December 19, 2011

Submission of comments on "Commission Guideline on Good Distribution Practice of Medicinal Products for Human use" (SANCO/C8/AM/an D(2010)380358

Comments from:

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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

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EFPIA welcomes the opportunity to comment on the proposals for GDP requirements. EFPIA considers two principles to be important in the development of this guidance: • Harmonisation of GDP requirements • Science and risk based decisions	
	Harmonisation of GDP requirements: Within the global environment that we now operate in EFPIA supports harmonisation of GDP requirements wherever possible. It is recommended that other guidances that have been developed or that are under development are considered as the EU guidance is finalised. For example WHO GDP, USP (current draft chapter).	
	Science- and risk-based decisions: EFPIA supports the key principles of science- and risk-based decision making to provide sufficient flexibility for implementation of GDPs. Specifically, such science- and risk-based rationales should be considered throughout the revised GDP Guideline in lieu of specific expectations put forward. Science- and risk-based decisions should be based on known characteristics of the product. For example: • overall supply chain qualification and validation activities;	

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	• need for physical segregation and separation of goods where today's current industry practice is to segregate goods by electronic means; • storage and transport conditions, incl. temperature monitoring during transport, residence time of deliveries at hubs; • returns to saleable stock within five days (6.9.ii.), as there is no clear rationale for such time period of any length. Further examples and respective comments are provided in the section "specific comments on text", below.	
	<u>EFPIA feedback provides comments on the text in the appropriate sections below but would also like to specifically make the following more general comments</u> • EFPIA understands that the GDP Guideline does not refer to Investigational Medicinal Products (IMP). However, paragraph 5.34 could be interpreted to cover IMP. Therefore EFPIA suggests that any ambiguity regarding applicability to IMPs is removed from the GDP text. • Also, EFPIA suggests that any ambiguity is removed from the text, that could imply that distribution outside the license system may be acceptable. • Chapter 9, 'Transportation': Transport conditions need not be identical to labelled storage conditions. Medicinal products may be transported at specified temperature ranges for specific durations provided continuous verification is applied (e.g. continuous temperature monitoring and scientifically based (stability data) assessment hereof before release).	

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	The use of cold chain programmes that employ validated packaging configurations for temperature maintenance over a pre-defined transport duration should be acceptable. The guideline should be sufficiently flexible to allow the use of validated temperature-control systems rather than stating specific references to availability of temperature monitoring data. The chapter "Temperature Control during Transport" should be better structured. As it is drafted, it is not clear enough. EFPIA suggests that paragraphs 9.19 to 9.23 are preceded by some introductory text, highlighting the fundamental principles and approaches. I.e. it has to be ensured that correct transport conditions are maintained between distributor and customer. This can be achieved in different ways, e.g. by validation of the shipping route, qualification of the shipping container, continuous temperature monitoring during each shipment, etc.. Where continuous temperature monitoring is used customers should be provided with a temperature data to demonstrate that products remained within the required temperature conditions during transport, if requested. • There is a gap in that "repackaging and relabelling" is not addressed. • The text should be more consistent in that the terms "distributor" and/or "wholesale distributor" are used consistently throughout the document. In the draft, usage of both terms in different section is confusing.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Introduction		"This chapter should reflect the evolution in technology used in the distribution industry (e.g. e-commerce) **Proposed change:** e-commerce, Direct to Pharmacy and Direct to Patient deliveries should be included	
Glossary		The second sentence of the definition of wholesale distribution of medicinal product i.e. Article 1(17) European Directive 2001/83/EC is unclear whether the wholesale distribution is covering the products storage and handling at a retail pharmacist level.	
Introduction, second paragraph, line 7		Suggest revising text below in Introduction – "…distribution objectives by observing GMP…" is probably not the intended text. **Proposed change:** "……It is necessary to exercise control over the entire distribution chain by observing good distribution practice of medicinal products. This policy ensures that the quality of medicinal products manufactured in accordance with good manufacturing practice (GMP) in, or imported into the European Union is maintained throughout the distribution network."	
Chapter 1, Principle, second paragraph		Principle states "…significant changes should be validated", **Proposed change:** "justified" or "qualified" may be more appropriate words. The distribution processes used should be well- defined and changes to them justified/qualified (/subject to a deviation or change control system).	
Chapter 1 Quality Risk Management		Quality Risk Management section does not clearly state the requirement to implement a formal Quality Risk Management Program.	

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		Proposed change: A Quality Risk Management program shall be in place to support the assessment, control, communication and review of risks to quality of medical products.	
1.2		The text as written suggests that a Responsible Person (RP) should be appointed at each Distribution site. Clarity is requested on this point. For example can one RP be assigned to multiple sites ? By comparison 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.	
1.3.		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. **Proposed change:** Use the same term throughout the document.	
Chapter 1 1.4, 1.6		Sections 1.4 and 1.6 refer to the size of the organisation and activities of a distributor with respect to the development of an appropriate quality system. **Proposed change:** Combine sections 1.4 and 1.6 to avoid duplication.	
1.8		No statement requiring the QS to ensure compliance with the provisions of a relevant license where applicable e.g. WDL. **Proposed change:** Include this as a bullet point here or elsewhere in the document.	
1.8 iii)		*´…within a satisfactory time period´*:- The time period agreed e.g. in a contract is acceptable and satisfactory. **Proposed change:** Change to read: *'...delivered to the right recipients within <u>the agreed</u> ~~a satisfactory~~ time period;'*	

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1.9		It is recommended that supply chain verification is included **Proposed change:** Include the requirement to verify (distribution) supply chain (MAA holder?).	
1.9 i)		It is advised to use consistent wording and role designations throughout the entire text. **Proposed change:** Change to read: *´…the suitability and competence of the contract acceptor ~~other party~~ to carry out…´*	
1.9 (ii)		The written agreement should be reviewed on regular basis **Proposed change:** ii) For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor *and should be reviewed on a regular basis*	
Chapter 2 2.1		**2.1 Says** : The wholesale distributor must designate a person as Responsible Person. ***The Responsible Person should fulfil his/her responsibilities personally and should be permanently available***. The Responsible Person should meet the conditions provided for by the legislation of the Member State concerned. **Comment:** We propose that personal accountability is maintained but that delegation may be allowed as per 2.5.x.. ('delegating his/her duties when absent…').	
Chapter 2 Personnel 2.3		In 2.3 it is stated that ''A degree in Pharmacy is desirable''. However in the previous sentence it is stated the qualifications of the Responsible Person should meet the conditions provided by the legislation of the Member State concerned and should be appropriate to fulfil the assigned duties. We consider this to be sufficient detail for inclusion in the GDP guideline. It is also in line with article 79 in 2001/83 which refers to the requirement for ''a qualified person designated as responsible, meeting the conditions provided for by the legislation of the Member State concerned'' . Reference to a pharmacy degree	

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		is additional to this requirement. **Proposed change:** Remove the reference to pharmacist.	
Chapter 2 Personnel 2.4		Section 2.4 states that the Responsible Person (RP) should carry out duties personally to ensure GDP Compliance. It should be possible that the RP delegates roles to trained individuals but they still have ultimate responsibility in ensuring GDP compliance. **Proposed change:** The Responsible Person should carry out his/her activities personally in order to ensure the wholesale distributor can demonstrate GDP compliance and that public service obligations are met. ***The Responsible Person activities may be formally delegated to appropriately trained individuals but the Responsible Person retains accountability for all such delegated activities.***	
Chapter 2 2.5		**Comment on iii),iv),vii):** 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). **Comment vi) :**places the requirement on the RP to perform the qualification and approval of suppliers and customers. For companies delivering direct to surgeries, pharmacies, hospitals etc, the customer base may exceed 10,000. The RP cannot physically perform this activity. With regards to approval of suppliers, this should be clarified to better explain the requirement. We would suggest that the RP is responsible for ensuring appropriate processes are in place to achieve both objectives and for confirming this via inspection/audit. **Comment on x):** Allows the delegation of duties only when absent, Roles need to be delegated even when not absent, provided it is clearly documented?	

