
Looking beyond the Global Pharma Horizon

CPhI Annual Industry Report 2015

Industry Expert Panel Submissions

Part 3.

Push-pull factors on growth



PANEL MEMBER

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Mega Trade Pacts and Their Impact On the Pharmaceutical Markets

Introduction

The passage of the Trade Promotion Authority (TPA-2015) Bill by the US Congress gives powers to the President, for the first time after 2007, to fast track the mega trade deals: a trade deal among 12 pacific rim countries and a trade and investment agreement with the European Union. After the Bill was passed, the US Trade Representative (USTR) Michael Froman, in a statement, said that the Bipartisan Trade Priorities and Accountability Act (TPA-2015) represents “the most significant upgrade to our approach to trade in over four decades, including the requirement that labour and environmental protections be fully enforceable; new requirements for taking on unfairly subsidized foreign state owned enterprises; strong and balanced intellectual property protections; and new consultations and transparency requirements.” He further claimed that “TPA will move us one step closer to delivering trade agreements like the Trans-Pacific Partnership (TPP) and the Trans-Atlantic Trade and Investment Partnership (T-TIP) which will open growing markets to “Made in America” exports, protect our workers, and ensure that America, not our competitors, sets the rules of the road on trade.”¹ The pacific rim countries negotiating the trade deal are Australia, Brunei, Canada, Chile, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, U.S.A. and Vietnam. The “companion agreement”

to TPPA is TTIP. President Obama is aiming to conclude the trans pacific deal in 2015 and the trans atlantic deal in 2016.

As both these deals are being negotiated in secrecy, their draft texts are not in the public domain. Whatever is written and discussed about these deals is based mostly on “leaked” texts; the 11 May 2015 version of the intellectual property (IP) chapter of the TPPA, and the proposed draft text of the TTIP leaked in March 2014. The European Commission disclosed some clauses in January 2015 for public consultation.

The academia, civil society, media and political commentators have all raised concerns about the impact of the TPPA on the public health and the TTIP on the inability of the governments to regulate the big corporations. This article seeks to assess effects of these mega deals on the pharmaceutical market by 2020.

TPPA-Key IP Provisions

The US negotiators want:

- Patent Law changes to make it easier to obtain “secondary” patent
- Regulatory Harmonization to fast track drug registration

¹ Third World Network, 20 April 2015

- 12-year Data Exclusivity to prevent generic competition
- Patent Linkage to prevent drug regulators from approving generic versions
- Patent Term Extension to keep the competition at bay
- Weakening of the early working provision (Bolar Exception) to delay entry of generics
- Empowering customs authorities to decide on “confusingly similar” trademarks

The deal would favour big companies like Pfizer, Roche, and Novartis if the 11 nations were to concede these demands. It would slow down and delay entry of generics in their markets. It would also force these countries to bear the burden of U.S. drug prices and create lucrative markets for patented drugs. No wonder that the Pharmaceutical Research and Manufacturers of America (PhRMA) has been lobbying for the TPPA.²

It is a different matter that the US domestic laws do not have some of these provisions.³ It is of even lesser importance that the Obama Administration wants to reduce drug costs for its citizens. It does not matter that it wants to dilute the patent monopoly for the benefit of its public. The contradiction between the demands on the Pacific Rim countries and the US domestic law could lead to one or more of three potential outcomes.

1. It could increase the cost of healthcare for 11 Pacific Rim countries
2. It could deny the U.S. citizens benefits of reduction in data exclusivity period for follow on biologics and higher standards of patentability
3. It could result in 11 Pacific Rim countries paying more for the medicines and providing justification to reverse policies of Obama Administration

The third and the last is the most likely outcome of the TPPA.

TTIP – Five Key Provisions

The US and the EU represent 60% of world GDP. They share 33% of world trade in goods and 42% of world trade in services,⁴ and yet they are home to only 20% of world population. A free trade agreement between the two,

covering 46% of world GDP, will potentially be the largest regional free-trade agreement.⁵

The free-trade agreements generally focus on tariff barriers to improve trade flows. Impact assessment of such agreements is relatively easy. The TTIP, on the other hand, aims to remove non-tariff barriers. Its societal impact on labour, employment, public health, markets, financial stability and governance are very deep and widespread but difficult to assess. Nevertheless, many have tried to assess and caution the negotiators based on whatever little is in the public domain.

The TTIP could also lead to harmonisation of North American Free Trade Agreement (NAFTA) and European Free Trade Agreement (EFTA) with the TTIP. The first will affect Canada and Mexico; and the second will affect Iceland, Norway, Switzerland and Leichtenstein in Europe and Canada and Mexico in North America.

The impact of the TTIP on the pharmaceutical sector has to be seen in the larger context and with reference to five key provisions being negotiated by the U.S. and the EU. They are:⁶

- Changes in intellectual property regulations
- Limits on pricing and reimbursement policies
- Attempts to limit transparency of clinical trials
- Increased corporate involvement in policy making + Dispute resolution mechanisms
- Setting a global standard

As is obvious, the intention is to push the EU to adopt the US standards and in return, the U.S. to raise its own barriers in the domestic market – “America sets the rules of the road on trade.” The most likely outcome of this trade deal is promotion of interests of the brand-name industry by delaying generic competition. The impact will not be limited to the U.S. and 28 Member States of the EU. It will extend not only to Canada, Iceland, Leichtenstein, Mexico, Norway and Switzerland but also to the developing countries and their generic industry. The new “standards” of IP, Drug Registration, Protection and Enforcement will hit the generic industry across the world.

