The Route To Patient Safety – Manufacturing Chemist

In the international pharma sector, failures in good distribution practice can have lethal results, which is why Ciaran Brady of PLS Pharma Logistics believes GDP training is imperative.

With pharmaceuticals, good distribution is not just a case of guaranteeing that a patient's supply of medicine is made available as and when it is needed – although that is, of course, essential. Rather it is a case of ensuring that the entire supply chain or distribution network is focused on supplying a quality product that complies at every point with regulatory requirements and is fit for use at the time that it reaches the patient. Any failings or faults within the chain, even seemingly innocuous failings, can seriously compromise the quality of the product and hence the safety of patients.

In this context, the supply chain extends well beyond the vehicles used to take the product from manufacturing facility to patient. It includes all the interconnected company processes, procedures and distribution points from sourcing of ingredients, through receipt of goods, order taking, picking and invoicing, warehouse maintenance and staff training.

Good Distribution Practice (GDP) is about much more than just the distribution of products. The MHRA recently defined GDP as

> *"the sum of all of the processes and activities designed and implemented to ensure that the quality of medicines is maintained throughout the distribution chain from manufacturer to patient, ensuring compliance with regulatory requirements at all relevant stages. It includes the storage and transportation of APIs, other ingredients and packaging components used in the production of the medicines."*

In effect, GDP extends to sourcing materials from approved suppliers and continues through manufacturing (under GMP) and on to delivery of the product to the final customer or patient.

This is a fairly simple observation that disguises a truly challenging picture. The supply chain is becoming more complex and global, raising serious practical questions about where the supply chain starts and ends, and precisely where control must be focused to guarantee quality all the way from ingredients to the final medicine. The more global and complex the distribution network, the more difficult it is to ensure that goods follow approved routes and that delays are avoided, that records are properly maintained and that quality is assured at every point.

The observation that climate change appears to be leading to some violent fluctuations in temperature and humidity in different locations around the world also needs to be factored into the equation. This raises genuine concerns about what happens to products as they wait to be loaded onto trucks, trains, ships or planes. One also has to take account of the risk that product might sit in the back of a truck that is caught in a traffic jam or has broken down.

The global growth of counterfeiting not only of finished product but also of APIs is also an issue. The implementation of GDP is essential for keeping counterfeits out of the legitimate supply chain/distribution network, and lapses in GDP can leave any pharmaceutical supply chain vulnerable to counterfeits.

Global warming

The suggestion that global warming has an impact on GDP is no idle claim. Both the FDA and MHRA single out temperature as a critical control parameter for ensuring pharmaceutical quality.FDA CFR 211.142states the need to ensure

> *"Storage of drug products under appropriate conditions of temperature, humidity and light so that the identity, strength, quality and purity of the drug products are not affected."*

These sentiments are also reflected in many other guidance documents (see table 1).

John Taylor, of the MHRA, has noted publicly that:

> *"The regulator expects companies to take the view that control and monitoring of the temperate chain is as important as the cold chain."*

He also observes that:

> *"Each shipment between countries and within countries of large geographical area should be treated as unique in terms of the range of temperatures the goods may experience."*

This recognises the huge temperature variations that ingredients and medicines may experience on any given journey and in any given location.

Despite this emphasis, poor temperature control during storage and transportation is a regular cause of failure during inspections. According to MHRA, 32% of all critical and major deficiencies are concerned with control and monitoring of storage and transportation. The insurance industry shares this perspective. John Perera, a risk management consultant with Royal & Sun Alliance, said:

> *"I have seen many cases where simple acts of ignorance have meant that millions of pounds of temperature-sensitive pharmaceuticals have had to be destroyed. Products have been stored in warehouses at the wrong temperature, or drivers have failed to set the right temperature within their containers. Simple, easily avoidable errors can put patients at risk as well as costing millions of pounds in damages. It is often down to the ignorance or lack of knowledge of one person, but there are also examples of a systematic failure from some manufacturers to set specifications and a systematic failure from distributors to adhere to them."*

Keeping out counterfeits

One of the biggest challenges for the pharmaceutical industry, and one of the main reasons why GDP is so important, is the increase of counterfeiting on a global basis. Various measures of the scale of the counterfeit problem have been published, and there were 10 recalls in the UK between 2004-7 in which counterfeits have reached the patient level.

