

PEPTIDES & PROTEINS

When it comes to peptide manufacturing, we are all Chinese

Jim Hampton, executive vice-president of business development at AmbioPharm, describes sourcing trends for raw materials, intermediates and finished goods in the peptide industry

China has become the world's factory, second only to the USA in terms of CO₂ emissions among major industrial countries.

Although we Westerners are responsible for our own carbon footprint, we generate a good share of China's as well. Inside China, per capita CO₂ emissions are only about 25% of those of the average person in the USA¹ (4.6 metric tonnes in China vrs 20 in the USA in 2007). About 31% of these emissions were caused by the manufacture of goods consumed outside China.

We Westerners are also largely responsible for Quality Control problems associated with importation from China. Baxter Healthcare recalled its heparin drug product because of problems arising from an impurity in API sourced from China. A US supplier manufactured the API in its subsidiary factory near Shanghai and, although the FDA was supposed to inspect the subsidiary, this inspection never took place. By its own admission, the FDA's inspection frequency of foreign drug and API manufacturers has been less than optimal².

A clear trend

In 1998, according to the US Census Bureau, the US-China trade deficit was \$56.9 billion; in 2009 it was \$268 billion³. During this ten-year period, most of us have grown used to 'Made in China' labels on many products in daily use.

Despite the risk, the trend in biopharmaceuticals is clear because we are all using more and more raw materials and intermediates manufactured in China. Amino acids, solvents and other fine chemicals used in peptide manufacturing are sourced from China, and used worldwide by peptide manufacturing Organizations (CMO's) to make drugs substances and intermediates.

Perceived risks

The first perceived risk is a misconception on the part of Westerners that Chinese management of Chinese companies is lax. According to recent survey⁴, Chinese managers of Chinese companies are setting the management agenda for the world. This group is described as a young, educated, largely English-conversant, ambitious cadre of talented people on the cusp of world-class success in business.

The same survey indicated that 60% of managers in China had degrees, followed by the US (37%), France (25%), and the UK (21%). What does this say about relative capabilities?

Regarding Western attitudes toward Chinese managers, their companies, and the products they supply to us, the authors of the survey report had four suggestions to minimize risk:

1. **Know your supplier:** Western perception of Chinese management is outdated and simply not realistic. Chinese management is highly motivated and competent. Audit your suppliers.
2. **Align priorities:** Inappropriate QC of imported Chinese goods is a prime example of mis-aligned priorities. If raw materials, intermediates and APIs imported from China contain impurities, we can blame our failure to specify, inspect and test.
3. **Invest in development in China:** Western manufacturing companies should invest in Chinese manufacturing sooner rather than later.
4. **Get ready for a new paradigm of Asian management:** We must be aware of and adapt to the Chinese agenda and also understand the potential impact this agenda will have on future economic relationships with the West. Think Japan in the 1980s.

Recently, companies such as Pfizer, Genzyme, Unigene and Charles River Laboratories, among many others, have announced significant new manufacturing facilities in China. Their subsidiaries here in the USA will buy the majority of raw materials and intermediates for biopharmaceutical manufacturing from Chinese suppliers.

Pfizer has said it will outsource 30% of its manufacturing, much of it to Asia, in order to take greater advantage of global manufacturing and R&D⁵. For instance, Pfizer will outsource most of its manufacturing of its cholesterol medicine Lipitor in preparation for competition from generic versions.

These plans follow Pfizer's announcement that it would shut down US manufacturing sites in Brooklyn, New York, and Omaha, Nebraska and sell a third manufacturing site in Feucht, Germany. These cuts, along with the closure of several research sites, are part of a plan to cut its worldwide workforce by 10%, or 10,000 jobs, and save \$2 billion/year in costs.

Risk management is the key

What fuels this trend towards sourcing raw materials for the manufacture of biopharmaceuticals, specifically peptides, from China? The answer is favourable price/value/risk ratios, a classic exercise in risk management. But, having assumed risk, what are our responsibilities as consumers in the transaction?

