



THE NEXT FRONTIER IN ENSURING THE QUALITY OF MEDICINES

Maintaining International Quality and Safety Standards in the Manufacturing and Supply of Active Pharmaceutical Ingredients

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LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
CDSCO	Central Drugs Standard Control Organization
CFDA	China's Food & Drug Administration
CMO	Contract Manufacturing Organization
CRO	Contract Research Organization
DRA	Drug Regulatory Agency
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FY	Fiscal Year
GDP	Good Distribution Practices
GAO	United States' General Accounting Office
GMP/cGMP	Good Manufacturing Practices / current Good Manufacturing Practices
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
QbD	Quality by Design
QbR	Question-Based Review
WHO	World Health Organization
WHOPIR	World Health Organization Public Inspection Reports

Additional definitions

Biopharmaceutical

A term used to describe and include both chemical based medicines (which are manufactured using a chemical process and products) as well as biologics which are medicines that are inherently biological products developed with biological sources and process. Throughout the paper, the terms biopharmaceutical, drug, medicine and medicinal product are used interchangeably.





EXECUTIVE SUMMARY

Traditionally the focus of medicines' safety and quality processes and procedures has been on finished pharmaceutical products. But manufacturing patterns and trends have changed considerably over the last few decades.

Biopharmaceutical products are now manufactured and assembled through a complex global assembly line with different suppliers used to source the individual components for a given product. Indeed, products for a given market can now be assembled from numerous suppliers and ingredients sourced globally. Over the past few years stringent drug regulatory authorities have begun to recognize how ensuring high standards of quality is not just about monitoring and testing the safety of a finished product but also screening and monitoring the safety and quality of its key ingredients wherever in the world they are sourced and/or manufactured.

In this context APIs have become the focus for increased regulatory attention in the US, EU, Canada and internationally through the WHO and ICH. The API is the core element of a given medicine. By and large, it is a chemically-synthesized molecule which interacts with one or more of the human body's components or an infectious micro-organism at the molecular level in order to create or initiate a curative effect. Today an estimated 70-80% of all marketed APIs are manufactured in China and India. Moreover, India imports as much as 90% of raw materials for API manufacturing from China. Yet regulatory and manufacturing standards in these two markets are not always aligned with international best practices. And even where regulations and relevant rules are in place, authorities in these countries face the huge task of enforcing these rules.

This state-of-affairs presents stringent DRAs and patients across the world with the real challenge of ensuring that the safety and quality of their medicines are not compromised anywhere – regardless of geographical location – within the production and distribution chain. Upholding the highest standards in API manufacturing is crucial to the interests of patient safety and public health. Failure to meet the highest quality requirements could result in impurities and contaminations which may lead to serious health risks and even fatalities.

In addressing this growing risk the past years have seen numerous import bans and product recalls issued on a nearly annual basis by DRAs on foreign API manufacturers, mostly Indian and Chinese, due to serious GMP deviations, regulatory violations, misconduct and intentional fraud. For example, numerous Indian manufacturers have received export bans due to GMP violations involving API manufacturing from the FDA, EMA, Health Canada and other authorities. This is in addition to wider problems of quality and safety of medicines from China and India. For instance, a recent investigation by the EMA led to the suspension of the marketing approval of nearly 700 generic medicines manufactured in India following an inspection by the French DRA (ANSM) which revealed systematic data manipulation of bioequivalence tests for the past five years at least.

This report findings can be grouped around four main or key areas that touch on this question and challenges regulators and patients face in maintaining the quality manufacturing and pharmacovigilance of API production and distribution.

Key finding 1: A drug regulator's world is now global, not local

This report's mapping of international API manufacturing practices confirms that drug and medical regulatory responsibility and pharmacovigilance is no longer confined or limited by geography or legal jurisdiction. Rather, to ensure the safety and quality of a given biopharmaceutical end product regulators and authorities must monitor and inspect a product all the way from raw material and API to finalized products. In practical terms it means that drug regulators in purchasing markets (such as the EU and US – the world's biggest biopharmaceutical markets) must now actively inspect and have a presence outside their respective legal jurisdictions.

Only in recent years have drug regulators in purchasing markets become cognizant of this new reality. However, recent legislative developments within the two leading stringent DRAs – the FDA and the EMA – suggest that divergent paths are being taken. While the EU’s Falsified Medicines Directive has shifted much of the responsibility of ensuring the quality of medicines imported into the EU over to the exporting country’s DRAs, the FDA’s new powers has broadened its authority and enabled it to apply swift measures to ensure public health.

The path taken by the EMA is striking, especially in light of the high number of Indian and Chinese API manufacturers within the annual number of GMP non-compliance reports issued by the EMA, as this report highlights. Indeed, shifting responsibility for quality assurance of imported medicines to foreign DRAs which may lack the capacity for effective enforcement and inspection is questionable, particularly where the official GMP standards are not as strong as international best practices. Nevertheless, the EMA has in the past stated that it is satisfied with the confirmations given by foreign DRAs under the new Directive, despite concerns raised by other organizations regarding foreign DRAs enforcement capabilities.

The approach taken in the US is different. Under the Safety & Innovation Act of 2012 and the Drug Quality & Security Act of 2013 FDA’s authority has been extended and strengthened considerably including: for administrative detention of suspicious drugs, definition of all actors’ responsibilities in maintaining quality throughout the entire supply chain, timeframes for the establishment of an electronic track and trace system, and a requirement of the FDA to identify every part of the entire supply chain of imported drugs. Moreover, the FDA and US Government has identified as a priority the need for greater levels of staffing and inspections rates in China and India by FDA officials.

Equally, the growing strength of India and China’s domestic exporters means that their DRAs must work toward not only upholding regional and national manufacturing and pharmacovigilance standards but also international standards.

Key finding 2: API manufacturing is plagued by concerns over substandard quality and GMP irregularities

The API manufacturing and pharmacovigilance environment in the two largest producing countries, China and India, is currently lacking with regards to both the presence of adequate GMP and pharmacovigilance regulations as well as their enforcement. China suffers from high levels of corruption, a large and wide-spread pharmaceutical counterfeiting industry, and a lack of resources for effective enforcement. Additionally, the CFDA does not regulate the chemicals industry which provides the raw ingredients for API manufacturing. In India the current official GMP standard – “Schedule M” – has not been revised since its issuance in 2005 and it is not as strong as international best practices as captured in ICH Q7 for example. Furthermore, the enforcement of existing standards are patchy and not backed up by a clear and strong national framework.

Analysis of both FDA and EMA warning letters show significant problems relating to quality control and integrity of API manufacturing in India and China. Examining the annual number of API-related GMP non-compliance reports issued by the EMA between 2010-2014 this report found that India’s and China’s share amounts to 38% and 27% respectively; by far the two largest violators. Both countries received the highest share of foreign letters by the FDA as well. This is particularly worrying as foreign inspection rates by the FDA and EMA are far behind equivalent inspection rates within the US and EU. The FDA is required by law to inspect domestic manufacturers once every two years; the US Government Accounting Office estimated in 2011 that the FDA would inspect foreign manufacturers only once every 9-13 years.

Key finding 3: Bilateral cooperation and dialogue between stringent DRAs and DRAs in manufacturing markets no longer a choice but a necessity

Given the new realities of living in a global production and marketplace regulators in purchasing markets must foster closer bilateral cooperation with regulators in manufacturing markets. This report has found that while this is an area where action has been taken in recent years (see for example the recent agreements between the CFDA and FDA) there is still considerable room for closer cooperation and harmonization of monitoring and inspection efforts.

Key finding 4: Adherence to international standards of API manufacturing and pharmacovigilance are still lacking

Agreeing on and enforcing international standards and best practices of API manufacturing and pharmacovigilance is of increasing importance to patients across the world. Although the emphasis in developed markets has been on ensuring domestic patient safety, it is equally imperative that medicines and APIs exported from manufacturing countries to developing country markets as well as produced for local consumption meet the highest international quality standards. Efforts at international harmonization have been in place for some time through, for example the ICH Q7 Guidelines, yet neither China nor India have adopted or enforced this measure in full.





INTRODUCTION

Traditionally the focus of medicines' safety and quality processes and procedures has been on finished pharmaceutical products. But manufacturing patterns and trends have changed considerably over the last few decades.

Biopharmaceutical products are now manufactured and assembled through a complex global assembly line with different suppliers used to source necessary components for a given product. Indeed; products for a given market can now be assembled from numerous suppliers and ingredients sourced globally. Over the past few years stringent drug regulatory authorities have increasingly begun to recognize how ensuring high standards of quality is not just about monitoring and testing the safety of a finished product but also screening and monitoring the safety and quality of its key ingredients in all parts of the world.

In this context APIs have become the focus for increased regulatory attention in the US, EU, Canada and internationally through the WHO and ICH. An API is the key ingredient in a given pharmaceutical product. The FDA and ICH defines an API as "any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body."¹ Put plainly, the API is the most fundamental and essential part of a medicine, as it is solely responsible for a given medicine's curative effect.

