Safeguarding public health

DG SANCO

SANCO-gmp@ec.europa.eu
ADM-GMDP@ema.europa.eu

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Subject **UK response to Public consultation on the revised Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use**

Please find attached the response of the Medicines and Healthcare products Regulatory Agency (MHRA) to the Public consultation on the revised Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use.

Given that the complexity of the supply chain for medicinal products has increased significantly since the publication of the current EU Guide to Good Distribution Practice, a revision of the guide is supported and welcomed by the MHRA.

Yours sincerely,

Maggie Jackman
Head of EU, International and Strategy

Medicines and Healthcare products Regulatory Agency (MHRA)
151 Buckingham Palace Road London SW1W 9SZ UK
T 020 3080 6000 www.mhra.gov.uk

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Chapter/section	UK Comment
Chapter 1 section 1.1	Comment: The use of “adulterated” implies that the product has been deliberately contaminated at some point, and does not accurately reflect the intention of the text. Proposed change: redraft to read “The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that product quality is maintained during storage and/or transportation.”
Chapter 1 section 1.2	Comment: This paragraph refers to the “responsible person”, section 2.1 refers to the “Responsible Person”. The text in section 1.2 should be aligned with later text.
Chapter 1 Sections 1.2 and 1.3	Comment: Reference to “management” and “senior management” – Is there meant to be a difference?
Chapter 1 Sections 1.1 to 1.8	Comment: Reference is made to “quality system”. Is this different to “quality management system” referred to in: Para. 1.9 - Management of Outsourced Activities, Para. 1.10 and 1.11 - Management Review and Monitoring.
Chapter 1 Section 1.11	Comment: This section states : ‘The outcome of this management review of the quality management system should be timely and effectively communicated.’ The management review and outcomes should also be documented Proposed change: redraft text to include documentation of the review and outcomes
Chapter 1 section 1.7	Comment: Change control should apply to any changes to the quality system, not just “critical” processes. It is possible to implement a proportionate change control system which can reduce the administrative burden for non-critical changes, this reduces the possibility of a number of small changes unintentionally creating a significant problem. Proposed change: redraft text to read “A change control system should be in place. This system should incorporate quality risk management principles, be proportionate and effective.”
Chapter 2 Section 2.1	Comment: The Responsible Person is required to be “permanently available”, but does not clarify who they are to be available to or in what capacity. Proposed change: “The Responsible Person should fulfil his/her responsibilities personally, and should be continuously available to provide support and advice to the wholesale distributor.”

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Chapter/section	UK Comment
Chapter 2 Section 2.2	Comment: The written job description of the Responsible Person cannot define his/her authorisation to take the decisions Proposed change: The written job description of the Responsible Person should define his/her responsibilities. The wholesale distributor should give the Responsible Person the authority and resources to fulfil his/her duties.
Chapter 2 Section 2.3	Comment: The minimum standards for a Responsible Person (education and/or experience) are not described in UK legislation, and are not likely to be unless described in the Directive at some point in time. Proposed change: "The qualifications of the Responsible Person should meet the conditions provided by the Member State concerned, and should be appropriate to fulfil the assigned duties. He/she should have appropriate competence and experience as well as knowledge of, and training in, GDP."
Chapter 2 Section 2.4	Comment: Reference is made to "and that public service obligations are met". Should this read "and that any public service obligations are met"
Chapter 2 Section 2.5	Comment: This section allows delegation of duties but Sections 2.1 and 2.4 require the Responsible Person to carry out his/her activities personally
Chapter 2 Section 2.8	Comment: The roles and responsibilities of all employees working in positions which could affect product quality should be defined and documented, rather than "key" positions. Proposed change: "The responsibilities and roles of employees working in positions which may have an impact on the quality of medicinal products should be defined in written job descriptions, in which any deputyship arrangements are also laid out."
Chapter 2 Section 2.9	Comment: There may be some individuals (such as the Responsible Person) with extensive duties, which in turn have significant potential to affect product quality. There may also be individual workers (product pickers or packers for example) where a very narrow range of duties can still have a negative effect on quality if the quantity of work is too high. It is more important to highlight individual workloads rather than duties. Proposed change: "Workload placed on any individual should not be such as to present unacceptable risk to product quality."
Chapter 2 Section 2.10	Comment: Does any GDP qualification exist? The aim of this section is to highlight training needs, and requires revision to reflect this aim. Proposed change: "All personnel involved in wholesale distribution activities should be

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	trained in the requirements of GDP, and should have assessed competence prior to commencing tasks."
Chapter 2 Section 2.10	Comment: Why single out training in aspects of product identification and avoidance of falsified medicines entering the supply chain? Section 2.1 requires training in GDP requirements one of which is Suspected falsified Medicinal Products set out in 6.13 to 6.15 Proposed change: Delete this specific requirement
Chapter 2 Section 2.12	Comment: In this section is it the personnel who need more stringent handling or the products? Proposed change: "Personnel dealing with any products which require more stringent handling conditions should receive specific training. Examples of such products include hazardous products, radioactive materials, products presenting special risks of abuse (including narcotic and psychotropic substances), and temperature sensitive products."
Chapter 2 Section 2.16	Comment: Reword from 'The storage of food, drink, smoking materials or medication for personal use in the storage areas should be prohibited'. Proposed change: 'The introduction of food, drink, smoking materials or medication for personal use into the storage areas should be prohibited'.
Chapter 3 Section 3.5	Comment: All areas should be adequately controlled, as no product will not have defined storage conditions (even if this is simply less than 25°C). Proposed Change: "Environmental controls should be adequate to maintain all parts of the relevant storage area(s) within defined temperature, humidity or light parameters."
Chapter 3 Section 3.10	Comment: Typographical error and tidying up the English. Proposed change: "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 so as not to be a source of contamination."
Chapter 3 Title	Comment: If products are sensitive to light or humidity would it not also be expected that areas are mapped appropriately, Proposed change: Change title to "Environmental Control".
Chapter 3 Section 3.14	Comment: Is the text likely to cause some degree of confusion as to where monitoring equipment should be located after mapping? Proposed change: "Storage areas should be mapped under representative conditions

