EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 Dec 2011

# Draft "**Commission Guideline on Good Distribution Practice of Medicinal Products for Human Use**"

## Comments from:

| Name of organisation or individual |
| --- |
| vfa.Research-Based Pharmaceutical Companies, Germany |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

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# 1. General comments

| General comment (if any) |
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| In general the principles and guidelines of the draft EU Commission Guideline on Good Distribution Practice of Medicinal Products for Human Use are broadly welcomed. They introduce a number of criteria that will help secure the pharmaceutical supply chain, and assure the maintenance of product quality.<br>Many pharmaceutical companies are organised as groups of legal entities. This structure requires a wholesaler license in addition to the manufacturing license. The quality system of these companies covers both parts of the business production and supply chain. The draft GDP guide does not reflect this very common structure. The quality risk management is referenced in the document but the level of detail and the overall structure of the document do not always reflect the changes that were introduced by this concept in the GMP-guidelines over the last years.<br>Principles like risk based approaches and design space are not taken into account. The document regulates many details that are addressed in the quality system of manufacturers. It is therefore necessary to reflect whether supply chains of manufacturers should be handled under GDP or might be better addressed under the GMP-guidelines. At the end two separate guidelines (one for manufacturers with additional wholesaler license and one for pure wholesalers) might be considered and might provide more clarity.<br>It is unclear how the issuance of this document will impact on Regulatory Agency inspections of the wholesale distribution chain, and clarity in this respect would be beneficial.<br>Further clarity is required in some sections to remove ambiguity and to ensure alignment across the clauses, and changes to the text are considered necessary as identified in section 2. |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>***(e.g. Lines 20-23)*** | Comment and rationale; proposed changes<br>***(If changes to the wording are suggested, they should be highlighted using 'track changes')*** |
|---|---|
| Page 5<br>Clause 1.2 | Comment:<br>Is this saying that a Responsible Person (RP), as required by Article 79(b) of Directive 2001/83/EC and referred to in Chapter 2, is required on each site; or that a person must be assigned as responsible for the Quality System on each site?<br><br>Can the same person be appointed for multiple sites?<br><br>A Qualified Person (QP) can be named on multiple Manufacturing Authorisations, and therefore only allowing an RP to be appointed to a single location is more stringent than the comparative GMP requirements.<br><br>Manufacturers that distribute (their own) products typically have a Quality Unit that has Quality oversight over wholesale and distribution activities. In such cases the responsible person for wholesaling may not have direct responsibility or may share the responsibility for the implementation of a distribution quality system.<br><br>Proposed change (if any):<br>Rephrase to alternatively allow for a Quality Unit to be responsible for the implementation of a quality system. |
| Page 5<br>Clause 1.3 | Comment:<br>Throughout the document the terms *wholesale distributor* and *distributor* are used seemingly synonymously. It should be clarified if both terms have the same meaning or whether there are any intended differences.<br><br>Proposed change (if any):<br>Use the same term throughout the document. |

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| Page 5<br>Clause 1.6 | Comment:<br>The Quality System elements required by every company should be the same irrespective of size, but it is recognised that the methodologies employed may vary.<br><br>Proposed change (if any):<br>Delete this clause. |
| Clause 1.11 | Comment: As senior management is responsible to perform the management review of the quality system, to whom should the results be communicated?<br><br>Proposed change (if any): define the audience for the communication |
| Page 8<br>Clause 2.1 | Comment:<br>How can this be practically implemented?<br><br>Section 2.8 describes the arrangements for deputies, and this seems to conflict with this section.<br><br>We propose that the roles and responsibilities of an RP are described in the guidelines without the requirement that one person (plus deputy) perform the role.<br>The justification for this is that the guidelines describe activities that lie within the responsibility of the MAH rather than the distributor. For example there may be a quality representative (or quality authority) at the distribution centre/ wholesaler responsible for those processes related to storage and transport, but there may be a separate quality representative responsible for processes like administrative release and recalls, and yet another person responsible for processes such as verification of customers. There is clear segregation of duties between these Quality functions, and such an organisation should be reflected in the guidelines as an alternative to a single RP. |