The issue

Over the years there have been a number of high profile and deadly scandals involving contaminated APIs that have prompted regulatory action. The most notable is the 2008 heparin scandal in which over a hundred US patients died using a heparin solution manufactured by Baxter.² In its subsequent investigations the FDA linked the contamination of the heparin with Baxter's API supplier; a manufacturer in China.³

Today an estimated 70-80% of all marketed APIs are manufactured in China and India.⁴ Moreover, India imports as much as 90% of raw materials for API manufacturing from China.⁵ Yet regulatory and manufacturing standards in these two markets are not always aligned with international best practices. And even where regulations and relevant rules are in place authorities in these countries face the huge task of enforcing these rules. This state-of-affairs presents stringent DRAs and patients across the world with the significant challenge of ensuring that the safety and quality of their medicines are not compromised anywhere within the production and distribution chain regardless of geographical location.

This report zeroes in on the existing gaps and challenges – both theoretically and on-the-ground – within API manufacturing and pharmacovigilance.

The report consist of 4 sections:

Section 1 provides a brief overview of the global API supply chain, its development and the globalization of production over the last few decades.

Section 2 reviews the current regulations, best practices and their enforcement as well as major gaps and challenges in the two global leaders in API manufacturing – China and India. This section includes a dedicated subsection analyzing a key source of information on the manufacturing environment in these two countries: warning letters issued by the FDA and EMA. The manufacturing challenges and quality concerns faced in these markets is highlighted by the overall number and rate of warning letters issued to API manufacturers by the FDA and by the EMA. These letters provide a unique and highly valuable source of information on the API manufacturing gaps and challenges in India and China.

Section 3 details the best practices and highest international standards for the manufacturing and distribution of APIs which ensure that the three essential pillars of a given medicine – safety, quality and efficacy – are maintained. These international standards and best practices are amalgamated into an API manufacturing “gold standard” set of international best practices.

Section 4 offers conclusions, final thoughts and an overview of the key findings of the report and concluding thoughts on what can be done by countries within the manufacturing and the purchasing markets to address the challenges presented in the earlier sections.







1

AN OVERVIEW OF GLOBAL API MANUFACTURING

The core component of all medicines, API manufacturing is today a truly global industry with production taking place all across the world. This raises opportunities as well as challenges.

The API is the core element of a given medicine. By and large, it is a chemically-synthesized molecule which interacts with one or more of the human body's components or an infectious micro-organism at the molecular level in order to create or initiate a curative effect.⁶ Today, advanced, high-end technologies enable scientists not only to create sophisticated molecules aimed at specific clinical conditions but also increase their efficacy by manipulation of their pharmacodynamics and pharmacokinetic features. Moreover, the introduction and rapid development of more advanced technologies (including biologic medicines) enable medical treatment to progress beyond merely treating the symptoms of illnesses and instead slowing the progress of, or even preventing, disease.⁷

As medicines have become more complex in their composition the need for high quality ingredients and manufacturing to ensure the stability, quality and ultimately efficacy and safety of a given product has only grown. Yet, more and more of the manufacturing supply chain and sourcing of relevant ingredients is in modern pharmaceutical manufacturing outsourced. Today there are multiple suppliers often in different countries and legal jurisdictions complicating the traceability of a given product and increasing the risk of missteps in the manufacturing and distribution supply chain. Indeed, the globalization and segmentation of the pharmaceutical supply chain is constantly growing and evolving. For instance, the number of Chinese and Indian API manufacturers for generic medicines has more than doubled in the past 8 years.⁸ Moreover, a recent survey shows that over 70% of big pharmaceutical companies are willing to consider outsourcing to CROs/CMOs in emerging markets.⁹ Today a finished medicine assembled in the US can contain raw materials which originate from China and an API which was manufactured in India.¹⁰

On the following page Figure 1 gives an overview of global API manufacturing and the leading countries of production.

1.1 Globalization of API production = Globalization of manufacturing regulations and pharmacovigilance

Apace with this fast-moving and constantly changing supply chain the challenges faced by DRAs everywhere – in purchasing as well as manufacturing markets – multiply. Indeed, the increased complexity and sophistication of modern day medicines (including biologic and biosimilar medicines) necessitate even stricter control and adherence to the highest manufacturing and production quality standards. But the globalization of production means that drug regulators in purchasing markets can no longer focus solely on verifying and enforcing standards within their own jurisdictions. Instead, these regulators must now ensure that quality standards are in place from day one with the sourcing of the most basic raw ingredients for a given product. However, it is impossible for purchasing market DRAs to inspect every API supplier and manufacturer around the world every year given their vast number, which is estimated at over 2,000 in India and China alone.¹¹ This fact necessitates not only the creation of a foreign inspection capability but also greater cooperation with regulators in manufacturing markets.

Compliance with international manufacturing standards is not required unanimously by all DRAs or in all countries. And even where it is, the “on the ground” reality may be different.¹² Serious GMP deviation occurs almost annually, sometimes repeated by the same manufacturer. What is more, the multiplicity of manufacturers on a global scale necessitates the reliance on regulation and enforcement by local DRAs, which, as will be discussed in the next section, can be quite poor

FIGURE 1 Global API Manufacturing - An Overview



United States

- The largest API market and leader in established API manufacturers
- High-end, up-to-date cGMP standard
- 136 FDA-approved API plants
- ~40% of generic medicines originate from India



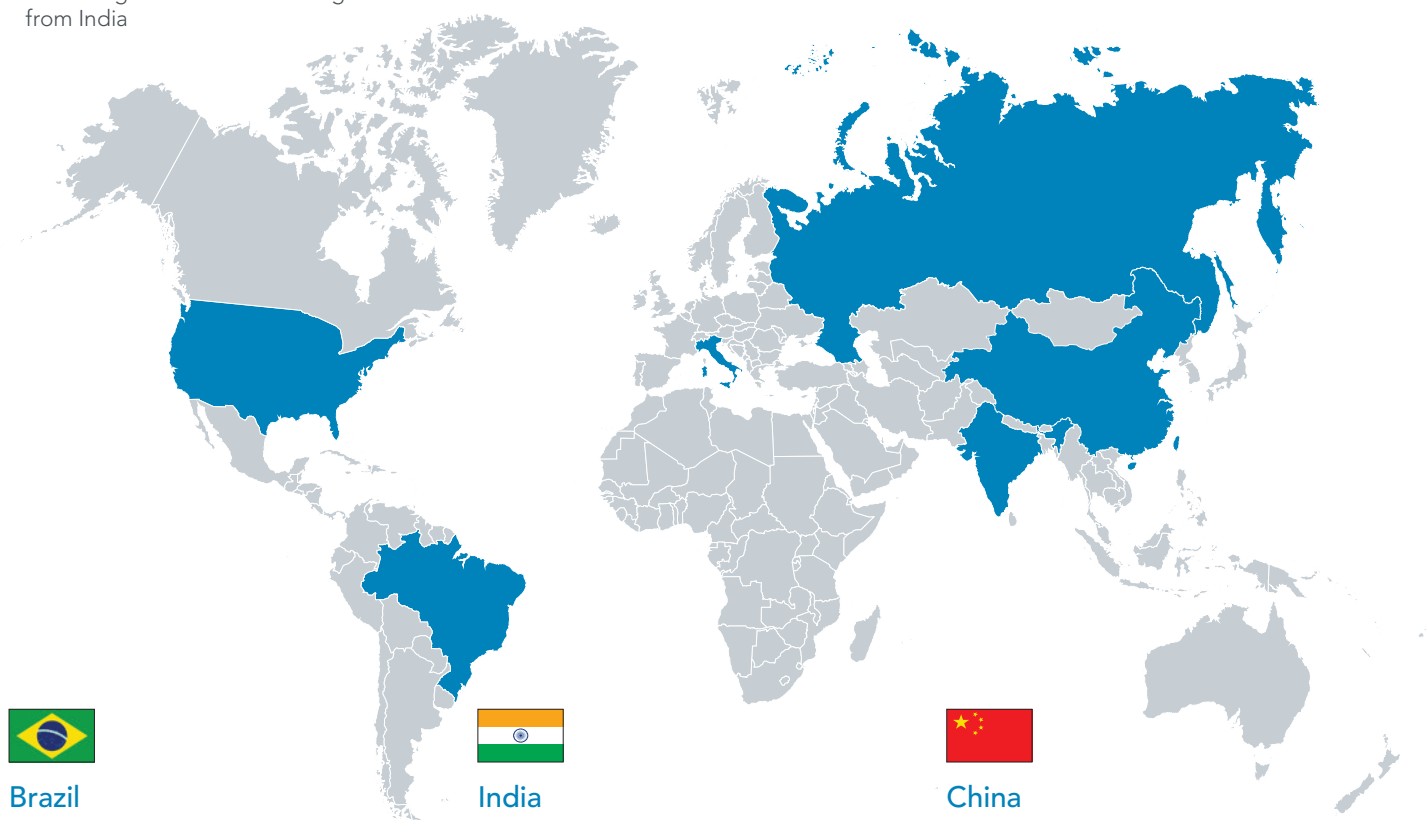
Italy

- Among global API manufacturing leaders
- 91 API manufacturers registered in EUDRA-GMDP; only 69 are FDA-approved



Russia

- 43 API manufacturers
- None FDA-approved
- GMP to be mandatory only from 2016



Brazil

- High-level GMP standard in legislation
- Recently approved for importing APIs into the EU without certification
- Only 4 API manufacturers are FDA-approved



India

- +1,400 API manufacturers, of these only 238 are FDA-approved
- The only manufacturing standard in place – Schedule M – was established in 2005 and has not been revised since then, despite significant difference in scope and detail with respect to WHO/ICH GMP standards
- Since 2013, India's DRA - the CDSCO – granted a GMP confirmation to +800 API plants, following EU requirements



China

- +1,100 API manufacturers
- Only 168 FDA-approved
- GMP revised to a higher standard in 2011, yet enforcement lacks resources and is ineffective
- 2015 to see FDA-CFDA collaboration on GMP inspection and doubling of FDA inspectors

Sources: EUDRA-GMDP; Thomson Reuters, 2014; Fierce Pharma, 2013; ECA Academy, 2013

and ineffective, and at times involves submission of falsified data.¹³ Because of this many stringent DRAs conduct routine inspections at foreign manufacturing plants which export medicines into their countries.¹⁴ Significantly the FDA and EU make their inspection findings and warning letters

issued publically available.¹⁵ (A detailed analysis of warning letters is provided in section 2.)

