Available online on 15 Sept, 2020 at https://ijdra.com/index.php/journal
International Journal of Drug Regulatory Affairs
Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article

Active Pharmaceutical Ingredients (API) Supply chain in Europe, United States, India, China and Canada

Mallikarjun Nagur*[,a], T.M. Pramod Kumar [a], Sangamesh Basayya Puranik[b]

[a]*Regulatory Affairs Group, Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagara, Mysore, Karnataka, India 570 015*
[b]*Head - Regulatory Affairs, Anthem Biosciences, Bangalore, Karnataka, India 560099*

Abstract

The main objectives of the review of the study Active pharmaceutical ingredients supply chain in India, Europe, United States, China and Canada. Active pharmaceutical ingredient supply chain management is the integration, planning, and management of all of the processes across the system of resources from the earliest raw material supplier through the sourcing, logistics, manufacturing, and distribution networks to the customer. The base of supply chain management is the efficient integration and planning of demand and supply across companies. Planning is not only at the tactical level, but also at the strategic level. Majority of the countries follow the Guidance for Industry Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. Roughly 80% of active pharmaceutical ingredients and 40% of finished drug product are imported into the U.S. from overseas from India and China. The pharmaceutical active ingredients supply chain used to be seen as a tool to supply products to market in an effective way, where the emphasis was on security of supply. Recent changes in the operating environment mean that companies are revisiting the components of their supply chains and identifying ways of extracting additional benefits from them.

Keywords: Active pharmaceutical ingredients, Supply chain, Logistics, Cold-chain, GMP, FDASIA, GDUFA, OECD

Article Info: Received 20 July. 2019; Review Completed 17 Jun. 2020; Accepted 15 Jul. 2020

Cite this article as:
Nagur M, Kumar TMP, Puranik SB. Active Pharmaceutical Ingredients (API) Supply chain in Europe, United States, India, China and Canada. International Journal of Drug Regulatory Affairs [Internet]. 15 Sept 2020 [cited 15 Sept 2020]; 8(3):1-10. Available from:
http://ijdra.com/index.php/journal/article/view/323

DOI: 10.22270/ijdra.v8i3.323
*Corresponding author Tel.: +91-9449262039;
E-mail address: mnagur613@gmail.com (Mallikarjun Nagur).

1. Introduction

Active Pharmaceutical Ingredients (API's), used as ingredients in sterile medicinal products, must be sterile unless the final dosage form is terminally sterilised, or produced by a process including a sterilising filtration step. API's intended for use in parenteral products must also comply with relevant specifications on pyrogens or bacterial endotoxins. (1)

Introduction on the global pharmaceutical API supply chain

Supply chain management is the integration, planning, and management of all of the processes across the system of resources from the earliest raw material supplier through the sourcing, logistics, manufacturing, and distribution networks to the customer. The base of supply chain management is the efficient integration and planning of demand and supply across companies. Planning is not only at the tactical level, but also at the strategic level.

API Importance

APIs are also known as bulk drugs or drug actives, and are responsible for rendering therapeutic action in a Medicine (Formulation). The philosophy of any new product development for APIs is innovation-led affordability and Quality by Design giving customers access to cost effective. (2)

Top challenges facing drug supply chains

Visibility: A lack of visibility into the supply chain may be the root of many challenges faced by the pharmaceutical industry. Today, the global pharmaceutical industry is knee-deep in a journey to solve the visibility problem by attaching product identifiers to every product and creating a system for all to access.

Logistics coordination: Differences in process permeate the industry, making any change in standards or control difficult to implement.

Compliance: Roughly 80% of active pharmaceutical ingredients and 40% of finished drug product are imported into the U.S. from overseas. Manufacturers in India and China, in particular, are a key source of the generic drugs prescribed to Americans in ever-increasing volumes.

In the U.S., the Food and Drug Administration is tasked with ensuring facilities based in foreign countries remain in compliance with Good Manufacturing Practices, a standard for aseptic production of pharmaceuticals.

It's not just manufacturing, though. Shippers and distributors will soon have to comply with regulations under the Drug Supply Chain Security Act, which requires any company wishing to sell pharmaceuticals in the U.S. to facilitate product "traceability" by 2023.

Enforcement of the first stage of the law has been delayed by one year, but meeting the new standards for traceability and serialization will require significant changes and investment through the supply chain.

Cold-chain shipping: While all API are sensitive to the rigors of cross-border shipping, biologics in particular are heat sensitive and susceptible to contamination. Keeping these drugs cold, then, is a crucial part of the supply chains that connect drug makers to patients. (3)

The main objectives of the review of the study Active pharmaceutical ingredients supply chain in India, Europe, United States, China and Canada.

