UPS Position Paper – European Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use,

November 2011

1. Introduction

The distribution of medicinal products in the European Union is regulated by, inter alia, directive 2001/83/EC, as enacted into the laws of EU national member states and implemented on the basis of the current guidelines on GDP (94 C 63/03). The enforcement of these is the responsibility of EU and national regulatory bodies. The European Commission (EC) has on 15th July 2011 issued draft guidelines for good distribution practice (GDP or the "guidelines") for a public consultation period open until December 31st 2011, with the objective of replacing in 2012, the GDP guidelines last issued in 1994. Once finalised and published the new EC GDP guidelines will have to be effectively implemented within 6 months of the publication date of the final version of the guidelines.

2. Problem

The guidelines seek to tighten the definition of the term "wholesale distribution" (WD) – trading, brokerage and storage of medicinal products – so as to regulate the periphery of this activity that was not previously directly addressed. The draft guidelines use the term storage for medicinal product that was previously considered to be in transit and define any period of refrigerated storage of medicinal products and medicinal products held on a premises for longer than 24 hours as a regulated activity requiring a GDP authorisation on a site by site basis, subject to full oversight and inspection by regulatory bodies. These requirements would significantly increase the cost of the medicinal product supply chains.

Clarification is sought on the practical application of this guideline and the interpretation of the wordings used in the draft guideline such as 'storage', 'deviation', 'normally', 'should', 'validation' – terms that could be interpreted as recommendations rather than strict requirements. More specifically and especially the following three areas of the draft GDP guideline have been highlighted by UPS as requiring further clarification: (A) Sections 9.1 and 9.4, (B) Sections 9.12 and 9.13, (C) Section 9.19.

(A) Sections 9.1 and 9.4

9.1 The required storage conditions for medicinal products should be maintained during transportation within the defined limits as described on the packaging information.

9.4 It is the responsibility of the distributor to ensure that vehicles and equipment used to distribute, store or handle medicinal products are suitable for their use and appropriately equipped to prevent exposure of the products to conditions that could affect their quality and packaging integrity, and to prevent contamination of any kind.

Comments

The responsibility for 9.1 needs to be more specifically defined as being the responsibility of the product owner (normally the marketing authorization holder or the shipper (on behalf of the product owner). As an example, UPS can ship on behalf of the pharmaceutical client as described in quality agreements and agreed work instructions from a UPS third party logistics (3PL) healthcare warehouse through the UPS small package delivery network. It is then the pharmaceutical client of UPS that

needs to define the service level requested from UPS in order for the pharmaceutical client to achieve compliance.

That said, considering that cost-effective compliance with 9.4 can be achieved through: (a) the use of a validated container or (b) a combination of stability data and lane mappings, would it then still be necessary for strict compliance with section 9.1 as well. There would be considerable cost increases associated with this stricter requirement. Controlled condition ambient LTL transportation can easily add 30% + to the current non-conditioned LTL costs. Specific condition ambient small package materials are many times the cost of currently used corrugate packaging for ambient shipments. In a market where billions of Euros are spent on the transportation of goods every year these percentages represent a significant increase for manufacturers and ultimately consumers to bear. (It is estimated that in 2011 greater than 10 billion Euros will have been spent on ground transportation and small package movement. Source : Datamonitor Pharma Vitae Profiles – May 09.) Clarification is required in this respect as to whether compliance to 9.4 in lieu of 9.1 would be considered as sufficient in this case. Also considering that in principle, a risk based approach can be utilized when planning transportation routes.

(B) Sections 9.12 and 9.13

9.12 Where transportation hubs are utilised in the supply chain, a maximum time limit of normally 24 hours should be set to await the next stage of the transportation route. Where medicinal products are held on the premises for longer than this defined time limit, the hub will be deemed to be acting as a storage site and required to obtain a wholesale distribution authorisation. For refrigerated product any storage at a transportation hub for any period of time would require that premises to hold a wholesalers distribution authorisation.

9.13 In the event that the transportation of medicinal products requires unloading and reloading e.g. at terminals and hubs, these premises should be audited and approved prior to deployment. Whenever any changes are made to the approved premises or functions, attention should be paid to the continued suitability of the changed premises or functions for their intended use. Particular attention should be paid to temperature monitoring, cleanliness and the security of unguarded intermediate storage facilities.

Comments

The 24 hour rule would prohibit the shipping of medicinal products through the UPS small package network on Fridays when stationary time over the weekend would be expected. An agreement with pharmaceutical clients to only use shipping days before Fridays or increased service levels for weekend delivery would be required in order prevent that medicinal products are held on the premises for longer than the defined time limit of 24 hours. This would have considerable impact on the smoothness and stability of the distribution network considering the creation of peaks. This impact would driver higher costs for all.

