EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20th December 2011

Submission of comments on 'Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use ' (SANCO/C8/AM/an D(2010) 380358)

Comments from:

Name of organisation or individual
European Industrial Gas Association (EIGA)

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)*
	It is understood that there is a requirement to amend how the regulations are applied to ensure that counterfeit products are not supplied for human use. The current Guidelines on GDP do not adequately address the requirements to ensure that counterfeit medicinal products do not enter the supply chain. The proposed Guidelines provides more clarity about all distribution activities and gives better guidance compared to the original text published in 1994. However, where the manufacturer of the medicinal product distributes the medicinal product to its customers using a network of storage sites which only handle the products manufactured under their control, there should be a possibility for these sites to be managed as an extension to the manufacturing licence. These sites will require a person to be responsible for the security and control of the product being handled by the site but does not necessarily need to a Responsible person as defined in this guide. The sites may not be owned by the manufacturing company but must be controlled by their QMS with respect to the handling and	

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	distribution of the medicinal products The manufacturing company's Qualified Person will retain the overall responsibility to ensure that the Quality Management System defined in the Marketing Authorisation is met and is in line with the general Quality Management System used on the manufacturing site. This would only apply to those products that are both stable and do not require specific storage requirements to maintain their quality. It is proposed that the degree to which distributors should fully comply with the Guidelines should be based on the results of Risk Management techniques. For example, as medicinal gases are only supplied in reusable cylinders (which are of a higher value than the medicinal products they contain) and are strictly regulated by the requirements of the Transportable Pressure Equipment Directive, they are not susceptible to being falsified. As a consequence, the full requirements of the Guidelines will place a significant burden onto the supplier without adding additional benefits to protect patient safety. There could be a benefit to add specific examples of different types of medicinal products that require different levels of control.	

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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)*
Paragraph 1.2		Comment: For some types of distribution activity, such as medicinal gases, the wholesale distributor may have several facilities for intermediate storage sites in the supply chain. These activities on these sites may be very limited, often only providing a backup facility for customers or overnight / over weekend storage of product being supplied directly to customers. In these cases it should be possible to have a Responsible Person who is named for more than one site. Proposed change (if any): A responsible person should be appointed by the management for each distribution site, who should have defined authority and responsibility for ensuring that the quality system is implemented and maintained. *Where the wholesale distribution activities on a site are limited, and the number of products handled and number of personnel restricted, it may be possible for the Responsible Person to have responsibility for more than one site.*	
Paragraphs 1.4 / 1.6		Comment: These two paragraphs appear to overlap in their purpose. It is proposed to merge the two paragraphs into one statement. Proposed change (if any):	

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		The size and complexity of distributor's activities should be taken into consideration when developing or modifying the Quality Management System, which should be organised in a way, that it reflects the size and structure of the organisation.	
Paragraph 1.11		Comment: Add the term 'documented' to the paragraph Proposed change (if any): The outcome of this management review of the quality management system should be timely and effectively communicated *and documented.*	
Paragraph 2.1		Comment: The paragraph does not explain the meaning of the term 'permanently available'. The availability of the Responsible Person on site would depend on the systems available and the type of products handled – and should be subject to a Risk Management review to identify the exact requirements to provide the appropriate level of patient safety. Proposed change (if any): The wholesale distributor must designate a person as *the* Responsible Person *for the site*. The Responsible Person should fulfil his/her responsibilities personally and should be ~~permanently~~ available *to control the activities on site. Where there is electronic or web based systems to provide the*	

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		relevant information and control of products to enable appropriate decisions to be made, the Responsible Person may not need to be on site. The Responsible Person should meet the conditions provided for by the legislation of the Member State concerned.	
Paragraph 2.3		Comment: Reference to 'A degree in Pharmacy as desirable' is not necessary as the paragraph indicates that the qualifications should meet the conditions provided by the legislation of the Member State. As an example, the QP for releasing medicinal product does not need to be a pharmacist in most member States. For medicinal gases, as the primary packaging (cylinder) for the product can not be changed, there are limited pharmacy type activities required to supply the product to the end user. As a separate point, the level of education of the RP should be appropriate to the wholesale distribution activities required. The responsibilities of the RP specified in Para 2.5, relate mainly to the Quality Management System and are not specifically related to pharmacy related activities. The requirements are also related to the type of products being handled. For example, with medicinal gases the wholesale dealing activities are all about the onward supply of product supplied in its the primary packaging. There is only very limited pharmacy actions required. Also, for medicinal gases, the required knowledge is limited to the understanding	