2. India and China

Pharma industry in India is playing a vital role in the healthcare area of the nation. With the implementation of product patent from the year 2005, there will be a tough competition for the global market share. Pharma companies will have to focus more intensively on R&D activity to survive the competition. As we are moving towards globalization, there is a need for strategic planning to meet the challenges posed by the product patent era. In the present context with the available expertise, manpower and skill, the Indian Pharma Industry will fight successfully for the global market share. (4)

The Indian pharmaceutical industry accounts for at least 35% of bulk drug filings in the US. Post-TRIPS, the Indian pharmaceutical landscape is set to change permanently. Local pharmaceutical majors are moving up the international value chain, focusing on generics marketing in Europe and the US to complement their already-strong presence in bulk active pharmaceutical ingredient (API) supply and to capitalize on the record number of drugs set to go off-patent over the next five years. (5)

India has the highest number of manufacturing facilities (332 sites) approved by the US FDA. Indian pharmaceutical companies have manufacturing opportunities in two segments - formulations and bulk drugs. (6)

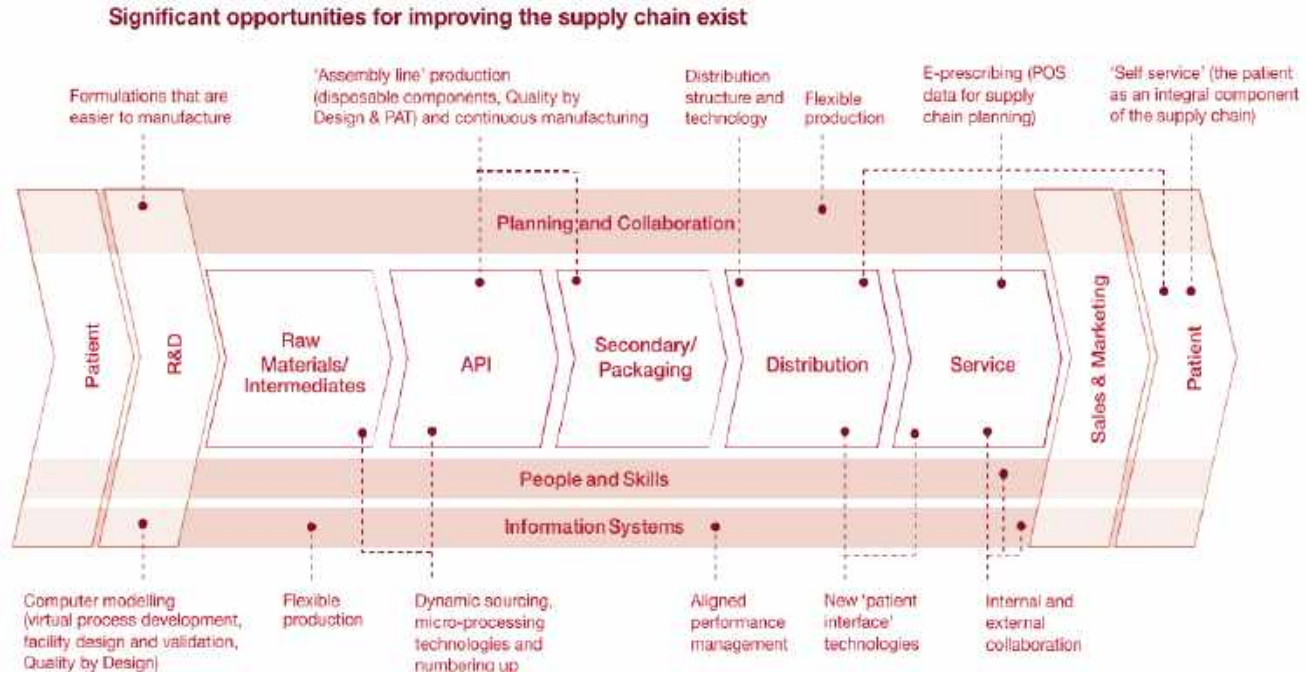

Figure 1. Opportunities for improving the supply chain

India also fears that the new law could be an attempt to check its exports of cheap generics (copied versions of off-patent medicines) to markets in Latin America and Africa as large Pharma companies, many of them based in the EU, feel threatened by the country's cheap but high-quality medicines. In addition to that, the US has made it compulsory for Active pharmaceutical ingredients (APIs) to be manufactured locally though nearly 80% of the raw material requirement is supplied by China and India. The decision has already sent Indian pharmaceutical exporters into a tizzy, as it will significantly impact Indian drug exports. Before the new

norms came into effect, US - based companies were allowed to procure APIs from countries like India and China, make the fixed formulations (final product) in the US and sell the drugs to the US government. Pharmexcil-India's pharmaceutical export promotion council and has approached the Commerce Ministry, requesting authorities to intervene and resolve the issue. (7)

Traditional generic drug companies are looking toward china for the supply of Active Pharmaceutical Ingredients (API) drugs. China is also a viable source for key intermediates and active ingredients as well. Today, there is also collaboration between India and China, as China is sufficient in supplying API and other intermediates for the key drugs. As indicated earlier India is well-versed in the field of generic drugs manufacturing. As the number of companies and intermediaries in the Chinese pharmaceutical industry continue to expand at an unprecedented rate, there are mounting concerns about the threat of counterfeit API's emanating from this country on the global pharmaceutical market.

