Cold Chains: Management, Compliance Complexities

Vincenzo Salvatore & Helen Roberts of the BonelliErede Healthcare Focus Team

consider key issues in cold chain supply & what are implications for stakeholders

Why is this important?

Regulations in the EU, US & other markets introduced updated 'Good Distribution Practice' (GDP) standards.

These standards are linked to inspections of sites and supply chain data, and to increased coordination between authorities that are publishing reports of inspections.

There are potential liabilities for non-compliance, for both companies and individuals. These liabilities will first be assessed in a country at national level, but may lead to inspections & sanctions such as fines, within the EU or other markets. Reputations of one member of a supply chain may affect others.

For healthcare professionals such as pharmacists or doctors, and for 'Qualified Persons', the compliance with GDP is a matter of professional conduct, subject to their own codes & penalties.

Launches of new biosimilars & specialty products have increased demand: 80 % of these products are temperature sensitive, and are often produced at only one site for distribution throughout the world.

Cold chain supply is also a global growth market: healthcare cold chain logistic services are estimated to reach nearly US$ 13.4 billion by 2020, from current US$ 8.5 billion (http://www.researchandmarkets.com/research/rcbr35/global_healthcare). Half of this growth is in the Far East & Asia.

Medicines are typically high market value products: one consignment may be worth at least on average US$ 40-50 million.

Insurers are aware of these risks and do require manufacturers, wholesalers and distributors to show active compliance with standards. Failure to do so may result in cancellation of cover and likely claims.

How GDP requirements are managed & monitored, by which company within a group and by which Responsible Person, are also important questions during M&A and outsourcing projects.

Common emphasis on risk management approach & auditability

Although there is no single global standard, recent guidance published by the EU, FDA, the World Health Organization & others do refer to:

- adopting risk-based assessments in the form of assessment, control, communication and review of risks
- the need for auditable quality agreements & written contracts between all those that are involved in the supply of medicines from production to patient
- proof that products have been stored at the temperature stated on the label and kept within approved temperatures during transportation

These common factors highlight the importance of good controls on data and on transfers of data, which are made in accordance with the new EU General Data Protection Regulation.

It is also key to review contracts & procedures with appropriate allocation of risks & responsibilities, refer to current law and appoint appropriate personnel to implement them.

Governance must also be considered: which Board Director of a manufacturer and of a marketing authorization holder takes responsibility for GDP - & who advises this Director on best practice, national & EU law?

Businesses that rely on third party or outsourced responsible persons must ensure that appropriate indemnities, reporting duties, audit rights & professional indemnity cover are included in relevant agreements.

EU GDP Guidelines - complexities

Article 80(g) of Directive 2001/83/EC states wholesalers must comply with GDP guidelines which came into effect in November 2013 (GDP guidelines).

GDP guidelines set out details under general headings: - principles, personnel, documentation, premises and equipment, deliveries to customers, returns, recalls, and self-inspections. It also requires auditable quality management systems, analysis of compliance capabilities, training, continuous monitoring and any other steps that are necessary to ensure compliance.

This may include 'gap analysis', and for example checking a tarmac gap', the time for which a consignment may wait in an airport hangar between flights, & what temperatures will apply in that time.

A 'gap analysis' may also include differences in laws, where products must be delivered to countries outside of the EU & North America.

GDP requires that products are transported in an acceptable range of temperatures with packaging that aims to maintain desired temperatures. 'Controlled Room' storage areas are usually certified and tested for these temperature ranges.

Where there are deviations between the actual & planned temperatures, deviation reports are required.

This implies companies have access to all relevant records about where & how medicines are stored. The implementation of the Falsified Medicines Directive will facilitate collection of this data; so before 2019 marketing authorization holders must ensure their contracts with wholesalers enable them to obtain this data, and to enforce breaches of contract if the data is not provided.

In the UK wholesalers are expected to retain supply records for no less than 5 years.