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		of the storage requirements and use of the product. The RP needs knowledge about the storage, handling and logistics of medicinal gases which ensures that the product is received by the patient in a the condition defined in the MA. The RP could be the QP (named on the Manufactures Licence) as they will have the relevant knowledge and experience. Proposed change (if any): 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. ~~A degree in Pharmacy is desirable.~~ He/she should have appropriate qualification, competence and experience as well as knowledge and training on GDP *specific to the products being handled*. In order to meet the qualification requirements, it may be appropriate for the QP named on the Manufacturers Licence to be named as the Responsible Person for wholesale distribution sites. Where appropriate the Responsible Person should be allowed to delegate their responsibilities to a nominated deputy on the distribution site. The delegate should have the appropriate level of qualification and competence and their name documented on a formal schedule.	
Paragraph 2.4 / 2.5		Comment: Although the Responsible person must be accountable and responsible to carry out his or her responsibilities, it should be possible for them to delegate some of their duties to a	

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		Nominated Deputy. Paragraph 2.5 (x) refers to the RP being able to delegate their responsibilities and refers to carrying out Self Inspections. The Nominated Deputy should be trained and competent in the quality management system used to control the distribution activities. The QMS should be audited to demonstrate that it is functioning correctly. The QMS should require the Responsible Person to ensure that the necessary activities are carried out and promptly documented. Proposed change (if any): 2.4. The Responsible Person should *be responsible for ensuring that* ~~carry out~~ his/ her activities *are carried out* ~~personally~~ in order to ensure the wholesale distributor can demonstrate GDP compliance and that public obligations are met. *Where the RP has a formal nominated deputy, the responsibilities and activities delegated to the deputy must be documented to ensure that all RP responsibilities are actioned.* *The nominated deputy must be suitably trained and suitably experienced in order to demonstrate that they are competent to carry out their appointed role.* *Where activities are managed by a nominated deputy, the RP shall perform Self Inspections to ensure that the deputy has followed the correct procedures.*	

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Paragraph 2.10		Comment: It is proposed to change the word 'and' to 'or, and to replace the phrase 'prior to commencing' to 'perform' as it reflects better the intent of the statement. Also, the experience needs to be relevant to the scope of the wholesale dealing activities and the person should be assessed to ensure that they are competent to carry out their specific tasks. Proposed change (if any): All personal involved in wholesale distribution activities should be qualified in GDP requirements by training ~~and~~ *or* should have *relevant experience with handling and storing medicinal* products. *They should be assessed to ensure they have the* appropriate competence to *perform* their tasks *effectively*.	
Paragraph 2.16		Comment: As food stuffs should be kept away from areas where medicinal products are stored and handled it is proposed to change the word 'storage to 'presence' to reflect better the requirements of the paragraph. Proposed change (if any): The ~~storage~~ *presence* of food, drink, smoking materials or medication for personal use in the storage areas should be prohibited.	

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Paragraph 3.3		Comment: The reference to segregated areas in paragraph 3.3 needs to reference the statement made in paragraph 5.24, where it refers to the use of electronic or computerised storage systems to provide the appropriate level of segregation. The word quarantined should be used to describe 'product awaiting further decisions as to their fate' Proposed change (if any): There should be ~~segregated areas~~ *a means of segregation* for the storage of *quarantined* products ~~product awaiting further decisions as to their fate~~ *including* 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.	
Paragraph 3.5		Comment: This paragraph should specify that the extend of the controls to be performed to maintain temperature, humidity or light should be compliant with the defined requirements specified in the Marketing Authorisation. Proposed change (if any): Where specific storage conditions are required, control should be adequate to maintain all parts of the relevant storage area	

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		within defined temperature, humidity or light parameters, *as defined in the Marketing Authorisation.*	
Paragraph 3.7		Comment: The paragraph should include the reference to local legislation requirements and reference to medicinal (not pressurised) gases in general. Proposed change (if any): Radioactive materials and other hazardous products, as well as products presenting special *safety* risks, such as fire or explosion (e.g. ~~pressurised~~ *medicinal* gases, combustibles, flammable liquids and solids) should be stored in a dedicated area(s) subject to *local legislation and* appropriate safety and security measures.	
Paragraph 3.11		Comment: It would be appropriate to refer to the need to carry out a Rsik Assessment to determine the level of pest control required – dependant on the nature of the products being stored. Proposed change (if any): *Risk assessments must be carried out to determine the appropriate level of pest control.* *Where required,* facilities should be designed and equipped so as to ensure protection against the entry of insects, rodents or other animals. A preventative pest control programme should	

