Privileged technologies move to the Pacific Rim

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It has long been recognized that the market for manufacturing both Active Pharmaceutical Ingredients and Drug products has moved to the Pacific Rim. Today, India has more active Drug Master Files than any other country. In 2011, Price Waterhouse Coopers considered China to be the most attractive Asian country for outsourcing the manufacturing of Drug Product. The estimated value of this was placed at $ 1.9 billion with an annual expected growth rate of 18% (1). Considering that the number of drugs that are currently manufactured in India and China, one might think that they would be potentially the leaders in technological advances in chemistry. That has not been the case to date.

Deloitte Touche Tohmatsu Limited and the Council of Competitiveness developed the Global Manufacturing Competitiveness Index (GMCI). In 2016, the US was ranked in second place and China was first while India ranked in the eleventh position. By 2020, they predict that the US will retake the first position while China will slip to second and India will move up to the fifth position. However, the US is ranked highest in advanced manufacturing technologies and is highly competitive in terms of the share of high skill and technology contribution to exports and labor productivity. The US continues to be among the global industries in research and development activities investing in Universities, R&D talent and venture capital investments. In addition, they expect the Asian area to continue to rise in these areas. China, Japan and South Korea will continue to improve due to technology and innovation while Taiwan and Singapore continue to improve as the focus on high tech exports (1).

Over the years, companies located in the US and in Europe have had the privilege of owning advanced technologies for the development and manufacturing of chemicals. Pharmaceutical companies have been able to take advantage of these improvements and advanced technologies to develop efficient methods to produce very complex molecules. Access to this technology has been critical and that and the cost to implement these technologies at scale have allowed companies in Europe and the US to maintain a technological advantage over companies in the Pacific Rim. When competing against low labor costs, the US has been able to maintain a competitive edge due to the technical superiority. However this has changed dramatically over the last few. The robust economies in the US and in China will allow for continued investments while the slug gist in Germany and the rest of Europe will minimize some of the investments there.

In the past, companies in India and China have been able to successfully adapt processes to fit more traditional older chemical methods. These regions have relied heavily on low labor rates to keep them competitive. However, the productivity and high efficiency of companies in Europe and the US has allowed these regions to compete successfully against low labor center. In fact, today, many companies in Europe and the US are fully booked and showing signs of growth and expansion.

As labor rates continue to climb in these regions, other factors also contribute to the need to get better. Increased regulatory oversight from both Environmental and FDA type agencies has also pushed companies to improve their chemical synthesis methods and reduce the overall environmental impact of their processes on the world. In addition, the complexity of the molecules today do not often lend to traditional chemical methods.

European and US companies have been able to rely on equipment and service suppliers. Also, western companies have the additional support of engineering firms to design and build the required equipment trains. This coupled with the technical support from research centers as well as the development engines in the US and Europe has helped the western companies maintain technical superiority. Analytical development in the west could also be a driver to keep technical here.

However as market dynamics shift, we see more of the support moving to India and China. Western companies have opened sales

offices followed by technical support centers in India and China to support the growing markets there. Other support areas such as analytical development have also seen movement to the Pacific Rim. This has opened up new markets for these companies and allowed access to greater technologies in China and India. In addition, we see an increase in the access to many of these technologies due to low cost improvements as well as increased awareness to the use and practicality of some of these improvements. Trade shows and high end technical presentations have helped fuel this as well.

Dr. Joseph Barendt, president of Chiral Technologies stated that "Despite a general perception that low-labor areas tend toward low-end technologies, we are seeing our customers in India and China adopt many of the high-tech, best practice approaches that you would expect to see in the US and Europe."

The cost of the equipment and the technology to use it has been a major concern for companies in China and India. The cost to install a new Simulated Moving Bed (SMB) system is in the millions and could be limited to a single product. This has been a deterrent for many companies. However last year, Laurus in India announced the installation of such a piece of equipment. Dr. Satyanarayana Chava, CEO of Laurus Labs feels that "We are in a race to establish cost leadership in single enantiomer synthesis using asymmetric synthesis vs chiral separations. Since achieving 100% ee through asymmetric synthesis is an undaunting task, Laurus utilized the concept of sync between asymmetric synthesis and chiral separations at industrial scale." He went on further to say that "Laurus developed a continuous chromatography method to separate this mixture in collaboration with Daicel." Novasep is reported to have done the development and pilot work in France and transferred the process to Laurus for commercialization. Today, Laurus is reported to produce about 200 kg of final product a day using a 5 x 350 mm diameter column configuration. For Laurus, Dr. Satya stated that "Using this approach Laurus achieved significant process efficiency by making process more yielding, environmental friendly and sustainable. Today, Laurus has gained significant expertise in using commercial scale chromatographic separations as a new approach towards achieving cost leadership."