Radio Frequency Identification (RFID) is referred to as the Automated Data Capture (ADC) technology due to the fact that it uses low-power radio waves to communicate between readers and tags on items such as medicines, component parts, food products, etc. RFID is one of the fastest growing technologies in the field of Supply Chain Management (SCM). There are an increasing number of RFID application technologies in a wide variety of industries. In the pharmaceutical industry RFID is increasingly being used to track and trace products movement on the global supply chain. As Kotler and Armstrong have observed: "An individual firm's success depends not only on how well it performs but also on how well its entire supply chain & marketing channel competes with competitors channels" (8)

Chinese Dominance in Indian Bulk Drugs Market

Bulk drug imports have grown substantially in the past, with India importing APIs worth USD3.9 billion in 2014-15 from about USD 800 million imported in 2004-05, growing at a CAGR of about 17% during the period. Majority of the drugs, worth USD3.3 billion, were imported from China in 2014-15, as the landed price of bulk drugs from China is 15-20% lower than the cost of producing them locally. The dominance of China in the bulk drug industry can be evidenced from the fact that our national healthcare programmes might suffer, if China snaps supply of APIs to India. India imports a large portion of intermediates used in manufacturing of various antibiotics, anti-hypertensive drugs, anti HIV / AIDS drugs and anti-TB drugs from China. Given the critical nature of these bulk drugs, any deterioration in relationship with China could potentially lead to a crisis for public health in India. As such, when the overall Indian domestic APIs industry is majorly dependent on its raw materials from China, we source just around 15% of its raw materials from China. This shields the Company from any supply side glitches and gives it a leverage to have control over its input costs by sourcing its materials from various suppliers.

Chinese API producers play on low cost manufacturing with high volume products. In the case of fermentation and chemical synthesis-based products, Chinese products are 15%-20% cost competitive. Additionally, Chinese APIs manufacturing industry is government supported whereas in India it is largely entrepreneur driven. The incentives offered by China for the export of APIs includes tax holidays, low interest rate loans and subsidy for effluent treatment plants and ensuring production facilities. However, the over-dependence on Chinese imports exposes the Indian pharmaceutical sector to price volatility and supply side shocks like the one witnessed during Beijing Olympics of 2008, when China decided to close many of its APIs plants due to pollution, thereby leading to a sharp spike in prices of many bulk drugs at that time. (9)

A case study in API supply chain integration

To illustrate the connection between integration and flexibility, consider a real-world case study of a newly launched product that involves three dispersed raw material suppliers, and Drug Supply (DS) and Drug Production (DP) production.

Three key raw materials are ordered from Asia and shipped by sea to the U.S. The critical lead time is 7-1/2 months, without any safety margins. DS manufacturing takes place in the U.S. Five chemical steps are required to produce the API. Intermediates are produced in campaigns. Quality release is carried out at the DS manufacturer, and testing is repeated at the DP manufacturer. DP is manufactured in the U.S as well, reducing transportation time. In this case, no extra time is needed for drug packaging.

Some of the process time inefficiencies can be seen in Figure. Supply chain planning adds safety buffers to the raw materials lead times to ensure on-time startup of DS and DP manufacturing. Average buffers are one-to-two months (pink on the diagram) depending on the shipping route, and the company's experience with the supplier. Some of the API manufacturing steps are inflexible, because of specialized plant, high asset utilization and other constraints, so buffers of up to 13% are needed to de-risk the API production. In addition, a safety buffer between DS & DP adds month or so to the timeline. QA/QC release (green) is repeated at several points as different manufacturers with different quality systems are involved.

The bottom half of figure shows the supply chain after simplification

In the simplified and integrated supply chain, buffers and QA time are substantially reduced. The total time is reduced by about three to five months, or 13% to 22%. By replacing incoming QA steps with certificates of analysis, four releases of nine are saved for each batch of final API: one for each raw material received into API production, and one receiving into DP. Per batch of API, QA cost savings are $2,000-$5,000. For a campaign with 20 API batches, and 40 first intermediate batches, savings add up to $180,000 per year. In addition, fewer QC method transfers and less validation work have to be done, saving at least another $100,000-to-$200,000 per

API. Processing fewer samples also reduces operational and technical errors, cutting the number of expensive out-of-specification (OOS) investigations.

With more stringent supply chain management, down times in production are reduced and inventory levels can be reduced. This typically translates to total supply chain cost avoidance. And with less (but better distributed) inventory, and fewer repeated QC steps, the supply chain can better accommodate unanticipated surges in volume. (10)