While this is a challenge affecting all types of medicines it is a particular concern for biologic medicines. This is because given the size,

complexity and inherent instability of a biologic, their development and manufacturing requires not only high levels of expertise and advanced technical infrastructure but also a considerable level of stability and technical capacity.¹⁶ Specifically, the manufacturing process must be consistent and not changed with new parts or processes introduced. Otherwise there is a risk that the quality and purity of the manufactured product is compromised.¹⁷

These challenges – of maintaining stability and consistency to ensure a high quality product – are particularly pronounced in relation to the manufacturing of biologics and make the outsourcing of this manufacturing difficult and technically testing.¹⁸ One reason for this is the lack of a robust regulatory framework which has the experience, resources and expertise to ensure that these challenges are met with appropriate quality assurance and adherence to high-level international manufacturing standards, as is the case with some leading destination countries in outsourcing pharmaceutical manufacturing.¹⁹ Indeed, one of the key challenges of the internationalization of the manufacturing of medicines more generally and APIs in particular is the considerable differences in standards and quality between pharmaceutical manufacturing plants across the world.

These are differences in geography brought about by both different formal regulatory requirements and standards as well as local production culture. For example, an academic paper examining the quality risk across 30 matched pairs of onshore and offshore biopharmaceutical plants owned by the same company discovered a significantly higher quality risk in offshore plants, as a direct result of less consistent adherence to the GMP standard.²⁰ Thus even within the same company it is clear that manufacturing standards can vary dramatically from one geographical location to another. The researchers suggest that lower educational level of offshore employees, a growing geographical distance between the plant and company headquarters, and cultural, economic and disparities in local capability are most likely to increase the quality risk of the products.²¹

These deviations and differences in manufacturing standards constitute a risk that should not be underestimated. The consequences can

range from the production and distribution of substandard medicines with reduced API to severe contamination which result in injuries and deaths. Indeed, over the years there have been a number of high profile and lethal scandals involving contaminated APIs. As mentioned, the most notable is perhaps the 2008 heparin scandal, in which nearly 150 patients in the US died as a result of an allergic or hypotensive response to a contaminated heparin solution, manufactured by Baxter.²² In its subsequent investigations the FDA linked the contamination of the heparin with Baxter's API supplier; a manufacturer in China.²³ The contaminant (in this case a substance whose physiochemical properties highly resemble that of heparin) was deemed by FDA officials to be deliberate due to its far lower production costs and the finished product manufacturer's inability to identify such an adulteration.²⁴ But there are also other cases. For example, over a hundred patients died in Pakistan in 2012 after taking a heart medicine which had been contaminated with an anti-malaria medicine's API during its manufacturing in a Karachi-based plant.²⁵

In addressing this growing risk the past years have witnessed numerous import bans and product recalls issued on a nearly annual basis by DRAs on foreign API manufacturers, mostly Indian and Chinese, due to serious GMP deviations, regulatory violations, misconduct and intentional fraud.²⁶ For example, numerous Indian manufacturers have received export bans due to GMP violations.²⁷ In addition, a recent investigation by the EMA had led to the suspension of the marketing approval of nearly 700 generic medicines manufactured in India following an inspection by the French DRA (ANSM) which revealed systematic data manipulation of bioequivalence tests for the past five years at least.²⁸

The following sections zooms in on the challenges and opportunities faced by both purchasing countries and their drug regulators as well as manufacturers and regulators on the ground in China and India. As the following section will detail, while it is unmistakably clear that there are serious gaps in both the existing regulatory framework and its enforcement in both of these countries, there are also real opportunities for greater cooperation and regulatory convergence between the relevant authorities in stringent purchasing markets like the US and EU and China and India.



2 INDIA AND CHINA – CHALLENGES AND OPPORTUNITIES IN API MANUFACTURING AND PHARMACOVIGILANCE

The globalization and segmentation of the pharmaceutical supply chain has resulted in a change of roles, as China and India have become the preeminent manufacturers of bulk drugs. Indeed, these two countries are now world leaders in API manufacturing, together responsible for ~80% of the global API market, meaning that very few pharmaceutical products in the world are assembled without their API having been manufactured in either of these two markets.²⁹

Yet regulatory and manufacturing standards in these two markets are not always aligned with international best practices.³⁰ As health and safety concerns have increased and API production has become more concentrated, DRAs around the world have increased their attention towards these two markets.³¹ This has been a process driven by DRAs in both purchasing as well as in India and China themselves.

Within purchasing markets, DRAs must deal with growing safety and quality concerns over imported bulk and finished drugs specifically from China and India.³² Within China and India, DRAs must answer to the growing demand for greater quality assurance from purchasing markets as well as local patients and health professionals by increasing enforcement and improving local manufacturing standards.

In this context, this section provides a detailed account of the current regulatory gaps and challenges in China and India, beginning with an in-depth analysis of API-related GMP Warning Letters Issued by the FDA and the EMA in the past five years.

2.1 Analysis of API-related GMP Warning Letters Issued by the FDA and the EMA, 2010-2014

Many DRAs perform annual inspections of both domestic and foreign pharmaceutical plants. When safety and quality issues are discovered, the DRA issues a warning letter to the plant details the problems and usually set a timeframe for their corrections. Warning letters issued by the FDA and the EMA are published within a publically available database.³³

Looking at API-related GMP warning letters issued by the FDA and the EMA it is possible to see a number of trends, such as continuous GMP violators, suggesting in which markets the main manufacturing and quality problems are concentrated.

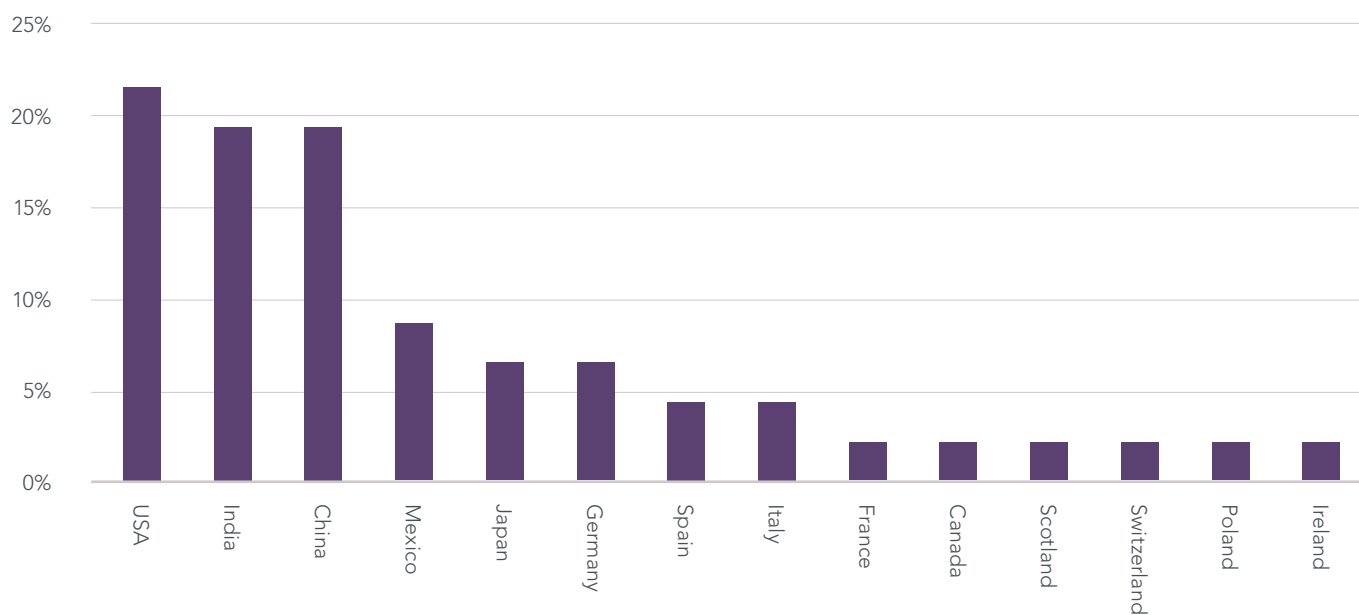
By and large the annual number of warning letters issued to pharmaceutical manufacturers by the FDA is growing.³⁴ It is worth noting a few basic points about these letters. For one, the annual share of GMP violations is not consistent, and can vary according to events such as the heparin crisis or China's promulgation of a new, better GMP standard.³⁵ Nevertheless, the importance of these letters cannot be overstated. These reports reflect negative outcomes of GMP inspections which were carried out by trained personnel from stringent DRAs. As such they provide a reliable account of the actual manufacturing standards and the quality of produced APIs for a given manufacturer, and, as a corollary in a given country.

