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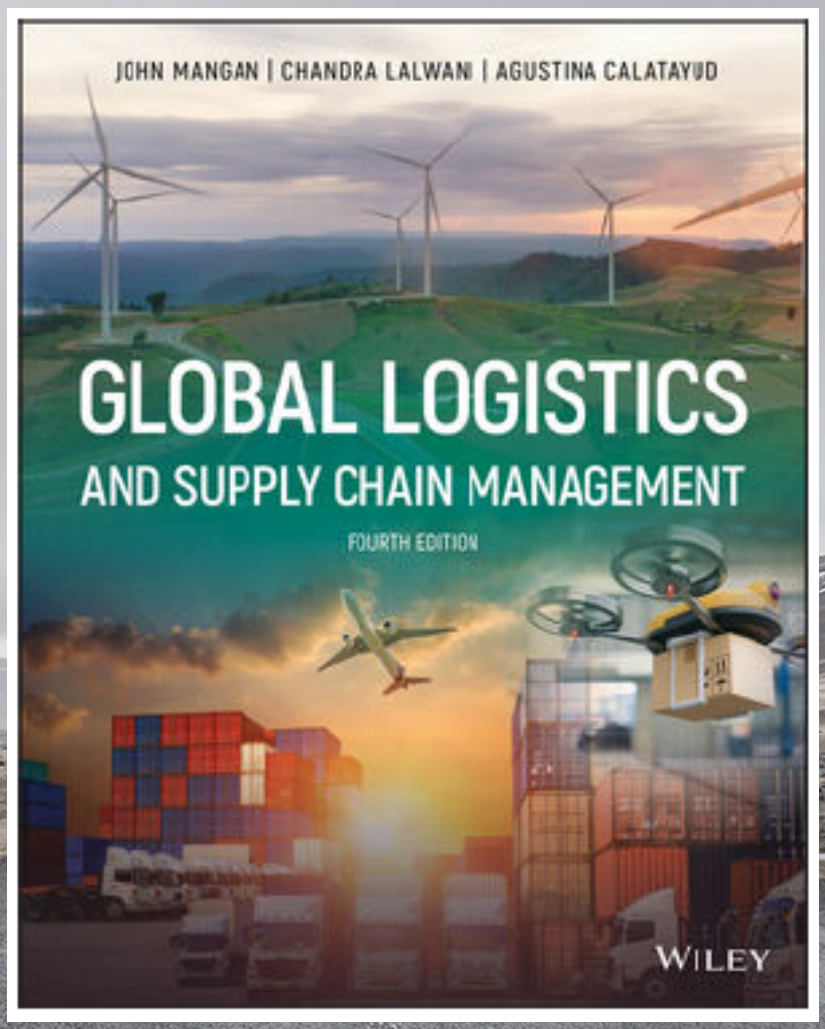

Patient Safety and the Pharmaceutical Supply Chain

Ciarán M. Brady

PLS Pharma Ireland & UK

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This case study focuses on patient safety in the context of the pharmaceutical supply chain, in particular in the European context. However, the lessons illustrated here are applicable in most other jurisdictions too.

OPERATION PANGEA

Shining a light on pharmaceutical crime and protecting consumers all over the world from counterfeit medical products.

Coordinated by INTERPOL, Operation Pangea, is a well-established international effort to disrupt the online sale of counterfeit and illicit health products. Just as importantly, Pangea works to raise awareness of the risks associated with buying medicines from unregulated websites. Since its launch in 2008, the Operation has removed more than 105 million units (pills, ampoules, sachets, bottles and so on) from circulation and made more than 3000 arrests. The combined efforts of police, customs, regulatory bodies and private sector companies have prevented potentially dangerous medicines from reaching unsuspecting consumers and have dismantled a number of illegal networks behind these crimes. Figure 1 highlights Operation Pangea successes since its establishment in 2008.