²William New, ip-watch.org on 05/06/2015

³Frederick Abbott, Bloomberg, 10/07/2015

⁴Wikipedia, the free encyclopedia

⁵World Economic Outlook Database October 2013

⁶TTIP – A Civil Society Response to the Big Pharma Wish List. Joint Position by commonsnetwork.eu

Future of the Pharmaceutical Market

The chronology of events indicates that the U.S. will first conclude the TPPA and use it as a benchmark to negotiate the TTIP. The 11 Pacific Rim countries, looking for access to the US market, are more vulnerable and prone to giving in to the USTR pressure than the EU. Among them, only three countries namely, Australia, Canada and New Zealand are known to evaluate trade-offs between the public health and other sectors. Japan has been a moot supporter of the US for pharmaceuticals in various trade forums. It is already practising most of what is being negotiated. This leaves seven countries. They may be lured by the preferential treatment in sectors like textiles, minerals, leather footwear, coffee, rice, rubber, wood and wood products, palm oil, fruits, fish and fish products, paper and pulp, etc. Consequently, the pharmaceutical industry will face disruptions across all major markets.

The brand name industry will be a major beneficiary of the trade pacts. It will be able to improve its price realization in the low-priced markets. It will be able to delay generic competition in all markets, including the US. and the EU. This would however be not without a certain cost. Its consumers (the patients) will be unhappy. Its customers (the doctors) will complain of unwarranted high prices of medicines, as they did for Novartis' Glivec.⁷ Businesses and corporations will be concerned for rapid rises in the healthcare cost of their employees. The law makers (parliamentarians), feeling cheated by the trade negotiators, will target the brand name industry for rise in medicine prices. The civil society and health activists will raise their banners for denying access to affordable medicines. The net outcome would be a poorer image of the brand-name industry.

The generic industry will suffer on several counts slowing down its growth and earnings.

- A major driver of growth for generics is new product introductions. As data exclusivity period and patent protection get longer, the new product introductions will suffer
- As the new product launches become scarce, generic companies will focus on a slice of the pie of older products. The resultant competition will lead to price

- erosion of even mature products, affecting their earnings
- Thus, two major drivers of growth, viz. new introductions and value, could have negative impact
- The remaining two drivers of growth, viz. new markets and volume, could provide opportunity to efficient manufacturers as they would drive volume and enter “new markets”, but it would be at the cost of existing players, as they will eat into their share
- As the patent linkage kicks-in in EU and other trading partners, the generics will face delays in obtaining marketing approvals
- Dilution of the early working provision (Bolar Exception) for marketing approval in other countries would require a generic company to manufacture the medicine locally in every country where it wishes to seek early marketing approval
- Not only patents, data exclusivity, and patent linkage, the TRIPs-Plus provisions related to protection of trademarks could question prominent display of international non-proprietary name (INN) or generic name of a product. It could prevent generics from using colours or shapes identical or similar to those of the original products⁸
- The fear of costly and lengthy infringement proceedings will keep generic companies at bay and limit them challenging even poor quality patents⁹
- The US proposal envisages empowering patent-holders to seek information of the entire supply and distribution chain in case of alleged infringement. The information so obtained could be used effectively to block the supply chain – transporters, warehousing agents and distributors
- The proposed border measures in the deal revive the fear of detention of goods in transit for alleged violations of patents and trademarks. The application of “confusingly similar” trademarks by the customs officials would most likely lead to seizure or detention of many generic consignments as it happened in case of a shipment of amoxicillin from India to Vanutan. The use of INN appeared confusingly similar to GlaxoSmithKline's brand Amoxil¹⁰

Thus, generic industry and the public health will be severely impacted. The generics decline will be discernible from the end 2017, if the TPPA is signed in 2015. It would begin from 11 Pacific Rim countries and accelerate with the

⁷ <http://bloodjournal.hematologylibrary.org/content/early/2013/04/23/blood-2013-03-490003.full.pdf>

⁸ UNTAID – The Trans-Pacific Partnership Agreement: Implications for Access to Medicines and Public Health March 2014

⁹ Ibid.

¹⁰ Ibid.

conclusion of TTIP in 2016. The decline will extend to the US and 28 EU countries, besides members of NAFTA (2) and EFTA (4). The full blown impact of these mega trade deals will be felt by 2020.

Encouraged by its success, the brand-name industry will be ready by 2020 to push the USTR to seek amendments to the TRIPs Agreement. Backed by some 50 signatories to TPPA and TTIP, the USTR will push for maximalist standards of protection and enforcement in the TRIPs Agreement. The moot question is if BRICS or any other new alignment of the developing countries would be able to thwart this grand design.

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PANEL MEMBER

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The Fertile Market of Sterile Injectables

Introduction

As life sciences firms have increasingly shifted their focus to therapeutic segments like Oncology, biologics have become a larger component of the pharmaceutical industry’s development pipeline. Further, novel drug delivery systems that provide targeted therapies are gaining prominence. These two factors, among others, have led to a rapid growth in the Sterile Injectable technologies and formulations’ market.

In this article, we provide an overview of the sterile injectable dose formulation market, the drivers behind its growth, and the various types of dosage forms that constitute the market. Following which, we assess the reasons for demand-supply inequity and the acquisitive strategies that have resulted thereof. We then conclude with a service provider’s view that summarizes how providers have responded to client needs and market trends.

Market overview

The global sterile Injectable market is at circa \$312 billion in 2014 and is projected to reach \$363 billion by 2017. The two largest segments are Biologics (52% share) and Small Molecule injectables (38% share), with a CAGR of 7% for the latter. Within Biologics, monoclonal antibodies (mAbs) account for the largest market share, followed by vaccines and insulin (see Chart 1). In the Small Molecule segment, Oncology and Anti-Infectives are the major contributors of the market (see Chart 2).