Looking specifically at API-related GMP violations, an annual average of 9.2 warning letters were issued by the FDA between 2010 and 2014. Their distribution by country of origin is provided in table 1 and figure 2 on the following page:

TABLE 1 API-related GMP Warning Letters Issued by the FDA, 2010-2014

	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014
No. of API-related cGMP warning letters	6	14	8	8	10
Distribution by country of origin:					
US	2	4	1	2	1
India		2		4	3
China	2	3			4
Japan	1	1		1	
Spain		1	1		
Mexico		1	3		
Italy			1		1
Germany			1	1	1

Source: FDA, 2015; analysis: Pugatch Consilium

FIGURE 2 Country of origin's share in API-related GMP Warning Letters Issued by the FDA, 2010-2014

Source: FDA, 2015; analysis: Pugatch Consilium

Two things stand out from the table and figure from the previous page:

- 1) The US, China and India are global leaders in API-related GMP violations with similar shares, and
- 2) The US is the only country in which consecutively at least one warning letter has been issued.

On the face of it this would suggest that quality concerns within the US are at least as serious as those of China and India. However, a different way of looking at this is that the annual rate of domestic and foreign inspections performed by the FDA is not equal. **In other words, China-based and India-based API plants, which outnumber their US counterparts, are under significantly less supervision than American manufacturing plants.**

Indeed, a 2011 report by the Government Accounting Office estimated that using the then rate of inspection the FDA would inspect foreign manufacturers once every 9-13 years.³⁶ In contrast the FDA was required by law to inspect domestic manufacturers once every two years; no such requirement exists for foreign manufacturers which market their drugs in the US.³⁷ In fact, a

more recent report from 2015 by the Department of Health and Human Services' Office of Inspector General shows that the annual number of inspections of US-based API plants is similar to the annual number of all of foreign-based API plants, all over the world.³⁸ For example, in the fiscal year of 2013 the FDA had conducted 252 inspections (43%) in the US and only 180 inspections (31%) in Asia.³⁹ This means that the rate of GMP violations by India-based and China-based manufacturers is much higher relative to the annual number of inspections in these countries. Furthermore, it also suggests that these figures represent only "the tip of the iceberg" and that the actual GMP violations by API manufacturers within these countries may be significantly higher.

Ironically, the FDA's frequent regulatory actions taken against US-based plants have resulted in an increase of offshoring, either by increasing foreign plants manufacturing scale or through CROs, which in turn has led to decreased FDA oversight of these activities.⁴⁰

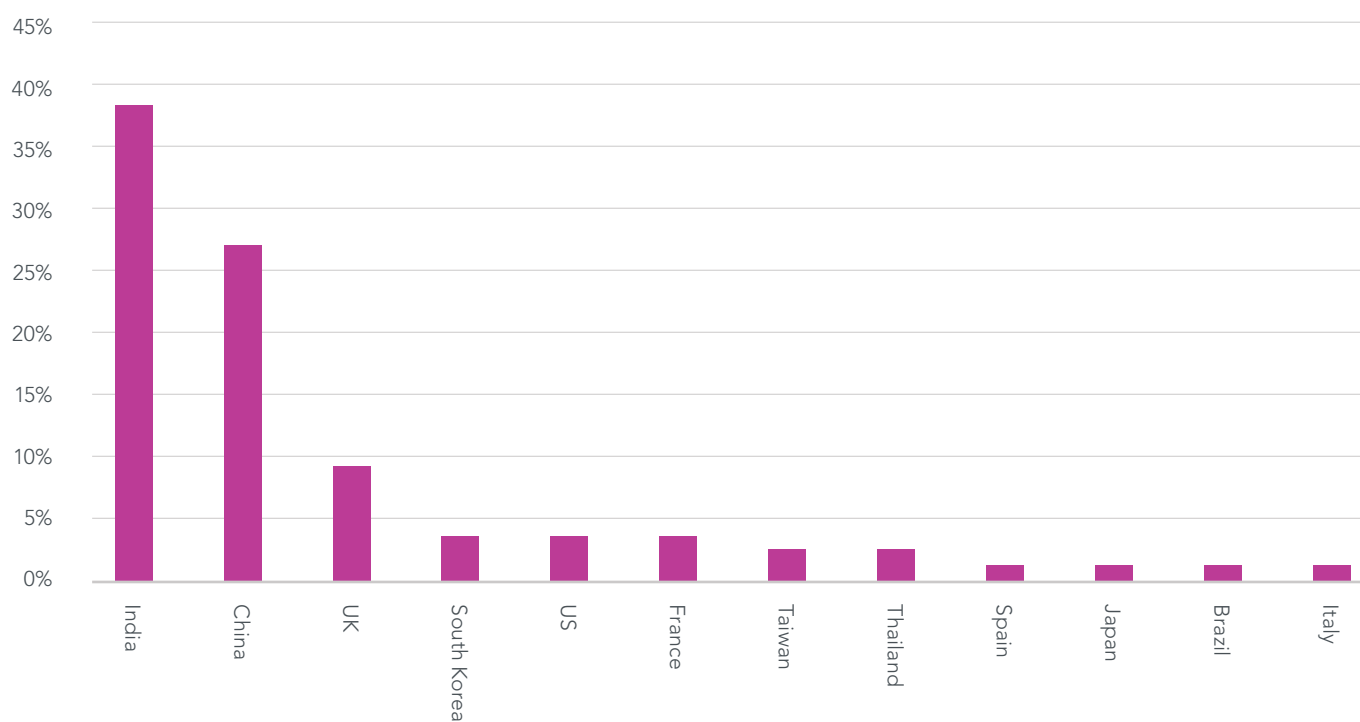
A similar story can be seen when looking at the country of origin's distribution of API-related GMP non-compliance reports issued by the EMA, provided in table 2 and figure 3 on the following page.



TABLE 2 API-related GMP non-compliance reports issued by the EMA, 2010-2014

	2010	2011	2012	2013	2014
India	3	3	11	9	8
China	3	3	4	10	4
UK	1		1	1	5
South Korea		1		2	
US		1	2		
France			2	1	
Taiwan	1				1
Thailand	1			1	
Spain					1
Japan					1
Brazil				1	
Italy				1	

Source: EUDRA-GMDP, 2015; analysis: Pugatch Consilium

FIGURE 3 Country of origin's share in API-related GMP non-compliance report Issued by the EMA, 2010-2014

Source: EUDRA-GMDP, 2015; analysis: Pugatch Consilium

Indeed, examining the annual number of API-related GMP non-compliance reports issued by the EMA shows that India's and China's share amounts to 38% and 27% respectively while the US' share is only 3%. In this case the EMA's the number of warning letters sent to China and India is even greater than that of the FDA.

Taken together, the figures and tables above show that more API manufacturers in India and China continuously violate GMP standard than in any other country inspected by the EMA. This is particularly worrying when considering the low rate of annual inspections: as mentioned, only 31% of the FDA's foreign inspections in 2013 were carried out in Asia. The story is similar for EMA. In 2013 the EMA had coordinated 391 GMP inspections outside the EEA;⁴¹ out of the 25 GMP non-compliance reports issued in 2013, China and India account for 36% each, or 72% together.⁴²

This means that the quality concerns for China and India are justified. It also means that just as for the US data these figures may only represent the "tip of the iceberg".

It is also worth noting that it is not just the EMA and FDA that have noted the API GMP violations in India and China. Other stringent DRAs have suspended the importation of medicines or API produced in facilities that found to have serious quality and safety concerns. For example, Health Canada in 2014 suspended the importation of finished products and APIs from three facilities in India.⁴³ The ban was based on inspections carried out by the FDA who found serious violations of quality and safety protocols at the manufacturing facility. In the press release announcing the ban Health Canada stated that it had "significant concerns with the manner in which data are collected and reported, raising serious doubts about the quality and safety of finished products and APIs produced at these sites".⁴⁴

2.2 Assuring quality in API manufacturing in China and India: Challenges and opportunities

Following the above analysis' results, this subsection provides an overview of China and India's API manufacturing environment and the key regulatory challenges and opportunities these countries face in improving the quality of API manufacturing.