Role of national regulatory authorities in EU

It is national regulatory authorities that are responsible for:

- interpreting how GDP guidelines will apply to distribution activities in their country
- enforcing remedial steps for deficiencies & penalties for infringements- Most authorities will take a pragmatic approach (see for example MHRA blogs by Stephen Todd).

Most authorities are relying on members of supply chains to decide for themselves how to apply 'risk-based' quality assessments, in the light of guidance of authorities.

The MHRA in April 2016 reminded companies of their duty to conduct due diligence - both initial and periodic (twice a month) - when dealing with suppliers:

- Authorised supplier holds a manufacturing or wholesale dealers licence
- Supplier complies with GDP (GDP certificate available?)
- Due diligence checks (including evaluation of on-site audits)

Guidance is also available from associations of wholesalers and other expert groups.

A Task Force of the European Compliance Association Foundation has developed a Guidance document to support Responsible Persons (RPs) for Good Distribution Practice (GDP). Code of Practice for RPs.

Other areas of complexity include returns of refrigerated products: - marketing authorization holders and wholesalers must assess the impact of temperature deviations on such products.

Pharmacists are expected to advise patients on temperature controls, to alert them to look for signs of improper storage, or to use cool bags.

Questions to Ask

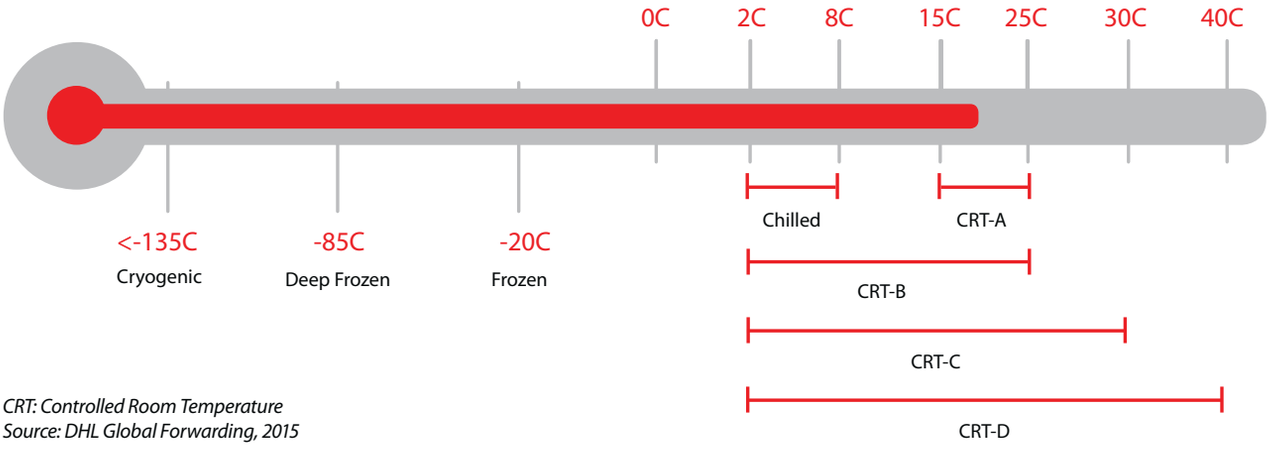
What impact will compliance with GDP in cold chain supply chains have on the cost of medicines?

It is difficult to find reliable estimates. This topic may be discussed at the G7 summit in Ise-Shima, Japan on May 26-27, when the French President raises the matter of international regulation of drugs prices.

How will differences of opinion on the interpretation of GDP guidelines between a marketing authorization holder or wholesaler, and a GDP inspector, or between members of a cold chain supply chain, be resolved?

This will be resolved under national law and in accordance with relevant contracts, as the EMA's sole role is harmonization & coordination between national authorities.

The contracts of members of a supply chain should be consistent, so that issues of interpretation of one contract are not litigated in different countries with different experts.



CRT: Controlled Room Temperature
Source: DHL Global Forwarding, 2015