To answer this, let us examine trends in the synthetic manufacturing of peptides. First, a little history. In 1998, China was virtually unrecognised internationally as a supplier of raw materials (including amino acids, resins and solvents) for synthetic peptide manufacturing.

Pre-2003, amino acids were sourced almost exclusively from Japanese (Ajinomoto), North American (Synthetech, ChemImpex), and European sources (Bachem, Senn Chemicals, Sygena). Today, most raw materials used in peptide synthesis ultimately come from China. Of course, there are inventories of amino acids that are derivatised in Japan, the USA and Europe, but the basic amino acids come from China.

What changed in peptides?

The dynamics of amino acid manufacturing changed dramatically in 2003 when the FDA approved Roche's HIV peptide drug Fuzeon (enfuvirtide) and Roche projected requirements for the Active Pharmaceutical Ingredient (API) of this drug at tonne scale at its facility in Boulder, Colorado. With over 100 manufacturing steps to make Fuzeon, each 1 kg of such a peptide requires 25 kgs of raw materials, even with a highly optimised manufacturing protocol.

In response to these requirements, many Asian companies began manufacturing relevant amino acid derivatives in multi-tonne batches to meet increasing demands. This increase in manufacturing scale drove down costs of raw materials for peptide synthesis worldwide.

Fifteen years ago, if the API requirement was over 500 grams/year, recombinant manufacturing technology was used and FDA-approved for peptides such as Forteo (pTH 1-34), Natrecor (nesiritide, BNP-32), and GlucaGen (glucagon 1-29). Even first-generation Angiomax (bivalirudin) was manufactured in a combined recombinant/synthetic process developed before 2000. Today, manufacturing under cGMP of Fuzeon (metric tonne/year), Angiomax (400 kgs/year) and other peptides (10-100kgs/year) is completely synthetic at very low unit costs relative to pre-2003.

Today, most amino acid derivatives used in the manufacturing of synthetic peptides are manufactured in Asia. As a result, the price for some Fmoc-protected amino acid derivatives has plummeted to 20% of 2003 prices.

Less expensive raw materials and newer manufacturing techniques have profound cost implications for the manufacture of synthetic peptides. Several Contract Manufacturing Organisations (CMOs) are now capable of manufacturing of highly-purified synthetic peptides under cGMP, using solid-phase chemistry and/or hybrid fragment condensation techniques at scales of 25-100 kg/batch.

At lower scales, fixed costs (labour, facilities, regulatory, etc.) and variable costs (raw materials) have a cost ratio of about 50:50. At very large scales, the fixed costs are amortised over many units and can fall to 20% of total cost, leaving the variable cost of raw materials to dominate at 80% of total cost.

As shown in Figure 1, CMOs sourcing raw materials and intermediates from Chinese suppliers have a significant cost advantage at larger scales because raw material costs as a percentage of total cost rises with scale.

CMO responsibilities

As a CMO sourcing raw materials and intermediates from Chinese suppliers for peptide synthesis under cGMP, how do we carry out our regulatory responsibilities? How do we manage the risks?

Firstly, we qualify and audit the manufacturing facilities of our amino acid and solvent suppliers on a regular schedule to insure that they employ Good Laboratory Practice (GLP). We maintain full traceability of raw materials as evidenced by the supplier's Certificate of Origin for each lot of each material. A Certificate of Analysis accompanies each lot of material released by the supplier's QC department.

Secondly, each incoming lot from suppliers is submitted to and released by our in-house QC testing laboratory to ensure purity and identity of all raw materials and intermediates used in cGMP manufacturing. Under cGMP, all testing results become part of the Batch Production Record. Small aliquots of critical raw materials are retained and stored properly for re-testing.

Thirdly, all critical raw materials used in cGMP manufacturing are commercially available from at least two qualified, audited suppliers. The results of these audits are formally documented and recorded in an audit report maintained by our QA department.