China

China is the world largest supplier of bulk drugs.⁴⁵ There are currently over 1,100 API manufacturers in China, but only 168 (~15%) of them are FDA-approved; of these, only 12 (~7%) are considered "established" companies with some years of experience in supplying major developed markets.⁴⁶

In 1998 a mandatory GMP standard was introduced, and was revised to meet the WHO GMP requirements in 2011 as a part of the 12th Five-Year Plan.⁴⁷ Manufacturers of sterile pharmaceutical products were given until the end of 2013 to adapt to the new requirements. As a result, ~40% of sterile pharmaceutical products manufacturers ceased production due to incapability to comply with the new GMP standard.⁴⁸ Manufacturers of non-sterile pharmaceutical products were given until the end of 2016 to adapt.⁴⁹

China has also initiated several reforms to strengthen its regulatory and legislative frameworks within recent years. For example, up until 2007 manufacturers of counterfeit medicines could only be held liable in accordance with the volume of counterfeit medicines seized; only later did the legislation change to account for harm and injuries caused.⁵⁰ In addition, the Chinese DRA (the CFDA) promulgated a Good Supply Practice standard, and has also issued measures for unannounced inspections of facilities in early 2015. Finally, a collaboration agreement between the USFDA and the CFDA was signed in late 2014, enabling joint inspections of facilities and increasing the number of FDA inspectors in China from 13 to 33.⁵¹

Despite these important steps to improve the regulatory environment China still suffers from high levels of corruption, a large and wide-spread pharmaceutical counterfeiting industry, and lack of resources for effective enforcement.⁵² Indeed, ineffective enforcement has been and remains a major challenge in China, for several reasons. First, evidence suggest high level of corruption which undermines the integrity of CFDA's inspections.⁵³ Second, inadequately-trained personnel often conduct hasty inspections while ignoring protocol, thus risking potential legal actions against violators.⁵⁴ Third, lack of uniformity in the regulatory requirements for publishing inspections results in their selective publishing and sensitivity to potential political considerations.⁵⁵

FIGURE 4 China's API manufacturing environment – strengths and weaknesses

Strengths	Weaknesses
<ul style="list-style-type: none"> • GMP standard revised to meet the WHO GMP requirements in 2011; mandatory for all sterile drug products manufacturers from 2014; non-sterile drug products from 2017 • Collaboration agreements signed with the USFDA • Efforts have been taken by the CFDA and Chinese Government to improve overall quality and fight corruption 	<ul style="list-style-type: none"> • On the ground API manufacturing quality level is still poor • Enforcement of regulatory requirements is largely ineffective • Regulatory gap excludes raw materials manufacturers from CFDA oversight, thus enabling manufacturers to avoid GMP compliance, creating a serious pharmacovigilance risk

Weak and ineffective enforcement has 'on-the-ground' results. A recent academic study which surveyed 47 manufacturers found severe GMP deviations in 93% of the manufacturers surveyed, as well as serious deficiencies in terms of quality assurance and deviations from ICH guidelines.⁵⁶ These findings stand in contrast to the number of Certification of Suitability granted annually by the CFDA which is constantly increasing. Furthermore, the CFDA has also supplied the EU with a GMP certification for over 650 API manufacturers.⁵⁷

China also suffers from a significant regulatory gap involving chemical products, which serve as raw materials for the production of APIs. In China, the manufacturing of chemical products used in the pharmaceutical industry is not regulated by the CFDA.⁵⁸ The CFDA oversees the regulation of API manufacturing, but not of the chemical industry which produces raw materials necessary for manufacturing of bulk drugs.⁵⁹ The CFDA also differentiate API manufacturers from manufacturers of finished products, resulting in an information gap between them which may constitute a potential safety risk.⁶⁰ (A similar gap existed up until recently in the US, as compounding pharmacies were regulated within the state level, beyond the scope of the FDA.⁶¹ In that case, the Drug Quality and Security Act of 2013 extended the FDA's authority over these pharmacies.⁶²) In China this gap has already resulted in one tragic incident, namely the Heparin crisis discussed above, as Baxter's Chinese supplier of the contaminant was registered in China as a chemical manufacturer, thus exempt from CFDA regulation and oversight.⁶³ At the time of research there was no evidence of government intent to address this gap.

This gap in the API supply chain is a clear pharmacovigilance risk which is now being recognized by stringent DRAs, as is evident in new

legislation such as the FDASIA which emphasizes manufacturers' responsibilities over the safety & quality of all the ingredients used in the manufacturing of their products.^{64, 65}

India

India has witnessed rapid growth in its share of the global API market over the last 15 years.⁶⁶ There are currently more than 1,400 API manufacturers in India, yet only 238 of them (~17%) are FDA-approved; of these, only 21 (less than 9%) are considered "established" companies with some years of experience in supplying major developed markets.⁶⁷

Despite their dominance in the global API market, Indian API manufacturers' technical capabilities are relatively limited and serious questions have been raised about their capacity to supply global API demand,⁶⁸ especially with regards to complex molecules and biosimilars.⁶⁹ Moreover, Indian manufacturers (API and finished products) remain under the spotlight of many stringent DRAs, as each year substantial GMP and data credibility issues are discovered.⁷⁰ One prominent example is Ranbaxy, an established India-based global biopharmaceutical company. Since 2008 five of its plants have been prohibited production and distribution of medicines and bulk drugs into the US, a consent decree of permanent injunction was issued, and a \$500 million fine was ruled to resolve cGMP violations allegations and making false claims and statements to the FDA.⁷¹

India faces regulatory challenges on two fronts:

1. The current official GMP standard is not in line with international best practices; and
2. Enforcement of existing standards are patchy and not backed up by a clear and strong national framework.

TABLE 3 Division of API-related regulatory authority and responsibility, Central versus State government, India

Functions undertaken by Central Government	Functions undertaken by State Governments
Statutory functions	Statutory functions
Laying down standards of drugs	Licensing of drug manufacturing
Laying down regulatory measures, amendments to Acts and Rules	Licensing of drug testing laboratories
Testing of drugs by Central Drugs Labs	Approval of drug formulations for manufacture
Publication of Indian Pharmacopoeia	Monitoring of quality of Drugs, manufactured by respective state units and those marketed in the state
Other functions	Pre- and post- licensing inspection
Participation in the WHO GMP certification scheme	

Source: CDSCO (2015); Torstensson, D. & Pugatch, M. (2010).

The current mandatory GMP standard – “Schedule M” – was introduced in 2005 and has not been significantly revised since then.⁷² While the Indian central authority DRA (the CDSCO) officially intends to revise “Schedule M” raising it to WHO GMP requirements by 2015, at the time of research no official changes have been made.⁷³ “Schedule M” is significantly weaker in comparison to existing international standards. This includes a number of important deficiencies. For example:

- the Schedule does not include a clear definition of API or when GMP is applicable in its synthesis process;
- quality management principles and responsibilities are not specified;
- the responsibility for record of quality-related activities, deviations from established procedures and notifying of GMP deficiencies is not specified; and
- quality risk management and the approval of all procedures which affect intermediates or APIs are also not specified.⁷⁴

In addition, the Indian regulatory framework does not contain a clear and acceptable definition of what constitute an adulterated drug, nor deterring penalties in cases of adulteration.⁷⁵

The lack of adherence to international standards is reflected in the number of manufacturers with international accreditation.

According to the CDSCO, in the beginning of 2015 there were 1,329 WHO-GMP certified pharmaceutical manufacturers in India.⁷⁶ However, the World Health Organization database of Public Inspections Reports – which reflects a positive outcome of GMP inspection, as opposed to Notice of Concern⁷⁷ – lists only 28 API manufacturers in India.⁷⁸ Furthermore, the 1,329 WHO-GMP certified pharmaceutical manufacturers constitute only ~13% of India’s 10,000 pharmaceutical manufacturers, most of which do not maintain this standard.⁷⁹ Indeed, many small and medium-size pharmaceutical manufacturers which supply the local Indian market are not incentivized to maintain a higher-level standard than the “Schedule M”, which is considered sufficient for the local market. India’s Drug Controller, G.N. Singh, was quoted saying that the allegations about Ranbaxy’s impropriety and poor standards did not “warrant withdrawal of drugs from the domestic market”,⁸⁰ and that by following US standards India “will have to shut almost all drug facilities”.⁸¹

In addition to a lack of a GMP standard corresponding to international standards, there is also the fact that there is divided authority between India’s central drug regulators and state and regional regulators. Since India is a Federal Republic consisting of 29 States and 7 Union Territories, each with its own local DRA, Indian regulation of manufacturing is split and can vary from one state/region to another. The Federal drug regulator – the CDSCO – has only limited legal authority over drug manufacturers, as is shown in table 3. As this table makes clear, on many critical

FIGURE 5 India’s API manufacturing environment – strengths and weaknesses

Strengths	Weaknesses
<ul style="list-style-type: none"> • Intention to revise the current GMP standard and raising local standards to comply with WHO GMP standard in 2015 • Some manufacturers independently maintain higher GMP standard than the official “Schedule M” 	<ul style="list-style-type: none"> • Current GMP standards still below international norms • Regulatory framework is split and varies between states / regions, causing overlaps, confusion and ineffectiveness • The Federal drug regulator – the CDSCO – has only limited authority, and can only enforce the official “Schedule M” GMP standard • Ambiguity regarding existing “double GMP standards” for exports and local market

issues of quality and safety regulations, there is divided authority between Central Government and the governments of individual Indian States. For example, while the CDSCO is charged with establishing standards of drugs and approving new drugs, State governments have the responsibility for approving drug formulations. That is, State governments approve what substances (for example, excipients in generic drugs) go into the manufacturing process and medicines.

