

# Taking a Leap Toward Global Supply Chain Efficiency - Part II



## INTRODUCTION

Pharmaceutical manufacturers face a number of challenges in the production and delivery of medicinal products (i.e., medicines, vaccines and biologics) via wholesalers and pharmacies to patients around the world. The purpose of this brochure is to outline and promote practical solutions to improve upon these challenges in global supply chain and product distribution that manufacturers, distributors, wholesalers, national regulatory authorities (NRAs) and other stakeholders need to overcome to ensure that medicinal products are delivered safely, reliably and efficiently to patients.

## ABSTRACT

Good distribution practices (GDPs) are key to the delivery of safe, authentic and high quality products to patients. Challenges to GDPs include issues related to sourcing of raw materials, shipping and storage, theft and falsification, and unauthorized delivery by unapproved pharmacies and websites. Serious product losses have been attributed to raw material supply and inadequate environmental control, including temperature verification. These GDPs failures can contribute to broader drug shortages as an entire batch might then be deemed unfit for purpose. Similarly, the potential introduction of falsified medicines due to poor GDPs are a real threat to public health and patient safety, and can lead to additional losses of product and drug shortages. For example, batches may be rejected if falsified medicines enter into the legal supply chain, or if adulterated medicines are not removed from the supply chain before dispensing to patients. Poor GDPs can also result in increased incidences of theft and less product being available to patients, or worse, made available again after improper handling and/or potential tainting. Enabling GDPs will also be addressed in this brochure.

## PROBLEM STATEMENT

The complexity concerning the production and supply of medicinal products, particularly for products that utilize globalized manufacturing processes and distribution channels, needs to be evident to NRAs and other stakeholders. GDPs are essential to the delivery of safe, authentic and high quality products to patients. There are numerous challenges to GDPs and hence necessary mitigating actions are required to secure and enable safe supply of medicinal products to all patients.



## A CALL TO ACTION

The complexity concerning the production and supply of medicinal products needs to be evident to NRAs and other stakeholders. GDPs are essential to the delivery of safe, authentic and high-quality products to patients and can assist in combating falsified medicines. Proper handling, storage and transport; oversight by NRAs; risk management approaches; and industry involvement are key elements for resilient supply chains and uninterrupted supply of quality products.

## EXECUTIVE SUMMARY



1. Strong GDPs, with the aim to reach global harmonization, are critical elements for ensuring that the medicinal products delivered ultimately to patients are safe and efficacious, and can assist in combating falsified medicines.



2. Proper handling, storage and transport requirements of medicinal products, which may vary by product, are crucial to ensuring that these products remain safe, efficacious, genuine and of unaltered quality.



3. Flexibility backed by appropriate risk management approaches is a key element of resilient supply chains, as it enables industry to adapt quickly to changing conditions (e.g., raw material shortages, increased demand, using alternative transportation route or means of delivery).



4. NRAs' oversight must ensure uninterrupted supply of quality products to patients, especially when changes in the supply chain are necessary.



## 1. **SOURCING RAW MATERIALS**

A secure and robust supply chain consists of multiple sources of ingredients, or raw materials, that a manufacturer uses to produce medicinal products. A shortage of any one of these ingredients may result in a supply disruption. Manufacturers of pharmaceutical products enable a robust supply chain by establishing multiple, redundant sources of raw materials as a safeguard against shortages. Manufacturers provide oversight of raw material suppliers, including vendor audits, as these measures ensure raw material suppliers meet the high-quality standards necessary for medicinal products. Additional assurance of raw material quality is provided by incoming testing of materials, which further assures that the material has not been altered during transfer from the raw material vendor to the medicinal product manufacturer. Enabling medicinal product manufacturers to establish multiple sources of raw materials (including alternative supplier of active pharmaceutical ingredients – APIs – addressed in dossier) is a key component of a healthy supply chain, since it enables manufacturers to react quickly to replace the depleted material.



## 2. REQUIREMENTS AND GUIDELINES

The ability of NRAs to converge on more harmonized requirements for robust supply chains within regions or preferably worldwide, is critical to ensure uninterrupted access of patients to the medicinal products they need. Currently diverging requirements - country to country - can cause interruptions to supply chains affecting supply (see example). Global convergence of regulations, scientific data requirements and interpretation of data are essential to reducing supply chain issues.