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		be in place.	
Paragraph 3.12		Comment: The text should include a reference that the environmental factors to be controlled would depend on the nature of the storage products and determined by an Environmental Risk Assessment. Proposed change (if any): Suitable equipment and procedures should be in place to ensure adequate control of the environment of medicinal products during storage. Environmental factors to be considered include, but are not limited to, temperature, humidity and cleanliness of the premises, *dependant on the products being stored and the information detailed in the Marketing Authorisation.* *An environmental Risk Assessment should be carried out to identify the equipment and procedures that should be in place to ensure adequate control of the environment of medicinal products during storage. These controls could include, but are not limited to, temperature, humidity, and cleanliness of the premises.* *Where the environmental factors do not have any impact on the safety and quality of the medicinal product, there is no requirement to control the storage environment.*	

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Paragraph 3.14		Comment: To align with the requirements of 3.5 add the reference 'Where specific storage conditions are required. Proposed change (if any): *Where the Environmental Risk Assessment identifies the need, the* storage areas should be temperature mapped under representative conditions and should take into account seasonal variations. An initial mapping should be carried out prior to the commencement of use. The mapping exercise should be repeated according to the results of a Risk Assessment exercise or whenever significant modifications are made to the facility or the temperature controlling equipment. *Where temperature monitoring is required*, the monitoring equipment should be located according to the results of the mapping exercise.	
Paragraph 3.23		Comment: The term Durability is unclear and needs clarification Proposed change (if any): *Data should be recorded either physically or electronically and protected against either accidental or unauthorised modifications.* *The data should be accessible as required.*	
Chapter 4		Comment:	

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		It is proposed that the text should indicate that paper as well as electronic format can be used. Proposed change (if any): Instructions, procedures, and records should be free from errors and each employee should have access to such instructions and procedures, *in paper or electronic format*, concerning his or her activities at any time. *Good documentation constitutes an essential part of the Quality Management System.* *Written documentation should prevents errors from spoken communication and permits tracing of batch history.* *Instructions, procedures, and records (in either paper or electronic format) should be free from errors.* Each employee should have access to such instructions and procedures concerning their activities.	
Paragraph 4.8		Comment: Text layout – Records needs to be a heading. Proposed change (if any): **Records**	
Paragraph 5.8		Comment: The paragraph should allow for all modes of supply of medicinal products to all types of customer. The medicinal gas industry tends to supply the end user directly and not supply via a third party – hence the clause should allow for this mode of supply	

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		Proposed change (if any): Wholesale distributors must ensure they *only* supply medicinal products to persons who are themselves in possession of a distribution authorisation or who are authorized or entitled to supply medicinal products to the public in the Member State concerned. *Alternatively they must ensure that where the product is supplied directly to the patient / healthcare user that they are appropriately qualified to receive the product.* Qualification of customers should be appropriately documented.	
Paragraph 5.17		Comment: Where there are specific requirements for the storage of medicinal products, the Guidelines should ensure that these requirements are met. For medicinal gases stored on the manufacturer's or the wholesale dealer's site have to follow the requirements in Annex 6 of the EC GMP Guide as well as meeting the requirements of any local legislation in individual Member States. Where this type of product is stored, it is not always possible for the different types of gases to be stored completely 'separately'. A quality risk based approach should be used to determine the appropriate storage requirements to ensure the quality, efficacy and safety of the medicinal products.	

