PHARMIG
Verband der pharmazeutischen Industrie Österreichs

Vienna, 23 December 2011

SANCO/C8/AM/an D(2010)

PHARMIG response to the European Commission Concept Paper: Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use

PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank the European Commission for the opportunity to comment on the draft Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use.

Please find following our comments.

Page 4, Introduction

"The wholesale distribution of medicinal products is an important activity in the integrated supply chain management... According to Article 1(17) of Directive 2001/83/EC, wholesale distribution is "all activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public."

Comment:

In our opinion it is necessary that Guidelines on Good Distribution Practice cover all means of distribution of medicinal products. This includes supplying medicinal products to the public by online pharmacies using parcel services for transport as well.

The scope of the guideline is not clearly defined. Is it restricted to finished products delivered to end customers (e.g. pharmacies, hospitals)? If not, what else is included (finished product, bulk, intermediates, APIs) and which parts of the supply chain are affected (inter-company transport, transport to end customers, etc.)? We suggest to include a chapter regarding the scope of the guideline.

Page 5, item 1.1

Comment:
It is deemed to be necessary to define the scope of the quality system. It should be clarified that medicinal products and active pharmaceutical ingredients (API) are covered whereas excipients are excluded.

Page 5, item 1.2
"A responsible person should be appointed by the management for each distribution site…"

Comment:
It should be clarified that a responsible person could be appointed for more than one distribution site. In organisations with several distribution sites the appointed person should be allowed to delegate responsibilities to appropriately qualified local staff.

Page 6, item 1.11
"The outcome of this management review of the quality management system should be timely and effectively communicated within the organisation."

Comment:
It should be clarified that the competent authorities are not the addressee of the management review.

Page 8, item 2.1

"The Responsible Person … should be permanently ~~available~~ reachable."

Comment:

We think that this requirement is excessive. In practise this could mean that it is necessary to have two Responsible Persons. If one Responsible Person meets the requirements for batch release the same level of availability should be sufficient here.

Page 8, item 2.3

"A degree in Pharmacy is desirable."

Comment:

We recommend to delete this sentence. Within the content of the paragraph there is no added value by this wording.

Page 8, item 2.4

"The Responsible Person should carry out his/her activities personally…"

Comment:

We think that this requirement is excessive and hard to meet in practise, e.g. in case of holidays or sick leave. It should be allowed to delegate responsibilities to appropriately qualified staff.

Page 8, item 2.5 ii)

"authorising the return to saleable stock of any returned medicines, provided the returned medicines have not left his/her area of responsibility;"

Comment:

It should be clarified that the Responsible Person cannot authorise return to saleable stock when the medicines went outside of his/her area of influence.

Page 9, item 2.5 x)

"delegating his/her duties when absent and keeping appropriate records relating to any delegation;"

Comment:

We suggest to delete "when absent". It should be allowed to delegate responsibilities to appropriately qualified staff also when the Responsible Person is not absent.

Page 9, item 2.5 xi)

"being involved in any decision to quarantine or dispose of returned, rejected, recalled or falsified products;"

Comment:

We strongly recommend to delete this requirement or at least the wording "any". The current wording would prevent conducting any recalls when the Responsible Person is absent (e.g. holidays or sick leave).

Page 11, item 3.4

"Medicinal products not intended for the Union market should be kept in segregated areas, e.g. different load carriers (pallets)."

Comment:

In facilities with random storage appropriate systems have to be in place to ensure segregation of goods in one storage room. It should be clarified that "segregated areas" does not mean different storage rooms.

Page 12, item 3.14

Comment:

We suggest to reword item 3.14 in a way that only requests qualification of storage areas without details on temperature mapping, etc. as this would be covered by the qualification.

Page 12, item 3.15

"All equipment used for storage … should be designed, located and maintained to a standard which suits its intended purpose."

Comment:

We suggest to reword to:

"All equipment used for storage … should be designed, located and maintained to ~~a standard which~~ suit~~s~~ its intended purpose."

Page 12, item 3.17

Comment:

We suggest to reword item 3.17 in a way that only requests qualification of equipment without details on calibration, etc. as this would be covered by the qualification.

Page 13, item 3.24

Comment:

We suggest to reword to:

"Data should be stored for at least 5 years."

This wording already includes data protection without requesting details for means of achieving it.

Page 14, item 4.8

Comment:
This item seems to be incomplete.

Page 15, Principle, paragraph 3
"Any distributor, not being the marketing authorisation holder, who imports a medicinal product from another Member State shall notify within reasonable time in advance the marketing authorisation holder and the competent authority in the Member State to which the medicinal product will be imported of his intention to import that product."