Harmonization efforts can be supported by industry and organizations (e.g., the World Health Organization – WHO; the Pan American Health Organization – PAHO; the Pan American Network on Drug Regulatory Harmonization – PANDRH; and the Asia-Pacific Economic Cooperation – APEC) that can develop and provide guidance or standards that all participating NRAs should adopt. Additionally, quality risk management is a key enabler to current supply chain requirements and needs to be expressed more clearly across NRAs. Moreover, better communication between agencies responsible for importation and the NRAs that receive and manage product registration information can help resolve documentation requests, including information related to any temperature excursions that may occur for products being imported.



### EXAMPLE

The ability of both manufacturers and NRAs to adapt to and find new solutions to manage this increased complexity is critical to assure the best possible and uninterrupted access of medicinal products needed by patients. Global convergence of regulations, scientific data requirements and interpretation are essential to achieve this goal. In this effort, WHO and the International Council on Harmonization (ICH) are key partners for NRAs, industry, patients and other stakeholders.

Many intended changes to manufacturing inputs and control parameters must first be reviewed and approved by NRAs prior to implementation and distribution of the post-change product. This review is important to minimize the risks associated with loss of integrity in the supply chain for medicinal products. Unfortunately, the variability in review time required by each NRA can often lead to a global divergence of pending regulatory approvals. The net result is fragmented implementation of these manufacturing changes between various regions and countries. As more changes are needed and overlap, a product process version may be years apart between countries causing supply chain inventory problems until all countries catch up and approve the manufacturing or quality control change.