(Source: IMS, 2014)

Chart 1. 2014 Sterile Biologics Market US\$ 162 B

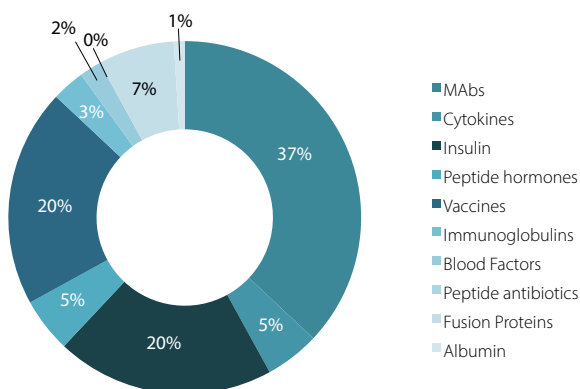
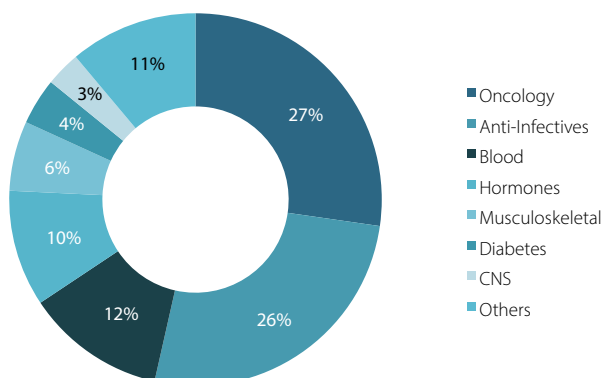


Chart 2. 2014 sterile Small Molecule Market US\$118 B



Market drivers

Approximately 2,400 injectable products are currently in the development pipeline (potent and non-potent), leading to growth on the innovative side of the market. Demand for cutting edge injectable capabilities should grow as ADCs and other high value products dominate the 'potent' development space. Nevertheless, the primary driver behind the growth in injectables is the generic market. Growth in the generic injectables is outpacing growth on the innovator side: The global, generic, sterile injectables market is projected to grow from \$37 billion in 2013 to \$70 billion in 2020 - a growth rate of 10%.

Market segmentation by technology

The Sterile Injectables formulation technologies market can be segmented into conventional and novel formulations. The 'Conventional Dosage' forms can be further categorized into Solutions, and Lyophilized / Water for reconstitution. Novel Drug Delivery Formulations have gained prominence in the last few years for enhanced disease targeting and to increase patient compliance. Some of them are:

- **Depot Injections – Microsphere & oil based:** A depot injection is an injection, usually subcutaneous or intramuscular, of a pharmacological agent which releases its active compound in a consistent way over a long period of time
- **Liposomes:** Liposomes are being used as carriers of various pharmacologically active agents like anti-neoplastics, antimicrobials, steroids etc. Liposome formulations are used to reduce toxicity and increase accumulation of the drug at the target site

- **Nanoformulation:** Nanoformulation enables the sheathing of drug particles with polymeric surfactants, which can then be layered onto a substrate for future delivery. This has helped in effective formulation of many insoluble molecules
- **PEGylated formulations:** PEGylation is the covalent attachment of Polyethylene glycol (PEG) to molecules of interest. It is the most commonly used non-ionic polymer in the field of polymer-based drug delivery. It increases solubility of the drug in aqueous medium, increases the half-life of the drug, reduces toxic side effects, stabilizes and improves therapeutic activity of the drug
- **Implants:** Implants are sterile solid preparations containing one or more active ingredients. They are of a size and shape suitable for parenteral implantation and provide release of the active ingredient(s) over an extended period of time

Key players in the innovator and generic space

Some of the large injectable players in the innovator (pharmaceutical and biotech firms) space are given in Table 1. Teva, Hospira, Hikma, and Fresenius Kabi, are some of the major generic players in this space.

Table 1: Key pharmaceutical and biotech firms with injectable products

Amgen	Genentech	Novo Nordisk
J & J	Sanofi	Abbvie
Eli Lilly	Pfizer	Roche Biogen

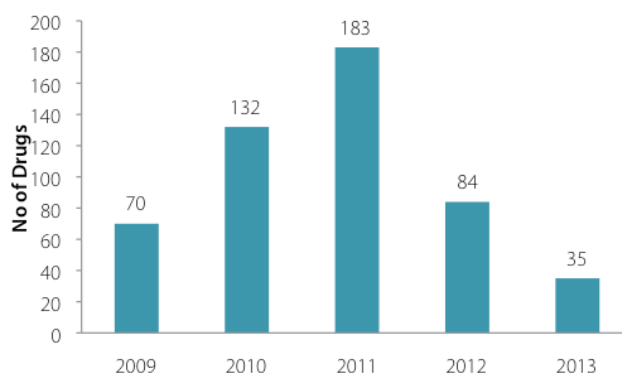
Market demand-supply equation

The development and manufacturing of sterile injectable products is both, complex, and capital intensive. Operational costs are high since injectables are toxic and infectious in their natural state and hence require a higher degree of quality and care in their manufacturing, packaging, storage, and distribution. Stringent regulations from FDA on manufacturing sites, pose a major challenge for both existing players, and for potential new market entrants. Competition from low cost manufacturing zones like India and China in the generic market has led to discontinuation of many products in the segment for economies of scale. Consolidation of captive/in-house manufacturing capacities have resulted in closure of many sterile manufacturing sites in the US and elsewhere which, in turn has led to product shortages in the US. Some of the other reasons for these shortages are:

- Mergers & Acquisition activities have resulted with single supply sources and capacity constraints
- FDA regulatory violations leading to Import alerts/bans at manufacturing sites
- Discontinuation of older injectable drugs in favour of newer, more profitable drugs
- Consolidation of supply chain by large pharma companies leading to shut down of their existing manufacturing sites
- Relatively less number of in the sterile injectable market that cater to the increasing demand of sterile dosage forms. The complex manufacturing process makes it even more difficult to transfer technologies freely between the sites. Some of the process related challenges are:

- Sterility: Bacterial and Fungal contamination
- Stability Issues (Crystallization)
- Extractables and Leachables from packaging materials: glass, metal or fibers in vials
- Transportation & Logistics

Chart 3: Sterile Injectables in short supply (Source: US FDA)



FDA has begun responding to shortages by expediting generic approvals for drugs that have shortages, shortening approval times for new production lines/new raw material sources to help increase supplies, and also allowing imports into the US for drugs under shortage from approved suppliers. This seems to be alleviating the problem, with the number of shortages reducing to 35 in 2013, from a high of 183 in 2011.

M & A Activity

The last few years have seen significant M & A activity in the sterile Injectable space. In a bid to quickly participate in a rapidly growing market, firms are acquiring specialist sterile injectable players to enhance their product portfolio and manufacturing capabilities. Some of the recent key deals are listed below:

- **Pfizer- Hospira (\$17 billion):** This provides a growing revenue stream and a platform for growth for Pfizer’s Global Established Pharmaceutical (GEP) business by combining Hospira’s generic sterile injectables products, including acute care and oncology injectables
- **Pfizer – InnoPharma (\$360 million):** At the time of the announced acquisition, InnoPharma’s portfolio included 10 USFDA approved generic products, a pipeline of 19 products filed with the FDA, and more than 30 injectable and ophthalmic products under development
- **Hikma - Bedford laboratories (\$300 million):** Hikma acquired Bedford’s product portfolio, intellectual property rights, contracts for products marketed under license,

raw material inventories, R&D and business development pipeline. This strengthened Hikma’s position in the US generic injectable market

- **Sun Pharmaceutical - Pharmalucence Inc.:** Pharmalucence was a privately held company based in Billerica, Massachusetts, which has sterile injectable capacity supported by R&D capabilities
- **Mylan – Strides Arcolab:** In December 2013, Mylan Inc. completed the acquisition of the Agila injectables businesses from Strides Arcolab Limited for up to \$1.75 billion. Through this acquisition, Mylan expanded its injectable product portfolio, pipeline, and capabilities, and as of December 2013, had more than 1,200 approved injectable products globally and more than 900 injectable products pending global approvals
- **Piramal - Coldstream Laboratories:** In early 2015, Piramal acquired Coldstream Laboratories, a Kentucky based injectable manufacturer to augment its formulation offering, while augmenting its ADC fill finish capabilities

Sterile CMO Market

Presently, the injectable CMO market is at US\$6bn and growing at a CAGR of 11% compared to the overall global CMO market which is growing at a CAGR of 7%. Outsourcing in the Sterile Injectable segment is still skewed towards US, followed by the EU. We anticipate this market to continue growing at 10% annually for the next 5 years and US to remain the most preferred outsourcing destination.

Some factors driving the growth are,

- Specialised technologies and dedicated capacities required for biopharmaceuticals products leads to high outsourcing of these products

- Preference to outsource products that require handling of high potency materials and containment suites
- Rapid growth of Pre-Filled syringes’ market leading to spike in the demand of CMOs
- De-risking of supply chain by brand manufacturers by adding a second source to their product manufacturing
- High growth in emerging markets resulting in local players looking at local CMOs to enter the geography

The major CMOs in the sterile injectable space include: Catalant, Baxter, Pfizer Centertsource, Akorn, Althea, Vetter, Piramal Pharma Solutions (ColdStream Laboratories), and IDT Biologica.

The Future

With over 900 approvals in the injectable space since 2000, the market is growing rapidly as firms invest more into development of new molecules and generics and ramping up their production capacities through acquisitions.

- Drug Delivery Systems like Liposomes, PEGylation, Depot Injections will see a spurt in the growth – especially in therapeutic segments that require efficient targeting of drugs
- Compliance issues and the high cost of injectable drugs will

- propel the Pre-Filled syringe market to attractive growth
- Biologic molecules will contribute to more than 50% of the research spend by top 15 companies globally, serving as a macro catalyst for injectables long term prospects
- Generic segment will continue its growth, and we expect that top generic players will consolidate their position with adding manufacturing infrastructure
- Emerging markets will drive the generic market expansion, with China and India leading the pack

Summary

The increase focus in biologics and targeted therapies, especially in the area of cancer has led to an increase in the need for injectable drugs. While biological drugs have a larger part of the injectable market, the small molecule injectables will have the higher growth. The complex process of manufacture, high capital and operational costs, and the compliance requirements for success has

led to a smaller number of players. These firms are being further reduced due to acquisitive activity in a sector that is rapidly consolidating. The supply crunch that was present a few years ago has been mitigated to some extent by FDA actions. In the future, we see a continued demand for injectable drugs especially in drug delivery systems and Pre-Filled Syringes.

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Innovation – can Pharmaceutical Manufacturing learn from the lessons in Auto Manufacturing in the US?

Introduction

In a 2008 article¹ titled, “Arguing by Analogy: What Pharma Can Learn from the Car Business,” the author of that article identified several key lessons that the pharmaceutical industry can learn from the automobile industry. At that time, the US auto industry was making a lot of headlines due to their business insolvency and related issues. Who could have imagined that companies like GM and Chrysler would be in such dire financial situation? The key lesson of the above mentioned article was that the pharmaceutical industry could possibly learn from what has happened to the US auto industry in the recent years.

Some characteristics of the auto manufacturing industry in the US that led up to the crisis in 2008, appear very similar to those that exist today in the pharmaceutical manufacturing business in the US and Western Europe:

1. Inefficiencies in manufacturing and the inability to streamline manufacturing.
2. Older plants and lack of investment in plant and technology.
3. Lack of innovation – age-old batch processes are still being used to make pharmaceuticals. The focus of pharmaceutical companies is in marketing and sales. Manufacturing assumes a secondary role.²
4. To stay competitive, the focus was on outsourcing to markets with cheaper labor rather than investing in modernization, new technology and improving efficiency and quality.
5. Lack of customer focus – pharma has two customers viz. the FDA and the patient. The patient is often forgotten. The patient relies on the FDA to ensure that the medical product is safe and effective. However, FDA does not even inspect many of the plants where our pharmaceutical products and the ingredients to make them are manufactured.
6. Lack of focus on quality and measurement of quality.
7. A reactive approach to problem solving rather than being proactive to solve their own problems. The auto industry blamed the unions for their decline and all their woes. Pharma today thinks FDA and the regulations are the major source of all their manufacturing problems. As if, if the FDA did not exist all, the plants would immediately upgrade their plants and processes and manufacture product that would be of very high quality.

¹Roger Longman, “Arguing by Analogy: What Pharma Can Learn from the Car Business”, The RPM Report, November 20, 2008

²Robin Pagnamenta, AstraZeneca to outsource manufacturing”, Times Online, September 17, 2007.