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		Proposal for iii): Ensuring that an initial and continuous training programme is implemented and maintained for all personnel involved in distribution activities. **Proposal for vi):** Ensuring processes and procedures are in place to qualify suppliers and customers. **Proposal for vii):** Ensuring an effective process for authorising the return to saleable stock of any returned medicines is implemented and maintained. **Proposal for viii):** Ensuring 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 **Proposal for x):** delegating his/her duties to appropriately trained individuals but the Responsible Person retains accountability for all such delegated activities and keeping appropriate records relating to any delegation;	
Page 9 Clause 2.10		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 **Proposed change :** All personnel involved in wholesale distribution activities must be appropriately trained in relevant aspects of GDP, and must have the appropriate competence and experience prior to commencing their tasks.	
2.16		**Recommend including "consumption" be added** **Proposed change:** The storage and consumption of food, drink, smoking materials or medication for personal use in the	

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		storage areas should be prohibited.	
Chapter 3 Principle		Recommend replacing word "conservation" with "storage".The **Proposed change:** Change and amend to read *´..., so to ensure proper storage ~~conservation~~ and distribution of the medicinal product.*	
3.2		The proposed wording is ambiguous in relation to how contracted premises need to be covered by a wholesale distribution authorisation. It should be sufficient to include the external storage as integrated part of an authorisation already existing. **Proposed change:** *'Where premises are not directly operated by the wholesale distributor, a contract should be in place ~~and the premises should be covered by a~~ to include them in the wholesale distribution authorisation.´*	
3.3		Current processes and technology do not require physical segregation (i.e. separation in space) of all goods. Current industry practice includes assigning quality status via an electronic inventory system. Both, physical segregation and segregation by electronic means should be included in 3.3. and consistently described also in 5.24, 5.25, and 6.15 of the guideline. **Proposed change:** Replace text in 3.3 to read: *´Products pending disposition should be segregated either physically or through an electronic system. This includes 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.* *Any system replacing physical segregation such as electronic segregation based on a computerised system shall provide equivalent security and should be validated.´*	

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3.4		Current GDP requirements apply GDP quality standards consistently to all products. We feel that there is no additional benefit or safeguard to patients by maintaining segregated areas for products to be distributed in- and outside the EU. The ability to access products authorised for different regions can also be controlled electronically according to section 3.3. In addition countries outside the Union market might apply the same, equal or better quality concepts based on an MRA or MoU. **Proposed change:** Proposal to delete text in section 3.4	
3.5		Products bearing a general indication as e.g. ´store in dry place´ - provide neither a specific nor a specified humidity limit. The requirements to control such conditions may be determined by an appropriate risk assessment. **Proposed change:** Amend the text to read: *´... humidity or light parameters. The requirements to control specific conditions may be determined based on an appropriate risk assessment.´*	
3.8		A facility with separate bays may be less robust than a single bay or a small warehouse with separate footprints and good procedures. Robust processes need to be in place for keeping inbound/outbound goods controlled and separate by either procedural, physical or electronic means. **Proposed change:** Amend the text to read: *´...There should be adequate separation between the receipt and dispatch areas and storage areas. Procedures should be in place for keeping inbound/outbound goods controlled. Reception areas where deliveries are examined at receipt should be...´*	
3.10		Typographical error in first sentence: Remove hyphen between ´and´ and ´free´. **Proposed change:** Correct and amend text to read:	

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		´Premises and storage facilities should be clean and free from litter and dust. Cleaning instructions and records should be in place. Cleaning equipment should be chosen and used in order not to be a source of contamination.´	
3.13		Amend for consistency with other parts of text :- • Illumination has to be considered to be in line with sect. 3.5. Cleanliness is covered by the requirements set forth in section 3.10 already. **Proposed change:** Change to read: *´... Environmental factors to be considered include at least~~, but are not limited to~~ temperature, humidity and illumination/light intensity and cleanliness of the premises*	
3.14		Storage areas and cold rooms might not require a seasonal mapping when located within a building and not having direct contact with the external environment. Such exclusion can be based on risk considerations. - Location of temperature monitor devices should be justified in the mapping report. **Proposed change:** Amend to read: *´Storage areas should be temperature mapped under representative conditions and should take into account seasonal variations except for areas where such outside interference can be excluded. ..... Location of temperature monitoring equipment should be justified ~~located~~ according to the results of the mapping exercise.´*	
3.16 & 3.17		Both sections include elements of calibration and verification of functionality. It is proposed to separate the two topics into each of the two paragraphs. - Calibration should be done for equipment based on risk and reliability considerations. - Risk assessment must be done to determine the necessity for having alarm systems and setting associated alarm levels.	

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		Proposed change: Change to read: ´3.16 Equipment used to control or to monitor the environment of the medicinal product should be calibrated based on a risk and reliability assessment. Calibration should be traceable to a primary standard. ~~and their correct operation and suitability for purpose verified at defined intervals by the appropriate methodology.~~ §3.17 ~~Calibration of equipment should be traceable to a primary standard.~~ Appropriate alarm systems should be in place based on a risk assessment to provide alerts preferably before ~~when~~ there are excursions ~~deviations~~ from pre-defined storage conditions. Alarm levels should be appropriately set ~~and~~. Alarms and their suitability should be regularly ~~tested~~ verified at defined intervals by the appropriate methodology to ensure adequate functionality.'	
3.19		- Relevant equipment should be determined in a conclusive enumeration based on risk considerations which shall include and focus on potential impact on product quality. - Security systems should be included here as well as it is proposed in section 3.9. - Equipment utilised in onward supply chain activities is addressed in chapter 9 ´Transportation´, i.e. section 9.6. **Proposed change:** Include to read: *'Relevant pieces of equipment shall be determined based on risk considerations and the potential impact on product quality. This would include at least ~~(but not be limited to)~~ cold stores, refrigerators, thermo hygrometers, or other temperature and humidity recording devices, air handling units, monitored intruder alarm and access control systems ~~and any equipment utilised in conjunction within the onward supply chain~~.'*	
3.20 – 3.25		The content proposed in these sections is closely linked with the regulations laid down in Vol. 4, Annex 11. Any redundancy	

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		or duplication of definitions and regulations with a slightly modified meaning would lead to ambiguous interpretation of requirements in the field of GDP (and GMP): **Proposed change:** It is strongly proposed to introduce a reference to Volume 4, Annex 11 ´Computerised Systems´ and/or to align with the wording in Annex 11.	
3.20		Before a computerised system is brought into use, it should be tested and validated to meet specifications and demonstrating fitness for purpose, **Proposed change:** Change and amend to read: *´Before a computerised system is brought into use, it should be demonstrated ~~confirmed~~ as being fit for purpose according to pre-defined user requirement specifications, testing programme and validation ~~capable of achieving the desired results~~.´*	
3.23		Deliberate fraud and sabotage committed by company personnel itself shall not be included as part of a guidance document. It is proposed to align with wording according to Annex 11, section 7.1. **Proposed change:** Change to read: *'…by physical and electronic means against damage.' Delete: 'wilful or accidental' from the text.*	
3.26		- Qualification and validation activities should cover both, key equipment and processes. - According Vol. 4, Annex 15 both, qualification and validation work should be planned and documented. **Proposed change:** Amend to read: *'Wholesale distributors should identify what qualification and/or validation activities are ~~work is~~ necessary to demonstrate control of key equipment and key processes ~~aspects~~ of their activities. … Qualification and validation activities should be planned and*	

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		documented. ...´	
3.27		- ´System´ could be incorrectly perceived as the whole system, instead of limiting to validation of the subsystems affected by the changes or upgrades only. - Common used terminology suggests to validate processes and to qualify systems and equipment to verify their correct installation and operation. **Proposed change:** Change to read: *'…after any significant changes or upgrades, <u>the affected</u> systems <u>or subsystems</u> should be <u>qualified</u> ~~validated~~ to ensure correct installation and operation.´*	
3.29		The term 'Re-qualification´ is neither familiar nor used throughout Vol. 4, Annex 15. Instead the periodic review process may be used to check qualification documentation for their adequacy on a periodical basis. In any case and after any change, all parts of the equipment affected by the change should be qualified. **Proposed change:** Change to read: *'Re-Qualification of equipment <u>affected</u> following repair or maintenance should be considered dependant on the scope of the changes made.´*	
Chapter 5 Principle		**Proposed change:** Include the need to comply with the provisions of a relevant licence where applicable (e.g. WDL)	
4.8		Comment: *Records* **Proposed change:** 4.8 Records (as Header) 4.8.1 … must be kept 4.8.2 .. should include 4.8.3 .. should be made	
Chapter 4.9 Chapter 4.10 Chapter 4.11		Proposed change: "Distribution records must be kept..." Proposed change: "Distribution records should include..." Proposed change: "Distribution and all other records should	

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		be ..."	
Chapter 5, Principle, 1st paragraph		First sentence requires that medicinal product is handled according to the specifications given in the packaging information. Packaging information typically does not provide specific handling instructions for distribution, storage instructions on the carton are intended for long term storage (only). **Proposed change:** Allow for shipping under conditions that are supported by scientific (e.g., stability data) that may differ from long term storage conditions.	
Chapter 5, Principle		**Proposed change:** Include the need to comply with the provisions of a relevant licence where applicable (e.g. WDL)	
Chapter 5, Principle, 3rd paragraph		It should be clarified whether the requirement to "notify the marketing authorisation holder and the competent authority" also does apply to the import of medicinal products for comparators used in clinical trials.	
Chapter 5, Section 5.1		It is not clear how the following applies to distributors who source their products outside the EU: '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…. " **Proposed change:** Consider all possibilities for legitimate supply of medicinal products originating outside the EU.	
Chapter 5, Section 5.1 to 5.10		In the case of a depository acting ON BEHALF OF its contract givers (usually the MAH or another wholesaler), it may be difficult to fulfil all the wholesale distribution obligations.	
Chapter 5, Section 5.2		This clause introduces a whole new bona fide checking process and implies that further activity must be undertaken to verify the supplying wholesale distributor meets GDP. This would add significant audit burden, and impede the sale of medicinal products. Should not all wholesalers be licensed by their	

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		competent authority, and therefore be compliant with the principles and guidelines of GDP? **Proposed change:** (New wording of section 5.2) Where the medicinal product is obtained from another wholesale distributor, wholesale distributors must verify that the supplying wholesale distributor holds the appropriate wholesale distribution authorisations.	
Chapter 5, Section 5.2, 5.3 and 5.8		**Proposed change:** It should be made clear exactly how a wholesaler's compliance with GDP's is to be performed. Is this statement to mean that all wholesale distributors must audit each other to ensure compliance to GDPs?	
Chapter 5, Section 5.4		It is unclear what is required by this clause. Does it mean that full traceability back to the original manufacturing site is required, including the supply route, transportation providers, etc? If so, this is level of traceability is not currently available. **Proposed change:** Define how far back the WDL holder needs to go – to the point of QP release, or back up the manufacturing chain.	
Chapter 5, Section 5.5		The section states that ''Appropriate qualification should be performed prior to any procurement.'' Our understanding (as per Glossary of Terms) is that this statement refers to the procurement of medicinal products and not for example of components used in the manufacture of medicinal products. **Proposed change**: Add ''of medicinal products'' after ''procurement'' in the first sentence of section 5.5.	
Chapter 5, Section 5.7		The examples given are considered to be over-prescriptive. It is the risk assessment which should identify and address potential risks. Those might be considerably different from the	

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		limited examples given here. **It is proposed:** if appropriate, to present these examples in a Q&A document later on. **Further, it is proposed to:** Change to read: *'A risk based approach should be used. ~~for this purpose considering:~~* *~~i) searches for the new supplier's reputation or reliability and its authorised activities;~~* *~~ii) certain medicinal products are more likely to be target of falsification;~~* *~~iii) large offers of medicinal product which are generally only available in limited quantities;~~* *~~iv) out of range prices.~~'*	
Chapter 5, Section 5.8		Wording is redundant: "must ensure they must supply…" **Proposed change:** "must ensure they supply …"	
Chapter 5, Section 5.8		**Proposed change:** In reference to "..distribution authorisation…", clarify this to be "wholesale distribution authorisation" to maintain consistency in terms throughout the document	
Chapter 5, Section 5.11		This section in unclear and gives opportunity to different interpretations. **Proposed change:** The section should be re-drafted, for example, for the following reasons: ○ It is not clear whether the wholesale distributor in question is located in the country where the product is intended to be distributed or in another Member State. ○ This section, as currently written, suggests that it is possible to distribute medicinal product in a Member State without Marketing Authorization, as long as, the product holds a MA in at least one Member State.	
Chapter 5, Section 5.12		This sentence is too restrictive, in that incidental damage to outside shipping containers which does not impact product	

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		quality or identity. **Proposed change:** Modify sentence to require assessment of potential impact of damage on product quality or identify.	
Chapter 5, Section 5.14		Since the MAH is responsible of the medicinal product that is on the market, it would be logical that the MAH is informed in every case when there is a suspicion of falsified medicinal product. **Proposed change:** "…and reported to the national competent authority and, *to the marketing authorization holder and/or manufacture."*	
Chapter 5, Section 5.14		The suspect of any falsification might include more than one (single) batch. It is advised to include the entire consignment as a whole. **Proposed change:** Change to read: *'In the event of any suspicion of falsified medicinal product, the consignment or batch affected should immediately be segregated and …'*	
Chapter 5, Sections 5.15 and 5.16		The terms "Union market" and "EU market" should be kept consistent.	
Chapter 5, Section 5.15		Does this require all wholesalers in the supply chain to have access to a proof of release to the market, or only the marketing authorisation holder or primary wholesaler?	
Chapter 5, Section 5.15		That is not necessary if goods are manufactured by a European site belonging to the same company. Certificates of analysis are available if needed.	
Chapter 5, Section 5.15		With respect to proof of release, reference is made to a ''control report'' and Article 51 of Directive 2001/83/EC. Since this term is not used specifically in Article 51, the expectation should be clarified. **Proposed change:** Clarify or remove the term ''control	

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		report''.	
Chapter 5, Section 5.16		In reference to "Distributors", should this be "Wholesale distributors" to maintain consistency in terms throughout the document?	
Chapter 5, Section 5.16		The term "Third Country" should be defined in the Glossary.	
Chapter 5, Section 5.16		This item needs to be clarified. Manufacturing / import authorisation need to be held by the entity in charge of releasing the products on the European market. This entity can not be the Distributor.	
Chapter 5, Section 5.17		It is stated that 'Medicinal products should be stored separately from other products…''. **Proposed change:** A definition of ''separately'' should be considered in this context to ensure consistency of interpretation. Alternatively, the following sentence could be added: '…or segregated electronically as per 5.24…'.	
Chapter 5, Section 5.17		Further clarity is required. Specifically is physical segregation required, or is spatial/ electronic sufficient (refer also to 5.24)? What is meant by 'other products'? Does this include medicinal products from other manufacturers/distributors, veterinary medicines, herbal medicines, food supplements, nutritionals, etc.?	
Chapter 5, Section 5.20 & 5.29; see also 6.12		The FEFO principle is mentioned in 5.20, 5.29, and 6.12. However, under certain circumstances FEFO is not possible. **Proposed change:** Text in 5.20, 5.29 and 6.15 should be revised to make clear that exceptions from FEFO should be permitted under limited and defined/controlled conditions.	
Section 5.21		It is not clear if properly packaged medical products can be stored on the floor.	