# 5 ways to Getting the Supply Chain in Sync - Part II



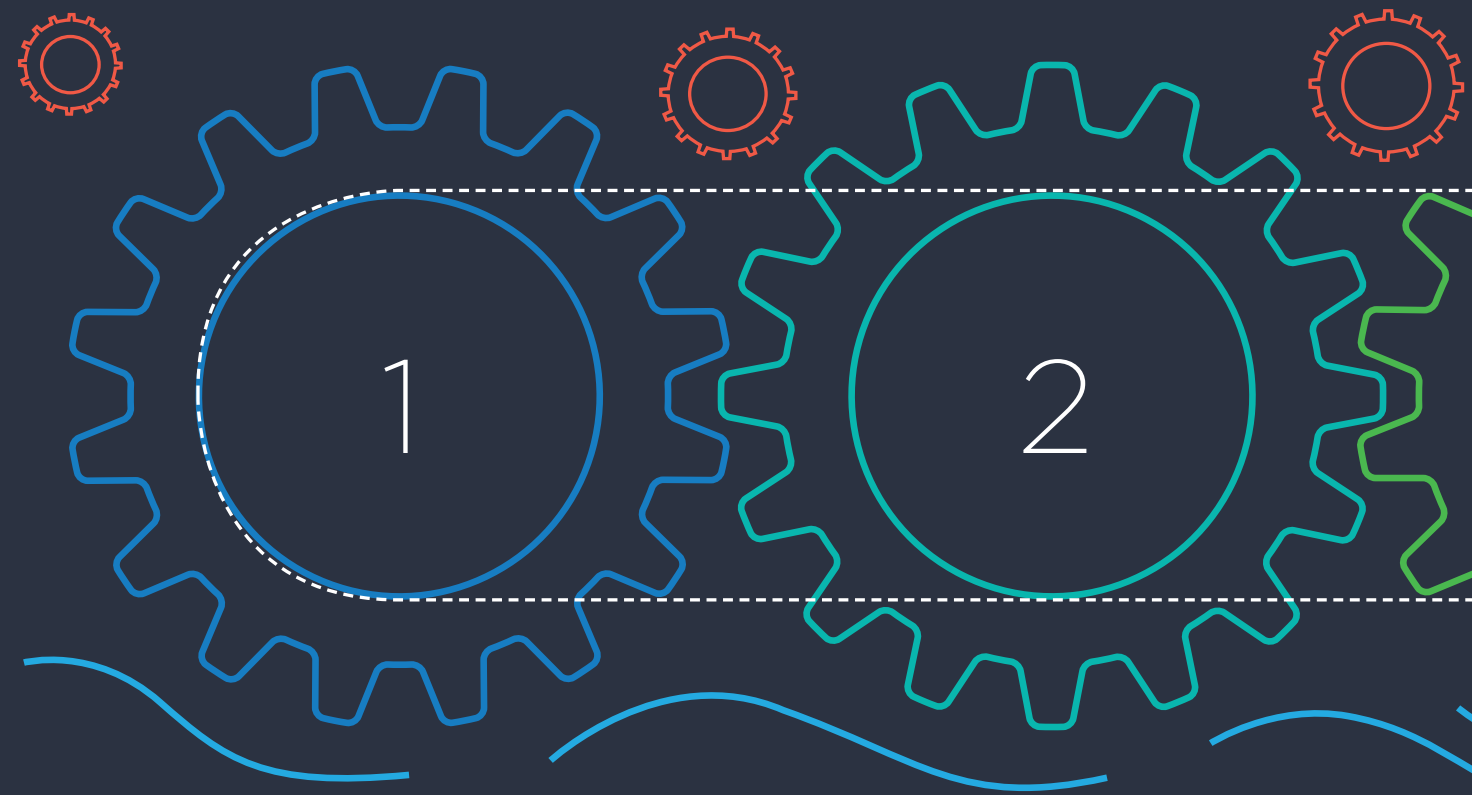
CHALLENGES

## SOURCING RAW MATERIALS

- Secondary vendors

## REQUIREMENTS AND GUIDELINES

- Non-harmonized local requirements
- Separate agency in charge of importation vs. registration



ENABLERS

- Vendor audits
- Identification testing

- Expansion of the quality management system to include quality risk management
- Train inspectors
- Help develop guidance and standards

## SHIPPING AND STORAGE

- Environment excursions:
  - Temperature
  - Humidity
  - Light
  - Vibration
  - Air pressure
- Disruption in transport

## INTEGRITY (THEFT AND FALSIFICATION)

- Products with fake identity, composition, source or history
- Internal and external theft

## IMPORT AND EXPORT

- Unauthorized import
- Unapproved pharmacies and websites
- Import holds



- Validated containers
- Monitoring
- Validated transport and cold chain

- Tamper-evident packaging
- Serialization
- Overt and covert special labeling components
- Anti-hijacking measures
- GPS tracking

- Internet surveillance monitoring
- Dedicated import and export staff

### 3. SHIPPING AND STORAGE

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Shipping medicinal products via wholesalers and pharmacies to the right patient at the right time with the assurance that product quality, safety, and efficacy are not altered at any level in the supply chain is challenging. This is mainly due to pharmaceutical manufacturers utilizing, in most cases, complex networks that encompass many warehouses across different countries with diverse transportation mechanisms prior to reaching patients.

Many potential transportation and storage hazards must be identified via a risk-based approach, assessed, and only then may a mitigation strategy be established and finally monitored for effectiveness using the knowledge, experience and understanding of the various sources of risk in the supply chain. Requirements and conditions necessary for individual products must be initially carefully established and appropriately used and interpreted.

Challenges to shipping and storage conditions include the following categories: atmospheric (e.g., temperature, humidity, light, and air pressure); mode of transport; duration and location of various stop over points along routes; shock and vibration among others. These risks can be experienced through different cycles and length of duration.

Enablers to counter such risks are varied, but include the use of validated certified transit containers for packages and properly qualified transport carriers. Accurate and valid procedures for testing and monitoring conditions during transportation exist but must be more universally adopted if stakeholders are to assure patients that they are receiving medicines that meet manufacturers' quality specifications after leaving a manufacturing site.

Closer collaboration and exchange among all stakeholders in the supply chain (NRAs, manufacturers, freight forwarders, logistics and service providers, distributors, wholesalers, pharmacies and patients) would vastly mitigate some of the issues caused by the complexity of today's supply chain.



## 4. INTEGRITY - THEFT AND FALSIFICATION

Product integrity (protection against theft and falsification) is of utmost importance to patients all around the globe. The use of medicinal products whose identity, source and history cannot be verified can lead to more harm than the conditions they are intended to treat. A falsified medicine is any medicinal product with a false representation of its identity (packaging and labelling, name or composition and the strength of its active pharmaceutical ingredients), its source (manufacturer, country of manufacturing, country of origin or marketing authorization holder) or its history (including the records and documents related to the distribution channels used)<sup>1</sup>.