Comment:
We recommend to include a reasonable timeframe for the notification to avoid this being done after the import of the medicinal product.

Page 15, item 5.1
"Wholesale distributors must obtain their supplies of medicinal products only from persons who are themselves in possession of a wholesale distribution authorisation, or who are in possession of a manufacturing authorisation which covers the product in question."

Comment:
To enable wholesale distributors to do so national competent authorities should maintain a system which publicly accessible lists holders of a wholesale distribution or a manufacturing authorisation and which notifies wholesale distributors on short

notice (e.g. e-mail alert) of any changes in the authorisation status of the listed companies.

Page 16, item 5.7

Comment:

This requirement is already covered by item 5.1. It lies in the responsibility of the authorising competent authority to assess the suitability, competence and the reliability of the applicant to supply medicinal products. The wholesale distributor is not in the position to scrutinise this in a sufficient way and has to rely on the due diligence of the responsible competent authority. Please see also comment on item 5.1.

Page 16, item 5.9

Comment:

This requirement is already covered by item 5.8. To enable wholesale distributors to do so please see also comment on item 5.1.

Page 17, item 5.14

"In the event of any suspicion of falsified medicinal product, the batch should immediately be segregated and reported to the national competent authority and, ~~where applicable~~ to the marketing authorisation holder."

Comment:

We recommend to delete "where applicable" since the marketing authorisation holder should be definitely informed in the event of any suspicion of falsified medicinal product in relation with the marketing authorisations within his responsibility.

Page 20, Principle, paragraph 1

"A special assessment of returned medicinal product should be performed before any approval for resale."

Comment:

We strongly recommend to delete this sentence. A wholesaler is not permitted to give approval for resale when the medicinal product has left his area of responsibility. This is in contradiction with the principles of GMP.

Page 20, item 6.9; page 21, items 6.10 and 6.11

Comment:

We recommend to delete these items for the same reasons as explained in our comment regarding Page 20, Principle, paragraph 1.

Page 21, item 6.14

"Distributors must immediately inform the competent authority and, ~~where applicable~~, the marketing authorisation holder of the medicinal products they identify as falsified or suspect to be falsified."

Comment:

We recommend to delete "where applicable" since the marketing authorisation holder should be definitely informed in the event of any suspicion of falsified medicinal product in relation with the marketing authorisations within his responsibility.

Page 23, Principle

"When outsourcing any activities a written contract should be drawn up. Both the contract giver and the contract acceptor must hold a ~~distribution authorisation~~ relevant authorization for the respective activities. The written and signed contract

should cover all ~~wholesale distribution~~ activities and clearly establish the duties and responsibilities of each party."

Comment:

We suggest to clarify that any outsourced activities should be subject to written agreements. The wording should reflect that outsourced activities do not necessarily require a distribution authorisation (e.g. transport of medicinal products). Furthermore not only wholesale distribution activities but also other operations can be outsourced.

Page 23, item 7.2

"An audit of the Contract Acceptor should be performed before the beginning of the outsourced activities and afterwards audits should be done periodically."

Comment:

Periodical audits should be defined as necessary based on the criticality of the contract activities and in case of changed contract activities.

Page 23, item 7.6

"The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements and, where applicable, an audit of the third party."

Comment:

An audit of the third party by the Contract Giver or the Contract Acceptor is not in all cases reasonable. It should be only required where it has been decided by risk assessment that an audit is deemed to be necessary.

Page 26, Principle, paragraph 3

"Medicinal products should be transported in accordance with the storage conditions indicated on the packaging information unless there are specific transport conditions for the particular product defined in accordance to paragraph 1."

Comment:

On a risk based approach it is possible to extend the transport conditions beyond the requirements for storage as indicated in the package information leaflet (PIL). Where this is not applicable the storage conditions of the PIL have to be strictly adhered.

Page 26, item 9.1

Comment:

Please see our comment on page 26, Principle, paragraph 3.

Page 26, item 9.2

"If a deviation has occurred during transportation, this should be reported to the distributor and recipient of the affected medicinal products."

Comment:

A definition of a relevant deviation is required. A deviation of 1°C for a time period of two minutes for a temperature controlled transport of medicinal products might not be relevant whereas the same deviation over a longer period of time may seriously adverse effect the medicinal product.

Page 26, item 9.7

"Equipment used for temperature monitoring during transport within vehicles and/or containers, should be maintained and calibrated at regular intervals at least once a year."

Comment:

This is an excessive requirement for short transports with very small deviations. Please consider the handling of non-removable monitoring devices in trucks.