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		Proposed change: "Medicinal products should be handled and stored in such a manner as to prevent spillage, breakage, contamination and mix-ups. Medicinal products be stored in a way that facilitates cleaning operations."	
Chapter 5, Section 5.22, 5.24 and 5.25		The section specifically mentions electronic segregation for expired stock, but only mentions segregation or physical segregation for others. Refer to comments made to 3.3, 5.24, 5.25 and 6.15. Clarity is required throughout the document on segregation requirements, especially on the use of electronic segregation vs. physical segregation.	
Chapter 5, Section 5.23		Stock inventories are performed regularly according to the national legislation and recommendations of statutory auditors. **Proposed change:** Stock inventories should be performed regularly. Irregularities should be investigated and documented.	
Chapter 5, Section 5.24		**Proposed change:** Clarify if 5.24 applies to all kind of product statuses or if there should be still physical segregated areas needed for recalled products and products suspected of falsification, as well as for medicinal product that are not intended for the Union market (3.4).	
Chapter 5, Section 5.24		"If required, medicinal products should be stored in segregated areas, which are clearly marked and their access restricted to authorised personnel". Why the "If required"? According to section 5.17 medicinal products "should be stored separately from other products..".	
Chapter 5, Section 5.25		Paragraphs 3.3., 5.24, 5.25, and 6.15 of the guideline address the concept of segregation and should be reviewed for consistency.	
Chapter 5,		**Proposed change:** clarify if/that systems	

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Section 5.26		segregation/quarantine is appropriate. Absolute clarity is required as different distributors will interpret words differently, especially when translated to various nations.	
Chapter 5, Section 5.27		Destruction is not only to be made according to the corresponding legal requirements and environment protection but for falsified medicine also in such a way that the falsified product is rendered useless to avoid any re-use **Proposed change:** "… for disposal of such products, with due consideration to the protection of the environment, and with the aim to render the product useless in order to avoid any re-use."	
Chapter 5, Section 5.28		Maintenance of records for all destroyed products should be in keeping with document retention policies and it is not necessary to keep such records indefinitely. **Proposed change:** In section 5.28, add ''for a defined period'' after ''should be maintained''.	
Chapter 5, Section 5.29		What is the purpose of the sentence: "the batch number should be recorded, where required"? Is the requirement to record linked to section 5.32? **Proposed change:** Define when the batch number is required to be recorded – is it by National legislation? Currently lots of variability and capability gaps.	
Chapter 5, Section 5.30		Packaging should provide a level of product protection, however, it is not practical to expect packaging to provide and maintain storage conditions during transport. This requirement for shipping containers is addressed in 9.14 of the guideline (Containers, packaging and labelling). In this context, "storage conditions" should not be the sole requirement for transports (ship to label). If special transport conditions are available and backed by adequate monitoring and scientific data (stability data) these should be accepted in	

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		line with shipping under storage conditions. Further, other means than the packing may ensure the right transport conditions – for example actively controlled vehicles could provide the temperature control during transport. **Proposed change:** Delete current text 5.30 and replace with: "The packaging and/or transport vehicle should be adequate to protect the product against the harmful effects of light, temperature, moisture and other environmental factors.''	
Chapter 5, Section 5.32		The section mentions "the safety features" but what are these – no context given – is this a cross reference to the Falsified Medicines Directive? **Proposed change:** Clarify and make this document stand alone (the safety features not mentioned in glossary either?)	
Chapter 5, Section 5.32, last sentence		Records of actual physical journey – how can this be complied with? What level of detail is required in the transport record? Should the requirement be to document and risk assess all routes and then have a system to report any anomalies/excursions from the normal route? It is not considered necessary nor practical that the actual physical journey undertaken can be tracked, and this documentation kept as a record for at least 5 years if this information is accessible until successful receipt of the products is confirmed, and records of receipt in good condition and temperature records for the entire journey are kept. Further, section 5.32 states: "Records should be kept so that the actual physical journey undertaken by the product can be tracked." It may be unreasonable to keep such documentation for 5 years if for example it is verified upon receipt that the actual physical journey was compliant and the products received in good condition.	

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		All in all, this is an unrealistic requirement and is not considered to influence product quality. It is unlikely to improve supply chain security, as falsification of these records would not be beyond the counterfeiters, as such it should be reconsidered. **Proposed change:** Change last sentence.	
Chapter 5, Section 5.32		Section 5.32 states: "…..,batch number at least for products bearing the safety features, where required;" Why doesn't batch number suffice? What does products bearing safety features mean and when wouldn't batch number be required? In case it should be interpreted in relation with the Falsified Medicines Directive, it is suggested to add a specific reference to the directive clause. **Proposed change:** Eliminate: "… ~~at least for products bearing safety features, where required; …~~"	
Chapter 5, Section 5.32		"For all supplies to a person authorised or entitled to supply medicinal product to the public, a document must be enclosed to ascertain...". It seems challenging to get all the requested information into "a" document. **Proposed change:** To allow for the documentation to come in more that one single document, it could instead be stated that "..documentation must be enclosed to ascertain...".	
Chapter 5, Section 5.33		**Proposed change:** (Spelling correction): "'operation" should be "operating".	
Chapter 5, Section 5.34		Different models for the distribution of pharmaceutical products are in place in different countries according to the local legislation. Nevertheless, in order to ensure safety, fight	

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		counterfeiting and supply with documentary evidence an adequate distribution the same requirements set for distribution in Europe should be in place also for the export in third Countries. At least exported medicinal products should be authorized both in EU and in the third country of destination and the customer should have a distribution license unless the local legislation provides for different requirements or the exportation is made on a tender basis.	
Chapter 5, Section 5.34, b.		This exception gives an impression that a person exporting from Europe does not need to control "export" customer. Would it be possible to define more clearly minimum requirements to control export customers. **Proposed change:** "The customer does not have to be holder of a distribution authorization but the person exporting medicinal products must control that the customer holds adequate certification to perform distribution of medicinal products."	
Chapter 5, Section 5.34 c.		Based on the regulation proposed in Litra c. the EU is accepting the handling of uncontrolled medicinal product in an uncontrolled environment. If this handling agent is not required to have a wholesale distribution authorisation, in consequence he is not required to stick to the GDP regulations and even more critical, might even not to be aware off. This practice might be acceptable in exceptional and limited circumstances, e.g. in a duty free zone or warehouse (Zollfrei- / Transitlager). **Proposed change:** Strongly proposed to adapt text to limit the practice mentioned to areas clearly and tightly specified (duty free zone or warehouse).	
Chapter 5, Section 5.35		Is it the document enclosure stated in 5.32 that is implied? **Proposed change:** Please make a reference.	

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Chapter 5, Section 5.35		"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 reason behind this requirement? It may conflict with the exceptions in section 5.34.	
Chapter 6 Complaints Principle		In line 2 it is stated that ‘’A special assessment of returned medicinal product should be performed….’’ It is not clear what is meant by a ‘’special assessment’’. **Proposed change:** Delete the word ‘’special’’ or clarify the requirement.	
6.2		Acc. 2.5. v) the qualified person is responsible to ensure that customer complaints are dealt with. The text proposed here might bear requirements too high for small companies, but it might be appropriate for large wholesale distributors. **Proposed change:** Proposal to omit paragraph 6.2 as it is sufficiently covered by 2.5 v) already.	
6.3 (and 6.1)		Change to 6.1: There should be a written procedure in place for the handling of complaints. A distinction should be made between complaints about the quality of a medicinal product and those relating to distribution. In the case of a complaint about the quality of a medicinal product, the manufacturer and/or marketing authorisation holder should be informed without delay in a timeframe as laid down in recall guidance documents (Subsequently, Competent authorities should be informed if a manufacturer/MA holder, on investigation, is considering action following possible faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product”) **Proposed change to 6.3:** Any complaint concerning a potential falsified product should be recorded with all the original details and investigated. The manufacturer and/or	