GDPs, including the European Union GDPs Guidelines, lay down some tools designed to prevent falsified medicines from entering the legitimate supply chain as well as prevent pharmaceutical theft from a general perspective. Qualification of suppliers and customers lies at the forefront of the fight against falsified medicines whereas supply chain participants are required to carry out “due diligence” checks to assess the suitability, competence and reliability of their suppliers and customers. Furthermore, all personnel must be regularly trained; the training of which should include aspects of product identification and identification of suspicious medicines entering the legitimate supply chain.

Despite all this, the tools provided by the GDP guidelines by themselves are not sufficient to adequately protect the supply chain from theft or falsification. This is why governments in numerous countries around the world have started implementing serialization requirements (at various levels) as well as asking manufacturers to include tamper-evident solutions on their packaging lines, which include both overt and covert technologies on their product packages. Individual companies (manufacturers and distributors) are also stepping up their efforts to increase security (protection against theft, diversion, tampering) through activities such as monitoring, use of global positioning satellite tracking, or implementing anti-hijacking measures. It is critical that systems be implemented in a step-wise, scalable manner, with realistic timelines and with suitable consultation with relevant stakeholders. These additional measures should also be established in conjunction with NRAs using globally recognized common standards so that fragmentation is minimized and harmonization is increased worldwide<sup>2</sup>.

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<sup>1</sup> European Union Falsified Medicines Directive (DIRECTIVE 2011/62/EU)

<sup>2</sup> IFPMA-EFPIA-PhRMA position paper “Serialization and Product Verification – Helping to Secure the Legal Supply Chain for Greater Patient Safety”.

## 5. IMPORT AND EXPORT

A trend that has impacted all manufactured products and pharmaceuticals in particular is the globalization of manufacturing. Prior to the late 1990's, many pharmaceutical companies produced APIs or bulk drug substance on site and completed finishing and packaging in close proximity. Currently, with globalization, manufacturing processes are much more specialized and spread among individual sites across the globe. For example, excipients, raw materials and pharmaceutical production often - if not usually - will take place in many countries. Also, once a pharmaceutical product is in its finished package form (and there may be multiple finishing sites) the product needs to be distributed to potentially more than 100 countries, each with its own regulatory requirements. Consequently, numerous NRA GDP requirements must be considered by manufacturers, wholesalers and other relevant stakeholders. However, a key subset of the GDPs that could be strengthened by NRAs are good import practices. Basically all imports begin as exports, i.e., raw materials and finished products being imported is exported from another country.

Regarding pharmaceuticals, all products that cross into another country's borders will go through customs and sometimes through that country's Ministry of Health. For finished medicinal products the manufacturer must:

1. have marketing authorization to import (sell) into the importing country; and
2. ship it to an authorized entity within the importing country.

Despite all these requirements and the development of compliant tools implemented by manufacturers, imports are a weak spot in the pharmaceutical supply chain due to the increased manufacturing complexity resulting from globalization. Nevertheless, many pharmaceutical manufacturers are strengthening their quality system by:

1. auditing their import brokers;
2. sharing importation data with importer of record; and
3. including importation control into their quality management system.

In conclusion, the movement of medicinal products across borders is a weak link in the pharmaceutical supply chain. Stakeholders in the supply chain need to work together to develop and integrate good import practices into GDP processes to help strengthen oversight and quality controls.





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## ABOUT IFPMA

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry's 2 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide.

Based in Geneva, IFPMA has official relations with the United

Nations and contributes industry expertise to help the global health community find solutions that improve global health.

## ABOUT IFPW

The International Federation of Pharmaceutical Wholesalers (IFPW) represents full-service pharmaceutical wholesalers, distributors and wholesaler associations in 26 countries, and provides a strong, effective platform to establish strong dialog within the global pharmaceutical community. The association is dedicated to helping its members and stakeholders advance the safe, efficient and continuous access to pharmaceuticals worldwide through the promotion of good distribution practices and services.

## ABOUT RX360

Rx360 an International Pharmaceutical Supply Chain Consortium. Rx-360's mission is to protect patient safety by sharing information and developing processes to improve the integrity of the health care supply chain and the quality of materials within the supply chain.



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