In 2015, cosponsored by the Chemical Engineering News and organized by the Green Chemistry Group (based in Pittsburgh) SFC China 2015 was organized. This was the first international conference on Supercritical Fluid technology organized in Asia. Larry Green, president of Green chemistry and a principle scientist in Discovery and Analytical Sciences group at Amgen was quoted as saying that the "China is no longer just a low-cost place to do work; the level of science as seen at this is high" (2).

Abhijit Tarafder, principle research chemist at Instrument maker Waters Corp. said that "Holding the SFC meeting in China is exciting for us. Although adoption of the technology is largely being driven by European and U.S. organizations, China is catching up" (2).

Other companies have also incorporated these technologies into their standard manufacturing procedures as well as looking at other technologies like flow chemistry. New and upcoming CDMO, Sai Life Sciences Ltd (India), have expressed keen interest and are exploring options to adopt such new technologies as part of their toolbox for innovator services. Sai Life Sciences has already invested in, and is regularly utilizing, large scale High Pressure Chromatography for cGMP production and Supercritical Fluid Chromatography.

Simulated Moving Bed is not new to China either. Asia-Giant Engineering was created in 1990 and focuses on various chromatography processes such as Simulated Moving Bed or Supercritical Fluid Chromatography. In 2011, they build a production line for extraction and purification of products for the pharmaceutical industry. Prior to this, they were using similar technologies to produce biodiesels. Hanbon Science and Technology in combination with Jiangnan University developed systems for the separation of natural products.

Seeing the expansion of the business, Chiral Technologies opened an office and support center in Shanghai in China which complements the existing facility in India. This allows Chiral Technologies a subsidiary of Daicel, to participate in the growing chromatography market in the Pacific Rim and be closer to its expanding customer base in this region. Chiral Technologies has expanded its operation to allow it to offer technical support and small scale separation capabilities in China and India.

Chemito, an engineering company that builds and supplies laboratory and pilot plant equipment based in India, has built and supplied a number of units around the world. In China Wuxi University (2000) and University of Shenjang (2013) have small scale SMB united in operation. In India, units were installed at the National Chemical Laboratories (Pune, 2002); Institute of Chemical Technology (Mumbai (2012) and Indian Institute of Chemical Technology (Hyderabad (2006). The training of students and the development of the expertise in these areas is critical to the incorporation of the technologies in the countries. In addition, many of the students who have been trained in western universities have returned home with the expertise and know how to implement many of these technologies.

Flow Chemistry is also seeing more of an influence on the manufacturing companies in India and China. A number of companies in China have already invested in flow chemistry. In India, Dr. Krishnamurthy is heading up a dedicated team at Piramal. Their objective is to improve the general economics of some chemical reactions and reduce the overall footprint of future expansions.

In China a number of companies have already invested in flow technologies. Porton Laboratories began a laboratory program with the goal of implementing continuous flow technologies. They have already applied this technology to produce a variety of intermediates at a semi-commercial scale and to enable development programs. They recognized that continuous flow technology could provide an improved level of process control desired by Quality by Design approaches and improve the process economics. George Chu, CEO of Eastar Chemical commented that "A number of the companies that we are interfacing with have asked us to assist them in developing continuous manufacturing in China. Our suppliers have recognized that they need to be able to innovate and improve the economics and environmental impact of their processes."

In 1990, the research group at Jiuzhou Pharma developed a new process and transferred it to the scale up group for commercialization. During scale, the identified that the process gave good product but the overall productivity was much lower than desired. A review of the process revealed that in order to produce the desired quantities, a very large investment would be required. However moving away from a batch environment could solve the problem and allow them to reduce both cost and improve productivity. Management accepted a proposal to fund the design work to develop continuous process. The pilot runs allowed for further optimize the process and control the operating parameters. After additional months, the new reactors were commissioned. The net result was a fivefold increase in productivity. This helped to keep the cost of goods reasonable and the product competitive.

Andres de-Vries, Director of Route Scouting Services at DSM stated that India and China are more inclined to buy new

assets and why not immediately flow/continuous assets, while Europe/North America have already too many assets, hence less easy to convince to invest in new assets. His opinion is that in principle the footprint and total cost are much lower than the new batch equivalents and the solvent requirements could 1000 to 10,000 times less in flow. This assumes that the process is properly designed.

