

# Buying APIs in China – A risk assessment

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### A RISKY BUSINESS?

Quality and safety are two concepts that are linked in all industries but they have a particular meaning for APIs because Quality concepts have been designed by health agencies to increase patient safety all over the world, China being no exception.

So, if the principles are the same in China, why discussing about a particular risk of buying APIs in China? The answer is simple and has different aspects.

First, thanks to its low cost and long history, the Chinese API manufacturing industry is well represented with many small, medium size and big companies. China is a very attractive place to manufacture APIs and source them at attractive prices for global markets. In contrast with a shrinking API industry in Europe, API manufacturing in China is a growing industry. It is supported both by exports and by the strong growth of the Chinese pharmaceutical market.

Second, the diversity of Chinese API manufacturers makes it difficult to grasp the industry. This comes from the growth of the industry, the history of China and the taste for entrepreneurship of Chinese people but also from the size and complexity of the country.

Third, one main difference between China and Western countries is the different way of thinking. When Westerners set rules and then observe them, Chinese admit that rules should be observed but may also include exceptions. When one applies this to quality and compliance, this certainly can lead to misunderstandings. While technical capability is often there, quality

management is often quite limited.

Fourth and last, China is a world of contradictions and one of these is the mix between developed and developing country features in all aspects. This stands for infrastructures, but it is particularly true for pharmaceuticals. Some plants are simply not acceptable by any quality standards and should stop producing. Other plants have very little to envy compared to some of the best European and US API manufacturers.

Even if all these aspects were present, buying APIs in China would not be risky if exports were tightly monitored by health agencies of the receiving countries. In fact even the most sophisticated health agencies such as the US FDA or other organizations like EDQM, are too limited in resources to inspect regularly and monitor all the plants exporting APIs in their respective countries or groups of countries. Chinese SFDA is more experienced and can be more efficient at these inspections. It can set up the infrastructure to monitor more efficiently and to act in case a site does not meet their quality standard for API manufacturing. Nevertheless, SFDA has not yet reached the same level of quality requirements as the western agencies and have had their share of problems to effectively deal with the quality issues.

Timing is also a very difficult hurdle for foreign and local agencies. While building an API facility in China and have it produce an API is much faster than having the production inspected, subsequent changes in the plant management and financial resources often occur. And it is frequent to visit inspected plants that are not meeting the

published by **B5** srl  
Via Cesare da Sesto, 10  
20123 Milano - Italy  
Tel. 0039 02 83241119  
Fax 0039 02 8376457  
www.b5srl.com

quality standards although it was met during a previous inspection.

One factor that also increase the risk level is the purchasing policies and practices of foreign firms, all countries included. Like in all industries, cost is one of the most important factors driving purchasing of APIs in China. In order to save money, one sometimes forgets basic quality assurance – one could cite the Heparin problem. Also basic technical communication is often neglected – one good example is the purchase of ethylene glycol instead of glycerol by a Spanish trader because of lack of simple QC check and correct reading of the label. This mistake led to tens of deaths in Panama. These safety factors put us at risk. Audits are often a formality that last one or two short days on site by auditors who know very little about the product. This simply is not enough to reach a decision if a site can be qualified or not. As Chinese API manufacturers are always eager to do business, are very flexible and have a rather undeveloped quality management, they often accept conditions implying that they have to cut corners to deliver.

So yes, buying API in China is risky because of this cocktail of circumstances and behaviors. But what are the consequences?

## CONSEQUENCES

The risk can be well appreciated with the occurrence of the negative events and their potential costs. EFCG has lobbied for quite a long time and pointed out to the European Commission of the potential negative consequences of buying from non inspected sources on the risks to patients' health. Agencies in Europe, after having been very soft on these issues have increased their requirements for API compliance. Many non compliant APIs of Asian origin had and will have to be replaced by compliant sources.

Pharmacovigilance has always been a very discrete field, particularly when severe adverse effects are recorded and action is undertaken such as withdrawal of a drug or change of an API source.

The Heparin case is probably the one which has been the most publicized. It has really shown what we can expect in cost of human lives but also in financial costs. The withdrawal of the Chinese source of Heparin created a shortage and affected the sales of many companies selling the product. The patients who needed the drug were also affected because replacement could not be found in certain countries. The reputation of the pharmaceutical companies involved have been damaged even if they could claim

they were not directly responsible of the manufacturing.

Because of the potential damages for their reputations, more and more pharmaceutical and generic companies refuse to buy APIs in China mainly because they could not be sure of the compliance and quality management of a Chinese source. They prefer not to risk their reputation even if this implies an economic disadvantage against their competitors.

Many companies estimate also that some Chinese API manufacturers can meet their compliance criteria but may not meet their development time lines, leading to launch delays that are unacceptable to their investors. These companies prefer to deal with Western or Indian organizations with better quality management, ensuring a better quality project management.

## HOW TO MITIGATE THE RISK?

The next question is how can this risk be avoided while keeping the cost advantage of buying in China. The Chinese API manufacturing industry is developing and improving quickly so they can not be ignored by any small or large pharmaceutical or generic company.

Dealing directly with API manufacturers in China for a foreign generic or pharmaceutical company either imply to have a very light involvement and therefore trust the manufacturer on many aspects of the API production and in particular quality, or be deeply involved and this means that a lot of resources have to be allocated to the management of the API project. Some would say that the amount of resources needed exceed by far the benefit of sourcing from China. Most of the companies have a limited involvement and experience major quality or timing setbacks mainly because quality management weaknesses and communication

difficulties have been ignored.

By far, the best approach is to use an appropriate intermediate who is able to bring the project and quality managements to the API project from the beginning. The role of this intermediate should not be limited to the simple sourcing role and not even to just the commercial/regulatory filing dual role that is often seen in generics. The intermediate should fill the quality management gap that is very often found in Chinese API manufacturers and should ensure the project is delivered to the customer as planned. This new type of local intermediate needs locally trained Chinese chemists, experiences Chinese quality assurance and quality control professionals and a good experience of Western quality management. The task of his team is to manage the project, interact with the manufacturer and the customer and solve issues.

Hundreds of API manufacturers in China are planning to export APIs in the next decade, at any cost. Finding a source is not a problem but transforming it into a low risk, reliable and overall economical supplier is the success factor for many generic and pharmaceutical firms. For many, the appropriate management resources are most probably outside their organization.

## Avoid China sourcing RISKS...

Eastar Pharma Products provides

- ✓ Sourcing and custom manufacturing of intermediates and APIs from China
- ✓ Quality and project management
- ✓ QA staff onsite at suppliers' facilities
- ✓ Tech support and QC lab in China
- ✓ Technology theft protection
- ✓ US and EU regulatory expertise
- ✓ Over 25 year of quality track record

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