Regarding the interpretation of refrigerated storage for any period of time as applied to cross docking activities, as an example, a shipment from a UPS healthcare warehouse to a central hub of a transportation service provider for consolidation would either require the shipment to be collected directly at the UPS warehouse for shipment without the hub stage, or for the hub to be GDP licensed. Both of the options would require considerable investment in either revising opening hours of the UPS GDP licensed facilities or for GDP licensing the hub of the transportation provider.

UPS does provide a next day delivery service for medicines but this impacts the cost charged to the pharmaceutical client. Furthermore if the medicinal product is being transported through the UPS freight forwarding network and customs holds the product for an extended period of time, the guarantee of the service level to the pharmaceutical client is not longer possible.

Further clarification is required for section 9.13. The definition of loading and unloading is unclear and could have several interpretations. If goods were transported in suitable packaging (carton, active pallet container, reefer trailer etc) and that packaging was opened and the goods repackaged then a conditioned environment could be a reasonable expectation. Such a conditioned environment should be audited for approval and acceptance. Would an SOP controlling time out of range matched with stability data be seen as a viable alternative ? On the other hand, if goods stayed in their packaging as shipped and were moved from one transport vehicle to another through a cross dock facility is the intent that that facility be audited and approved ? UPS has over 280 such locations in Europe, other providers many more and the audit costs for each by every user of their services would be significant.

(C) Section 9.19

9.19 Validated temperature-control systems (e.g. thermal packaging, temperature-controlled containers, and refrigerated vehicles) should be used to ensure correct transport conditions are maintained between the distributor and customer. Customers should be provided with a temperature data to demonstrate that products remained within the required temperature storage conditions during transit, if requested.

Comments

The use of the term 'validated' in terms of validation required for transit containers needs to be further clarified. Passive packaging may be validated but not all semi-active or active containers are validated. For example, the Pharmaport container is validated whilst other containers that are currently available on the market may not be.

Vendors providing ground transportation may or may not have validated trailers. It would be very difficult to identify transportation companies that provide validated trailers and most often the increase in cost (estimated at 30%) for use is prohibitive to the UPS pharmaceutical clients.

In the case that non-validated containers are used would a qualification process be sufficient to ensure regulatory compliance is maintained?

There also needs to be a more specific definition that the responsibility for providing temperature data is not the responsibility of the shipper but of the product owner.

3. Discussion

UPS has launched a global campaign to extend its activity in the transport and distribution of medicinal products, around the world. An increasing number of these are sensitive to temperature; require specialised transport and facilities which UPS and others are developing. In some cases contingency-only (not planned storage) cool space may be installed in currently unregulated transportation facilities.

These facilities and services are subject to detailed contractual obligation and extensive oversight by the pharmaceutical companies as an extension of their regulation. The UPS network, and those of its competitors involved in transport as opposed to warehousing, have not previously required

authorisation. For reference, UPS does have a Good Distribution Practice (GDP) licensed storage building and a Good Manufacturing Practice (GMP) secondary repacking contract logistics regulated Distribution Centre in Roermond, the Netherlands.

The extension of full regulatory oversight to transportation facilities equipped with refrigerated equipment for the safe transit of Healthcare products, would add considerable cost to this activity. It may jeopardise Public Health by delaying or arresting investment in infrastructure, required to achieve the safe and timely delivery of these medicinal products to patients.

4. Solution

UPS seeks to distinguish the staging or temporary transit from the warehousing or storage of medicinal products, and conditions required while in transit.

5. Rationale

Substantial amounts are being invested in the network, to improve the security of medicinal products transiting in them. All employees handling medicinal products are being trained to use the equipment responsibly. The draft guideline has not assessed the impact of overlaying GDP Regulatory oversight on facilities already substantially regulated by Security and Transport agencies. The EU and its member states do not have unfettered jurisdiction over Airport facilities regulated by International law. Considerable delay and cost would be inevitable. Good Distribution Practice (GDP) is reaching these facilities through the contractual terms and inspection/audit competences of the licence holders contracting transport.

6. References

6.1 Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use, http://ec.europa.eu/health/files/eudralex/vol-4/2011-07_gdpguidline_publicconsultation.pdf

6.2 Directive 2011/62/EU of the European Parliament and of the Council, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:174:0074:0087:EN:PDF

6.3 Directive 2001/83/EU of the European Parliament and of the Council, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf