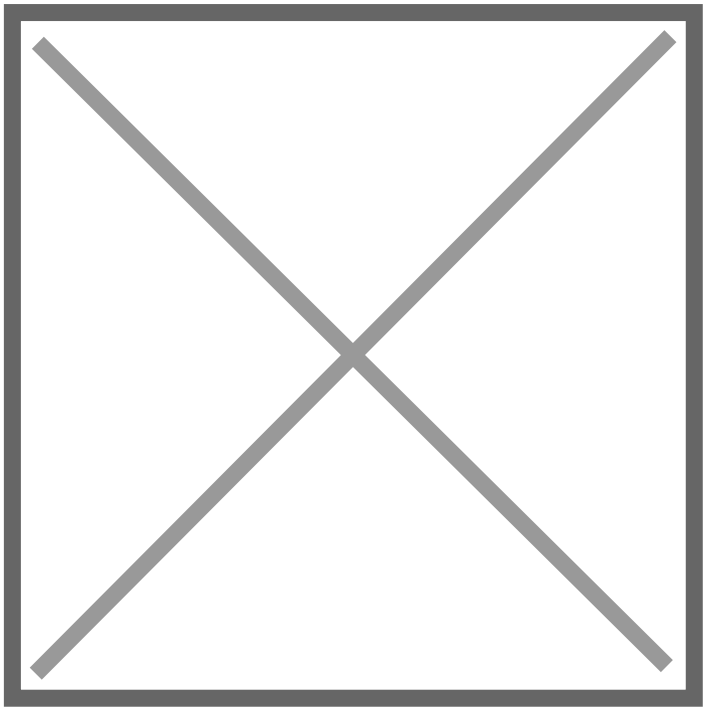
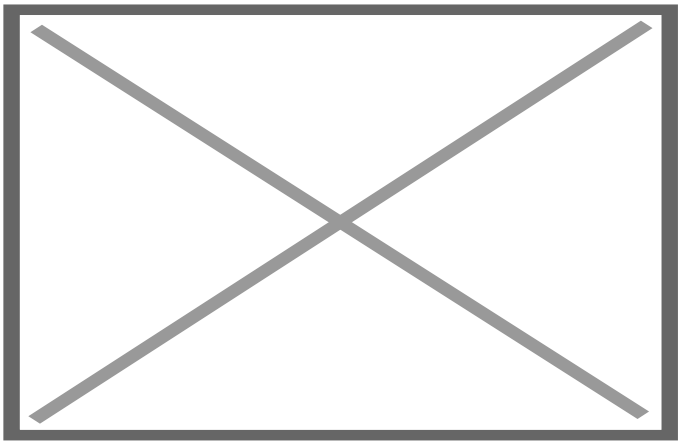
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Quality assurance is key

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Biologics manufacturers are striving hard to adhere to international quality standards. Better regulatory policies by the government will go a long way in aiding the industry

In recent years, licensing and quality control for manufacturers and national regulatory authorities has become more complex. The National Institute of Biologicals (NIB) has been working since 1992 as an autonomous organization under the Ministry of Health and Family Welfare, Government of India, to strengthen the regulations on biologicals in India. The institute assures and reviews quality of biological products available through domestic manufacturers and importers. The operations are carried out in the state-of-the-art facility of the institute and in close co-ordination with government regulatory authorities, such as the office of Drug Controller General of India and the Indian Pharmacopeia Commission.

Indian companies are ramping up their facilities in adherence to quality standards for both the regulated and unregulated markets of the world, but they still have a long way to go. Ã¢â?¬Å?One area that could be improved upon is the availability of more current good manufacturing practices (cGMP)-approved manufacturing facilities,Ã¢â?¬? says Mr Chinny Rao, executive director, Transgene Biotek. Ã¢â?¬Å?This can sometimes sit alongside a dearth of knowledge concerning the exact standards and parameters prescribed by foreign regulators, and the absence of government support in dealing with or overcoming foreign government restrictions on imports. In commercial terms this just adds to delays in manufacturing time lines and also cost increases.Ã¢â?¬?

Quality is priority

Companies dealing in biologicals say adhering to quality parameters is of utmost importance to them. Dr Esmail Samiwala, senior VP, USV, says USV's focus is to maintain the highest quality standards at all stages. Ã¢â?¬Å?USV believes in the concept of one quality and one development for both regulated and semi-regulated markets. The EU and the US cGMP standards along with Indian GMP standards are strictly adhered to while manufacturing at both drug substance and drug product manufacturing plants,Ã¢â?¬? he says. The companies, as a part of their yearly training calendar, provide training to employees on-the-job to maintain quality standards. Updating employees about the regulatory requirements and ensuring that the new standards are implemented in a time-bound manner are regular practices at all manufacturing plants.

