# AIPES comments on:

# Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use

Date: 23 December 2011

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| 1 Principle | 5 | All distribution activities should be clearly defined and systematically reviewed and all criticalsteps of distribution processes and significant changes should be validated. | The distribution process is in constant change. It is possible to qualify, but not to validate. | How is a significant change defined and how should it be validated? |
| 1 | | Definition of quality system | | What quality system should be established, according to ISO standards ? |
| 1.2 | 5 | A responsible person should be appointed by the management for each distribution site, who should have defined authority and responsibility for ensuring that a quality system is implemented and maintained. | | How should a distribution site be defined? (e.g.include subsidiaries and offices that perform marketing and sales and are involved in order management but not physical distribution?) |
| 2 | | Responsible persons | | Some national legislations (eg. Spain, Portugal) demand the responsible person to be a pharmacist. This would be a concern on a EU level. Can the responsibility be delegated to non-pharmacist personnel ? |
| 2.1 | 8 | The Responsible Person should | | Does this mean 24 |

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| | | fulfill his/her responsibilities personally and should be permanently available. | | hour coverage seven days a week, or coverage during business hours with call out for RPs as needed? |
| 2.3 | 8 | A degree in pharmacy is desirable. | Should not be too specific on the qualifications required as a degree in Pharmacy may not be necessary. | |
| 2.5 iii) | 8 | Approving the initial and continuous training program for all personnel involved in distribution activities | | Need to better define training and what it is being approved against. |
| 2.5 viii) | 9 | Approving any contract between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to wholesale distribution and/or transportation of medicinal products | | Needs to be defined. (Subsidiaries and offices are working under agreements made centrally on behalf of the site) |
| 2.12 | 9 | Personnel dealing with medicinal products requiring more stringent handling such as hazardous products, radioactive materials as well as products presenting special risks of abuse, narcotics or psychotropic substances, or temperature sensitive products should be given specific training. | | This is too general – what is meant by 'specific training'? |
| 3 | | Qualification an validation of equipment and premises | Validation should be covered by "qualification". | |
| 3.3 | 11 | There should be segregated areas designated for the storage of products awaiting further decisions as to their fate. | | Suggest additional wording in brackets: There should be segregated areas (including those defined electronically) designated for the storage of products awaiting further |

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| | | | | decisions as to their fate. |
| 3.4 | 11 | Medicinal products not intended for the Union market should be kept in segregated areas. | It is not clear why this is required as current legislation ensures strict control of the stock / warehouse and current systems track product and batches. This would not, therefore, add any additional safety. | |
| 3.7 | 11 | Radioactive materials and other hazardous products, as well as products presenting special risks of fire or explosion (e.g. pressurized gases, combustibles, flammable liquids and solids) should be stored in a dedicated area(s) subject to appropriate safety and security measures. | Radiopharmaceuticals should not be included as they are always in transit, labeled to the end user and are not stored. | Should refer to <u>medicinal</u> products e.g. "hazardous medicinal products, as well as products presenting special risks of fire or explosion (e.g. pressurized gases, combustibles, flammable liquids and solids) should be stored in a dedicated area(s) subject to appropriate safety and security measures." |
| 3.10 | 12 | Cleaning equipment should be chosen and used in order not to be a source of contamination. | | Unclear how equipment can be chosen to ensure it is not a source of contamination? |
| 3.15 | 12 | All equipment used for storage and distribution of medicinal products should be designed, located and maintained to a standard which suits its intended purpose.Planned preventive maintenance should be in place for key equipment | | How is key equipment vital to the operation defined? |

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| | | vital to thefunctionality of the operation | | |
| 3.17 | 12 | Alarm levels should be appropriately set and alarms should be regularly tested to ensure adequate functionality. | This is impractical for any piece of equipment used in the supply chain. | |
| 5.8 | 16 | Wholesale distributors must ensure they must supply medicinal products only to persons who are themselves in possession of the distribution authorisation or who are authorised or entitled to supply medicinal products to the public in the Member State concerned. Qualification of customers should be appropriately documented. | | Require clarification on who is responsible for 'Qualification of customers' as it implies it is the wholesalers. |
| 5.10 | 16 | Wholesale distributors should monitor their transactions and investigate any irregularity in sale patterns to avoid diversion of medicinal products at risks of being misused and to ensure fulfilling any public service obligation imposed on them. | The statement is too ambiguous; there should be a risk-based analysis based on product. | |
| 5.16 | 17 | Distributors receiving medicinal products from third countries for the purpose of importation, i.e. for the purpose of placing these products on the EU market, must hold a manufacturing / import authorization. | | What is the definition of third countries? Are PIC countries included/excluded? Is a distributor defined as just a third party who doesn't own goods or import? |
| 5.32 | 18 | For all supplies to a person authorised or entitled to supply medicinal product to the public, a document must be enclosed to ascertain the date; name and pharmaceutical form of the medicinal product, batch number at least for products bearing the safety features, where required: quantity supplied; name and address of | | Need to define 'public' e.g. individual versus hospital pharmacy? |

