter, especially for the development and manufacturing of advanced biologics, have often meant that the most efficient entry strategy into the Chinese market is through partnering with a China-based drug maker that has experience in developing a drug locally. Here, we discuss different drug development processes in China and the regulatory steps that should be considered by a multinational pharmaceutical company that is planning on entering the Chinese market.

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China's rapid economic growth and increases in consumer spending has provided a financial opportunity for drug makers. By filling a burgeoning host of unmet medical needs, the development and commercialisation of both novel and biosimilar drugs brings to market an array of drug products that are in high demand. Economic growth correlates with increases in disease incidences in China, which are common during the urbanisation of a developing country. The underlying drivers of these increases, include: (1) the rise in the middle class and urbanisation that shifts healthcare culture towards increased self-awareness in terms of health and regular medical screening, leading to higher detection rates of disease in the population; (2) the introduction of new technologies, allowing for better recognition and detection of health problems that may have been

previously undiagnosed; (3) increases in affluent lifestyles, raising life expectancy and thus age-related diseases, and high fat diets that escalate cardiovascular problems, chance of developing diabetes, and other obesity-related diseases; and (4) industrialisation, which positively correlates with higher incidences of respiratory diseases and cancer due to various toxic pollutants that are released into the environment.

In addition to the above, the increase in medical insurance spending and improvements of healthcare infrastructure and medical capabilities has meant that China is projected to become the second largest market for pharmaceutical products by the end of the decade. In mid-2014, as part of governmental healthcare reforms for meeting demands of higher quality healthcare services, the construction of foreign-owned hospitals are now also permitted. All of

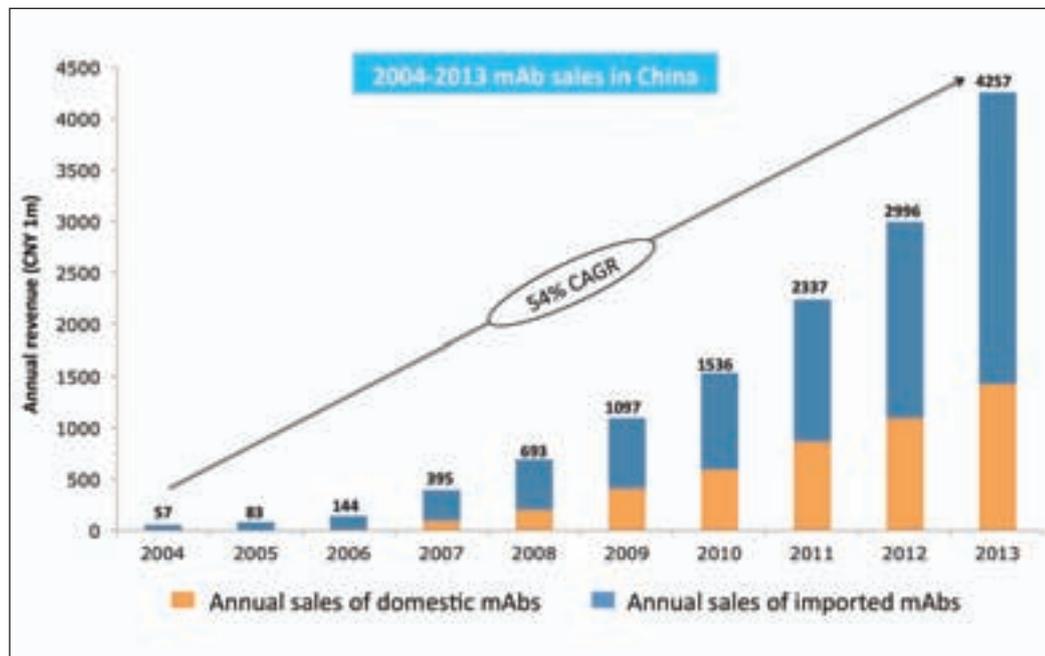


Figure 1
Increase in domestic and imported mAb sales between 2004-13 (data from IMS)