During the Pangea 2020 week of action (3–10 March 2020), authorities in participating INTERPOL countries saw a rise in fake medical products related to COVID-19. They inspected more than 326,000 packages, of which more than 48,000 were seized. The operation resulted in 121 arrests worldwide and the seizure of potentially dangerous pharmaceuticals worth more than US$14 million. The COVID-19 outbreak offered an opportunity for fast cash as criminals took advantage of the high market demand for personal protection and hygiene products. Law enforcement agencies taking part in Operation Pangea found 2000 online links advertising items related to COVID-19. Of these, counterfeit surgical masks were the medical device most commonly sold online, accounting for around 600 cases during the week of action. The seizure of more than

Figure 1 Operation Pangea (Source: Reproduced with permission of INTERPOL[1])

34,000 counterfeit and substandard masks, 'corona spray', 'coronavirus packages' or 'coronavirus medicine' reveals only the tip of the iceberg regarding this new trend in counterfeiting. 'Once again, Operation Pangea shows that criminals will stop at nothing to make a profit. The illicit trade in such counterfeit medical items during a public health crisis shows their total disregard for people's wellbeing, or their lives', said Jürgen Stock, INTERPOL's Secretary General.[2]

The pharmaceutical industry has a vital role, and responsibility, to ensure the products it manufactures, distributes and delivers are fit for purpose and safe for the patient. Falsified/counterfeit medicines are a growing concern with the resilience of the pharmaceutical supply chain under constant pressure as economic conditions continue to pose significant challenges for business and consumers globally. Assuring supply chain integrity and patient safety is today more important than ever. All of us depend on safe medicines, medical devices, healthcare products and equipment including personal protective equipment (PPE) at various times in our lives. There is much better understanding of this following COVID-19. A risk-based approach should be used on a global and local basis to ensure continuity of supply. The pharmaceutical supply chain is somewhat unique in that compliance at every point along the supply chain is essential.

In the pharmaceutical industry, a manufacturer's responsibility begins at sourcing materials from approved suppliers, continues through manufacturing under **good manufacturing practice (GMP)** and on to delivery/distribution of the finished product to the final customer under **good distribution practice (GDP)**. The entire supply chain and the distribution network are focused on supplying a quality product that complies at every point with regulatory requirements. Any failings within the pharmaceutical supply chain can seriously compromise the quality of the product and patient safety.

The pharmaceutical supply chain extends well beyond the vehicles used to move bulk pharmaceutical materials, ingredients and components to the manufacturing facility and finished products from the manufacturing facility to distributors/wholesalers worldwide. It also must ensure compliant delivery to hospitals, pharmacies and even supermarkets, where the consumer can now purchase medicines. As patients, we would like to be guaranteed that the excellent quality under which medicines are produced, in the manufacturing facility, extends all along the legitimate distribution chain.

GMP ensures that products are manufactured batch upon batch, year upon year, to the appropriate and consistent quality standards and in accordance with regulatory requirements. Driving higher standards and compliance in the distribution chain is essential for continued success. As mergers within the pharmaceutical industry continue apace, and more blockbuster drugs come off patent, there is continued pressure on the industry, governments and patients worldwide. As a greater number of new products require cold chain distribution, temperature-controlled transportation will be the standard required throughout the supply chain for the majority of pharmaceutical products going forward.

WHAT IS GDP?

GDP together with GMP (sometimes called GMDP) should encompass the full supply chain that is necessary to make and sell pharmaceutical products (Figure 2). The critical need is to establish controls and manage risks at all points along the supply chain so that all partners handling and