BHS Filtration supplies continuous filtration equipment as well as other process equipment. Their continuous pressure and vacuum filtration equipment have been installed for bulk and final pharmaceutical production and the BHS Rotary Pressure Filter and Continuous-Indexing Vacuum Belt Filter have the benefits of reproducible cake thickness for reproducible wash ratios and drying and eliminate the need for in-process sampling. Both units provide for maximum displacement washing and drying of non-bound (free) moisture. CIP, demonstrated by riboflavin testing, full containment and automatic cake discharge are integrated into the technologies. This equipment integrates into continuous operations and can reduce cost not just in labor but can operate in a closed system making it more environmentally favorable and safer to operate for the worker. In 2007, they opened their technical center in India and in 2010, significantly increased their manufacturing footprint in China.

Western suppliers of technology have recognized this need had have position themselves to support these developments and established themselves in the Pacific Rim. In November, 2015, Cemtrix announced they delivered a flow technology train in India. Rufouz Hitek, based in India has been delivering plug flow reactors from any years. Corning has a technical support group based in Pune, India to support the growing market there.

Today, modern technology allows for companies using 3-D printing to develop and produce small scale reactors for the manufacturing of complex chemicals. This could significantly reduce the cost of equipment in the future. Any reduction in cost should have an impact on the ability for companies to invest in new technology and implement these technologies in their plants.

As we have seen, the manufacturing of the equipment for both continuous chemistry as well as Simulated Bed Chromatography, it is important to develop a scientific base for these technologies. This includes the development of technical expertise in these regions. This can be supported from local universities as well as a greater awareness of the technologies available. To this end, we have seen an increase in the number of organized symposiums and technical meetings in both India and China. Over the last few years, there have been a number of international conferences held in China and India focusing on some of the current technologies such as Simulated Moving Bed and Continuous Reactions. This brings a number of experts from around the world and will help these technologies to grow in the region.

The chemistry is not the only processes in drug manufacturing that has been developing. We have seen work done on continuous dosage manufacturing. Recently in China, the Peking University held a conference looking at Continuous Manufacturing. The forum was the first of its kind in China which included not only case studies from some of the largest pharmaceutical companies but representatives from the FDA, EMEA and the CFDA. Dr. Jiinbin Tang, Vice President, APC Pharma China at the GEA commented that "It was very satisfying to see that, not only were all our most important Chinese customers present and participating in the symposium, regulatory agencies such as the EMEA, US FDA and CFDA also took part. It's extremely encouraging for Chinese companies to hear the clear statement from governing bodies that there are no regulatory barriers to continuous manufacturing." This gave a clear message. From the regulatory agencies around the world, there were no barriers to adopting these technologies. Also considering the number of industrial representatives from big pharmaceutical companies it is apparent that these technologies are more common in the west.

Mr Xu Jiaqi, Director of the Center for Drug Evaluation, China Food and Drug Administration (CFDA CDE), gave the keynote speech, "Medical Progress and Advanced Technology," which set the scene for further presentations on end-to-end pharmaceutical production and the continuous perfusion culture of mammal cells to produce biologics. "Continuous pharmaceutical manufacturing is an emerging technology that may very well inspire the pharmaceutical industry to adopt more efficient and cost-effective manufacturing. These discussions did not include just the production of the API's but included the manufacturing of the actual dosage. Companies like GEA, supplier of a wide range of continuous manufacturing vessels which include the dosage preparation were present as well (3).

There are other support requirements for the implementation of new technologies. A major concern could be the development of more sophisticated analytical methods. Several companies have already invested in the Pacific Rim and built modern analytical facilities to support the market place and test materials.

Irvine Pharmaceutical Services commissioned a new analytical service operation in 2014 in Hanzhou China too. This operation was designed to support the large multinational pharmaceutical companies who require robust quality services in the Pacific Rim. In addition, it will supply them with a footprint in China which will help them to better understand the overall region.

In 1991, SGS China was formed as joint venture between SGS and China Standard Technology Development Corp under the State Administration of Quality Technical Supervision. Their analytical services support the supply lines for many different industries as well as pharmaceuticals. For the shifting markets with more advanced technologies, it also supports the approval of the products which are produced.

Like the markets, technology has become more globalized. Innovation is no longer limited to companies in the US and Europe. Markets have already started to adjust to the new realities greater technology competition and the reduction of low cost centers around the world. It will be interesting to see how this plays out in the future and the ability of companies in Europe and the US to maintain their technical edge in the future.

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