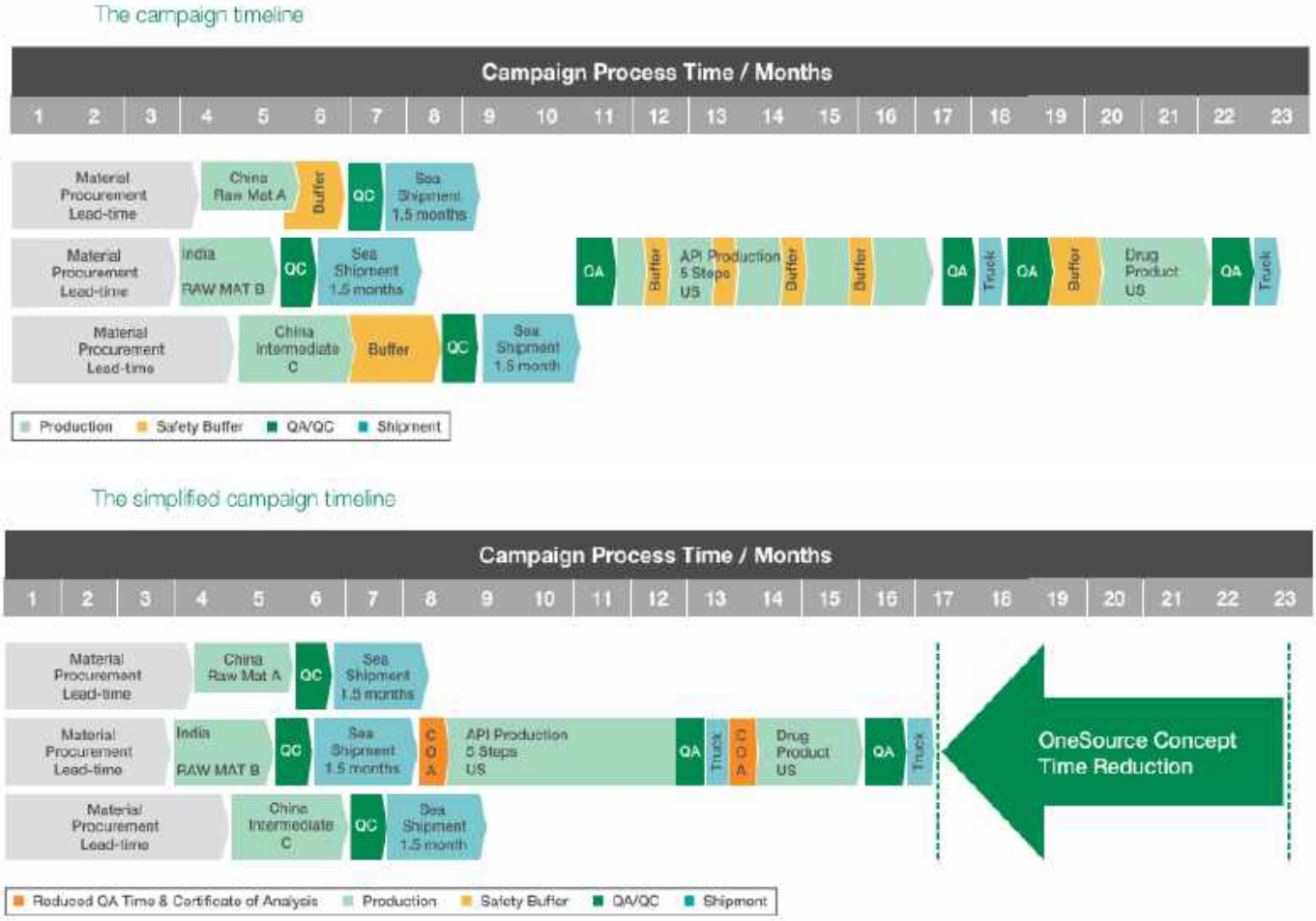

Figure 2. Campaign Process time/Months

3. Four steps to a better supply chain

To create a harmonized and integrated supply chain, it's critical to:

a) Implement a strong and uniform quality system

Apply it, too, with regular audits at your suppliers. Measure performance with strict KPIs such as right first time (RFT). With a small, stable network of quality suppliers, a harmonized system can be achieved with several measurable benefits:

- Safety margins in ordering lead times can be substantially reduced or eliminated. As soon as the network is qualified, and regular auditing established, there will be no returns for re-work. This will create stability in the supply chain. In our example, at least two months were recaptured.
- The manufacturing process becomes transparent. A strong quality management process with quality leaders at the raw material suppliers allows for quality agreements that can be enforced. With such a system, suppliers' certificates of analysis (COAs) can be trusted, and time savings achieved. In our example, this removed at least a month from the timeline.
- Network partners can provide capacity flexibility. With harmonized process validation for chemical APIs, a network partner can serve as an extension of internal manufacturing to accommodate unforeseen demand. A strong and enforced quality system is the foundation of this capability.

b) Reduce the number of interfaces, and standardize operational models

Standardize project management internally, and with suppliers, to allow for direct and clear communication. Share data with a collaboration tool such as SharePoint. With such a system:

- Important information can be communicated quickly and reliably. For example, toxicology classifications of raw materials can be exchanged immediately and special handling requirements consistently conveyed. This will prevent lengthy reworks of intermediates or DS, or last minute changes to plant configurations.

- Supply chain breakdowns can be avoided. Real time and transparent information means fewer disruptions due to miscommunication. Also, where a problem needs to be addressed by changes to the upstream system, it can be recognized and the changes initiated without delay.

c) Optimize intermediate inventories

Identify the bottlenecks and add safety stocks on the downstream side. Bottlenecks usually appear in API production rather than DP due to the latter's shorter manufacturing cycles and faster change-over times. You can add safety stock appropriately if you have a view of demand and of the whole supply chain, and if suppliers and API manufacturers collaborate. With safety stocks rationalized:

Large and expensive API safety stocks may be eliminated. Safety stocks of precursors or starting materials may obviate the need to hold stocks of API. In our example, a stockpile of one intermediate significantly reduces lead time.

• Demand responsiveness may be increased without holding excess DP. Inventories of intermediates for API synthesis can provide flexibility to demand changes without the need to hold expensive excess stocks of DP.

d) Validate more than one production site

Validate two production sites, ideally within the same company network, and file for them both during the initial set-up. Harmonized quality systems, manufacturing, and QC setups will simplify such an approach. For biologic APIs, it is also possible to cross-validate two production sites. Harmonized operations and quality systems will make this substantially simpler. With more than one production site, a company has the flexibility to respond to unanticipated demand. With biologics, for instance, single use fermenters can be quickly added to expand capacity if enough downstream process capacity is available.