In the late fifties and early sixties, the automobile industry in the US was highly profitable and Japan had then just started entering the automobile manufacturing business. The automobile industry in the US was focused on engine power, vehicle speed, artful design, luxury and size of cars, but not so much on reliability and defects. Quality was of lesser importance. US automobiles were then generally competitive with European products and superior to Japanese products.³ In fact, people like Edward Deming found a voice in Japan rather than at home, here in the US. Deming championed statistical process control and started working with Japanese companies as early as 1947-1950 to better design products and improve product quality.

Rather than trying to improve quality by improving manufacturing through innovation and investment in new technology, the US auto manufacturers responded to the competition by shifting manufacturing to low labor-cost countries like Mexico. The main difference between the Japanese automakers and the US automakers, was that the Japanese implemented state-of-the-art quality management programs, measured quality and invested in innovative technologies to continuously improve the quality of their automobiles. Meanwhile, the US automakers pursued cost savings by looking for cheaper sources of labor.

Rather than trying to improve quality through innovation and investment in new technology, the US auto manufacturers responded to the competition by shifting manufacturing to low labor-cost countries like Mexico

As the result of nearly one hundred years of experience with many ups and downs, the US pharmaceutical manufacturers today undoubtedly have attained a higher regulatory and compliance standards compared to those in Asia. In addition, the FDA inspects US plants quite frequently, on an average once every two and a half years.⁴ However, the current trend is that pharmaceutical manufacturing is gradually being outsourced to countries with lower labor

cost without due consideration of regulatory standards in those countries, which have far less cGMP and regulatory history and experience. Facing cost pressure, rather than investing in quality, technology and innovation to reduce cost, the industry is relying on outsourcing where quality is far less guaranteed, as opposed to if the same products were manufactured in the US. Those of us, who have been involved with cGMP and regulatory compliance for a number of years in pharmaceutical manufacturing, know that the high quality standards and quality cultures cannot be achieved overnight by reading some books, manuals or FDA Guidance Documents. It is a culture that requires a number of years of training, experience and practice. Usually, a site or a manufacturer evolves into a high quality one over time, sometimes even through making some unfortunate mistakes. Pharmaceutical manufacturers in countries with cheaper labor are primarily in business by providing lower cost and are facing competition even internally in their own countries. Any experienced pharmaceutical manufacturing expert will agree that it is difficult to maintain low cost while investing in compliance. There is a cost to compliance. Quality is not cheap. I visited an Indian pharmaceutical plant in 2008, which exports several products to the US market, and while the manufacturing facility was very impressive, the lack of knowledge and the true spirit of cGMP, even among senior quality and regulatory staff was apparent.

It is well known that cost of labor is only around 20% of the entire COGS for pharmaceutical products.⁵ Thus, it is difficult to understand how the cost of labor alone can justify the significantly lower cost of manufacture of pharmaceuticals in countries where outsourcing currently is predominant. One might then ask the question as to why there is such a rush to outsource? Is the cost saving really due to cheaper labor, or is it due to being able to manufacture in a less regulated or unregulated environment?

Many of the countries which have lower labor costs are in the process of evolving into regulatory cultures, however, it will probably take them several years before they can attain comparable regulatory standards that have already been achieved by many US pharmaceutical manufacturers. FDA's inspection of foreign facilities has always been an issue. On April 24, 2008, during Senate hearings on the heparin fiasco, Dr. Janet Woodcock, the FDA stated that the FDA's

³Joseph M. Juran, "Made in USA: A Renaissance in Quality", Harvard Business Review, July-August, 1993.

⁴GAO-10-961

⁵Prabir K Basu, et al, "Analysis of Manufacturing Costs in Pharmaceutical Companies", Journal of Pharmaceutical Innovation 3(1):30-40 - February 2008

capacity to inspect generic drug manufacturing facilities “has not been commensurate with this global expansion”⁶ According to Dr Woodcock, “We cannot be the quality-control unit of the world.” Dr Woodcock also mentioned that with increasingly large numbers of pharmaceutical ingredients manufactured abroad, it makes it nearly impossible for the agency to ensure the safety of the drugs sold in this country.

The FDA inspect foreign plants at a much lesser frequency than domestic plants. A US Government Accountability Office Report issued in September, 2010 stated:

“Using a list the FDA developed to prioritize foreign establishments for inspection, the GAO estimated that the FDA inspected 11 percent of foreign establishments on this list in fiscal year 2009. At this rate, the GAO estimated it would take the FDA about 9 years to inspect all establishments on this list once. In contrast, in that same year, the FDA conducted 1,015 domestic inspections, inspecting approximately 40 percent of domestic establishments. The GAO estimated that at this rate the FDA inspects domestic establishments approximately once every 2.5 years. Further, FDA’s approach in selecting establishments for inspection is inconsistent with GAO’s 2008 recommendation that the FDA inspect, at a comparable frequency, those establishments that are identified as having the greatest public health risk potential if they experience a manufacturing defect, regardless of whether they are a foreign or domestic establishment. Instead, its foreign inspections continue to be driven by the establishments listed on an application for a new drug, instead of those already producing drugs for the US market.”

Thus, unless a serious quality issue arises, the probability that a foreign plant will get inspected while it is manufacturing product for the US market is very low (perhaps once every 11 years!). The FDA has considerably increased its resources for inspecting foreign pharmaceutical plants. However, it still has a considerable way to go.

When a product is outsourced, it is likely to be due to it being inefficient to manufacture in-house because the process is old and it has a poor performance record. Therefore, plants in countries like India and China are inheriting the poor technology from the West while they are evolving in their regulatory cultures. This is not improving

quality of the pharmaceutical products, but is in fact creating quality risks instead.

The status of science and technology of pharmaceutical product development and manufacturing is antiquated compared to other industries. Lack of research, innovation and publicly available knowledge base or “Technology Commons” in manufacturing science is startling for an industry so critical for the wellbeing of people. Will the increased reliance on outsourcing have the same consequences for the pharmaceutical industry as that of the US auto industry? If a major incident several times bigger and more severe than the heparin incident happens, will there be knee-jerk reaction from the FDA or the US Congress about outsourcing and quality of outsourced drugs? Will that lead to severe drug shortages in the US?