Mr Chinny Rao, says, Ã¢â?¬Å?In addition to regular internal auditing of our facilities and processes, we also adhere to cGMP, ISO and EU guidelines as standard practice.Ã¢â?¬?

India's biggest vaccine manufacturers, such as Serum Institute of India in Pune, Panacea Biotec in New Delhi, and Bharat Biotech in Hyderabad, who manufacture a variety of biological products, follow quality parameters strictly. As a result of this, these firms have emerged as major exporters, matching international quality expectations. The quality audits have been part of the regular programs in order to ensure that overall quality concerns of the companies are addressed.

At Panacea Biotec, vaccines account for about 70 percent of revenues. It has ultra-modern production facilities complying with international standards and cGMP. Similarly, Bharat Biotech International too has been observing the highest quality standards at its manufacturing units. Ã¢â?¬Å?We are aware that our products are administered to children and adults worldwide. We have to maintain the highest standards of quality. Absolutely no compromise will be tolerated at Bharat Biotech for quality,Ã¢â?¬? says Dr Krishna M Ella, CMD, Bharat Biotech.

The biopharmaceutical manufacturing facility at Reliance Life Sciences in Mumbai is already approved by the European Medicines Agency (EMA).

Mr KV Subramaniam, president, Reliance Life sciences, says, Ã¢â?¬Å?The manufacturing facilities at Reliance Life Sciences are built as per US Food and Drug Administration (FDA) and EMA standards.Ã¢â?¬?

Talking about his company, Dr Cyrus Karkaria, president, biotechnology, Lupin, Ã¢â?¬Å?Lupin adheres to quality demanded by developed markets because at the end-of-the-day that is where we want to be and we are striving to get there as soon as possible. The opening up of the US biosimilar pathway would lead to a world of opportunities for companies, such as Lupin, in India.Ã¢â?¬?

Setback in quality

In the recent past, there have been instances where some of the major companies dealing in biologics have suffered setbacks in quality adherence. In April 2010, the WHO ordered recall of Shantha Biotechnics's pentavalent vaccine, Shan5, from the market after finding some white sediments in the vials of certain samples. The recall was ordered as a precautionary measure. Shan5 is a DTwP-hepatitis B-Hib vaccine.

Speaking about the current status of Shan5, Dr Harish Iyer, CEO, Shantha Biotechnics, says, Ã¢â?¬Å?Getting the pre-qualification approval from the WHO for Shan5 is a high priority for us. We are working hard towards making necessary changes, so that we can again start supplying it by 2014 to the agencies. We hope to start bidding for tenders for the pentavalent vaccine in the next round.Ã¢â?¬?

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- Dr Harish Iyer
CEO, Shantha Biotechnics

Ã¢â?¬Å?There have been certain disruptions, but I am confident that we will bounce back in 2013. We have initiated corrective and preventive measures to ensure compliance with the WHO pre-qualification guidelines and are in touch with the WHO in this respect. We are confident that with these corrective and preventive measures, we will be able to get re-listing of our pentavalent vaccine in the list of WHO pre-qualified vaccines.Ã¢â?¬?

- Dr Rajesh Jain
joint managing director, Panacea Biotec

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- Dr Krishna M Ella
CMD, Bharat Biotech

Ã¢â?¬Å?There are many local and international companies in the Indian market and price erosion across all products is a problem. Because of the evolving Indian regulatory system, players who launched their products about four-to-five years ago were spending less on development as compared to the present costs of development. With the existing regulatory system, the cost of development and time spent on it are increasing manifold.Ã¢â?¬?

- Dr Esmail Samiwala
senior VP, USV

In August 2011, Panacea Biotec, which was among the first companies to launch a pentavalent vaccine, had their WHO pre-qualification approval withdrawn after a routine audit due to inadequate quality assurance processes. The statement by the WHO states that EasyFive was not found to be unsafe, but procurement was to be stopped until the manufacturer implemented corrective measures.

Reacting to it, Dr Rajesh Jain, joint managing director, Panacea Biotec, says, Ã¢â?¬Å?There have been certain disruptions,

but I am confident that we will bounce back in 2013. Our performance has been affected by the delisting of pentavalent vaccine from the WHO's list of pre-qualified vaccines, following a routine site audit by a WHO team in July 2011.We have initiated corrective and preventive measures to ensure compliance with the WHO pre-qualification guidelines and are in touch with the WHO in this respect. We are confident that with these corrective and preventive measures, our pentavalent vaccine will regain its WHO pre-qualified vaccine status.Ã¢â?¬?