Page 26, item 9.8

"Dedicated vehicles and equipment should be used, where possible, when handling medicinal products or, on a risk based approach, other products (e.g. APIs, food supplements)."

Comment:

On the basis of a risk assessment it should be allowed to transport also other products or materials on vehicles dedicated for medicinal products.

Page 27, item 9.9

"Deliveries should be made ~~directly~~ to the ~~address~~ consignee stated on the delivery note and must be handed into the care of the consignee. Medicinal products should not be left on alternative ~~premises~~ consignees."

Comment:

It should be considered that a consignee might have several addresses. Therefore the delivery should focus on the consignee instead of the particular address. However, a delivery to alternative consignees should not be permitted.

Furthermore it should be possible to deliver different consignees in one tour. Therefore we recommend to delete the requirement that deliveries should be made directly.

Page 27, item 9.12

"Where transportation hubs are utilised in the supply chain, a maximum time limit of normally ~~24~~ 72 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~~ temperature controlled product any storage at a transportation hub for any period of time would require that premises to hold a wholesalers distribution authorisation."

Comment:

We recommend to extend the maximum time limit of non-temperature controlled products to 72 hours since the proposed 24 hours might be too short for transport in countries with large geographic dimensions or over weekends with consecutive holidays.

The requirement that all transportation hubs where a product is held on the premises for more than 24 hours will need a wholesale distribution authorisation will be hard to meet in practise. In fact every airport Europe-wide would be required to obtain a wholesale distribution authorisation. Within inter Europe flights parts of the travel route can be replaced by road transport on short notice. In these cases the storage facilities being used are not known in advance.

The term "refrigerated product" should be replaced by "temperature controlled product" since it is often the bigger challenge to protect the product from coldness than from heat.

Regarding the last sentence: it should be clarified if that applies to refrigerated products in a cool box, too. International shipping of refrigerated products in cool boxes by air with carriers (TNT, DHL, World Courier; GNN) would be impossible. In addition, how should storage times in customs area warehouses be handled?

Page 27, item 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~~ covered by the quality system."

Comment:

The requirement for an audit means in practice that all airports Europe-wide have to be audited. It should be sufficient to cover these premises by the risk assessment within the quality system.

Page 27, item 9.18

"Transportation of medicinal products comprising highly active and radioactive materials should be transported in safe, dedicated and secure containers and vehicles."

Comment:

It is deemed to be necessary to define API classes for "highly active" medicinal products. The definition should also give examples for medicinal products explicitly not covered by this definition, e.g. antibiotics should be excluded as they contain highly active APIs but are definitely safe to transport as a finished product.

Page 28, item 9.19

"~~Validated~~ Qualified temperature-control systems … should be used… Customers should be provided with a temperature data to demonstrate that products remained within the required temperature storage conditions during transit, if ~~requested~~ agreed in advance."

Comment:

Since every vehicle has its own control device for temperature mapping the request to provide temperature data can, especially when more than one vehicle was used for the transport, only be met if this was agreed in advance.

Page 28, item 9.20

"If ~~refrigerated~~ temperature controlled vehicles are used, the temperature monitoring equipment used during transport should be maintained and calibrated at regular intervals or at a minimum of once a year. Temperature controlled vehicles should be qualified. This includes temperature mapping under representative conditions and should take into account seasonal variations. Customers should be provided with data to demonstrate that products remained within the required temperature storage conditions during transportation, if ~~requested~~ agreed in advance."

Comment:

The term "temperature controlled vehicle" should be defined in the annex. It is not clear if the term "refrigerated vehicle" used in the draft document refers to vehicles with +2/+8 °C transport conditions only or if every vehicle with a cooling equipment is meant (e.g. vehicles with temperature range controlled room temperature).

Page 31 and 32, Annex

Comment:

To include all elements given in EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, Annex 15, we recommend to widen the definitions of qualification and validation as following:

"Qualification is a part of validation. It includes all actions taken to demonstrate and document that all facilities, systems and items of equipment that influence the quality of a product have been set up and installed properly, work correctly and actually lead to the expected results; including also design qualification, installation qualification, operational qualification and performance qualification."

"Validation means documented evidence which provides a high degree of assurance that all processes, methods or systems that influence the product quality will

consistently result in a product that meets its pre-determined specifications and quality characteristics."

Furthermore, we suggest to include definitions for storage, transport and temperature controlled vehicle.

The term "Holding" is defined by "Keeping or storing medicinal products". In contradiction to that there is a distinction between the terms "holding" and "storing" in the introduction at page 4, paragraph 6: "All obligations related to wholesale distribution activities (such as exporting, holding, or storing) also apply to these actors.".