In addition, State governments have the ultimate responsibility when it comes to ensuring that GMP practices and safety and quality procedures are in place and are being followed by manufacturers, sellers and distributors of medicines and pharmaceuticals. This administrative distribution have resulted in discrepancies and lack of uniformity among the various State DRAs, creating overlaps and confusion, as well as differences in their overall effectiveness.⁸²

As is discussed below, the EU’s reliance on GMP certifications issued by the CDSCO presents a serious gap and potential threat to patient safety. The Falsified Medicines Directive (which entered into force in 2013) requires that every non-EU manufacturer adhere to EU equivalent GMP standard. Specifically, the EU’s policy of, in effect, outsourcing the inspection and verification of GMP standards to local Indian authorities is problematic and a potential threat to patient safety.

However, the CDSCO has no legal authority to enforce any GMP adherence throughout India, especially since the WHO GMP is not the formal manufacturing standard in India. In fact, the CDSCO can only impose compliance with a

standard if it is officially established within the legislative framework. Since “Schedule M” of 2005 is the only official mandatory standard, the CDSCO can only issue “recommendations” for manufacturers to comply with higher standards such as the WHO GMP, as it did in a memorandum sent to India’s territorial DRAs in 2014.⁸³ Nevertheless, while 1,329 manufacturers have been accredited as WHO-GMP certified, WHO inspections of Indian manufacturers revealed continuous major GMP violations and data adulterations.⁸⁴

As mentioned, there is also the issue of divided authority and GMP compliance being under the purview of state and regional DRAs. Following the coming into force of the Directive the CDSCO has granted GMP certification to more than 800 APIs in just under two years.⁸⁵ In addition, the number of the Certifications of Suitability granted annually by the CDSCO has tripled from 50 granted in 2007 to over 150 granted in 2013.⁸⁶





3

CREATING AN INTERNATIONAL GOLD STANDARD FOR API MANUFACTURING

Clearly there are real challenges to ensuring manufacturing quality and the safety of medicines in China and India. Yet, the growth and development of India and China as the two dominant players in the international manufacture of APIs also carries with it some real opportunities for regulatory convergence.

Simply put if stringent regulatory authorities and their counterparts in India and China can successfully build on existing efforts of cooperation and harmonization it is possible that international standards of quality manufacturing can be more firmly anchored within existing national and regional regulatory frameworks. As the previous section discussed in some areas there has been greater cooperation – such as a closer dialogue between the CFDA and the FDA – but more needs to be done. This section discusses existing international best practices of high quality API manufacturing and puts together a template or ‘Gold Standard’ for API manufacturing and pharmacovigilance.

3.1 Building a Gold Standard

In 1999, the Active Pharmaceutical Ingredient Committee (an industry body within the European Chemical Industry Council) provided 3 principles which serve as basis for following its GMP standard:

1. “Development should ensure that all products meet the requirements for quality and purity which they purport or are represented to possess;”
2. “During drug development all information directly leading to statements on quality of critical intermediates and APIs must be retrievable and/or reconstructable;”
3. “The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented”.⁸⁷

Unfortunately, these principles do not serve as a mandatory code of practice by all API manufacturers around the world, nor is there international agreement on compliance to an international GMP standard. The incidents and the current state-of-affairs detailed in the preceding section emphasize the pressing need for a “gold standard” in API manufacturing.

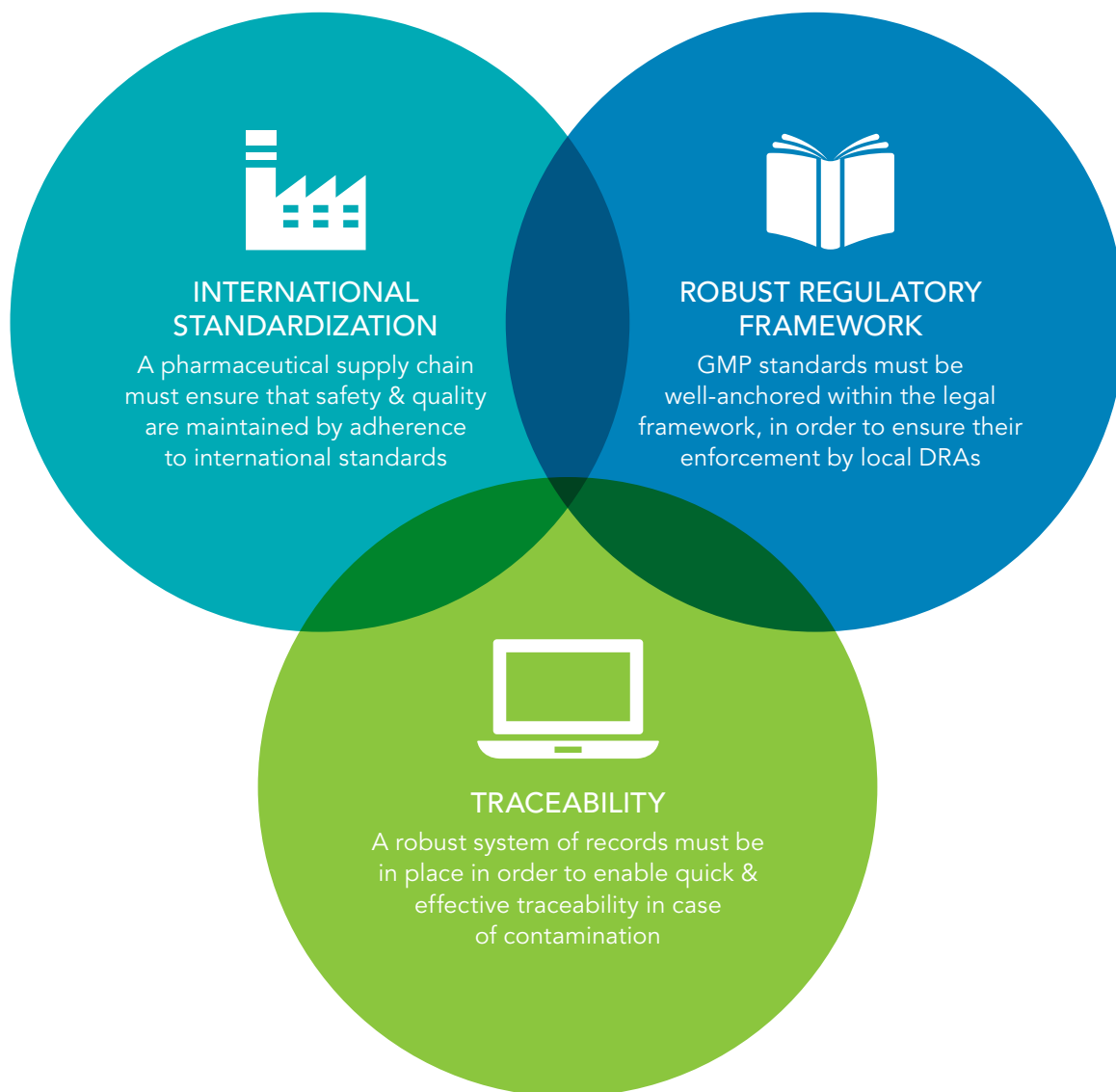
A “gold standard” is not a mere technical account of the manufacturing standards which should be adhered to. A holistic perspective and a broad conception of manufacturing and pharmacovigilance requires taking into account factors which constitute the environment of the pharmaceutical supply chain. Figure 6 on the next page provides a summary of the three main characteristics a “Gold Standard” needs to capture.

The commercial manufacturing of a medicine requires that all of its properties, such as purity, potency and stability, are maintained through the entire manufacturing process.⁸⁸ This can be achieved by adhering to high-end and internationally accepted manufacturing standards, such as the ICH’s Q7 GMP for APIs or similar-level GMP standards. These standards provide a minimum requirement for the establishment of a formal system of controls at a biopharmaceutical manufacturer, which, if stringently applied and put into practice, helps to prevent instances of contamination, deviations, failures, and errors.⁸⁹

3.2 The ICH Q7 – GMP specific for APIs

In November 2000 the ICH released a GMP standard for the production of APIs with the intention of ensuring “that APIs meet the requirements for quality and purity that they purport or are represented to possess”.⁹⁰ The

FIGURE 6 Three essential elements of pharmacovigilance within API manufacturing



standard was developed through a tripartite (US, EU, Japan) expert committee.⁹¹ While some stringent DRAs have later established their own GMP standards the ICH standard has become an accepted international best practice. For instance, the WHO revised its prequalification program GMP standard and adopted the ICH's Q7 principles in 2009.⁹² Table 4 on the following page provides an overview and summary of the standards core elements and is cited verbatim from ICH's standard.

Though comprehensive and detailed at the time of issue, the ICH Q7 is not without issues.