When a product is outsourced, it is likely due to it being inefficient to manufacture the product in-house

If the main driver for the pharmaceutical industry to outsource is to take advantage of cheap labor, then within a few years, is it likely that even India and China may face competition from other countries around the world with even cheaper sources of labor. How many foreign offices will the FDA have and how many inspectors will the FDA need in 2050 to assure the quality of our drugs? What the US corporations save in cost of pharmaceuticals by outsourcing is ultimately outweighed by the increased headcount and increase of the FDA budget. We have to remember that it is the US taxpayer who funds the FDA. The patient is not only saving money, but is also now at the risk of receiving a lower quality product.

Promoting “Quality by Design” (QbD) in developing and manufacturing medical products, using Process Analytical Technology (PAT) etc. and pushing for Quality Metrics in manufacturing are therefore the right approaches to the problem at hand. Approaches like QbD and PAT are proactive and they attempt to fix problems before they occur rather than the current reactive approach of assuring quality through inspection of the products after they

⁶Jesse C. Vivian, “FDA Inspection of Foreign Drug Companies”, e-Connect, December 15, 2008.
⁷GAO-10-961

have already been manufactured. According to Deming,⁸ “Inspection does not improve quality, nor guarantee quality. Inspection is too late. The quality, good or bad, is already in the product.” Quality by Design is practised by other industries such as the Japanese auto industry since the early 1960’s or perhaps even earlier. If products are designed and manufactured using the 21st century principles of science and engineering, then quality can be designed into the products and thus quality can be assured no matter where the product is manufactured. Therefore, implementing QbD will reduce the need for inspection by the FDA of manufacturing facilities, while ensuring a greater degree of quality of the medical products for our patients.

The main impediment to implementing QbD in pharmaceutical product development and manufacturing today is that the 21st century science, required to design

and manufacture our medical products by QbD, are not available. Therefore, the US government and the pharmaceutical industry should learn a lesson from the current situation of our auto industry and encourage investment in fundamental science and engineering to design and manufacture pharmaceutical products so that robust and cost-effective manufacturing processes can be developed. Greater savings can be easily achieved with innovative science and technology. It is important for the pharmaceutical industry to learn from other industries such as the automobile industry and invest in research and innovation to ensure that our medical products continue to be safe and of high quality. Like other industries such as the chemical and petrochemical industries, pharmaceutical research results should not be proprietary, but should be shared in public to create a viable knowledge base for the common good.

Addendum: Follow up Q&A on future trends

1. *Do you think quality cultures should come from the industry or the regulators?*

Quality culture is ultimately the responsibility of the industry. However, the FDA’s enforcement is weak. I often wonder (theoretically of course), what would happen if the FDA did not regulate manufacturing at all. In that case, I think the consumers will become more alert and will ask questions as to where and how the drugs are being manufactured. If I had a choice between buying a prescription drug from Pfizer or an unknown generic in a foreign country, I would not hesitate to pay a higher price to buy it from Pfizer for example. Today, consumers perhaps falsely think that since FDA regulates manufacturing, all manufacturing is equivalent.

2. *Do you know any manufacturers trying to implement any initiatives from the car industry?*

I know that some of the manufacturers have been inspired by the car industry experience. But, I cannot give you specific examples of direct one-to-one relationship between the OPEX or quality initiatives between the two.

a. *Can you predict if this will happen?*

It is already happening. Deming’s work with the car industry in Japan is being followed in most six sigma

and lean initiatives. Quality management principles are the same.

3. *Chinese and Indian industries are becoming gradually more expensive, do you believe that within the next 5 years cheaper industries will open up, or do you believe manufacturing will continue in China/India and that their regulations will improve?*

Chinese and Indian industries are going to become increasingly expensive as they try to comply with the regulations more and more, in addition to their labor costs increasing. Manufacturing will continue in India and China for several more years. However, I will not be surprised to see that other countries, with cheaper labor costs, becoming outsourcing partners for the western manufacturers. Isn’t it the most logical thing to happen? Why not? Also, if continuous manufacturing technology becomes well established, it will lead to manufacturing returning to the west.

a. *Can you make any predictions about outsourcing?*

It will continue to grow. There is no incentive or disincentive currently for the industry otherwise.

4. Just as a general thought, you mentioned that FDA costs are becoming increasingly high, do you believe the industry should support its costs e.g. through a levy? (Would this help.)

I think if a company decides to source an ingredient, intermediate or a final product from a company outside the country, then they should submit a proposal for that to the FDA. FDA should train and support private certified inspectors, who would be assigned to inspect and certify to the FDA that these outsourcing partners are qualified to do so. FDA can review and spot check on these inspections. These facilities abroad should be inspected at least once a year. The entire cost of this should be borne by the industry. There are a large number of qualified and well-trained people with experience available today. The FDA just needs to develop a program for training and certification. Pressure vessels, such as boilers, are inspected and certified by reputed inspection agencies, such as Lloyds of London. Why can't we develop a similar system? Why do taxpayers have to pay for the cost of inspection?

5. Overall, the context of the article puts a compelling (and worrying) case for the future if nothing changes, what do you predict the consequences for this will be?

a. Will the industry gradually improve its standards abroad?

Some of them definitely will do.

b. Will the FDA become further over stretched and fail?

FDA will undoubtedly become further stretched, but I cannot say that they will fail. However, if a catastrophic incident occurs, then I am not sure what the reaction of the public and the congress will be, a knee-jerk reaction may lead to severe drug shortages.

c. Will even lower cost markets emerge?

I firmly believe that they will.

d. Will the industry take the lead on pushing quality cultures?

Big pharma, which has a lot at stake, has already been pushing for quality cultures for a long time. They are also leading most of the OPEX efforts. However,

most of our drugs are generics and they are being outsourced. I am not sure about that part of our manufacturing.

e. Will manufacturing begin to return to the US and Europe?

Only if continuous manufacturing takes hold. Then we can have manufacturing on-demand on-site.

f. Do you think the patient may instigate change at all?