Focusing on these four steps will drive down inventory costs, and shorten the timeline from raw materials to finished product. Adopting standardized processes and common metrics will improve end-to-end transparency, accommodate unforeseen variations in demand, and lower the risks associated with complexity.

Transparency in supply chain

Many small local final formulation firms who procure APIs in the global market, mainly from the API-manufacturing firms located either in India or China sometimes find that navigating the market is challenging, especially when procuring the non-WHO GMP or SRA approved APIs. Furthermore some API manufacturers who could not directly export their goods had to go through a state-owned trading company; many Chinese API manufacturers still use such trading companies. These traders may have a tendency towards non-transparency. Moreover there is no public database that can track the API manufacturers and quality assessments.

Usually when a final formulator procures APIs from global merchant market he should use USFDA audits along with internal audits aiming on the supply chain, technical processes and facilities in order to validate the quality of the API manufacturer directly. The direct contact of the final formulator with the API manufacturer provides the necessary transparency to the supply chain. A manufacturer would know the process better and would be able to do necessary quality control checks directly, provide any requested certification. Many smaller final formulators without the resources and experience rely on a trader to source the APIs. (11)

4. Europe

In Europe following ICH Q7 Manufacturing Practice for Active Pharmaceutical Ingredients. (12)

Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.

Figure 3. New rules for imported API

New rules on API "Written confirmation"

- Confirming compliance of the plant with GMP or equivalent rules
- Issued by the competent authority of the exporting non-EU country
- Issued per site and API (not per batch or consignment)
- One written confirmation can cover several APIs
- Duration of validity is established by exporting non-EU country

New rules on API "Waiver 1": non-EU country is

"Listed" List is set up by the European Commission following a request from a non-EU country

The list is based on an assessment of equivalence of:

- GMP rules
- Regularity of inspections
- Effectiveness of enforcement of GMP
- Rapid alert system for non-compliant producers

New rules on API "Waiver 2": "Exceptional circumstances"

"Exceptionally", and where this is necessary to ensure the availability of medicines, the need for the written confirmation can be waived by a EU Member State if a EU Member State has inspected the plant and found it compliant. (13)

5. Canada:

Securing Active Pharmaceutical Ingredients (APIs)

This is the first step in the supply chain and includes sourcing the API from an external supplier or manufacturing the API in-house. The majority of the APIs are provided by suppliers located in China and India. The API supplier must adhere to Good Manufacturing Practices (GMP), while the API must meet the specific quality standards.

Inconsistencies with how inspection results from different regulatory authorities are applied by Health Canada to foreign sites have the potential to disrupt supply:

Health Canada has been inconsistent in how it interprets and acts on inspection results from different regulatory authorities for API and finished dosage form manufacturing sites. It is often not clear to generic manufacturers what compliance actions will be taken and why. In some cases, "terms and conditions" have been added to the Drug Establishment License (DEL), such as testing of product by an independent third-party. The DEL holders are often unclear as to what steps they need to take to remove these conditions and what the timelines are. In other cases, the compliance action taken by Health Canada can be more extreme than that taken by the country that has physically inspected the site.

There have been instances where Health Canada has banned the product from being sold in Canada due to inspection findings from the United States Food and Drug Administration (USFDA). Meanwhile, the USFDA has not imposed any restrictions on continued import and sale of the product in the U.S. market. As a result of the lack of clarity on why Health Canada's actions differ from those of other regulators, it takes an unpredictable amount of time and effort for the generic manufacturers to resolve these issues. During this time, they are unable to sell the particular generic drug in Canada and are at risk of losing their market share to other generic drugs or branded drug products and paying penalties to their contracted customers.

Health Canada is trying to protect Canadian patients by taking compliance actions; however, the unpredictability and lack of transparency for these actions is causing disruption in the industry. These actions have several possible impacts, including interrupted access for Canadian patients, reduction in the number of generic drugs available in the market, increased costs to industry (e.g. third-party testing, loss and disposal of product that has passed its expiry date) and in some cases, increased amount spent on a particular type of drug as the only option available may be the branded drug product.

Case Study

This example is for a generic drug used to treat symptoms of migraine headaches. The market size was approximately $6.1M with approximately 67% captured by the generic drug manufacturers and 33% belonging to the branded drug company as of October 2014.

Issue: The API site for one of the generic manufacturers was inspected in November 2014 by USFDA for GMP compliance. USFDA issued a Warning Letter to this site, however no compliance actions were taken in the U.S., and the product remained on the market. On the other hand, based on the warning letter from the USFDA, Health Canada asked the generic manufacturer to voluntarily quarantine all drugs containing the API manufactured at this site. Furthermore, Health Canada also requested the API site to voluntarily stop shipping their product to Canada. Despite numerous requests for clarification by the Canadian Generic Pharmaceutical Association (CGPA) on behalf of the generic manufacturers' on what steps were needed to lift the restrictions, none were provided by Health Canada.

Impact on patients: As of January 2016, the branded drug company has regained significant market share and has now captured 87% of the market while the generic drug manufacturers' market share has declined significantly to only 13%. As the branded drug product now has majority of the market, the result is that patients, governments and insurance companies are spending more on prescription drugs since the generic drug price is on average 41% of the price of the branded drug product.