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		marketing authorisation holder and National Competent Authority should be notified of suspected product falsifications without delay in a timeframe as laid down in recall guidance documents.	
6.3		The term "product" in "potential product defect" and it is unclear whether it also includes packaging and labelling as in the definition of "falsified medicinal product". **Proposed change:** Add definition of "falsified medicinal product".	
6.5		'If necessary, appropriate follow-up actions should be taken after investigation and evaluation of the complaint.' **Proposed change:** Any appropriate Corrective and Preventive actions should be taken after investigation and evaluation of the complaint, including where required notification to the national competent authorities.	
6.7		Acc. 5.32 every consignment is accompanied by a delivery document. When relying on controlled delivery pathways, one can expect this delivery information still to be available. The delivery document is a powerful piece of information to track the history and extract information on the quality of the returned goods. **Proposed change:** Amend to read: *'…any specific storage requirements, ~~and~~ the time elapsed since the medicinal product was originally dispatched and the tracking of the products journey based on the delivery records available.'*	
6.7		Not practical to perform a risk assessment for every return (where volumes very high) **Proposed change:** Returned products must be handled according to a written, risk-based process taking into account the product concerned, any specific storage requirements and the time elapsed since the medicinal product was originally	

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		dispatched.	
6.8		Clarify if this is physical or system segregation – if physical, a different pallet location or a separate dedicated area of the warehouse? **Proposed change:** Returned medicinal products should be kept segregated from saleable stock until a decision is taken regarding their disposition (physical and/or warehouse management system segregation)	
6.9		Clarify that **all** the following sections i) to v) must be complied with **Proposed change:** Medicinal products which have left the premises of the distributor should only be returned to saleable stock if all the following are confirmed:	
6.6 – 6.12 Returns whole section		**Proposed change:** Use a table to show the allowed timescales for returns for both cold chain and ambient product for both licensed and unlicensed returns.	
6.9 (ii)		• There is no rationale why 5 days is appropriate. • 5 days is not practically achievable for a variety of reasons: holidays, weekends, time for receipt, return communications and logistics arrangements. • 5 days does not guarantee that nothing has impacted product quality. **Proposed change** ii) medicinal products returns from a customer not holding a wholesale distribution authorisation should only be returned to saleable stock if they were returned within fifteen working days of original dispatch. By exception, a longer period can be accepted providing this is documented in a risk assessment and all other criteria in this section are satisfied. **Supplementary proposal:** It is strongly proposed to rethink	

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		if wholesalers not having an authorisation are allowed to return goods into the legally controlled channel.	
6.9 (ii)		**Proposed change:** • Clarify here that there should be no cold chain returns from unauthorised sites, or what is the period allowed – 1 day? • Clarify if the returns period applies to ambient products only. Is this overridden by National Law where applicable (some countries have tighter/looser requirements). • For ambient returns from ***licensed*** premises, what is the time limit (is there one)? Does "licensed" also include a site with a Manufacturing License for example (which may not have a wholesale distribution licence). Recommend genericising this to "site licensed to store medicinal products?"	
6.9 (ii)		Point (ii) stipulates a maximum time (5 days from dispatch) within which medicinal products must be returned if they are to be returned to saleable stock. The rationale for defining this time period is not evident. We would prefer such decisions to be made on a risk management basis taking into consideration properties of the product concerned. For products requiring low temperature storage (referred to in section 6.10) a number of criteria are given to be used in making decisions concerning return to saleable stock. **Proposed change:** Remove reference to 'five days' time period in 6.9 (ii) and combine this point with 6.10.	
6.9. iii)		Specifications and predefined conditions include the adjective proper. **Proposed change:** Change to read: '…handled under ~~proper~~ specified/predefined conditions;'	
6.9 (iii)		**Proposed change:** iii) it is demonstrated by means of due	

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		documentation that the medicinal products have been transported, stored and handled under proper specified/predefined conditions;	
6.9 iii)		**Comment:** It is not useful to add this paragraph, because if packagings are unopened and undamaged, we can consider that products have been transported, stored and handled under good conditions.	
6.9 (v)		**Comment:** V) Attachment of a copy of the original delivery note will only cause troubles for the distributor, and it does not ensure that the product is not falsified, if you can falsify a product then there will be no problem in falsifying the delivery note. If electronic tracking systems/computerised distribution systems are used that will always allow records of the units originally distributed (with unique unit IDs) for a particular distribution to be accessed in the event of a return or incident during transport with or without a delivery note.	
6.9 (v)		Typographical errors: ''th the'' and ''upplied'' **Proposed change:** Correct text in 6.9 (v) to ''evidence that the product was supplied''.	
6.9 (v)		Comment: Conditions described under v) list general requirements with priority. If these pre-requisites are not fulfilled, the check required under III and IV is not necessary. **Proposed change:** Move requirements v) up to become II).	
6.9 (v)		Does this point mean that if no batch number was recorded on dispatch, no returns are allowed, or is it just confirmation that the bx being returned is one that the distributor has had in saleable stock? **Proposed change:** "the distributor has reasonable evidence that the product was supplied to that customer and the batch number of the dispatched product is one that is known to have been distributed from that location, that a copy of the original	

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		delivery note is attached and that there is no reason to believe that the product has been falsified."	
6.10.		The requirement needs to be clarified. If it means 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 cold/frozen product to stock. Activities such as unpacking, inspection, repacking and transfers to cool stores typically happen under ambient conditions. The requirement should state that the time period and conditions of these activities (bullet points) are considered. **Proposed change:** "....evidence that the product has been handled in accordance with the manufacturer's/MA holders requirements, while out of the distributor's possession."	
6.10		Medicinal products may be returned to saleable stock if a stability profile or associated stability information is available to support exposure conditions that differ from the labelled storage conditions. **Proposed change:** ''Medicinal products requiring low temperature storage conditions can be returned to saleable stock …. if there is evidence that appropriate conditions have been maintained throughout transport and storage of the product."	
6.10		The bullet point headings in section 6.10 are not clear with respect to the evidence required before return to saleable stock is considered. For example, bullet point 3 in refers to ''examination of the product'' This could involve visual evaluation of the product for integrity or alternatively a programme of product testing. **Proposed change:** Delete bullet points in 6.10 and replace with a general statement about maintenance of appropriate storage conditions (see proposed text 6.10 above) and that there is no evidence to suggest that product integrity has	

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		been compromised.	
6.10		"Medicinal products requiring low temperature storage conditions can be returned to saleable stock only if the batch number of the dispatched product is known and there is evidence that the product has been stored within the authorised storage conditions throughout the entire time. The evidence should include...". If this section also applies to the transport prior to the wholesaler getting the products into possession, the reference to "storage conditions" should be supplemented with a reference to "transport conditions" if such are available and backed by adequate monitoring and scientific data (stability data).	
6.10		**Proposed change:** "low temperature storage" should be made more specific e.g. 2-8 or "cold chain". Text: "No returns from unlicensed sites are allowed (proposal) In addition to criteria defined in 6.9, evidence should include: -must be a known delivery to customer -returned batch known to have been delivered from the sending site -examination of the packaging (clarify re: opening of packaging versus tamper evident labelling) -confirmation of correct temperature control and security during original delivery and collection/return journey -signed declaration by the RP of the licensed returning site to confirm correct storage and handling The above evidence must be signed for by RP accepting the return. Time limit for these returns to be defined.	
6.11.		Disposal of returned product should not require individual approval by a Responsible Person if requirements and process	

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		are regulated by procedures/SOPs. Approval of procedures/SOP's regarding the disposal of returned products by the responsible person is the better alternative. Return to saleable stock should be approved by responsible person. **Proposed change:** <u>All handling of returned stock should be recorded. Return to saleable stock should be approved by the Responsible Person.</u>	
6.12		Providing the product has an acceptable minimum shelf life the use of both FIFO and FEFO should be considered acceptable. See also comment made to 5.20 and 5.29 regarding exceptions from FEFO.	
6.13		The text proposed is redundant with ruling set in 2.11. **Proposed change:** Proposal to omit paragraph 6.13.	
6.14		Since the MAH is responsible of the medicinal product that is on the market, it would be logical that the MAH is informed in every case when there is a suspicion of falsified medicinal product. **Proposed change:** <u>Distributors must immediately investigate suspect falsified medicinal products. After preliminary investigation, they must inform the National Competent Authority and the manufacturer and/or marketing authorisation holder</u> of the medicinal products they identify as falsified or suspect to be falsified 22. A procedure should be in place to this effect.	
6.14		In reference to "Distributors", should this be "Wholesale distributors" to maintain consistency in terms throughout the document?	
6.15		Refer to comments made to 3.3, 5.22, 5.24 and 5.25. Clarity is needed on the use of electronic segregation vs. physical segregation. There might be an electronic system in place ensuring the same security as if it was physically	