the above factors contribute to a vast market and demand in newer and higher quality drugs at local and affordable prices. Biologic drug products, especially monoclonal antibodies (mAbs), are currently the top-selling pharmaceutical products in the world, and annual sales revenue of antibodies in China is rapidly increasing (see Figure 1). Biosimilar products remain as key revenue contributors (96% of biologic sales). In China, biosimilars are usually classed as innovative drugs until the drug has entered the Chinese market. An important recent regulatory development for biologics in China was the release of a draft biosimilar guideline (in late 2014) by the Centre for Drug Evaluation (CDE) which mirrored those of the EMEA and the US FDA. After review by the industry, the full guideline was released on February 28 (<http://www.sfda.gov.cn/WS01/CL0087/115103.html>) with immediate implementation. This final version is similar to the draft, where biosimilars are still required to enter the same regulatory pathway as innovative drugs, but are scored against different criteria. However, at present, it is unclear whether biosimilars will benefit from quicker approvals. So far, only one truly innovative biologic product (worldwide) has been developed locally, named Conbercept (Ophthalmology. 2014 Sep;121(9): 1740-7; Mol Vis. 2008 Jan 10;14:37-49), which is used for treating age-related macular degeneration.

Thus, there is an enormous space for the development of novel drugs, including novel-like first-in-market biosimilars.

Perception of drug making in China

The majority of 'advanced' biologics (recombinant proteins, mAbs, etc), and new generation antibody technologies (bispecific, domain antibodies, antibody drug conjugates, etc), have shown high efficacy in treating a broad spectrum of diseases, with proven mechanisms of action at least at the pre-clinical stage. The approval of an anti-CTLA-4 mAb in the US in 2011, marketed as Yervoy, has paved the way for the discovery of immunotherapies that have performed considerably well in clinical trials. Many of the advanced biologics that are currently sold in China are imported and sold at a high premium. Thus, the production of locally-made biologics would be highly competitive in terms of affordability to the local populace and may possibly be attached to government reimbursement schemes.

Currently, only 21 mAbs have been approved by the China Food and Drug Administration (CFDA). Foreign pharmaceutical companies often perceive that they will face a complex and fluctuating registration environment and vague requirements from Chinese regulatory authorities when seeking to import their products. Due to these uncertainties and difficulties, it is now seen as highly advantageous and most efficient for foreign pharmaceutical companies to partner with local Chinese companies when bringing a drug into the Chinese market. This is especially the case for Chinese companies that have the knowhow, experience, manufacturing capacity and are very familiar with Chinese

law and the regulatory environment. The latter is of extreme importance not only in establishing drug development strategies but also in tracking the latest updates on regulations and obtaining preliminary recommendations and progress of a drug's registration. Efficient communication with government bodies (CFDA, local FDA and the CDE) may also avoid misguided product R&D. Moreover, cultural and language challenges are often mitigated when partnering with a local company, especially during implementation of clinical trials in Chinese hospitals, in which communication with local medical staff is key in the rapid recruitment of patients and for mediating logistics.

Highlighted below are the time-limiting steps that affect regulatory procedures, and also details on strategies that may aid the expedition of a biologic drug product (emphasised on recombinant proteins and monoclonal antibodies) through the drug approval process in China.

Preparing an Investigational New Drug (IND)-enabling package for China

The whole process for chemistry, manufacturing and controls (CMC) and pharmacology studies for an IND-enabling package in China may take approximately 18 months for completion (see Figure 2). Collectively, there are not many differences between the early CMC processes for an IND-enabling package in China compared with other countries. Upon identification of a leading biologic drug candidate, the first step in the CMC process is to generate a stable cell line overexpressing the candidate drug. In China, alike the rest of the world, CHO cells are often used as the host