Suggested solution: Health Canada's actions should be consistent with those of their trusted regulatory partners. If actions are taken to restrict products or facility

activities, Health Canada should publish clear guidelines on what needs to be done to lift the restrictions. (14)

6. USA

Today, a large number of generics and over-the-counter medicines in the U.S. are imported, much of it from India. Approximately 80 percent of active pharmaceutical ingredients (APIs) the substances in medicines responsible for their therapeutic effects in U.S.-marketed drugs come from outside the U.S.

Guidance for Industry Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

APIs and intermediates should be transported in a manner that does not adversely affect their quality.

Special transport or storage conditions for an API or intermediate should be stated on the label.

The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall. (15)

The US Government Accounting Office (GAO) published a report on the challenges that FDA faced in assuring the safety of the API supply chain given that reliance on APIs produced by foreign manufacturers has risen dramatically and the complexity of the global pharmaceutical supply chain has increased significantly over the past two decades. The report found that while FDA had increased inspections of foreign API manufacturers (up 27% from 2007 to 2009, for example), its rate of inspection for foreign establishments was still far below that for domestic manufacturers. In addition, most foreign inspections were scheduled far in advance, conducted under controlled circumstances, and typically occurred during much shorter time frames. GAO also determined that FDA still lacked important information about foreign API manufacturers

On a positive note, GAO recognized that FDA had begun to implement initiatives designed to improve its oversight of the drug supply chain, including increased training by overseas offices, the development of programs for control of APIs and other drug products entering the United States, and a push for risk-based inspections rather than a set schedule. The GAO concluded, however, that FDA needed to implement changes more rapidly to better assure the safety of drugs on the US market

Since that report, new legislation has affected FDA‘s ability to schedule and conduct inspections of API manufacturers. As a result, inspections of foreign manufacturers have increased dramatically--along with warning letters-while inspections of domestic manufacturers have decreased.

Impact of GDUFA

The most important piece of legislation affecting FDA’s ability to improve the safety of the pharmaceutical supply chain is the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012. The Generic Drug User Fee Amendments (GDUFA), included as part of FDASIA, instituted a Generic Drug User Fee Program that was agreed to by FDA and the generic-drug industry, specifically the Bulk Pharmaceutical Task Force (BPTF) of the Society of Chemical Manufacturers and Affiliates (SOCMA), the European Fine Chemicals Group (EFCG), and the Generic Pharmaceutical Association (GPhA).

The user fees are intended to provide additional funding for FDA ‘s drug approval and inspection efforts with the goal of increasing the safety of generic drugs and the ingredients used to produce them, increase the speed of the drug approval process, and the transparency of the industry. One of the main goals of GDUFA is to ensure that foreign facilities are inspected at a rate equal to that of domestic facilities. The fees raised through GDUFA have enabled FDA to hire approximately 1000 additional employees, making it possible for the agency to complete more inspections and speed up the approval process for abbreviated new drug applications (ANDAs) and the review of drug master files (DMFs).

Further developments with FDASIA

Several other aspects of the FDASIA legislation have also impacted the API and formulated-drug supply chain. For instance, FDASIA requires FDA to identify facilities involved in the manufacture of generic drugs and associated APIs. “Prior to FDASIA, FDA didn’t ‘t know how many facilities were producing formulated drugs or APIs in the US, let alone how many companies around the world were manufacturing APIs and formulated drugs and exporting them to the US,” says John DiLoreto, executive director of BPTF. Before the self-registration process began, the industry estimated that there were 1700-2000 manufacturing sites around the world. After the registration process was complete, that number was reduced to approximately 1300. DiLoreto believes that some consolidation of manufacturing plants occurred as companies looked to reduce the GDUFA fees they would have to pay by consolidating operations.

In the most recent report on foreign and domestic drug establishments issued by FDA , the agency identified a total of 12,949 registered drug establishments in 2014, including 9330 domestic and 3619 foreign (slightly up from 12,613 in 2013. Of those 12,949 facilities, 4383 were registered as finished drug product (FDP) establishments, and 1495 were registered as API establishments. (If a site produces both finished drug products and APIs, it is placed in the FDP category.) The

remaining 7071 establishments fell into the "other" category, which includes facilities that produce, compound, or process medical gases, medicated feed, and some biologic drugs.

FDASIA also grants FDA the authority to confiscate and destroy unsafe APIs and drug products being imported into the US. With its increased ability to track the manufacturing activities and inspection histories of API and drug manufacturing sites, the agency can determine if APIs or finished drug products were produced at a facility that has not been FDA-inspected or is not in compliance. The agency has also published guidance on what conduct it considers as delaying, denying, limiting, or refusing inspection, actions that can result in determination of a drug to be adulterated. In addition, under GDUFA, all drugs produced in an unregistered facility or in a facility for which the GDUFA fees have not paid are considered "misbranded" (16, 17)

"Together, these new capabilities of the agency make it possible for potentially unsafe APIs and drug products to be removed from the marketplace completely," DiLoreto says.

FDA is also using the information on establishments to prioritize them according to the level of risk each represents. Rather than inspect facilities on a set schedule as was the case in the past-typically once every two and one-half years on average for domestic facilities and once every 10 years or more for foreign manufacturing sites-the agency now determines which facilities to inspect based on the overall level of risk they pose, which is determined using a model that takes into account inherent risk, outbreaks, recalls, adverse events, and compliance history. (18) This move has led to a dramatic increase in foreign inspections and a concomitant decline in domestic inspections.