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| | Proposed change (if any):<br>The wholesale distributor should designate one or more people as a Responsible Person(s). The Responsible Person(s) routine duties should be described in writing, including those that may be delegated. The Responsible Person(s) maintains personal responsibility for the Quality System, even though duties may be delegated. |
| Page 8<br>Clause 2.3 | Comment:<br>Recommend deleting the Pharmacist requirement. Instead specify a set of criteria similar to the requirements in Article 49 of Directive 2001/83/EC but tailored specifically to GDP.<br><br>Proposed change (if any):<br>Delete 'A degree in Pharmacy is desirable'. |
| Page 9<br>Clause 2.5 | Comment:<br>The RP should have responsibility for the specified processes but not necessarily specific tasks. The guidelines must allow for routine duties to be appropriately delegated (i.e. delegate the task but not the responsibility).<br><br>Proposed change (if any):<br>iii) Ensuring that an initial and continuous training programme is implemented and maintained for all personnel involved in distribution activities.<br>vi) Ensuring an effective process is implemented for the qualification and approval of suppliers and customers.<br>vii) Ensuring an effective process for authorising the return to saleable stock of any returned medicines is implemented and maintained.<br><br>See 1.2. Allow also for a Quality unit independent from the responsible person to take care of certain tasks like complaint and recall handling. |

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| Page 9<br>Clause 2.10 | Comment:<br>Section 2.10 uses the word qualified in relation to GDP training. This should be changed to state that all 'personnel must be appropriately trained in relevant aspects of GDP' as the word 'qualified' has a much further reaching meaning<br><br>Proposed change (if any):<br>All personnel involved in wholesale distribution activities should be appropriately trained in relevant aspects of GDP, and should have the appropriate competence and experience prior to commencing their tasks. |
| Clause 2.16 | Comment: There should be an exception for bottled water or water fountains in work areas to avoid unnecessary traffic into and out of the GDP areas for the sole purpose of drinking water. |
| Clause 3.2 | Comment: It should be clarified that only premises used for product handling/storage purposes are concerned to ensure clarity which type of premises need to be covered by the authorisation. |
| Page 11<br>Clause 3.3 | Comment:<br>There is confusion throughout the document with respect to the need to physical vs. virtual segregation.<br><br>Refer to sections Ref: 3.3; 5.22; 5.24, 5.25 and 6.15. It is recommended that a consistent requirement with regards to the use of electronic segregation is stated throughout the document.<br><br>Proposed change (if any):<br>Products pending disposition should be segregated from saleable stock, either physically or through a validated electronic warehouse management system. These include any product suspected of falsification, returned products, rejected product, product awaiting disposal and recalled product. The appropriate degree of security should be applied in these areas to ensure that such items remain separate from saleable stock. |

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| Page 11<br>Clause 3.3 | Comment:<br>Change 'as to their fate' to 'pending disposition'<br><br>Proposed change (if any):<br>Products pending disposition should be segregated from saleable stock, either physically or through a validated electronic warehouse management system. |
| Page 11<br>Clause 3.4 | Comment:<br>In a manufacturer's warehouse (if acting as a wholesale distributor) typically products for the EU and other countries are stored within the same warehouse/area. Other means of ensuring prevention of mix ups are applied. This should be permitted to avoid unnecessary significant additional costs for segregation of areas.<br>E.g. a validated Warehouse Management System (WMS) is capable of providing appropriate system segregation, and physical segregation should not be necessary where a validated WMS is used.<br><br>Proposed change (if any):<br>Delete this clause. |
| Page 11<br>Clause 3.8 | Comment:<br>This is very subjective, as 'adequate separation' could be defined by space or physical segregation and should be more clearly defined. It should be phrased in a way that allows also organisational separation, e.g. different times for receipt and dispatch. |
| 3.10 | Comment: **Premises and storage facilities should be … free from …dust.**<br><br>Remark: In full automatic high bay warehouses this can not be guarantied at any time. Usually such facilities are not accessible for humans. Dust can be detected from inspection platforms on racks at any level. |