First, its scope is, broadly speaking, limited to chemically-synthesized APIs. This potential gap is particularly important with the growth in biologic drugs and their follow-on biosimilars. Second, since it was issued almost 16 years ago it has not been thoroughly revised to meet current issues. For example, its approach to process validation is mainly technical, focusing on the synthesis and scale-up process, while more current approaches (as taken by the FDA and the EMA) are more holistic and focus on "building quality into the process" by continued verification.⁹³ Third, throughout the ICH Q7 standard rather flexible terminology is employed, such as 'should' instead

TABLE 4 ICH's Q7 GMP for APIs – selected core elements

Policy area	Policy improvements needed
Quality management	<ul style="list-style-type: none"> • Quality should be the responsibility of all persons involved in manufacturing • Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel • There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities • No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s)
Personnel, Buildings and Facilities	<ul style="list-style-type: none"> • The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing • Personnel should avoid direct contact with intermediates or APIs • All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded
Process equipment	<ul style="list-style-type: none"> • Production equipment should only be used within its qualified operating range
Documentation and Records	<ul style="list-style-type: none"> • All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures • Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch
Materials management	<ul style="list-style-type: none"> • Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials • Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s)
Production and in-process control	<ul style="list-style-type: none"> • Any deviation should be documented and explained. Any critical deviation should be investigated • Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs
Storage and Distribution	<ul style="list-style-type: none"> • Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary) • 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 should be transported in a manner that does not adversely affect their quality; 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
Validation	<ul style="list-style-type: none"> • Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes • Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed
Contract manufacturers and other parties	<ul style="list-style-type: none"> • All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide; contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites • All agents, brokers, traders, distributors, repackers, and relabellers should comply with GMP as defined in this Guide; Agents, brokers, traders, distributors, repackers, or relabellers should maintain complete traceability of APIs and intermediates that they distribute.
APIs in Clinical trials	<ul style="list-style-type: none"> • A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials • Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs

Source: ICH, 2000, quoted verbatim.

TABLE 5 Major differences between the ICH's Q7, the FDA and the EU's GMPs

	FDA	EU	ICH Q7
Determine appropriateness of, and/or need to change, product specifications	Required	Required	Not specified
Determine the need to change manufacturing control procedures	Required	Not specified	Not specified
Account for previous reviews of product annual review / product quality review	Expected	Required	Not specified
Inclusion of starting materials and packaging materials in product annual review / product quality review	Not specified	Required	Not specified
Inclusion of contract manufacturer responsibility in product annual review / product quality review	Not specified	Required	Not specified

Source: Grazal, J. G., Lee, J. Y. (2008). "Product Annual/Quality Review: US–EU Comparative Analysis and Interpretations", *Pharmaceutical Technology*, Vol. 3, Issue 32.

of 'must',⁹⁴ thus leaving potential for variation from one implementing body to another.

In addition, as GMP standards have evolved, the ICH Q7, which was not thoroughly revised since its issuance in 2000, lacks regulatory requirements that are now required by most stringent DRAs. In this regard, the ICH has recently issued a Q&A paper which addresses some of its inherent gaps and issues.⁹⁵ Yet differences between the ICH Q7 and more current GMP standards still exist. Table 5 gives an overview of these major differences.

3.3 Enforcement and application

While having appropriate standards and guidelines in place is of obvious importance, simply adhering to the GMP textbook is not enough to ensure that quality is maintained, for several reasons.

First, many, if not most, of the world's API manufacturers rely on different suppliers for raw materials, or starting materials, which are often imported. For example, Indian API manufacturers import up to 90% of raw materials from Chinese suppliers.⁹⁶ In most mature markets with stringent regulations manufacturers of finished products are legally responsible for ensuring the use of high-quality ingredients throughout all stages of the production process.⁹⁷ Thus, it is the responsibility of an API manufacturer to ensure that only high-quality ingredients of pharmaceutical grade are used.

Second, a decrease in the level of quality of raw materials and starting ingredients as well as the bulk drug (the finished API) can occur due to improper conditions of storage and transportation, such as temperature and humidity control. These deviations in quality can lead to changes in the bulk drug's physiochemical properties, stability, and its safety profile.⁹⁸ The longer and more geographically spread out supply chains are, the greater the risk there is for degradations caused by poor storage and transportation techniques.

Third, impurities in raw ingredients can result from various sources, such as organic or inorganic or solvent residuals.⁹⁹ Impurities can also be the result of deliberate adulteration. Yet their detection by the API manufacturer is not guaranteed. First, a relatively advanced technological capability is required; yet not all API manufacturers are competent in this respect.¹⁰⁰ Second, following compendial standards does not always ensure detection of unpredicted contaminations as a result of different manufacturing processes.¹⁰¹ And finally, deliberate adulterations may be planned specifically to surpass any testing.¹⁰²

In this respect, stringent DRAs have begun implementing new risk-based approaches, whose underlying premise is that quality cannot solely be tested. Instead quality should be built-in to existing processes and through design.¹⁰³ One part of this approach as implemented by the FDA

is the QbR. This specific development enables manufacturers to submit a product development report from which “reviewers will learn how drug substance and formulation variables affect the performance and stability of the drug product”.¹⁰⁴ In addition, the QbR review template contains standardized review questions.¹⁰⁵

The globalization of biopharmaceuticals means that DRAs across the world share the responsibility of ensuring that high quality is maintained in local manufacturing for domestic and exporting purposes as well as in imported raw materials. Yet DRAs differ not only in their capabilities but also in the regulatory framework which empowers them. For instance, as noted the Indian DRA does not have the authority to enforce international GMP requirements.¹⁰⁶

Where a robust regulatory framework is in place as well as the resources to ensure its enforcement on the ground, the integrity of the local pharmaceutical supply chain can be secured. Ideally that would be the case for each country. Unfortunately considerable gaps still exist in some DRAs, mainly in poor enforcement capabilities and/or inadequate regulatory framework, either due to poor standards and/or lack of authority. As the examples of China and India illustrate, this is a key concern for patients and regulators around the world as regulators and patients in purchasing markets are relying on the regulatory authorities in manufacturing countries and their raw ingredient suppliers to maintain adequate levels of quality and safety control.

In this context, the first essential element of a robust regulatory framework concerns its scope and extent of authority and oversight of the various components of the pharmaceutical supply chain. Where regulation is not comprehensive or there is a lack of application and enforcement of existing rules and regulations the risk of manufacturing and circulation of substandard and counterfeit medicines is much greater.¹⁰⁷ For example, recent research shows that medicines manufactured by WHO-approved manufacturers perform as much as five times better than medicines manufactured by non-WHO-approved manufacturers, mainly due to a significantly higher portion of substandard medicines containing less than 75% API, originating from Indian and Chinese manufacturers.¹⁰⁸ Yet this research also

underlines the fact that having higher standards in place is not enough, they must also be enforced. For instance, this study also shows that a similar percentage of substandard medicines were manufactured both by Chinese WHO-approved and non-WHO-approved manufacturers.¹⁰⁹

In addition to a comprehensive regulatory framework it is essential to ensure effective, sufficiently-resourced on-the-ground enforcement of these regulations. Indeed, while adopting high-level manufacturing standards is laudable, it is nevertheless an essential yet insufficient condition for successful quality assurance. Lack of actual enforcement might result from three major factors. First, some DRAs lack the resources, either financial or human resources to conduct routine inspections. Inspections necessitate advanced technical knowledge and skilled personnel. Second, a high corruption rate also hinders effective enforcement of regulation. For example, in 2007 it was revealed that the head of the Chinese CFDA (then called SFDA) had taken bribes during his 8-year tenure in return for the approval of over 150,000 medicines, at least six of them fake.¹¹⁰ Third, matters of jurisdiction and federal authority can also hinder enforcement. For example, as discussed, enforcement of GMP in India is under the authority of each Indian state or regional DRA, and the Indian central DRA – the CDSCO – has only limited authority in this respect.¹¹¹

The third element is the establishment and maintenance of a secure and robust track-and-trace system, which enables quick and effective tracing and tracking in cases of contaminations. The FDA and the EMA have begun implementing new regulatory requirements of electronic barcoding and serialization which have been anchored within legislation, and are expected to deter counterfeit medicines. In the US, as of January 1 2015, all actors within the supply chain – manufacturers, wholesalers, dispensers etc. – are compelled under law to establish systems of record keeping and medicine verifying. In addition, by 2020 all of the marketed medicines by all these actors must bear a unique product identifier.¹¹² In the EU a similar model was implemented within the Falsified Medicines Directive of 2011,¹¹³ ensuring that “any medicine sold in the EU can be verified at point of dispensing using individual pack level serial numbers before being given to the patient”.¹¹⁴



By keeping an electronic record of a given medicine's pedigree – “a statement of origin that identifies each prior sale, purchase, or trade of a drug, including the date of those transactions and the names and addresses of all parties to them”¹¹⁵ – DRAs that introduce such measures would be able to conduct quick and effective tracking and tracing in cases of contaminations, while also deterring circulation of counterfeit medicines.