Only if a catastrophic incident occurs. Today, a patient thinks since he/she is buying the drug from a pharmacy, and the FDA is there to protect them; the drug must therefore be safe. Very few know how the drug is actually made, what the GMP's are, where the drug is made and whether the plant was even ever inspected. Even when we buy a piece of clothing, the label says where it was made, but not for a drug. Isn't that strange?

6. Any general thoughts on how this will develop over the next few years (5-10)?

Nothing much will change unless there is a serious or catastrophic incident. (Which I sincerely hope does not occur). The recent quality metrics guidance will not ultimately make a particularly large impact, as the metrics does not have any teeth, it does not reflect the quality culture. Manufacturing the metrics to look good is easy.

7. If you are not sure how the industry will change, how do you think the industry should be improved? (there may be no easy fix).

Outsourcing has to be regulated. I am not against outsourcing, however, outsourcing should only be approved if the company responsible for it can demonstrate that the outsourced product will have a superior quality, or at least an equivalent quality.

8. Any further information on how we might set up a technology commons ground (are we any closer to this than last year)?

The industry has to take the lead here. It can learn from SEMATECH, the semiconductor industry. Currently, the industry is too protective about its technology. They should come together and develop technologies

that can be widely used by everyone. Industry and government should support research in academia, to conduct research and develop new technologies or fill the gaps in technology. There should be texts, rules and procedures as to how to design equipment and processes. Pharma needs to learn from the chemical and petrochemical industries, which have invested in research into how to design and operate equipment, how to estimate physical properties of raw materials and mixtures, etc.

9. We are just really looking for your thoughts and predictions on how you think this situation will now evolve over the next few years.

I may be totally wrong. So, you must take my opinions with a grain of salt. But, I do not see things changing much unless there are some major problems with drug quality or drug supply.



PANEL MEMBER

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The real need for generic medicines

Introduction

In an ideal world, there would be total freedom of access to healthcare with safe, effective, and affordable medicines available to all. Unfortunately, this is not – and cannot be – the reality. An aging and increasing population places ever greater demands on healthcare systems that have already been strained for several years. Add to this the economic stresses of recent times, and the rising burden of cost to health systems appears unsustainable.

Meeting the challenge requires a holistic approach, although one key area of focus remains controlling pharmaceutical costs. European countries have employed a multitude of tactics, including mandatory price cuts, changes in reimbursement levels, delisting of products, prescribing formularies, tendering for medicines supply, and increases in patient co-payments. These have worked to some degree, actually decreasing the growth in pharmaceutical expenditures in some countries.

In the EU, generic medicines have played a significant part in this aspect of cost control to date. However, given that over the next 10 years, the number of original brands losing their market exclusivity – and the savings opportunities to be had from generics – will be dramatically reduced,

the role that generic medicines have historically played in sustaining health systems in the EU will be diminished.

Providing affordable healthcare that meets acceptable standards is a major challenge in most European countries. Resources are pulled in many directions, and European economies struggle to raise sufficient funds from taxation to cover their budgets.

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Public expenditure on health in the EU reached an average of 8.7% of GDP in 2012,¹ having increased from 5.7% in 1980. On average, Western European countries spend 8 to 12 percent of their gross domestic product on healthcare – a proportion that has remained stable despite the global economic crisis, according to the Organization for Economic Cooperation and Development—despite the increasing demand. The specific proportion of GDP spent

on healthcare varies widely between Member States: it is above 11% in Austria, Denmark, France, Germany, and the Netherlands; below 6% in Estonia, Latvia, and Romania.²

Spending on pharmaceuticals, on average, accounted for almost a fifth of all healthcare expenditure across EU member states in 2012, making it the third largest spending component after inpatient and outpatient care. The economic crisis has had a significant effect on the growth in pharmaceutical spending in many European countries. Between 2000 and 2009, annual pharmaceutical expenditure per capita grew on average by 3.7% in real terms in EU member states, but fell in the following three consecutive years. On average, pharmaceutical spending fell by over 2% per year in real terms between 2009 and 2012 across EU member states.³

Pharmaceutical spending is closely related to GDP per capita and, over time, tends to follow GDP growth which in the current economic climate will fail to deliver sufficient funds to support the growth in healthcare costs.

Lowering pharmaceutical costs is seen as an important element of achieving sustainable healthcare, and even before the recession, many European countries attempted to control pharmaceutical expenditures via a mix of price and volume controls directed at physicians and pharmacies. They also relied on policies targeting specific products. In Germany, pharmaceutical companies must now enter into rebate negotiations with health insurance funds for new innovative medicines, putting an end to the previous free-pricing regime. In 2010, Spain mandated a price reduction for generics and introduced a general rebate applicable for all medicines prescribed by NHS physicians. In France, price reductions or rebates on pharmaceuticals have often been used as adjustment variables to contain growth in health spending, while in the United Kingdom, caps were introduced on pharmaceutical companies' profits on sales to the National Health Service (NHS).⁴

Some countries have started to shift healthcare costs to patients, via co-payments, new reimbursement policies and deregulation of certain therapies in order to reduce the burden on the provider. However, savings produced by all of these efforts can quickly be eradicated by changing

demographics and the availability of new, more expensive medicines.

Population aging is one of the greatest social and economic challenges for the European Union and is the result of a low fertility rate, the gradual progress of baby boomers toward retirement age, and increased life expectancy at birth. It is estimated that the increase in the proportion of people aged 65 and over will rise from 17.4 % in 2010 to 25.6 % in 2030 and to 29.5 % in 2060.^{5,6} Because an aging population has different healthcare requirements – such as a higher demand for mental health care, homecare and assistance and social capital and self-management services – health systems will need to adapt so they can provide adequate care and remain financially sustainable. Another consequence of the changing demographics is that the workforce will increasingly consist of older workers. This will in turn put pressure on healthcare systems as they attempt to cope with the need to maintain a healthy workforce.