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| | Proposed change (if any): A possible contamination with **dust has to be removed before the materials/goods are transferred to GMP production areas.** |
| Page 12<br>Clause 3.13 | Comment:<br>Humidity should not be specified as a requirement.<br><br>All medicinal products are subject to stability tests according to ICH requirements, and humidity variations within the European Union would not be expected to have any impact on product quality.<br><br>Proposed change (if any):<br>Delete humidity. |
| Page 12<br>Clause 3.19 | Comment:<br>Change 'would' to 'may', and remove the requirement for humidity.<br><br>Proposed change (if any):<br>Adequate records of repair, maintenance and calibration activities for key equipment should be made and the results should be retained. Relevant pieces of equipment may include (but not be limited to) cold stores, refrigerators, thermometers, or other temperature recording devices, air handling units and any equipment utilised in conjunction within the onward supply chain.<br><br>Comment: The term "equipment utilized in conjunction with the onward supply chain" is not well defined.<br>Proposed change (if any): "Equipment utilized in conjunction with the onward supply chain" should be better described, e.g. trucks or other means of transport |
| Page 12<br>Clause 3.20 | Comment:<br>Change to state 'requires validation' (ref. GMP annex 11). |

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| | Proposed change (if any):<br>Before a computerised system is brought into use, it should be validated. |
| Page 13<br>3.24 | 3.24 Comment: **Back up data should be stored … at least 5 years …**<br><br>Proposed change (if any): Back up data should be retained for a period stated in national legislation but not shorter than the longest shelf-life of the product plus one year, or a minimum of 5 years (whichever is longest). |
| Page 14<br>Clause 4.5 | Comment:<br>It is recommend that this is changed to 'longest shelf life plus 1 year, and a minimum of 5 years'<br><br>Proposed change (if any):<br>Documents should be retained for a period stated in national legislation but not shorter than the longest shelf-life of the product plus one year, or a minimum of 5 years (whichever is longest). |
| Page 15<br>Clause 5.2 | Comment: To avoid that each individual wholesaler and each individual manufacturer must exchange licenses, causing an extreme additional bureaucratic effort, it may be better to develop a controlled data base that allows each wholesale party to determine the license status of a business partner. |
| Clause 5.3 | Comment: To avoid that each individual wholesaler and each individual manufacturer must exchange licenses, causing an extreme additional bureaucratic effort, it may be better to develop a controlled data base that allows each wholesale party to determine the license status of a business partner. |
| Page 15<br>Clause 5.4 | Comment:<br>It is unclear what is required by this clause? |

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| | Does this mean that full traceability back to the original manufacturing site is required, including the supply route, transportation providers, etc. If so this level of traceability is not currently available. |
| Clause 5.7 | Comment: Should be combined with 5.5. |
| Page 17<br>Clause 5.15 | Comment:<br>It is the obligation of the Qualified person of the manufacturer/importer to release the batch to the market. If the wholesaler has checked the manufacturing license additional checks of the batches should not be necessary unless the wholesaler does not trust the manufacturing license or the GMP-status anymore. |
| Page 17<br>Clause 5.17 | Comment:<br>Further clarity is required. Specifically is physical segregation required, or is spatial/ electronic segregation sufficient (refer also to 5.24).<br><br>What is meant by 'other products'? Does this include veterinary medicines, herbal medicines, food supplements, nutritionals, etc. |
| Page 17<br>Clause 5.22 | Comment:<br>Specifically mentions electronic segregation for expired stock, but only mentions segregation or physical segregation for others.<br><br>Refer to 3.3, 5.24, 5.25 and 6.15. Clarity is required throughout the document on segregation requirements. |
| Page 17<br>Clause 5.24 | Comment:<br>Refer to 3.3, 5.22, 5.25 and 6.15.<br>Clarity is needed on the use of electronic segregation vs. physical segregation. |
| Page 18 | Comment: |