Finally, all these elements that compose a robust regulatory framework must be well-anchored within the national and/or regional legislation. Indeed, legislation constitute the backbone of the regulatory framework: it defines the regulator's scope and extent of authority, set stakeholders' responsibilities and impose penalties and legal remedies in case of violations. Where legislation is lacking or too broad, actual deterrence by legislative means – such as fines and legal remedies – might be ineffective. As mentioned, up until 2007 in China manufacturers of counterfeit medicines could only be held liable in accordance with the volume of counterfeit medicines seized; only later did the legislation changed to account for harm and injuries caused.¹¹⁶

The 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) serves as a good example of legislation which expands the drug regulator's authority in order to “address the challenges posed by an increasingly global drug supply chain”.¹¹⁷ One prominent measure within this law is the FDA's extended authority to perform administrative detention of any drugs which are suspected as adulterated or misbranded, “until FDA has had time to consider what action it should take concerning the drugs, and to initiate legal action, if appropriate”.¹¹⁸ In addition, the FDA has issued guidelines on the “Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection”, as well as established higher penalties for adulterated and counterfeit medicines.¹¹⁹

Looking at pharmacovigilance and model frameworks for API production the EU Directive 2011/62/EU of 2011 serves as a good example of a “pharmacovigilance” legislation. This Directive, also referred to as the Falsified Medicines Directive, was adopted and published mid-2011 and entered into force only in January 2013. It has introduced several measures, such as stringent labeling, packaging and record-keeping requirements. It has also introduced a new requirement under which imported APIs are subjected to two conditions:

“(a) the active substances have been manufactured in accordance with standards of good manufacturing practice at least equivalent to those laid down by the Union...; and

(b) the active substances are accompanied by a written confirmation from the competent authority of the exporting third country...”¹²⁰

What this legislation provides is a *de facto* quality assurance by imposing high-end manufacturing standards for APIs as a pre-condition. This also bears international significance, as it also applies to APIs which will be assembled into finished products within the EU and will be exported into other countries.¹²¹

3.4 A ‘Gold Standard’

The three elements of a ‘gold standard’ described above are summarized below in Figure 7.

FIGURE 7 A 'gold standard' of API manufacturing

The manufacturing level

- Ensure adherence to high-end, up-to-date international standards of good manufacturing practices, such as the ICH Q7 or the WHO GMP for Active Ingredients
- Ensure exclusive use of high quality ingredients originating only from authorized and regulated suppliers
- Ensure that high-end, up-to-date international standards of Good Distribution practices are maintained by suppliers of raw materials as well as by distributors of the finished bulk drugs
- Implement and maintain a risk-based strategy, with an emphasis on building quality into the product by understanding stringent DRAs regulatory requirements

The regulatory level

- Provide local drug regulators with broad authority and oversight, in order to cover as many actors in the pharmaceutical supply chain as possible, including manufacturers of raw materials
- Ensure that the roles and responsibilities of all actors involved are set, in accordance with WHO and ICH guidelines
- Maintain an effective, sufficiently resourced enforcement mechanism adhering to international standards of safety and quality as well as additional regulatory requirements, using highly skilled and trained personnel
- Establish and maintain a secure and robust "Track & Trace" system of all marketed biopharmaceutical products and their ingredients, according to international standards, and make it mandatory for all actors in the pharmaceutical supply chain
- Ensure the existence of an exhaustive and robust legislative framework, which:
 - Defines the responsibilities of every actor involved in API manufacturing
 - Ensures adherence to high-end international standards of manufacturing and distribution
 - Deters misconduct (e.g. GMP deviations, data adulteration etc.) and substandard and counterfeit medicines circulation by offering heavy penalties and legal remedies



4

KEY FINDINGS AND CONCLUSIONS

This report has highlighted serious regulatory and quality gaps in API manufacturing in China and India, specifically in adhering to high-end manufacturing standards and their enforcement by local drug authorities.

These gaps illustrate how securing the integrity of the pharmaceutical supply chain - from the production of raw materials to the dispensing of a final product in hospitals and pharmacies – is a shared concern of all actors and stakeholders, manufacturers, wholesalers, distributors and regulators in all jurisdictions.

The central research question this report has looked at is: With API production increasingly concentrated in India and China, how do drug regulators in purchasing markets (such as the FDA and EMA) better ensure the safety of patients in their markets?

This report findings can be grouped around four main or key areas that touch on this question and maintaining the quality manufacturing and pharmacovigilance of API production and distribution.

Key finding 1: A drug regulator's world is now global, not local

This report's mapping of international API manufacturing practices confirms that drug and medical regulatory responsibility and pharmacovigilance is no longer confined or limited by geography or legal jurisdiction. Rather, to ensure the safety and quality of a given biopharmaceutical end product regulators and authorities must monitor and inspect a product all the way from raw material and API to finalized products. In practical terms it means that drug regulators in purchasing markets (such as the EU and US – the world's biggest biopharmaceutical markets) must now actively inspect and have a presence outside their respective legal jurisdictions.

Only in recent years have drug regulators in purchasing markets become cognizant of this new reality. However, recent legislative developments within the two leading stringent DRAs – the FDA and the EMA – suggest that divergent paths are being taken. While the EU's Falsified Medicines

Directive has shifted much of the responsibility of ensuring the quality of medicines imported into the EU over to the exporting country's DRAs, the FDA's new powers has broadened its authority and enabled it to apply swift measures to ensure public health.

The path taken by the EMA is striking, especially in light of the high number of Indian and Chinese API manufacturers within the annual number of GMP non-compliance reports issued by the EMA, as this report highlights. Indeed, shifting responsibility for quality assurance of imported medicines to foreign DRAs which may lack the capacity for effective enforcement and inspection is questionable, particularly where the official GMP standards are not as strong as international best practices. Nevertheless, the EMA has in the past stated that it is satisfied with the confirmations given by foreign DRAs under the new Directive, despite concerns raised by other organizations regarding foreign DRAs enforcement capabilities.¹²²

The approach taken in the US is different. Under the Safety & Innovation Act of 2012 and the Drug Quality & Security Act of 2013 FDA's authority has been extended and strengthened considerably including: for administrative detention of suspicious drugs, definition of all actors' responsibilities in maintaining quality throughout the entire supply chain, timeframes for the establishment of an electronic track and trace system, and a requirement of the FDA to identify every part of the entire supply chain of imported drugs. Moreover, the FDA and US Government has identified as a priority the need for greater levels of staffing and inspections rates in China and India by FDA officials.

Equally, the growing strength of India and China's domestic exporters means that their DRAs must work toward not only upholding regional and national manufacturing and pharmacovigilance standards but also international standards.

Key finding 2: API manufacturing is plagued by concerns over substandard quality and GMP irregularities

The API manufacturing and pharmacovigilance environment in the two largest producing countries, China and India, is currently lacking with regards to both the presence of adequate GMP and pharmacovigilance regulations as well as their enforcement. China suffers from high levels of corruption, a large and wide-spread pharmaceutical counterfeiting industry, and a lack of resources for effective enforcement. Additionally, the CFDA does not regulate the chemicals industry which provides the raw ingredients for API manufacturing. In India the current official GMP standard – “Schedule M” – has not been revised since its issuance in 2005 and it is not as strong as international best practices as captured in ICH Q7 for example. Furthermore, the enforcement of existing standards are patchy and not backed up by a clear and strong national framework.

Analysis of both FDA and EMA warning letters show significant problems relating to quality control and integrity of API manufacturing in India and China. Examining the annual number of API-related GMP non-compliance reports issued by the EMA between 2010-2014 this report found that India’s and China’s share amounts to 38% and 27% respectively; by far the two largest violators. Both countries received the highest share of foreign letters by the FDA as well. This is particularly worrying as foreign inspection rates by the FDA and EMA are far behind equivalent inspection rates within the US and EU. The FDA is required by law to inspect domestic manufacturers once every two years; the US Government Accounting Office estimated in 2011 that the FDA would inspect foreign manufacturers only once every 9-13 years.

Key finding 3: Bilateral cooperation and dialogue between stringent DRAs and DRAs in manufacturing markets no longer a choice but a necessity

Given the new realities of living in a global production and marketplace regulators in purchasing markets must foster closer bilateral cooperation with regulators in manufacturing markets. This report has found that while this is an area where action has been taken in recent years (see for example the recent agreements between

the CFDA and FDA) there is still considerable room for closer cooperation and harmonization of monitoring and inspection efforts.

Key finding 4: Adherence to international standards of API manufacturing and pharmacovigilance are still lacking

Agreeing on and enforcing international standards and best practices of API manufacturing and pharmacovigilance is of increasing importance to patients across the world. Although the emphasis in developed markets has been on ensuring domestic patient safety, it is equally imperative that medicines and APIs exported from manufacturing countries to developing country markets as well as produced for local consumption meet the highest international quality standards. Efforts at international harmonization have been in place for some time through, for example the ICH Q7 Guidelines, yet neither China nor India have adopted or enforced this measure in full.

Conclusion and final thoughts

Together these findings add up to a new reality for regulators and patients alike. The globalization of biopharmaceutical production combined with the concentration of API manufacturing in markets where standards of quality, production practices and pharmacovigilance are not always aligned with international best practices mean that geographical and legal jurisdictions are less important and cooperation and regulatory convergence are instead at the top of the agenda. Regulators in stringent regulatory markets have begun to recognize and put into place new processes and procedures to face this new reality. There is also a growing recognition and international discussion of the quality and safety concerns in API manufacturing markets; indeed the FDA has been at the forefront of this. However, stronger efforts are needed in the area of bilateral cooperation and international regulatory convergence. Strong standards of API manufacturing are in place within the ICH Q7 and international industry best practices, but greater efforts are needed to adopt and actively apply these standards in manufacturing markets. The international ‘Gold Standard’ amalgamated in this report is a good starting point and highlights the need for a more comprehensive and holistic approach to what is in effect becoming the international regulation of API manufacturing.



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