Bharat Biotech, one of the major exporters of vaccines to international organizations such as the WHO, too adheres to the highest quality standards. But, in 2011, the WHO suspended supply of its hepatitis B vaccine through UN procuring agencies after it found deficiencies in the implementation of good manufacturing practices and quality management of the company during a site audit of a production plant at Hyderabad. The WHO, however, did not recommend recall of Revac-B+ that was already distributed, since the suspension was precautionary and an interim measure.

Regulatory landscape requires reforms

Delay in approvals after submission of dossiers to regulators is a pain point for the industry. Mr Chinny Rao of Transgene Biotek says that advantages of manpower availability and lower costs of manufacturing, which gives the industry in India its underlying momentum, can sometimes get Ã¢â?¬Å?outweighed by certain localized disadvantages, most of which typically relate to bureaucracyÃ¢â?¬?.

CHALLENGES

Reference standard not available in time: For example, official monographs of filgrastim, interferon and erythropoietin were included in pharmacopoeia in 2007, but reference standard is not available yet.

No chapters or guidance for finished products: All requirements mentioned in pharmacopeia monographs are in place for drug substance only.

Specifications more relaxed than innovator product: Quality requirements by pharmacopoeial authorities are considerably different in approved drugs and contradictory to biosimilars requirement. Manufacturers can use monograph for evaluation of quality of product for release purpose. However, compliance to monograph is not sufficient when purpose of the study is to establish biosimilarity.

Source: *Kemwell India*

The lack of standard procedures on what needs to be done to attain regulatory clearance by companies in India and abroad is a major drawback. The company heads are of a view that a haphazard approach by a few officials to set criteria that companies must clear to get green signal is not at all helpful.

Ã¢â?¬Å?It's a little bit of guessing on both sides, which in turn means that time is wasted in exploring or researching what you think will be required. Furthermore, if you have export aspirations, this can add to the workload because more often than not what is generally required here is what will be expected in foreign markets as well. And the absence of standard practice often means having to go back and forth wasting precious time and resources,Ã¢â?¬? adds Mr Rao.

Pointing towards the lack of clarity on stem cells and biosimilars, Mr KV Subramaniam, president, Reliance Life Sciences, says, Ã¢â?¬Å?India does have a biosimilar regulatory framework in place. But for stem cell-based therapies, such a framework is obscure. For biosimilars, current guidelines are quite stringent and, therefore, any biosimilar player faces challenges in terms of longer clinical development time lines and higher development costs.Ã¢â?¬?

One of the challenges of biologics manufacturing here in India has been the absence of government support to what is a fledgling industry. All countries, where the pharmaceutical and biotech industries are very successful, have a single regulatory agency. As compared to that, India has a rather complex structure with many agencies, such as the Drug Controller General of India, the Review Committee for Genetic Manipulation, the Genetic Engineering Appraisal Committee, and the Directorate General of Foreign Trade (DGFT) among others.

Ã¢â?¬Å?India has a strong biologics regulatory framework that involves four-to-five ministries in the Government of India and many agencies that jointly regulate the development, manufacture and supply of biologics. It makes for a very complex regulatory system. Comparatively, all countries where the pharmaceutical and biotech industries are very successful, have a single regulatory agency such as the EMEA (in Europe), the FDA (in the US), TGA (in Australia) and ANVISA (in Brazil), which oversee and regulate all aspects of the industry,Ã¢â?¬? says Dr Krishna Ella of Bharat Biotech.

Sharing a similar view, Dr Samiwala of USV says, Ã¢â?¬Å?Development of products for the Indian market is a little different when compared with the development program of Europe. The difference is in the number of times regulatory submissions during the development and time lost in follow-ups. Apart from this, there is some non-clinical and clinical development requirements specific to India. As the company's thirst is to reach other semi-regulated and regulated markets, merging the development programs for India and other markets is the biggest challenge.Ã¢â?¬?

Dr Hemanth Nandigala, director, Virchow Biotech, has a different view. Ã¢â?¬Å?Contrary to common belief on hassles, we feel that India has an excellent biological regulatory approval system. We have been operating across multiple markets and we can say this with reasonable experience,Ã¢â?¬? he says.

On an optimistic note, Dr Cyrus Karkaria, president, biotechnology, Lupin, says, Ã¢â?¬Å?There have been delays but most of

the times they have been pre-empted by engaging the regulatory forces. They have been co-operating with the industry by coming up with a separate set of guidelines. Once those guidelines are out, then the process would be more seamless and understood clearly.Ã¢â?¬?

Rahul Koul in New Delhi