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| | | the supplier, name and delivery address of the consignee (actual physical storage premises, if different) and applicable transport and storage conditions. | | |
| 5.35 | 19 | If the medicinal product is supplied to a person in a third country authorized or entitled to supply medicinal products to the public, the rules for document enclosure apply as for supply of the medicinal product established in the EU. | | What is the definition of 'a person'and what does 'authorised or entitled to supply medicinal products to the public' mean? Requires clarification. |
| Chapter 6 Principle | 20 | A special assessment of returned medicinal product should be performed before any approval for resale. A consistent approach amongst all partners within the supply chain is required to be successful in the fight against falsified medicinal products. | | What is meant by 'special assessment'? e.g. complete re-test or risk assessment etc |
| 6 | | Medicinal products returns from a customer not holding a wholesale distribution authorization should only be returned to saleable stock if they are returned within 5 days…. | Many of our customers are hospital pharmacies which may not hold a wholesaler license, but are by way of their "qualification" (pharmacies) to be treated like a wholesaler. | |
| 6.9i | 21 | The medicinal products are in their unopened and undamaged secondary packaging and in good condition; | | Need a standard for what defines 'good condition' as otherwise is too open to interpretation. |
| 6.9iv | 21 | They have been examined and assessed by a sufficiently trained and competent person authorised to do so | | Need some guidance on 'sufficiently trained and competent person' as interpretation can vary. |
| 6.9v | 21 | | | Two typographical |

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| | | | | errors in this paragraph. |
| 6.11 | 21 | All handling of returned medicinal products including their return to saleable stock or disposal should be approved by the Responsible Person and recorded | | Who is in charge? RP of the manufacturing plant – or RP of the Distributor / Wholesaler? |
| 6.13 | 21 | There should be documentation in place that describes how the distributor increases their staff's awareness of the risks of falsified medicinal products entering the supply chain. | | This should be covered in training records. |
| 6.23 | 22 | The effectiveness of the arrangements for recalls should be evaluated regularly. | | This should be evaluated annually or to timescales specified by Health Authorities. |
| Chapter 7 Principle | 23 | When outsourcing activities a written contract should be drawn up. Both the contract giver and the contract acceptor must hold a distribution authorisation. | | 'Activities' may cover a wide range, should be more clearly defined. Does 'distribution authorisation' mean a wholesaler licence? – needs to be clarified. |
| 7.6 | 23 | 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 an audit of the third party. | | The level of audit needs to be risk assessed and appropriate to the level of activity being assessed. |
| 7.8 | 23 | The Contract Acceptor must forward any information that can influence the quality of the products to the Contract Giver in accordance with the requirement of the contract. | | How would the Contract Acceptor know? Needs to be clarified as difficult otherwise to see how they can comply. |
| 8.3 | 25 | Audit of subcontracted activities should be a part of the self-inspection programme. | | This needs to be made clearer e.g. whoever is doing the subcontracting must |

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| | | | | have a self-inspection programme. |
| Chapter 9 Principle | 26 | Medicinal products should be transported in accordance with the storage conditions indicated on the packaging information. | Transport temperature conditions do not apply unless specified on the package. | |
| Chapter 9 Transportation | 26 | | General comments:<br>1) The contribution of this guidance to decrease the introduction of falsified medicinal products entering the market is not clear as it doesn't address falsified medicines per se, only the distribution thereafter.<br>2) Packaged medicinal products are not easily recognizable therefore transport companies will have difficulties when they are not specifically contracted to carry these pharmaceuticals. | |
| 9.1 | 26 | The required storage conditions for medicinal products should be maintained during transportation within the defined limits as described on the packaging information. | Transport temperature conditions do not apply unless specified on the package | |
| 9.4 | 26 | 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 | How is contamination defined and how do you control it? This cannot be guaranteed for an Airline operation? | |