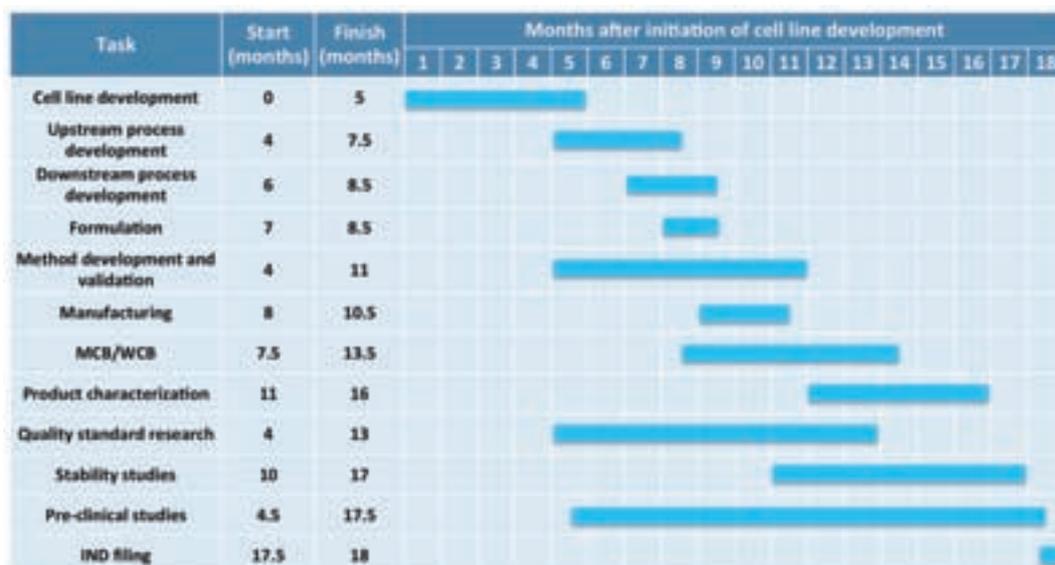
expression cell line, in which information on the cell line history is of extreme importance to regulators. After cell line generation, the process development steps, purification, formulation optimisation and product biophysical characterisation follow routine procedures in finding the best condition for the cell line in producing high-titers of high-quality drug that meets its functional purpose. After scale up and transfer of these optimal conditions to manufacturing, the first production batches of protein are then available for characterisation and testing.

In China, it is necessary to perform a minimum of a six-month real-time stability study on production material (compared with three months for the US FDA), thus adding a few months on to the generation of an IND-enabling package. Moreover, three manufacturing lots of clinical grade material must be characterised prior to IND submission, versus one in the US. Analytical QC testing methods to characterise protein biophysical properties require internal validation for testing by the CDE, but there are generally no extra requirements in China to this end. Methods to assess protein stability are routine. Furthermore, the bioassays required for quality control are usually assessed on a case-by-case basis, but there is increasing preference given to stable and reproducible cell-based functional assays, even for the more difficult cells, such as immune cells.

Pharmacology and toxicology

The CFDA's preclinical pharmacology requirements for an IND application of a biologic are not significantly different to those stipulated by the