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		segregated, for instance fully automatic warehouses.	
6.15		The statement may need rephrasing. The meaning of legitimate medicinal products is not defined and understandable (to be honest: Quarantined, rejected, etc goods would be illegitimate too, when applying the same definition). **Proposed change:** Rephrase to read: 'Any suspected falsified medicinal products found in the supply chain should immediately be ~~immediately~~ segregated physically and securely ~~*segregated from legitimate medicinal products*~~.'	
6.16, 6.23		Sections 6.16 and 6.23 both refer to the periodic testing and evaluation of recall arrangements. **Proposed change:** Combine 6.16 and 6.23 to one statement.	
6.16		It is not intended to test the procedure itself, but to challenge the processes laid down in the procedure with so called 'fire drills'. **Proposed change:** Amend to read: *'The processes laid down by the recall procedure should be ~~periodically~~ tested periodically.'*	
6.18		In reference to "Distributor", should this be "Wholesale distributors" to maintain consistency in terms throughout the document?	
6.20		The content of delivery documents and records is extensively described by paragraphs 4.10 and 5.32 already. It is proposed to add the remaining statement to paragraph 6.18. **Proposed change:** Change to read: *'6.18 The distributor must follow the instructions of a recall message, which should be approved, if required, by the competent authorities. The distribution records should be readily available to the person(s) responsible for the recall.'* Then omit paragraph 6.20.	

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6.20		States here that distribution records should detail batch numbers, but previous sections have not clarified if batch number must be recorded on dispatch. **Proposed change:** Clarify – include statement re: "bracketing" of bx numbers if specific bx numbers are not recorded per delivery. Add text: "Where distribution records do not detail specific batch numbers of product for each delivery, there must be a process to ensure specific batches can be identified and recalled from customers".	
6.21		Need absolute clarity on definition of "stored separately in a secure area" **Proposed change:** As per previous comments need to define separate (systems quarantine, unique pallet location, different dedicated area of the warehouse?). A table showing the different categories of product requiring "separation" and valid options for achieving this would be very useful. E.g. returned goods, recalled goods, suspect counterfeits, under investigation goods….and options include different pallet location, systems separation, caged, locked areas etc. this is a real area of ambiguity.	
6.23		"The effectiveness of the arrangements for recalls should be evaluated regularly". Clarity required on what is regularly? Is a risk based approach to be applied? If so could this be specified?	
7. Contract Operations		From the definitions available so far and from this chapter, it is not fully clear whether transportation of medicinal products 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.	

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Chapter 7, Principle llines 2-3		We completely agree on the requirement to have necessary contracts in place. We also emphasize the importance to have formalized agreements in place defining quality related activities and responsibilities between contract giver and acceptor. Nevertheless, we think that the obligation that both contract giver and acceptor must hold a distribution authorization is an overwhelming requirement for small local business units sub-contracting distribution activities to authorized distributors in their respective countries. **Proposed change:** We propose to give a possibility for local business units to sub-contract distribution activities without having themselves a distribution authorization. We propose to insist on having an adequate quality system in place to ensure appropriate application of GDP requirements and requiring existence of an agreement defining quality related requirements and responsibilities between contract giver and acceptor.	
7 - Principle		In reference to "..distribution authorisation...", should be "..wholesale distribution authorisation.." to maintain consistency in terms throughout the document?	
Chapter 7 Principles		**Proposed change:** Specify that this relates to outsourcing **distribution** activities, as opposed to cleaning for example?	
7.1		In reference to "The Contract Giver is responsible for the activities contracted out". Should this be "accountable" instead?	
Glossary Chapter 5 7.5		In the case of a depository acting ON BEHALF OF its contract givers (usually the MAH or another wholesaler), it may be difficult to fulfil all the wholesale distribution obligations (especially sections 5.1 to 5.10).	
7.5.		Storage exceeding more than 24 hours can occur everywhere in the world. Many activities within the distribution are performed by carrier´s subcontractors, like airport handling	

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		agencies, port terminals etc. Establishing the supervision and controls envisioned in the draft document may be impossible. If transport of medicinal products is considered an activity falling under the definition of wholesale distribution then all global transport providers (DHL, ToF, etc), all air and ocean carrier (Maersk, Lufthansa etc.) and all port and airport terminals might be considered to become wholesale distributors. Transport is a critical activity within wholesale distribution and the GDP draft requires that distributors must apply supervision and control over service providers for transport operations. That supervision is not practically possible, e.g. a wholesale distributor has no influence and knowledge at which port terminal the goods will be handled / stored by ocean carriers. The same is true for handling agents at airports. It should be avoided therefore, that transport service providers have to become wholesale distributors with an independent license. **Proposed change:** 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.	
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 an approval of the arrangements and an audit of the third party". It is not clear who actually needs to perform the audit from this statement?, some guidance in this would help clarify	
7.6.		There are cases that an audit is not possible or required to allow for the outsourcing of activities.	

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		Proposed change: The requirement to audit should be accompanied by an "if required" statement,	
7.6		It is impossible to evaluate and approve a third party at any time, in particular for transportation. It is possible to have a list of third parties used by the Contract Acceptor. **Proposed change:** Arrangements made between the Contract Acceptor and any third party should ensure that the wholesale distribution information is made available in the same way as between the original Contract Giver and Contract Acceptor. A list of all third parties used by the Contract Acceptor should be available.	
Section 7.6		Comment: Should also apply to transporters.	
Chapter 9 Transportation Principle		1) The entire chapter 9 should be carefully reconsidered and revised to reflect scientific and risk based approaches and to be practically achievable and necessary to assure product quality. The concept of risk-based approach for the decisions of storage and transport conditions should be applied throughout the distribution chain. These decisions should be science-based and based on known characteristics of the product. 2) Chapter 9 should be reviewed to provide more clarity on monitoring requirements during transportation. Chapter 9 should provide an overview over the different possible control strategies, for instance through a clear matrix introduced to visualize the respective cold chain, 8-15, ambient categories (etc.) and the corresponding requirements for control, risk assessment, monitoring in both primary and secondary distribution. 3) Specifically, 3a) the use of stability data for transportation of medicinal	

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		products, which means that medicinal products may be transported at specified temperature ranges for specific durations if adequate stability data are available. Furthermore the EFPIA suggests alignment of this guideline with the recently issued draft USP <1079> which allows that "drug products can be transported at temperatures outside their labelled storage temperatures if stability data and relevant scientific justification demonstrate that product quality is maintained." 3b) storage conditions and transport conditions need not necessarily be identical. For temperature sensitive products, exposure ranges and durations outside of labelled storage conditions should be permitted provided that this approach is supported by adequate stability data therefore for the transportation of medicinal products. We suggest using the term storage conditions instead of warehouse conditions. 4) Further comments: 4a) Monitor only in case of cold chain products and justify not monitoring the temperature of each shipment for non cold chain products; 4b) The use of qualified temperature-control systems should be acceptable rather than stating specific references to availability of temperature monitoring data. The use of cold chain programmes that employ validated packaging configurations for temperature maintenance over a pre-defined transport duration should be acceptable 4c) For all temperature sensitive products continuous verification should be provided. 5) Chapter 9, Principles, 3rd paragraph, proposed change: Change sentence to ''Medicinal products should be transported in accordance with appropriate storage conditions which are supported by stability data and should be protected during transportation against harmful effects of light, temperature,	

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		and other adverse environmental factors."	
Transportation 9.1		This statement infers a requirement to monitor all shipments for storage conditions. Determination of the best possible controls should be based on a risk assessment including product, packaging and transport route etc. Clarification on the definition and requirements for "packaging information". If this relates to the storage information as stated on the original pack (artwork) then we will have more restrictive transport conditions to fulfil. We support "packaging information" to be defined as the information declared on the goods, e.g. labels of pallet/outer carton, and the delivery note (transport/stowage conditions based on the stability data available and the distribution risk assessment). This would then be more visible to the personnel involved in the supply chain. This modification is necessary in order to be consistent with Section 5.32 line 6 **Proposed change:** "The required transport and storage conditions for..." adding "If not justified otherwise, the required storage conditions for medicinal products should be maintained during transportation	
Transportation 9.2		Deviation should be defined more precisely. It should be specified who has the obligation to report the deviation. **Proposed change:** "The required transport conditions for pharmaceutical products should be maintained within acceptable limits during transportation. If a deviation has been observed during transportation, this should be reported to the distributor and recipient. Wording should be consistent throughout the guideline. In that context ´consignee´ is the commercial term more appropriate.	