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| | | of the products to conditions that could affect their quality and packaging integrity, and to prevent contamination of any kind. | | |
| 9.5 | 26 | Delivery drivers (including contract drivers) should be trained in the relevant areas of GDP | Need to take into account that not all pharma operations use own vehicles and control external drivers / all aspects of the shipment.<br><br>Sufficient if delivery drivers receive delivery instructions in line with GDP. It should be risk-based;train dedicated delivery systems and give proper instructions for non-dedicated drivers - this is especially so for low use, high frequency products using integrators. | |
| 9.6 | 26 | There should be procedures in place for the operation and maintenance of all vehicles and equipment involved in the distribution process, including cleaning and safety precautions. Particular attention should be paid to the fact that cleaning agents should<br>not have an adverse effect on product quality. | What about airlines and companies using external transportation? The guideline has not taken into account consolidated shipments / low volume distribution of medical products. It would be extremely difficult to assess adverse effects of any cleaning agents used - but in any case the packaging is designed to protect the product from | |

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| | | | adverse conditions found in normal distribution. | |
| 9.8 | 26 | Dedicated vehicles and equipment should be used, where possible, when handling medicinal products. Where non-dedicated vehicles and equipment are used procedures should be in place to ensure that the quality of the medicinal product will not be compromised | What about Airlines and pharma companies using external transportation? The guideline has not taken into account consolidated shipments / low volume distribution of medical products | |
| 9.9 | 27 | Deliveries should be made directly to the address stated on the delivery note and must be handed into the care of the consignee. Medicinal products should not be left on alternative premises. | | Suggest the following additional text (in red): Deliveries should be made directly to the address stated on the delivery note and must be handed into the care or left according to the instructions of the consignee. Medicinal products should not be left on alternative premises. |
| 9.10 | 27 | In case of emergency deliveries outside normal business hours persons should be designated and written procedures should be available. | | Suggest the following additional text (in red): Deliveries should be made directly to the address stated on the delivery note and must be handed into the care or left according to the instructions of the consignee. Medicinal products should not be left on alternative premises. |
| 9.12 | 27 | Where transportation hubs are utilized in the supply chain, a maximum time limit of normally | Not possible to achieve. What about weekend deliveries, | |

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| | | 24 hours should be set to await the next stage of the transportation route.<br>Where medicinal products are held on the premises for longer than this defined time<br>limit, the hub will be deemed to be acting as a storage site and required to obtain a wholesale distribution authorization. For refrigerated product any storage at a transportation hub for any period of time would require that premises to hold a wholesalers distribution authorisation | emergencies and problems, airline cancellations, (ash-cloud s etc).<br><br>Oversea Sea freight takes several days. Should shipping lines obtain wholesale / distributor license...?<br><br>Products that are packed and labeled to end user must be considered to be in transit – not stored. | |
| 9.13 | 27 | In the event that the transportation of medicinal products requires unloading and<br>reloading e.g. at terminals and hubs, these premises should be audited and approved<br>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<br>or functions for their intended use. Particular attention should be paid to temperature monitoring, cleanliness and the security of unguarded intermediate storage facilities | Impossible to achieve. What happens in case of a vehicle break down and there is need to transfer the load to another vehicle? What happens if the external driver/company receives instructions from his forwarding agent to perform change of plan?<br><br>Need to take into account that not all pharma operations use own vehicles and control external drivers / all aspects of the shipment. | |
| 9.14 | 27 | Medicinal products should be transported in containers that have no adverse effect on the quality of the products, and that offer adequate protection from external influences, including contamination. | | Need to define 'containers'. If this means primary containers it is not relevant for GDP. |
| 9.15 | 27 | Selection of a container and | | Suggest the |