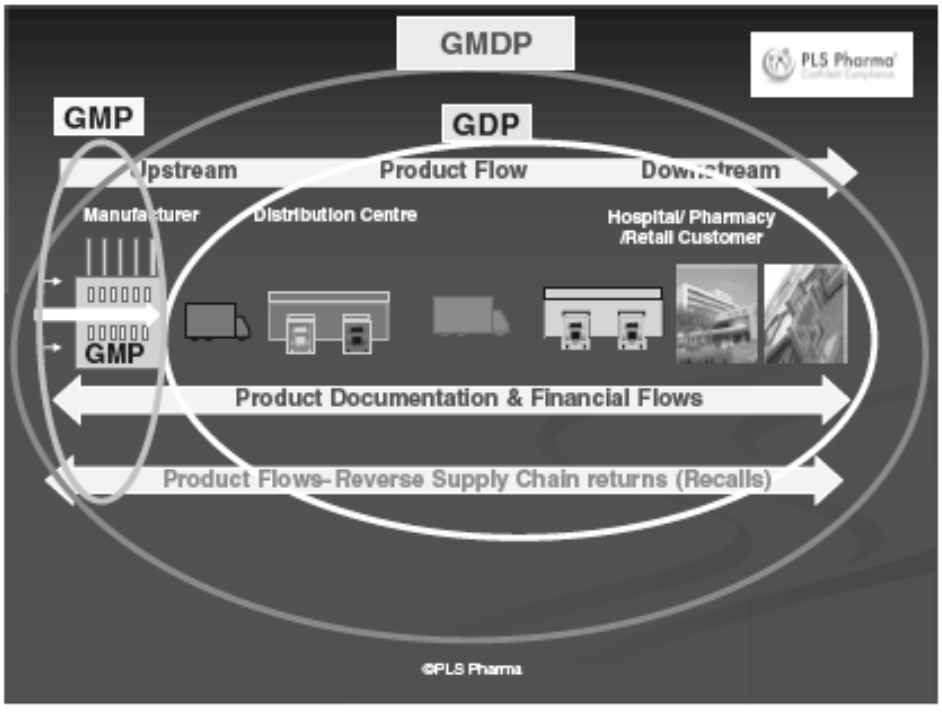

Figure 2 GMP and GDP (GMDP) in the pharma supply chain (Source: Reproduced with permission of PLS Pharma[4])

transporting pharmaceuticals do so within compliance. GDP can be defined as 'that part of quality assurance which ensures that the quality of medicinal products is maintained throughout all stages of the supply chain from the site of manufacture to the pharmacy or person authorised or entitled to supply medicinal products to the public'.[3]

The importance of GDP in Europe for example is clarified in the EU GDP Guideline 2013/C 343/01 (EU GDP Guideline) on GDP:

> The wholesale distribution of medicinal products is an important activity in integrated supply chain management. Today's distribution network for medicinal products is increasingly complex and involves many players. These Guidelines lay down appropriate tools to assist wholesale distributors in conducting their activities and to prevent falsified medicines from entering the legal supply chain. Compliance with these Guidelines will ensure control of the distribution chain and consequently maintain the quality and the integrity of medicinal products.

This EU GDP Guideline represents a substantial increase in standards as it raises the bar for all players in the pharmaceutical supply chain, including outsourced providers. For the first time, manufacturers performing GDP activities with their own products must also now comply with GDP.

Areas covered by the guidelines now include, for example, outsourcing, quality risk management, change control, CAPA (corrective and preventative actions), brokers, management responsibilities and more responsibilities for the 'Responsible Person' (RP); the RP or person responsible depending on national legislation is named on European WDA (Wholesale Distribution Authorisation) licences. These licences are issued by local regulators in the country of operation, and the role, responsibilities and qualification vary by country. The RP has legal and compliance responsibilities to ensure the licence is complied with as outlined in the EU Guidelines and local regulatory requirements.

Transportation is receiving increased regulatory focus at inspections. It is a complex area to manage with increasing challenges concerning security, temperature management and more requirements for track and trace technology. As many facilities and equipment are often used during distribution (including temporary storage facilities, unloading and reloading at hubs etc.), this presents greater complexity as products move across increasingly complex supply chains. Some European regulators have put limits on the number of hours products can remain in temporary facilities without a WDA and have defined when storage should occur in such facilities under a WDA licence to protect the quality of the products during transportation.[5]

DEFICIENCIES FOUND IN PHARMACEUTICAL SUPPLY CHAINS

Regulators continue to see deficiencies in pharmaceutical supply chains.[6] Some examples of deficiencies found include the following:

- Inadequate temperature management for warehouses/vehicles and temperature excursions in storage and transportation of pharmaceutical products.
- Lack of understanding of the pharmaceutical supply chain in GMP and GDP.
- All distribution activities were not clearly defined and systematically reviewed.
- The Quality Management System (QMS) did not set out the responsibilities, processes and risk management principles in relation to the activities conducted or controlled from the site.