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		Proposed change: Change to read: ´If a deviation has occurred during transportation, this should be reported to the distributor and consignee recipient of the affected medicinal products.'	
Transportation 9.5		Need to specify who has control/oversight and who provides training to the *delivery drivers* We question the need to specify what drivers should undertake GDP training. Training of personnel and driver qualification is the responsibility of the service provider. Terms of delivery will normally be defined in a contract/service level agreement (e.g. as per Ch 7 EU GMP Outsourced Activities). The term 'delivery drivers'' is also ambiguous since products may be transported throughout the supply chain via other modes of transport than road e.g. rail and air where the driver also has responsibility to adhere to delivery terms and agreements but need not necessarily be trained in GDP. This will be a significant administrative burden. It is unclear how this section differs from sections 2.10 to 2.14. **Proposed change:** Clarify requirement or delete as redundant. "… The RP should approve GDP training plans and be involved in the construction and delivery of training materials."	
Transportation 9.6		Who is expected to be overall accountable for this? Taking into account that most vehicles and equipment for transport of medicinal products, such as trailers, containers, and airplanes are not owned by the manufacturer/distributor, the mentioned requirement will be virtually impossible to control and enforce. Particular attention to Cleaning agent - is that necessary when product is packed as finished good in shipment boxes and wrapped pallets. It is too detailed for this guideline	

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		Proposed change: The second sentence beginning ‘’Particular attention..’’ should be deleted.	
Transportation 9.7		Why at least once a year? Rather than specifying a maximum time period it is technical common sense to set calibration intervals based on risk and reliability assessments relying on experience and specification characteristics of the temperature monitoring system involved. The shipping cycles (time of circulation) for such monitoring systems have to be kept in mind as well. **Proposed change:** Change to read: ´Equipment used for temperature monitoring during transport within vehicles and/or containers, should be maintained and calibrated against primary standards and at regular intervals based on a risk and reliability assessment or at a minimum of once a year.’	
Transportation 9.8		Why is there a distinction being made for dedicated and non-dedicated vehicle as same standards should apply for both? If this distinction is to remain then additional guidance is required or some examples to provide a greater consistency in approach. What exactly is meant by "dedicated"? It would be useful to accurately define which kind of items can be transported. This would refrain from any dangerous uncontrolled conduct that might hazard the quality of the transported products. These procedures would normally include an appropriate cleaning regime, as is requested in point 9.6. It is considered impractical to use 100% dedicated pharmaceutical deliveries/drivers. Therefore, this clause 9.8 is acceptable to EFPIA only because flexibility is provided through the insert "as possible **Proposed change:** Delete this requirement, and add clause to state that proper handling instructions should be provided.	

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Transportation 9.9		When shipping by sea or air, deliveries are often made in port or airport, where the medicinal products are made available for consignee's pick-up rather than handed over directly to the consignee at his premises. Deliveries are not always made directly to the address on the delivery note due to the use of cross-docking and/or consolidation services (as stated in 9.12) **Proposed change:** Reworded to: "Deliveries should be made to the address stated on the delivery note and made available for consignee's pick-up as agreed, except where cross-docking and/or consolidation services are contracted, and are part of the approved supply chain. Medicinal products should not be left on alternative premises".	
Transportation 9.10		Comment: Please clarify section in further detail	
Transportation 9.12		We need to understand the definition of a hub. Does this requirement also apply to transfer docks; overnight warehousing; overnight lorry stops, etc.? Is transit in Port, Airport during customs considered as storage? If yes, this requirement could result in a need to issue wholesale licenses for all transport service providers (e.g. at airport hubs) engaged in pharmaceutical transport and therefore it will be impossible to transport medicinal products; in particular for direct delivery between wholesales of laboratories and pharmacies. It seems to be impossible to require a wholesale distribution authorisation for all transporter hubs all around Europe. The rationale for this time limit is not evident. The maximum holding time should be part of the contractual agreement and based on risks involved. We consider that this would introduce additional administrative requirements without necessarily enhancing public health. All hubs must be able to store product over a public holiday, a weekend or adverse weather conditions which exceeds the 24 hours limit. While cleanliness,	

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		pest control and appropriate environmental control must be ensured (e.g. through contracts, etc.), the requirement to hold a wholesale license seems excessive. In addition, it would result in additional inspection activities of supervisory agencies. All airports worldwide simply execute a transfer of cooled goods. Sea freight would dictate products will be sitting in containers at Port docks for potentially a few days before loading in vessel. These and other scenarios would require a wholesale distribution authorisation to be obtained, would this be entirely practical? Would the Competent Authorities expect to broaden the scope of inspection activities to include airport terminals and similar transit storage facilities in order to issue wholesalers distribution authorizations? This cannot be fulfilled for all bonded storages passing the border. How this can be regulated by the pharmaceutical industry? There is not commitment from the customs offices to work accordantly! Previously this has been 36 hours. What is the rationale to reduce this to 24 hours? Why is 24 hours any more controlled than 36 hours? Demanding an authorisation on an involuntary basis is imposing a legal threat. The requirement for all hubs dealing with refrigerated products to hold a wholesalers distribution authorisation seems quite extensive taking into account the number of airports, ports and forwarders dealing with cold chain products. It will place a restriction on cold chain distribution activities, and could result in product shortages on the market. Also, for refrigerated /cold chain product shipped in qualified temperature controlled packaging do the same rules apply as stated for refrigerated product? The emphasis should be on prior audit and approval of these	

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		facilities. As this section reads, any airport or transportation hub where a connection needs to be made during the transport of a refrigerated (presumably also including frozen products and APIs) will require a wholesale distribution authorisation, unless the receiving vehicle (truck or airplane) is already waiting for the product to be loaded when it is delivered. This is not a realistic expectation, nor does this requirement take into the impact of weather delays and other variables. **Proposed change:** Change sentence to permit the use of transport hubs for goods in transit as per contractual agreements with the transporter, and delete reference to 24 hour requirement, and the reference to the requirement to hold a wholesalers distribution authorisation for transport hubs which handle refrigerated products.	
Transportation 9.13		Clarify if this includes airports, ports. It is our understanding that marketing authorisation holders will not normally have to audit all transport hubs. Distributors using hubs would be expected to specify this in contractual agreements, and an audit would be performed to ensure that a quality system, including oversight of the hubs is in place. If the above interpretation is acceptable, then the sentence in 9.13 need not be changed. If not clarify. Audits are conducted for some of the stations for x docking but not to every hub level in-market. To audit all terminals and hubs before deployment and after any subsequent changes to the approved premises should be subject to a risk assessment, like stated in section 3.26, in order to use the quality resources where they make most sense. In this risk assessment issues like packaging type (e.g. a sealed container) and product type (e.g. temperature sensitivity) should be taken into consideration. This requirement as written would require that wholesale license holder's audit a very high number of operations	

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		internationally. **Proposed change:** Remove the requirement to audit all hubs and terminals prior to use and add language that allows a risk based approach and for the use of quality agreements between the distributor and the transport provider to clarify facility and quality requirements. In the event that the transportation of medical products requires unloading and reloading e.g. at terminals and hubs, the requirements the premises have to meet have to be defined. Particular attention should be paid to temperature monitoring, cleanliness and the security of unguarded intermediate storage facilities.	
Containers, Packaging and Labelling 9.14		Text should be added regarding mitigation of cargo theft. **Proposed change:** "Medicinal products should be transported in secure cargo containers that have no adverse effect on the quality of the products, and that offer adequate protection from external influences including contamination."	
Containers, Packaging and Labelling 9.15		Transit storage is not limited to customs only. Transit storage is also happening at hubs and terminals. Clarification is required around the statement: "….the validation status of the packaging and shipment containers". **Proposed change:** Proposed to add: ´...; the estimated maximum time for transportation including transit storage at customs, hubs, terminals and the validation status of the packaging and shipment containers.'	
Containers, Packaging and Labelling 9.16		To reduce the risk of theft of certain medicinal products including narcotics, psychotropic, hormones, (in line with section 9.17) the labelling requirement should allow for omitting, coding or paraphrasing the specific description of the product type, in a way that still enable unambiguous identification.	