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| | | packaging should be based on the storage and transportation requirements of the medicinal products; the space required for the amount of medicines; the anticipated external temperature extremes; the estimated maximum time for transportation including transit storage at customs the validation status of the packaging and shipment containers. | | following additional text (in red):<br>Selection of a container and packaging should be based on the storage and transportation requirements of the medicinal products; the space required for the amount of medicines. When applicable; the anticipated external temperature extremes; the estimated maximum time for transportation including transit storage at customs the validation status of the packaging and shipment containersetc. |
| 9.16 | 27 | Containers should bear labels providing sufficient information on handling and storage requirements and precautions to ensure that the products are properly handled and secured at all times. The containers should enable identification of the contents of the containers and the source. | | Need to define 'containers'. If this means primary containers it is not relevant for GDP.<br><br>Suggest the following additional text (in red):<br>"When applicable, the package~~Containers~~should bear labels providing sufficient information on handling and storage requirements and precautions to ensure that the products are properly handled and secured at all |

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| | | | | times. The containers should enable identification of the contents of the containers and the source."<br><br>What is meant by the last sentence - what is contents and the source? |
| 9.18 | 28 | Transportation of medicinal products comprising highly active and radioactive materials should be transported in safe, dedicated and secure containers and vehicles. In addition, these safety measures should be in accordance with international agreements and national legislation. | | Suggest the following changes in text (in red): Transportation of medicinal products comprising highly active (Comment: what is meant by this? Needs clarifying) and radioactive materials should ~~be transported in safe, dedicated and secure containers and vehicles. In addition, these safety measures should~~ be in accordance with international ~~agreements~~ and national legislation. |
| 9.19 | 28 | 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 | For low volume / high frequency shipments this will be labour intensive and very expensive to achieve without any safety benefit. | |

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| | | required temperature storage conditions during transit, if requested | | |
| 9.20 | 28 | Customers should be provided with data to demonstrate that products remained within the required temperature storage conditions during transportation, if requested. | Who is defined as the customer? This will be very difficult to achieve in practice. | |
| 9.21 | 28 | If cool-packs are used in insulated boxes, they need to be located such that the product does not come in direct contact with the cool-pack. Staff must be trained on the procedures for assembly of the insulated boxes (seasonal configurations) and on the re-use of cool-packs. | Suggest the following additional text (in red):<br><br>"If cool-packs are used in insulated boxes, they need to be located such that the product, when necessary, does not come in direct contact with the cool-pack. Staff must be trained on the procedures for assembly of the insulated boxes (seasonal configurations) and on the re¬use of cool-packs."<br><br>This is more GMP related as the product will never come in direct contact with a cool-pack. | |
| 9.22 | 28 | There should be a system in place to control the reuse of cool-packs to ensure that incompletely cooled packs are not used in error. There should be adequate physical distinction between frozen and chilled ice packs. | Need adequate controls to distinguish between frozen and chilled but they don't need to be physically distinct.<br><br>This is more GMP related defining | This will apply to new cool-pack as well as re-used ones. |

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| | | | packing rather than transport. | |
| 9.23 | 28 | The process for delivery of sensitive products and control of seasonal temperature variations should be described in a written procedure. This procedure should also cover unexpected occurrences such as vehicle breakdown or non-delivery. A procedure should also be in place for investigating and handling temperature excursions. | | Need to define sensitive products |
| Annex Glossary of Terms<br><br>Validation | 32 | Action of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification). | The validation is defined as the full pharmaceutical validation and this is not possible for a number of operations in the transport of pharmaceutical products. | |
| Annex Glossary of Terms | | Additional term to be added | Add the following term and definition into the glossary<br><br>Term: In transit<br><br>Definition:Addressed packages that are to be delivered without opening the delivery package to the end destination. The packages will be on planned routes to end users and will suffer no undue delay or interruption of the route. Planned routes to end users can include change of carriers and/or transport mode(s). | |

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| Annex Glossary of Terms | | Additional term to be added | Add the following term and definition into the glossary<br><br>Term: Low volume product<br><br>Definition: Type of product that is produced in low volume but has a high frequency of delivery. These products may be delivered using planned routes using multiple carriers including integrators and by all modes. The products have a short shelf life (typically less than 6 months) and may be made to order for the patient. Typical low volume product examples are radiopharmaceuticals, contrast media, cold kits used with radiopharmaceuticals, serums and antidotes. | |
| Annex Glossary of Terms | | Additional term to be added | Term: Storage<br><br>Definition: Long term holding of the medicinal goods in a controlled environment according to the prescribed product specifications, the storage ensures the quality of the goods | |

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| | | | to expiry. | |