- The QMS procedures were not following current compliance expectations.
- Adequate GDP training and re-certification was not taking place as per the QMS.
- The Licence Holder and Responsible Person had failed to meet their obligations to comply with the GDP Guidelines.
- Outsourcing partners (for example Transportation Providers) used were not carrying out GDP duties and responsibilities under signed agreements as documented under the QMS.
- Transportation standards of vehicles, equipment and GDP training falling short of current compliance requirements.
- Supply chains not demonstrating temperature compliance, no documented risk assessment and route qualification available for review.
- No proof from temperature devices used or vehicle printouts providing proof that product was distributed as per label claim for the duration of the shipment – including road, air and sea as well as temporary storage on route.
- Inadequate training of key staff, including management, in GDP.
- Bona fides of suppliers, customers and outsourced partners not established and maintained.
- No risk assessment had taken place to prevent the possible entry of falsified medicines into the legal supply chain.
- Validation of systems and equipment not documented.
- Management review and monitoring using KPIs not demonstrating RP oversight and how non-compliances are successfully reported and closed out on time to enhance changing compliance standards.
- Changes of activities in the business, physical, financial and product flows not clearly documented. Supply chain mapping not in keeping with current operations.

WHAT ARE FALSIFIED OR SUBSTANDARD MEDICINES?

A falsified medicine is defined by EU GDP Guidelines as any medicinal product with a false representation of: its *identity*, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients; its *source*, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder or its *history*, including the records and documents relating to the distribution channels used. A falsified medicine could be a genuine product but with a falsified history, source or identity.

Falsified Herceptin 150 mg powder concentrate for solution

Falsified Herceptin units were identified as having been stolen from a hospital in Italy before being re-introduced in EU markets. It is understood that unauthorised wholesalers operating in Cyprus, Hungary, Latvia, Romania, the Slovak Republic and Slovenia supplied the stolen medicines to authorised Italian wholesalers who subsequently exported the falsified products to other EU markets.[7]

Toxic diet pills

A 21-year-old student from Shrewsbury in the UK died in hospital on 12 April 2015 after becoming unwell. Police said the tablets were believed to contain dinitrophenol, known as DNP, an industrial chemical. Two tablets were a lethal dose – but unfortunately the student had taken eight. DNP is highly toxic and is not intended for human consumption. An industrial chemical, it is sold illegally in diet pills as a fat-burning substance. Users experience a metabolism boost, leading to weight loss, but taking even a few tablets can be fatal.[8]

Untrained, unsuspecting consumers are vulnerable to the potentially lethal outcomes of buying medicines online. Increasing numbers of consumers are choosing to source their medicines this way, having stated cost, convenience and privacy as some of the key reasons they choose to purchase online. A global marketplace exists for falsified/counterfeit medicines, and organisations know where the maximum profits can be made through, especially illegal, websites.

The introduction of serialisation and safety features to medicinal products commenced on a phased basis in 2019. Following the introduction of the Falsified Medicines Directive (FMD) in 2011/EU/62, this Directive introduced harmonised European measures to fight medicine falsifications and ensure that medicines are safe and that the trade in medicines is rigorously controlled. The main provisions of the Falsified Medicines Directive are to introduce the following:

- A new obligatory authenticity feature (referred to as a safety feature) which must appear on the outer packaging of designated medicines
- More robust rules regarding the control on starting materials and inspection of producers of active substances and excipients contained in medicines
- More robust controls on the wholesale distribution of medicines, including introducing controls for the first time on entities involved in brokering medicines
- A common, EU-wide logo to identify legal online pharmacies and to establish a notification system for entities offering to supply medicines to the public over the Internet