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| Clause 5.25 | Refer to 3.3, 5.22, 5.24 and 6.15<br>Clarity is needed on the use of electronic segregation vs. physical segregation.<br><br>The use of validated computer systems should prevent the need for product status labelling.<br><br>Proposed change (if any):<br>Delete 'The products and the areas concerned shall be appropriately identified.'. |
| Page 18<br>Clause 5.29 | Comment:<br>Providing the product has an acceptable minimum shelf life the use of both FIFO and FEFO should be considered acceptable.<br><br>Proposed change (if any): Exceptions from FEFO should be permitted. Exceptions should be controlled by SOPs (defined exceptions/defined justifications for exceptions) |
| Page 18<br>Clause 5.30 | Comment: The sealing requirement should be defined more precisely (to avoid misinterpretation). Not every shipping box or every pallet can be sealed. |
| Page 18<br>Clause 5.32 | Comment:<br>This clause implies the need to have full track and trace, of all batches of medicinal product.<br><br>The phrase 'products bearing the safety features' should be clarified. The detailed requirement in the Falsified Medicines Directive shall be described in a delegated act. This clause should only cross reference the delegated act. In particular the level of detail in the transportation records should be remained open to allow the European Commission's delegated act to give the framework as foreseen in the Falsified medicines Directive. |
| Page 20 | Comment: |

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| Clause 6.3 | Product Quality complaints are referred back to the manufacturing site for investigation, and should only be reported to the national competent authority as per GMP chapter 8, clause 8.8. Otherwise Wholesalers may have to notify authorities about any product complaint they are informed about including all minor complaints.<br><br>Proposed change (if any):<br>The last sentence : "The national authority should be notified without delay" should be replaced with a statement as in 6.1., e.g. "<br>The complaint should be notified to the manufacturer/MA holder without delay. Falsifications should be notified to the national authority without delay." |
| Page 20<br>Clause 6.5 | Comment:<br>Change to read:<br>'If necessary, appropriate follow-up actions should be taken after investigation and evaluation of the complaint, including where required notification to the national competent authorities'<br><br>Proposed change (if any):<br>If necessary, appropriate follow-up actions should be taken after investigation and evaluation of the complaint, including where required notification to the national competent authorities. |
| Page 21<br>Clause 6.9ii | Comment:<br>Section 6.9ii; The limit of five days is not justified by scientific reasons and does not reflect this concept of risk management assessments. It is an arbitrary number for allowing returned product to be placed back into saleable stock, and does also not take into consideration weekends/ national holidays, and the need to arrange suitable return logistics. Based on this a longer period of time could be justified.<br>The emphasis should be on verifying correct handling and storage to ensure that product quality is not compromised.<br><br>Proposed change (if any): |

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| | Medicinal products returns from a customer not holding a wholesale distribution authorisation should only be returned to saleable stock if they were returned within thirty days of original dispatch or the storage conditions of the customer are proved to be in accordance with this guideline. |
| Clause 6.10 | Comment: **Medicinal products requiring low temperature …throughout the entire time …**<br><br>Comment: The requirement is unclear. If it means to say that all listed steps have to be performed under authorised storage conditions (e.g. 2-8 deg C) it will become virtually impossible to return these products to stock. Al least unpackaging, inspection, repacking and transfers to cool stores typically happen under ambient conditions. The requirement is unnecessarily strict, as - with the exception of very few extremely sensitive products that are labelled accordingly (cool chain)- many products requiring low storage temperatures can be exposed to ambient conditions for the normal duration of some activities (such as transport to and from a cooling device or area, packaging of shipment etc.) without any quality impact. The requirement does not reflect the concept of risk assessment. The conditions should be assessed per product or per class of products. |
| Clause 6.11 | Comment: Disposal of returned product should not require individual approval by a Responsible Person if requirements and process are regulated by procedures/SOPs. |
| Page 21<br>Clause 6.12 | Comment:<br>Providing the product has an acceptable minimum shelf life the use of both FIFO and FEFO should be considered acceptable.<br><br>Proposed change (if any): Exceptions from FEFO should be permitted. Exceptions should be controlled by SOPs (defined exceptions/defined justifications for exceptions) |
| Page 21<br>Clause 6.15 | Comment: Refer to 3.3, 5.22, 5.24 and 5.25.<br>Clarity is needed on the use of electronic segregation vs. physical segregation |
| 7 Contract | Comment: From the definitions available so far and from this chapter it is not fully clear whether transportation of medicinal products |