In fiscal year (FY) 2014, the total number of foreign and domestic high-risk human drug inspections by FDA was 918, which exceeded the agency's target of 750 (3). In FY 2013, 443 domestic and 365 foreign high-risk establishments were inspected (total of 808); 43 GMP-based warning letters were issued as a result of those inspections. (19) Overall in FY 2013, FDA conducted 967 domestic and 604 foreign GMP inspections (19). In FY 2014, those numbers were 780 and 757. FDA estimates that in both FY 2015 and 2016, there will be 591 domestic and 843 foreign inspections.

Both the agency and the industry are adjusting to the risk-based inspection approach, according to DiLoreto. "When FDA first indicated that it would be decreasing domestic inspections so significantly, BPTF was initially concerned that domestic facilities would not be receiving inspections often enough, particularly those exporting to Europe, because the European Medicines Agency (EMA) requires pharmaceutical manufacturers importing products into the European Union to have had an inspection within the previous three years," notes DiLoreto. The agency has addressed those concerns and established an agreement with EMA. "One of the primary goals of GDUFA was to achieve inspection parity between foreign and domestic facilities, but the change to a risk-based program allows FDA to better utilize resources," he adds.

International agreements

An additional step in the right direction was made in December 2014 when FDA Commissioner Margaret Hamburg signed an agreement with Chinese officials to collaborate on inspections in China that builds on an initial agreement signed in 2007. (20) China also finally agreed to provide additional visas for more FDA inspectors, which will allow the agency to boost its number of employees from 13 to 33.

FDA is working with EMA on joint inspections and trying to establish mechanisms for sharing of inspection data, according to DiLoreto. BPTF would like to eventually see EMA and FDA inspections results considered to be equivalent. There are, however, concerns on the part of some manufacturers about how confidential business information can be adequately protected under such a scenario.

On-going issues

Despite the numerous advances that FDA has made in addressing concerns about APIs and formulated drugs manufactured overseas, there are still many challenges facing the agency. Some foreign governments still do not welcome the agency, and inspections of foreign facilities still suffer from many restrictions. DiLoreto does believe, however, that the situation is improving in many countries, as indicated by the recent agreement in China.

There is also the issue of the dramatic increase in warning letters issued to foreign manufacturers that has occurred along with the rise in foreign inspections. DiLoreto expects these problems to be resolved once these manufacturers have been educated about GMP requirements and become familiar with the expectations of FDA. "It is not surprising that issues are being found at facilities that are being inspected for the first time. These facilities will implement the required improvements, and the number of citations will decline as more effective quality programs are put in place," he observes.

It is also important to remember, according to DiLoreto, that many of the FDA inspectors now on the job are still quite new. "It takes at least two years for an FDA inspector to be fully trained, because it takes time for him/her to gain the practical experience needed for the job," he says. "A large percentage of current FDA inspectors don't have that two years of experience yet, and while new inspectors are on the learning curve, issues can arise," DiLoreto continues. These difficulties, however, should also be resolved in the next few years, he notes.

Table 1. Compression Study of Active Pharmaceutical Ingredients supply chain of United States, Europe, India, China, and Canada

Particulars	United states	Europe	India	China	Canada
Guidelines	Food and Drug Administration (USFDA)	European Medicines Agency (EMA)	Central Drugs Standard Control Organization (CDCSO)	Chinese Food and Drug Authority (CFDA)	Canadian Food and Drug Act (CFDA)
Pharmacopoeia	United States Pharmacopoeia (USP)	European Pharmacopoeia (EP)	Indian Pharmacopoeia (IP)	Chinese pharmacopoeia (CP)	-
Federal Regulators	Review authorizes, new Drugs brand and generic under Food and Drug Administration (USFDA)	Review authorizes, new Drugs brand and generic under European Medicines Agency (EMA)	Review authorizes, new Drugs brand and generic under the Food and Drugs and Acts (FDA) & European Medicines Agency (EMA)	Review authorizes, new Drugs brand and generic under the Food and Drugs and Acts (FDA) European Medicines Agency (EMA)	Review authorizes, new Drugs brand and generic under the Food and Drugs and Acts (FDA)
Guidelines followed for API (Active Pharmaceutical Ingredients)	ICH Topic Q 10	ICH Topic Q 7 (European Medicines Agency)	ICH Topic Q 7	ICH Topic Q 7	ICH Topic Q 7
International fora	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)
API Exporting	Less	Less	More	More	More
Manufacturer Guidelines	GMP	GMP	GMP	GMP	GMP
Extent of Price Controls	-	-	High	High	Moderate
Cost of API Production	High	High	Low	Very Low	Medium
Regulatory of API	Stringent	Stringent	Medium	Low	Medium
Cost of API Production	High	High	Low	Low	Medium
Quality of API	High	High	Medium	Very Low	Medium

7. Conclusion

The pharmaceutical active ingredients supply chain used to be seen as a tool to supply products to market in an effective way, where the emphasis was on security of supply. Recent changes in the operating environment mean that companies are revisiting the components of their supply chains and identifying ways of extracting additional benefits from them. In this sector in particular, the supply chain of interest is not simply the physical processes of conversion and distribution of materials.