Falsified medicines are fake medicines that pass themselves off as real, authorised medicines. The EU has a strong legal framework for the licencing, manufacturing and distribution of medicines, centred around the Directive on falsified medicines for human use, so that only licenced pharmacies and approved retailers are allowed to offer medicines for sale, including legitimate sale via the Internet. The European Medicines Agency is working closely with its partners on the implementation of these laws. This legislation will enhance visibility, improve patient safety and better manage and measure pharmaceutical supply chain performance where medicines are manufactured stored, transported and distributed. The introduction of serialisation will help to ensure a safe secure falsified free supply chain. Good Supply Chain Management, coupled with best-in-class good distribution and manufacturing practice, is a minimum requirement in helping to stem the flow of falsified/counterfeit products to protect the legal supply chain and patient safety on a local and global basis.[9]

NEW MANDATORY LOGO FOR SELLING MEDICINES ONLINE

Taking the UK as an example, anybody selling medicines online to the public needs to be registered with the MHRA (Medicines and Healthcare Products Regulatory Agency) and to be on the

MHRA's list of UK-registered online retail sellers. They also need to display on every page of their website offering medicines for sale the new European Common Logo which is registered to the seller. The registered EU Common Logo will contain a hyperlink to their entry in the MHRA's list of registered online sellers.[10]

Anybody buying medicines online can check whether the website is legitimately registered and will be able to click on the logo which will take them through to a list of approved sellers. If the registered person retails a medicine through a third-party marketplace website, then the third-party marketplace service provider must display that registered person's EU Common Logo on every page of their website that offers the registered person's medicine for sale to the public from that service provider's site. Under the rules of the new scheme, the medicine being offered online must be licenced in the member state where the member of public who buys the medicine is based.

CONCLUSION: THE WAY FORWARD

If we are to deliver patient safety, there is a need for all stakeholders in the pharmaceutical industry to work in partnership to ensure supply chain integrity, quality and compliance. Regulators across the world are working with manufacturers, distributors and other stakeholders involved in pharmaceutical supply chains to embrace and drive higher compliance standards.

EU Guidelines and Directives, together with the introduction of serialisation and the EU Common Logo, will continue to raise standards in the management of the pharmaceutical supply chain. There will also be more focus following COVID-19 on medical devices healthcare and equipment suppliers including essential PPE supplies. The resilience of supply chains and availability to deliver continuity of supply will continue to bring challenges. The need to protect the legal supply chain and improve standards from sourcing to final delivery is essential if we are to keep our families safe.

The critical need to establish controls, review real risks in increasingly complex supply chains and understand where individual responsibilities start and finish is essential. Legislation and good practices oblige pharmaceutical manufacturers and distributors to exercise control over the distribution chain and ensure that the quality of medicines is maintained. Critical in this regard is control of the environmental conditions under which medicines are stored and transported. As global temperatures increase, the need to carefully transport all products within their specific temperature ranges will remain a significant challenge.

Optimising the pharmaceutical supply chain is a competitive necessity, but delivering patient safety should never be put at risk. Suppliers, manufacturers, distributors and outsource partners who transport and distribute products must ensure that the high level of product quality achieved by observing GMP is maintained throughout the distribution network as products are transported and delivered on a global and local basis.

While the regulators are doing all they can to heighten awareness, everyone working in this area must ensure that they act as part of the team delivering best practice and patient safety all along the supply chain. Now, more than ever, education, training and awareness are essential to

maintain and continuously improve quality, integrity and supply chain performance and standards and to reduce risk. Operating without supply chain integrity and product authenticity will not deliver patient safety all day every day.

'GET REAL, GET A PRESCRIPTION'[11]

A campaign in the UK to heighten awareness of the risks of buying counterfeit medicines using the Internet, 'Get real get a prescription', helped to educate consumers about the real dangers of buying counterfeit medicines online and that such a transaction could end in death.

NOTES

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