The US-based Centre for Medicines in the Public Interest has predicted that counterfeit drug sales will reach US $75bn (b55bn) globally in 2010, which would represent a 90% increase on 2005. The WHO suggests that counterfeits account for around 1% of sales in developed countries to more than 10% in developing countries, and medicines purchased over the Internet from sites that conceal their physical address are counterfeit in at least 50% of cases.

GDP is a minimum requirement in helping to stem the flow of counterfeit products into legitimate pharmaceutical supply/distribution channels. The practice of parallel distribution, and the complex interfaces between manufacturers, distributors and repackagers, especially around withdrawal of product and subsequent approved disposal, are all areas of potential weakness that counterfeiters are only too willing to exploit. There is also a substantial risk associated with returns, and specific training is required to help staff deal effectively with them.

Indeed, the need for all stakeholders in the pharmaceutical industry to work in partnership to ensure supply chain integrity and that only bonafide suppliers and customers are allowed to supply and sell is a must if we are to ensure patient safety at all times.

As the recently published Orange Guide notes in its introduction,

> *"The great majority of reported defective medicinal products has resulted from human error or carelessness, not from failures in technology."*

From this it is apparent that individuals within companies must do everything expected of them to meet the requirements of GMP and GDP; by implication, they must first understand what those requirements are and where their own activities come under the remit of GDP and/or GMP.

Training is therefore an essential pre-requisite to the implementation of GDP, and that message does appear to be getting through. RSSL Pharma Training is one organisation that runs GDP courses and according to training manager Lyndsey Wright, uptake has increased dramatically in the past year.

> *"The distribution network has sometimes been seen as something external to the production of pharmaceuticals. Now the industry realises that there is no point in exercising fine control over every aspect of production if there is no equivalent control of the product once it leaves the premises. That is not to say that no-one recognised this before, but there have been shortfalls in how the responsibility for product safety was passed on through the supply chain/distribution network and how it was enforced."*

Key components

There are several key components to getting GDP right, with training being just one aspect of the wider requirement for personnel to be adequately managed, motivated and resourced. Manufacturers, wholesalers and distributors need also to consider and address their overall quality systems, documentation, premises (especially warehousing) and equipment, deliveries to customers (transportation and supply chain), returns, recall procedures and self inspections.

But there are other issues to address, such as the need to ensure that identification is not lost, that contamination is avoided and that products are secure at all times. It is one thing to be certain that the right product has been loaded properly into an appropriate vehicle with all the right documentation, but everything else that happens thereafter is beyond the direct control of the manufacturer.
Choosing the right supply chain/distribution network partners is not just a matter of choosing a distributor with the appropriate licence, because all the intermediaries that touch, move and handle the product ought to be considered too.

It is the unknown interventions that should concern us all. Selecting, establishing and maintaining the bonafides of all suppliers and customers is an essential but complicated aspect of GDP, especially in a global pharmaceutical market characterised by takeovers, mergers, increased regulator expectations and downward pressure on costs.

Summary

In summary, everyone involved in the business has a responsibility under GDP to protect patient safety. This responsibility extends from the technical department that deals with preparing the documents under which suppliers are contracted and under which shipping instructions are written, through to the IT manager responsible for record-keeping and data storage, because traceability is essential for successful recall.

While there are guidelines that can assist pharmaceutical manufacturers and distributors in achieving higher standards of compliance, training is a critical ingredient for success. It is people who manage the systems and the process, and who must ensure that GDP is adhered to.
Having well-trained and highly motivated staff will go a long way to ensuring that GDP is managed successfully throughout the supply chain/distribution network, and that pharmaceutical products are handled, transported and delivered with best-in-class GDP standards and full compliance.

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