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| Operations | must be considered a "wholesale distribution operation" or not and, if transportation must be considered an "outsourced activity". As written the requirement might result in the need for all transport providers to formally apply for wholesale licenses. |
| Clause 7.5 | Comment: If transport of medicinal products is considered an activity falling under the definition of wholesale distribution then all transport providers (DHL, ToF etc) would become wholesale distributors. Is this the intention of this guideline?<br><br>Proposed change (if any):Make it more clear that transport is a critical activity within wholesale distribution and that wholesale distributors must apply appropriate supervision and control over service providers for transport operations. It should be avoided though, that transport service providers have to become wholesale distributors with an independent license. |
| Clause 7.6 | Comment: There might be cases where an audit does not make sense (e.g. technical support for taxes) . It should be allowed to allow for the outsourcing of activities in justified cases.<br><br>Proposed change (if any): The requirement to audit should be accompanied by an statement "unless well justified exemptions". |
| 9 Principle | Comment: Sentence 3 should be rephrased to allow for deviations from standard storage conditions, if supported by stability data. Storage conditions on the packaging are meant to limit changes to the product during long term storage. They do not necessarily indicate that short term temperature excursions affect product quality negatively. If short term excursions from standard storage conditions are affecting product quality, this is typically indicated on the product label/packaging in a way that "closed cool chain must be maintained". Currently labelling regulations do not require to define transport conditions on the label or on packaging. CPMP QWP 609 explicitly states that a limitation of allowable transport conditions to labelled storage conditions should only be made if necessary. Else stability data should be used to justify excursions. |
| 9.1 | Comment: see above : If wholesalers and manufacturers have to ensure 2-8 deg C transport of all cold products and conditions of less than 25 deg C for all products labelled accordingly, then transportation costs for medicinal products will increase significantly without adding to the quality of the products. Also, only in limited areas of the world are transportation services offered that reliably |

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| | provide the necessary temperature ranges.<br><br>Proposed change (if any): Allow for other transport conditions if supported by stability data. |
| 9.2 | Comment: Deviation should be defined more precisely and it should be stated who should do the reporting. |
| 9.12 | Comment: **Where transportation hubs are utilised supply chain …for more than 24 hours ….**<br><br>Remark: This is always the case for – over the weekend – national distribution, where usually trucks are deloaded on Friday evening or Saturday morning at a hub and local distribution to pharmacist is started on Monday morning! These hubs are not maintained as warehouses from the point of documentation, pallet turn over handling, temperature mapping and calibration, etc. Therefore hubs can not be compared to a storage site - at the same GDP level!<br><br>This can not be fulfilled for all bonded storages passing the border. How can this be regulated by the pharmaceutical industry? There is no commitment from the customs offices to work accordingly! |
| 9.12 | Comment: **For refrigerated products any storage at a hub… for any period of time …**<br><br>Remark: What does it mean, any time? Do the GDP count in minutes? Does the hub need to implement any GDP rule at a level of a storage site?<br><br>Proposed change (if any): In case **refrigerated products should remain in the hub longer than required by an uninterrupted distribution,** these hubs need premises equivalent to storage sites and have to be authorised as distribution wholesalers.<br><br>Comment: This requirement indirectly results in a need to issue wholesale licenses for all transport service providers engaged in transport of medicinal products. All hubs must be able to store product over a public holiday or a weekend which exceeds the 24 |

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| | hours limit. While cleanliness, pest control and appropriate environmental control must be ensured (e.g. through contracts, audits etc) the requirement to hold a wholesale license seems excessive and does not reflect the concept of risk management. |
| 9.19 | Comment: Temperature data should not be handed to customers as customers do not have the required knowledge to interpret such data. Rather it should be the obligation of the shipper (wholesaler) to ensure through appropriate contract with the transport provider that appropriate conditions are maintained during transport. In case of deviations the manufacturer should be informed and decide if the product quality is affected. |
| 9.20 | Comment: **… refrigerated vehicles …should be … calibrated …at minimum once a year. This includes temperature mapping … (on) seasonal variations …**<br><br>Remark: This should be maintained as any other qualification process. Complete data once and re-qualification in case of significant changes! An approach of ICH Q9 (risk based) should be allowed. Usually this can be verified during audits of the distribution contractors performed by the pharmaceutical industry. The adequacy of maintenance program and qualification should be assessed during these audits.<br><br>Proposed change (if any): …**adequate qualification and maintenance of the used refrigerated vehicles should be regularly evaluated by the contract giver**. This should include temperature mapping under representative conditions and take seasonal variations into account. |

Please add more rows if needed.