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		Reference should be made to specific storage requirements specified in the Marketing Authorisation. Proposed change (if any): Medicinal products should be stored *as defined by the Environmental Risk Assessment (para 5.24) carried out for each type of product handled.* *It may be necessary to store medicinal products* separately from other products and protected from harmful effects of light, temperature, moisture or other external factors. Particular attention should be paid to products where specific storage conditions are ~~required~~ *specified in the Marketing Authorisation.*	
Paragraph 5.21		Comment: Not all products need to be stored off of the floor – specifically, medicinal gases should be placed directly on the floor. Proposed change (if any): Medicinal products should be handled and stored in such a manner as to prevent spillage, breakage, contamination and mix-ups. Medicinal products should not be stored directly on the floor *unless the package is designed to allow such storage (as for medicinal gas containers).*	

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Paragraph 5.32		Comment: For deliveries made by distribution sites operated by the manufacturer as part of the same distribution network using common information systems, it should be possible to have some of the required data available electronically. There is a need to clarify if all the information referred to should be available for each supply in printed format or whether it could be available for reference in a validated electronic information system. Proposed change (if any): Records, *either as a paper based document or available electronically on-line in a format that can be printed* should be kept so that the actual physical journey undertaken by the product can be tracked.	
Paragraph 5.33		Comment: Text change – to change the word 'operation' to 'operating' Proposed change (if any): Proposed change (if any): A person exporting medicinal products must thus hold a wholesale distribution authorization or a manufacturing authorization. This is also the case if the exporting wholesale distributor is ~~operation~~ *operating* from a free zone.	
Chapter 7		Comment:	

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Principle		There needs to be clarity as to the level of controls required for Contract Operations. The text specifies that 'both the contract giver and the contract acceptor must hold a distribution authorisation'. There are numerous activities that can be outsourced, from cleaning to pest control that should be covered by a contract but not require the contractor to hold a distribution licence. It should be clarified in what extend these activities are subject to a distribution licence. It may be more appropriate for them to be included as part of the Manufacturing Licence or Wholesale Distribution Licence of the Contract acceptor. Proposed change (if any): When outsourcing activities a written contract should be drawn up. Both the contract giver and the contract acceptor should hold a distribution authorisation *if they are responsible for the wholesale dealing of any medicinal products.* The written and signed contract should cover all wholesale distribution activities and clearly establish the duties and responsibilities of each party. Written contracts should be established for any activity likely to impact on GDP related activities.	
Paragraph 9.7		Comment: The control of temperature during transportation should be controlled as detailed in the Manufacture Authorisation and be	

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		in line with the storage conditions indicated on the packaged information Proposed change (if any): *Where specific transport conditions are required by the Marketing Authorisation, the* equipment used for temperature monitoring during transport, within vehicles and /or containers, should be maintained and calibrated at regular intervals at least once a year.	
Paragraph 9.12		Comment: Risk assessment should be used to determine the appropriate timings where product can be stored within a distribution hub. The time limit should take into account the type of product, the extent of the supply chain and should incorporate the outcomes established from the risk evaluation. A time limit of 24 hours may be acceptable in some cases (especially where product is stored over a weekend or where supply distances are long. Proposed change (if any): Where transportation hubs are utilised in the supply chain, ~~a maximum~~ time limits ~~of normally 24 hours~~ should be set when products are dispatched on the next stage of the transportation route. *The time limit should be based on the specific storage requirements of the product (defined in 3.5)*	

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		and the security of the site where the product is held. Where the medicinal product is not subject to deterioration during the storage on the hub site, the time interval may be extended to cover weekend / statutory holiday periods. Where medicinal products are held on the premises for longer than this defined time limit, the hub will be deemed to be acting as a storage site and required to obtain a wholesale distribution authorisation. For refrigerated product any storage at a transportation hub for any period of time would require that premises to hold a wholesalers distribution authorisation.	
Paragraph 9.18		Comment: It would be helpful to add a new paragraph to this section dealing specifically with the unique requirements for medicinal gases stored in cylinders Proposed change (if any): *9.19 Medicinal gases should be transported in safe and secure vehicles in accordance with the requirements laid down in international and national transport (ADR) regulations.*	
Paragraph 9.19		Comment: Exception should be possible for this requirement depending on type of product being transported. For medicinal gases distributed as a cryogenic liquid, the method of storage is governed by the type of vehicle used and the storage of the product prior to loading.	

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		Proposed change (if any): *Where the medicinal product needs to be stored under specific temperature conditions, the* validated temperature-control systems (e.g. thermal packaging, temperature-controlled containers, and refrigerated vehicles) should be used to ensure correct transport conditions are maintained between the distributor and customer. Customers should be provided with a temperature data to demonstrate that products remained within the required temperature storage conditions during transit, if requested.	
Paragraph		Comment: Proposed change (if any):	
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Please add more rows if needed.