Figure 2
An example of a timeline for generation of an IND-enabling package



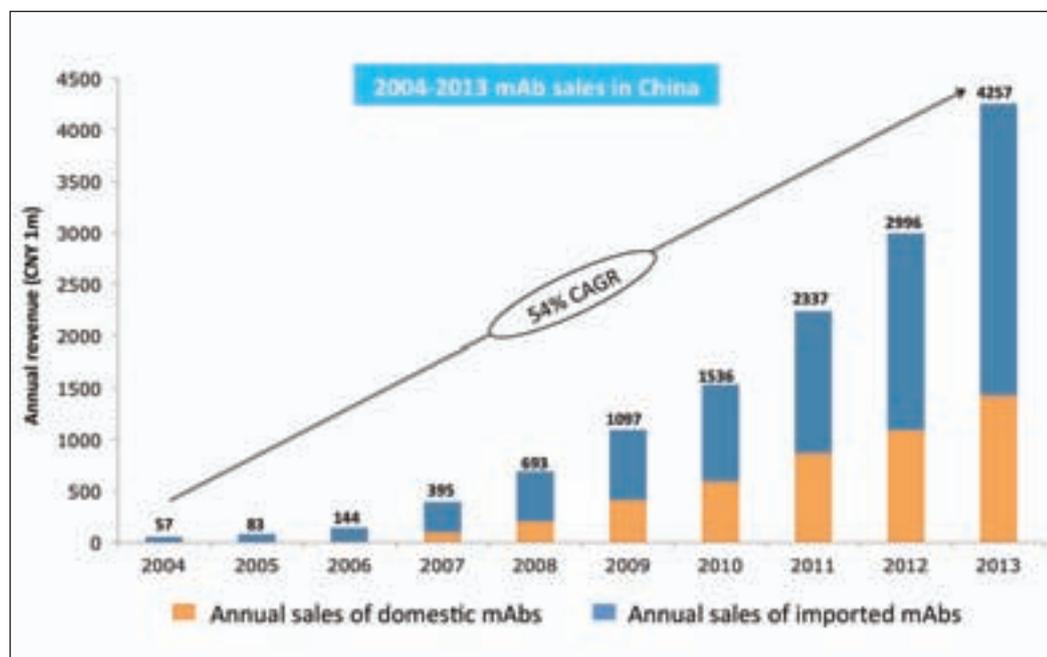


Figure 3
Strategies for clinical studies with the 'green channel' approval in place

ICH. Thus, the materials required by the CFDA satisfy and are deemed surplus to those set by the US FDA. The major items regarding the CFDA's requirements that differ from the US FDA's for pre-clinical pharmacology studies are described below.

Animal studies that are conducted outside of China can be used for an IND package in China. Animal studies are generally conducted using the lead drug candidate if the molecule is cross-reactive to the drug target in small animals. If no cross-reactivity is present, a surrogate molecule/antibody may be used to obtain a mechanism of action for the drug, and data derived from these studies could be deemed satisfactory. However, in China, the final lead drug may have to be tested directly in animals, and if the drug only recognises the human target, it might be necessary for the *in vivo* animal study to be conducted in a humanised rodent or non-human primates. Contract research organisations (CROs) in China are currently developing humanised animal models for this purpose. However, at this present time, it may be more efficient to carry out these studies in collaboration with academic labs that have mature *in vivo* screening platforms, as they would also be acceptable in the IND-filing document.

Similar to the US, all safety studies that are carried out in China should be conducted in labs that are compliant to GLP standards. For repeated dose toxicity studies, each animal group, including those administered with intermediate dose-strengths, usually require recovery observations,

compared to US FDA requirements where only the control and high-dose groups are necessary. For anti-tumour drugs, the US FDA requires a three-month repeated-dose study according to ICH S9, whereas the CFDA requires a six-month repeated-dose study. For safety pharmacology, a rodent CNS safety test may be required in animals, even if the drug does not cross-react with the rodent protein equivalent. For reproductive toxicity, the CFDA requires a much earlier stage study than in the US, where fertility and embryo-foetal studies may be required for Phase I studies by the CFDA, but only before Phase III for the US FDA. These are examples of studies that would not logically fit into typical *in vivo* preclinical plans, but may still be requested by the regulatory bodies.

Post-IND filing

After filing the IND application, the authorisation waiting period in China is lengthy, and could take up to 12-18 months or longer. This is dependent on the queue and post-review recommendations. Due to the CFDA's requirement for having long-term stability studies for the establishment of a calculated expiration date of the product (testing for three months on top of the expiry date recommendation) some companies conduct this testing during the authorisation waiting period. Since long-term toxicity and stability studies may delay the first-in-man studies in China, companies that also plan to register their drug product globally are increasingly looking towards submitting their

IND applications in Australia. In Australia, the IND approval process and first-in-man studies are much quicker, so that Phase I data from these studies could be used to plan more optimised Phase I or Phase I/II studies in China, after clinical study approval in China.