Conclusion:

Chinese suppliers recognise the need to maintain facilities and train their staff to meet world standards for raw materials and intermediates for peptide synthesis. However, the regulatory responsibilities of CMOs manufacturing drugs and drug substances under cGMP remain constant, regardless of where raw materials are sourced.

With effective risk management on our part as CMOs, suppliers in China will continue to reduce our costs for raw materials and intermediates, and we will reduce the price of the APIs we manufacture for our clients, especially at increasing scale.

For further information, please contact:

Jim Hampton

Executive Vice President of Business Development

AmbioPharm, Inc.

1024 North Dittman Court

North Augusta

SC 29842

USA

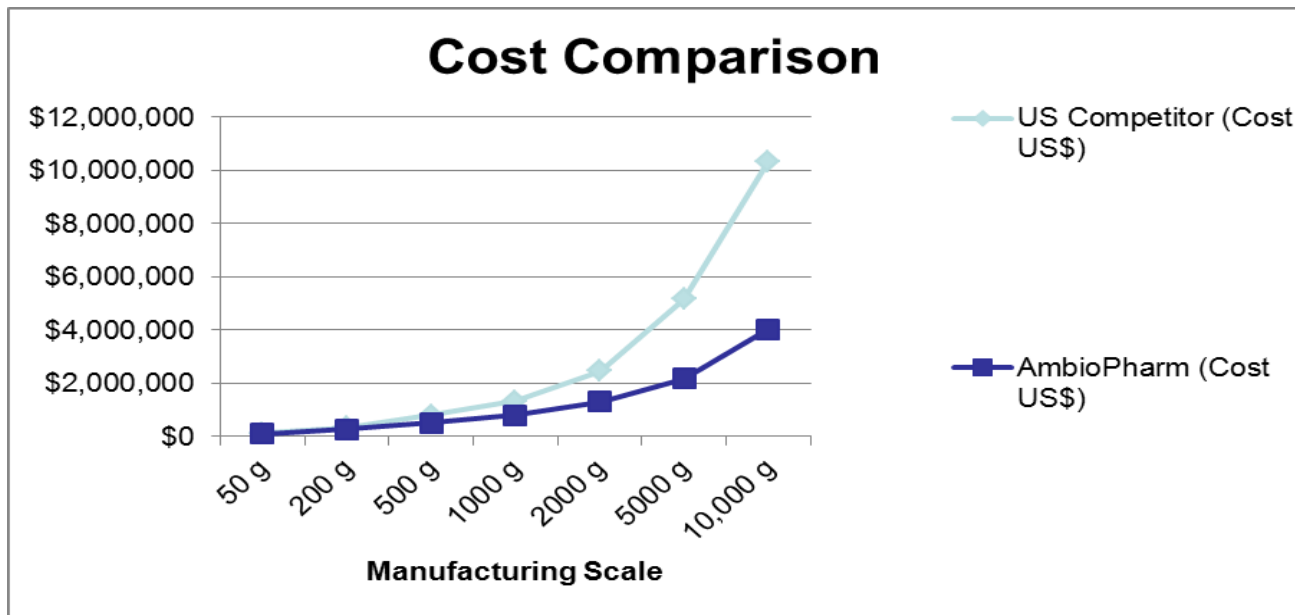
Tel: +1 415 921 3593

E-mail: jim.hampton@ambiopharm.com

Website: www.ambiopharm.com

Illustration, as supplied:

Figure 1 - Cost Comparison of two CMOs using solid-phase chemistry for peptide synthesis under cGMP after sourcing raw materials and intermediates from Asian & Western suppliers



References:

¹ 2007 data calculated by US Department of Energy's Carbon Dioxide Information Analysis Center (CDIAC)

² Speech before Congressional Committee by Andrew C. von Eschenbach, M.D., FDA Commissioner, November 1, 2007

³ SOURCE: U.S. Census Bureau, Foreign Trade Division, Data Dissemination Branch, Washington, D.C. 20233

⁴ survey conducted by The Institute of Leadership & Management

⁵ Pfizer November 30, 2007 Analyst Meeting in Hong Kong