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EU countries have seen an improvement in lifestyle trends such as a reduction in tobacco consumption and occupational injuries. Nevertheless, much of the burden of disease in EU countries is still linked to lifestyle factors, such as alcohol consumption, unhealthy diet, lack of physical activity, and obesity. Although there is considerable variation between countries, the EU currently has the highest level of alcohol consumption in the world (an average of 10.1 litres per person per year), while 53% of adults are either overweight or obese, and 16.7% are considered obese.

An aging society and poor lifestyle are linked to chronic diseases and conditions that have traditionally included cardiovascular disease, diabetes, and asthma/COPD. As survival rates and durations have improved, this type of disease now also includes many varieties of cancer, HIV/

AIDS, mental disorders (such as depression, schizophrenia and dementia), and disabilities such as sight impairment and arthroses. Chronic diseases are now responsible for most of the disease and deaths in Europe. Expenditures on chronic care is rising across Europe, consuming increasingly greater proportions of public and private budgets.⁷ Many of the diseases of ageing however, can be managed by the prescribing of a generic medicine.

New diagnostic and treatment options are improving survival rates for patients in many chronic diseases such as cancer, HIV/AIDS, and they are, in turn, driving demand for new medicines. For example, the new wave of treatments for hepatitis C offering the promise of halting disease progression, preventing the occurrence of end-stage renal disease and liver cancer. Such innovations, however, often come at a high price.

So where do generic medicines fit in? The value of generic medicines does not just lie in the role that they play in reducing the cost of therapies for post patent expiry usage of key medicines. They increase patient access to well established and proven therapies in many disease areas, however they represent only a very small part of the healthcare budget. In Europe, over half of prescription medicines are generic, but these only represent 25% of the

total medicine expenditure. As a tool, generic medicines provide a cost-effective solution to managing the budget spent on medicines, without compromising prescription freedom or therapeutic choice. Generic medicines stimulate innovation, both within the generic sector and the discovery and development of new medicines. With drug budgets under scrutiny, generic medicines can help control costs whilst still allowing headroom for additional expenditure required for new medicines, addressing unmet clinical needs. Generic medicines represent many of the therapies required for the treatment of diseases in an ageing population and as such provide a safe, effective and affordable solution. Growth in the generics sector should be seen as a positive step and as essential component of cost containment. Any existing negative incentives should be removed without delay if the full benefit of generic medicines is to be realized. Positive measures aimed at increasing usage of generics can provide a far more sustainable solution to cost containment rather than the arbitrary lowering of prices of generic medicines which may only result in marginal savings and could act as a disincentive for increased usage. Sustainable policies for pricing and reimbursement are essential if generic medicines are to be an effective resource in controlling long term costs. Without generic medicines, the cost of healthcare would surely be unaffordable.

References

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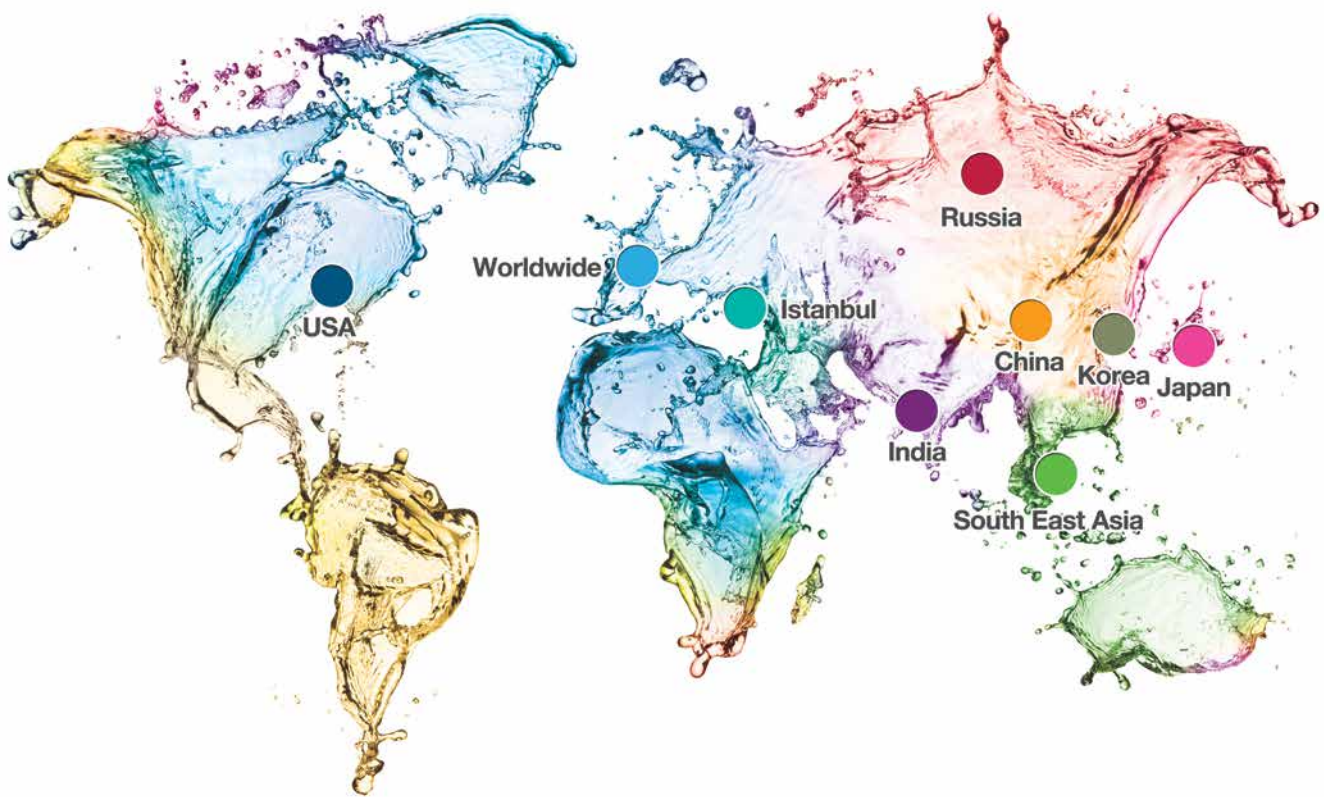
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