Acknowledgements

I would like to express my gratitude to International Journal of Drug Regulatory Affairs (IJDRA) who gave me the opportunity to publish the article.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Active Pharmaceuticals Ingredients Committee of CEFIC Committee report 1999 [Internet]. CEFIC; 1999 [cited 2019 Apr 28]. Available from:

http://academy.gmp-compliance.org/guidemgr/files/3STERILEAPIGUIDE9912.PDF.
2. IP & Regulatory expertise, will continue focus on new product development & filings for focused market. Management Discussion & Analysis [Internet].2017 [cited 2019 Jul 07]. Available from: https://www.jubl.com/annualreport2017-18/MDA.pdf.
3. Top challenges facing drug supply chains [Internet]. Biopharmadive; 2019 [cited 2019 May 5]. Available from: https://www.biopharmadive.com/news/top-challenges-facing-drug-supply-chains/521876/.
4. Sen Anindya, Gokarn Subir, Vaidya Rajendra. Growth and Structural Changes in the Pharmaceutical Industry in India, The Structure of Indian Industry [Internet]. New Delhi: Oxford University Press; 1999 [cited 2019 Apr 22]. Available from: http://www.ijplsjournal.com/issues%20PDF%20files/july2010/4..pdf.
5. Pandey Shivanand. India's Pharmaceutical Industry on Course for Globalization: A Review. International journal of pharmacy & life sciences. 2010; 1(3):133-40.
6. Study on Indian Pharmaceutical Industry. Export-Import Bank of India [Internet]. Eximbankindia; 2015 [cited 2019 Apr 27]. Available from: https://www.eximbankindia.in/Assets/Dynamic/PDF/Publication-esources/ResearchPapers/39file.pdf.
7. Alamelu R, Amudha R, Cresenta Shakila Motha L, Nalini R. Pharma Export Comforts and Confronts in India. Asian J Pharm Clin Res. 2016; 9(4):1-3.
8. Kalyan Bollampally, Sam Dzever. The Impact of RFID on Pharmaceutical Supply Chains: India, China and Europe Compared. Dian. Journal of Science and Technology. 2015; 8(S4)L:176-188.
9. Management discussion & analysis. Nutraplus India Limited 26th Annual Report 2015-2016 [Internet]. Sun pharma; 2015-2016 [cited 2019 Mar 12]. Available from: https://www.sunpharma.com/sites/default/files/annual/SPIL%2024th%20Annual%20Report%202015-16.pdf.
10. Patheon one source [Internet]. Patheon; 2019 [cited 2019 Mar 13]. Available from: doingbusiness@patheon.com
11. Smarta RB. Emerging Challenges of API Industry [Internet]. Interlink Pharmabiz; 2014 Oct 02 [cited 2019 Mar 12]. Available from: http://www.pharmabiz.com/NewsDetails.aspx?aid=84972&sid=21.
12. ICH Topic Q 7 Good Manufacturing Practice for Active Pharmaceutical Ingredients [Internet]. ICH; 2000 Nov [cited 2019 Jun 10] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-7-good-manufacturing-practice-active-pharmaceutical-ingredients-step-5_en.pdf.
13. API - the new approach for third countries what are the consequences should we expect shortage of medicinal products in the country? Perspectives from an acceding country [Internet]. EMA; 2013 May 06-07 [cited 2019 Mar 25]. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-active-pharmaceutical-ingredients-new-approach-third-countries-what-are-consequences_en.pdf.
14. Ensuring a consistent supply of safe, effective and high quality generic medicines for Canadians [Internet]. Canadian Generic Pharmaceutical Association Deloitte; 2016 Oct 17 [cited 2019 Mar 20]. Available from: https://canadiangenerics.ca/wp-content/uploads/2016/11/10.17.16DeloitteGlobalSupplyChainReport_ENG_FINAL.pdf.
15. ICH Guideline 2010. Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients [Internet]. FDA; 2001 Sept [cited 2019 Mar 20]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-q7a-good-manufacturing-practice-guidance-active-pharmaceutical-ingredients#P911_62718.
16. Washington DC. Drug Safety: FDA Faces Challenges Overseeing the Foreign Drug Manufacturing Supply Chain 2011 [Internet]. GAO;2011 Sept 14 [cited 2019 Mar 20]. Available from: https://www.gao.gov/assets/130/126943.pdf.
17. Rockville MD. Annual Report on Inspections of Establishments in FY 2014 [Internet]. FDA; 2017 [cited 2019 Mar 20]. Available from: https://www.fda.gov/media/103023/download.
18. Washington DC .Department of Health and Human Services, Fiscal Year 2015 Food and Drug Administration Justification of Estimates for Appropriations Committees [Internet]. cdc.gov; 2015 [cited 2019 Mar 20]. Available from: https://www.cdc.gov/budget/documents/fy2015/fy-2015-cdc-congressional-justification.pdf.
19. Washington DC. Department of Health and Human Services, Fiscal Year 2016 Food and Drug Administration Justification of Estimates for Appropriations Committees [Internet]. hhs.gov; 2016 [cited 2019 Mar 20]. Available from: https://www.hhs.gov/sites/default/files/budget/fy2016/fy2016-general-departmental-budget-justification.pdf.
20. M. Mansou. United States: FDA And China Agree To Collaborate On Inspections 2014 [Internet]. pharmtech; 2015 May 04 [cited 2019 Mar 20]. Available from: http://www.pharmtech.com/better-control-api-supply-chain