Fast-tracking the regulatory process

In July 2012, the US FDA opened a new category that provides a ‘Breakthrough Therapy Designation’ to drugs that can be used alone or as a combination for treatment of life-threatening diseases. These drugs must show substantial improvement on existing drug therapies during early clinical development. If designated as such, the US FDA expedites the development and review of the drug, and can be reviewed within 60 days of its application. This means that a potentially life-saving drug could be brought to patients earlier and companies can make quicker returns on their assets.

In China, local pharmaceutical companies may have their drug in a ‘fast-track’ stream, in which a ‘special review’ process is enabled. Usually, novel drugs are fast-tracked, which include drugs that are novel worldwide, address a significant unmet medical need or have clinical benefits over existing therapies. These drugs would benefit from being prioritised in the IND application waiting queue, and thus undergo a quicker review process. It is important to have close communication with the CDE so that any changes required in the IND application may be supplemented during the review process.

Access to government grants may provide small companies financial aid in the development phase of a project. One scheme, named the ‘Mega Drug Innovation Development Project’, gives novel and well-planned projects that fulfill unmet medical needs monetary support in the development of their drug. However, financial benefit is not the only advantage as this allows the drug to enter into what is called the ‘green channel’. Not only does the drug maker obtain closer communication with the regulatory body, it may provide a better chance for the drug to obtain approval for all Phase I-III studies from only one application. Thus, clinical studies may be conducted in an overlapping fashion, where results from one phase can be used to plan and immediately be implemented into the following phase before the end of the trial, resulting in the saving of months of valuable time before BLA filing (see Figure 3).

Another set of government grants, named the 973 and 863 programmes, have been available to companies that are interested in collaborating with

academic laboratories for basic research studies. These applications are only usually successful when applied in collaboration with academic laboratories specialised in the same field of research. The advantages after obtaining these types of grants include recognition by academic circles and potential investors, and may help to create the opportunity for a ‘special review’ process. All of these grants are difficult or not possible for foreign companies to obtain unless they are working in collaboration with a local entity.

Other considerations

At the end of 2014, the CFDA released a new guideline on multi-region clinical trial (MRCTs) for consultation, in which both internal and external sites should be open to CFDA inspection. The patient subjects in these trials should be representative of the local population – in this case China, or other similar Asian populations. According to this guideline, foreign sponsors are encouraged to carry out MRCTs, which focus on critical unmet medical needs in China and to conduct pivotal studies there. Foreign sponsors need to apply for the MRCT application to conduct MRCTs in China and can use MRCT data for BLA application. However, foreign sponsors need to apply for IND and BLA applications besides the MRCT application, which means that foreign sponsors must go through three rounds of applications followed by three review processes (MRCT review, imported product IND review and imported product BLA review) if they seek to use any MRCT data to enter the Chinese market. Due to the lengthy approval times in China and added stringency in the application requirements for MRCT data, this brings fewer advantages that foreign companies had previously expected, as MRCT material was hoped to quicken the drug approval process. This highlights the changing (or maturing) regulatory system in China that needs to be followed carefully in order to align with the Chinese drug development process. Local and foreign companies have been sought for input in drafting these guidelines, but it is unclear whether these will be tailored to advantage the development of drugs by local companies.

Conclusions

Although China has opened its market to the world, Chinese technological advances have often lagged behind the demand for high-quality products meaning that the latest products are only available for the wealthier population. China is often criticised for the lack of innovation; for the

foreseeable future, at least in the large macromolecule biologics industry, this may still be the case as there is a massive market for the development of biosimilar drugs. To lower risk, start-up biopharma companies have generally followed a business model of first developing and launching biosimilar/me-too/me-better products before truly investing in new generation and first-in-class (worldwide) product development. Nevertheless, China's drug regulatory system has now started to take a more complete shape, and it will be interesting to see how China's growth will affect global sales and availability of these drugs, not only to the developing world, but also globally. **DDW**

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