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		Proposed change: "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". Delete the rest.	
Transportation of Products requiring special Conditions 9.17		To what level of controlled drug do these requirements apply? What is meant with "additional control systems"?	
Transportation of Products requiring special Conditions 9.18		Define "highly active". Does this mean both dedicated container and dedicated vehicle? Clarify if a dedicated container within non-dedicated vehicle is acceptable.	
Temperature Control during Transport 9.19		Requirement Part 1: • These paragraphs appear to be focussed on cold chain/sensitive products, but the title is simply 'Temperature Control during Transport' and 9.19 as currently written does not provide any differentiation, i.e. it reads as though validated temperature-control systems should be used for all shipments. This change would add significantly to the costs of distribution and potentially restrict suppliers to a small number of logistics providers. • The decision of whether or not to require validated temperature control requirements for a particular product/shipment should be made on a risk based approach to monitoring as many other forms of control, if applied, could provide equivalent, if not better, better assurance. For example a qualified supply chain. • Many different players/shipping/transport providers could be used in the complete supply chain – Consideration should be used to qualify rather than validate as full validation may be not possible with some shippers. The term validated should be replaced with qualified to be consistent with existing guidance such as PDA technical Report No. 39. • This clause would require the use of a temperature	

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		monitoring device in every shipment, and considering the times and temperatures associated with these deliveries is considered unnecessary. If a qualified system is used this should provide sufficient assurance that product has been transported under appropriate conditions.
		• Recommend that this is limited to time and temperature sensitive products only, as defined by WHO
		• The term "transport conditions" is too broad. The critical variable that needs to be controlled is temperature.
		• Temperature restrictions during transport can be controlled in different ways, e.g.
		  ○ Validation of the shipping route
		  ○ Qualification of the shipping container
		  ○ Continuous temperature monitoring during each shipment
		In section 9.19 mainly the third method is considered.
		
		Requirement Part 2
		• This statement could imply that temperature data should be available for all deliveries if requested. As an alternative to monitoring all shipments, we advocate the use of cold chain programmes that employ validated packaging configurations for temperature maintenance over a pre-defined transport duration. A validated temperature-control system should provide adequate assurance that the temperature is maintained.
		• 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 product is affected. (See response for 9.2).
		• The challenges of requiring temperature confirmation/data	

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		at the end of a delivery of, for example ambient product to a pharmacy, should not be underestimated (how to demand that a customer downloads temperature data for example). This "secondary" transport to the end-customer presents the biggest challenge whereas "primary" transport between 2 company owned locations is much easier to control and verify. A risk based approach is more pragmatic and aligned with current Pharma industry direction. • Requirement should be clarified if it refers to that refrigerated, frozen or all products. **Proposed change:** 1. Do consider that large temperature-controlled containers/refrigerated vehicles are normally limited in numbers in e.g. airport terminals. Not all airports are equipped to handle large temperature-controlled containers. 2. Risk assessment of every route should be used to determine controls required, and those controls should be verified /validated. Where risk assessment determines that assurance of adequate controls is not sufficiently robust, temperature monitoring should be used to record temperature during every transportation. 3. Where monitoring is required, this should be reviewed for each transportation. There should be confirmation that the defined transport controls were in place for each transportation. For cold chain product transportation, every transportation should be monitored. 4. Last sentence of paragraph 9.19 is redundant with last sentence of paragraph 9.20 and contains a typographical error. "If requested" at the end of each section (9.19 and 9.20): is it linked to a request from customer to get the data? Please clarify.	

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		5. 9.19. should read "…provided with temperature data…" NOT "….provided with a temperature data…."	
Temperature Control during Transport 9.20		• Align the wording with paragraph 3.14. • Combine 9.7 and 9.20 to one item. • Combine 9.19 and 9.20 to one item. The requirements for refrigerated vehicles should not be so prescriptive as to require mapping of each vehicle, but should allow for other means of establishing and qualifying appropriate shipping carriers e.g. certification to an industry standard. Temperature monitoring of refrigerated vehicles, including mapping under representative conditions and seasons is extremely constraining and may be difficult to apply and manage. If individual shipments are monitored and reviewed at destination prior to release this requirement seems over stringent. This requirement should be managed like any qualification process: Complete data generated once and re-qualification in case of significant changes! A risk based approach (ICH9) should be allowed. The adequacy of the (re-) qualification program can be assessed during audits. Refrigerated vehicles are only suitable for goods which have to be transported under refrigerated conditions (2-8-°C). Other temperature-controlled vehicles (e.g. not more than 25 °C, or 2-40 °C) should be considered as well. Therefore, the term temperature controlled vehicles should be used in lieu of refrigerated vehicles. **Proposed change:** "9.20: If temperature controlled vehicles are used, the temperature monitoring equipment used during transport should be maintained. This includes temperature mapping under representative conditions and should take into account seasonal variations."	

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Temperature Control during Transport 9.21		It has to be described, how the correct handling of the cool packs is assured. It is a potential risk for Frozen Packs to be in contact for freeze sensitive products.	
Temperature Control during Transport 9.22		Section 9.22 states that there should be. It is not clear what is intended by ''adequate physical distinction between frozen and chilled packs''– does this refer to e.g. appearance of the ice packs or is physical segregation required? **Proposed change:** Delete sentence beginning ''There should be adequate segregation...'' or clarify expectation.	
Temperature Control during Transport 9.23		Section 9.23 refers to several different concepts and quality systems e.g. the delivery of products (track and trace?), the control of seasonal temperature variations (validation?), the handling of unexpected events and investigation of temperature excursions. The intention is not clear. **Proposed change:** Make a general statement that specifies the requirement to have a documented cold chain management programme. State that provision for emergency access to cold storage should be made in case of a breakdown/failure in transport.	
Glossary		The terms "qualification" and "validation" should be defined in the glossary in relation with GDPs and specifically with transportation.	
Glossary		There is no definition of GDP (used in the guideline e.g. 8.2 and 9.5) and also no definition of 'distributor' (used in the guideline e.g. 9.4) **Proposed change:** Add definitions for ''GDP'' and ''Distributor'' to the Glossary.	
Glossary: Brokering		Reference to "…in point 17 of this article" provided in the definition of the term "Brokering" is hard to understand. **Proposed change:** Delete " as defined in point 17 of this	

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		article" and amend last sentence to read: (Wholesale distribution as defined in Article 1 point 17 of Directive 2001/83/EC, as amended).	
Glossary Free zones and free warehouses – (a)		Need to be clarified as the definition is not clear.	
Glossary		Suggest adding the definition for "Medical Product", for example are devices in the scope of this document?	
Glossary		Suggest to add the definition for "Traceability "	
Glossary		**Proposed change:** Add definitions for "adulterated", "critical process", "cold chain"?	
Glossary		Specify Segregation-Separation physical-electronically (see for example text in section 3.3 and 5.24). Import should be defined in Glossary of Terms (similar to export) (Chapter 5, Principle, third Paragraph).	

Please add more rows if needed.