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	and should take into account seasonal variations. An initial mapping exercise should be carried out in a storage area 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 environmental control system. Monitoring equipment should be located according to the results of the mapping exercise so as to, as a minimum, monitor any storage areas exposed to extremes of temperature, humidity or light."
Chapter 3 Section 3.14	Comment: Clearer guidance could be given around the expectations for temperature monitoring i.e. Maximum and minimum temperatures recorded on a daily basis and the actions to be taken in the event of a temperature excursion Proposed change:
Chapter 3 Section 3.15	Comment: "Planned preventive maintenance" . Should this be "Planned maintenance should be documented and be in place…"
Chapter 3 Section 3.17	Comment: It is not clear what "traceable to a primary standard" means.
Chapter 3 Section 3.19	Comment: "Relevant pieces of equipment would include …". Should this refer to "Key equipment would include …"?
Chapter 3 Section 3.28	Comment: Corrective and preventive actions (CAPA) is used in para. 1.8 vi). Minor point should we just use the abbreviation here.
Chapter 3 Section 3.5 & 3.13	Comment: These two sections repeat each other Proposed change: Rationalise the text
Chapter 3 Section 3.27	Comment: this section implies all systems must be validated, yet 3.26 requires validation based on risk assessment. Also this section requires 'Prior to implementation and after any significant changes or upgrades, systems should be validated to ensure correct installation and operation'. It is not possible to validate something prior to implementation. Proposed change: Replace with 'Before commencing to use a piece of equipment, process or procedure to assure the quality of medicinal products and after any significant changes or upgrades, systems should be validated to ensure correct installation and operation'
Chapter 4	Comment: This section states that documents should not be hand written but then goes

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Chapter/section	UK Comment
Section 4.3	on to stay that if this type of entry is required then space should be left for it?
Chapter 4 Section 4.7	This section refers to both SOPs and documents. Is the intention for these terms to be used interchangeably? If so then does the same apply to the previous sections in this chapter?
Chapter 4 Section 4.6	Comment: For what purpose should all documentation be available? Is it reasonable to expect the license holder to have all documentation "readily available" if documentation has to be held for a minimum of 5 years? Proposed change: "All documentation should be made available on the request of the Competent Authority granting the wholesale dealer's authorisation."
Chapter 4 Section 4.7	Comment: The text for supersede versions of documents should be re-ordered. Proposed change: "Documents should be reviewed regularly and kept up-to-date. Version control should be applied to SOPs. After revision of a document a system should exist to prevent inadvertent use of the superseded version superseded or obsolete SOP documents should be removed from workstations and archived."
Chapter 4 Section 4.8	Comment: There is only one word "Records". Is that correct or should the para. 4.8 be deleted and the rest renumbered?
Chapter 4 Section 4.8	Comment: The text just says "Records", is this supposed to be a sub-section?
Chapter 4 Section 4.9	Comment: The records required by Directive 2011/62/EU go further than just invoices and delivery slips. The guidelines contain a specific section for brokering activities (Chapter 10), and it may be better to refer to record keeping requirements for brokers in that section. Proposed change: "Records required by National legislation, in either written or electronic form, must be made and retained for any wholesale transaction in medicinal products."
Chapter Section 4.11	Comment: Typo Proposed change: Change "taken" to "undertaken"
Chapter 5	General comment: The whole chapter seems to largely re-iterate the requirements of the Directive, rather than providing guidance to the authorisation holder.
Chapter Section 5.3	Comment: Section 3 does not fully convey what is required in the Falsified Medicines Directive. Article 1(15) amends Directive 2001/83/EC: in Article 76, paragraph 3 is replaced by the

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Chapter/section	UK Comment
	following: 3. Any distributor, not being the marketing authorisation holder, who imports a medicinal product from another Member State shall notify the marketing authorisation holder and the competent authority in the Member State to which the medicinal product will be imported of his intention to import that product.……. 4. In the case of medicinal products which have been granted an authorisation pursuant to Regulation (EC) No 726/2004, the distributor shall submit the notification in accordance with paragraph 3 of this Article to the marketing authorisation holder and the Agency. ……..
Chapter 5 Principle	Comment: Medicinal products supplied under the limited exemptions from a Marketing Authorisation, described in Article 5 of Directive 2001/83/EC, will not have a Marketing Authorisation granted by the EU or a Member State. The text also seems to simply restate certain parts of the Directive rather than providing a description of the principle objectives of the section. Proposed change: "All actions taken by the distributor should ensure that the identity of the medicinal product is not lost and that wholesale distribution of medicinal products is in accordance with the approved storage conditions for those products. The wholesale distributor should use all means available to ensure that the provenance of received products is known, to minimise the risk of falsified medicinal products entering the legal supply chain. All key operations should be fully described in the quality management system, in appropriate standard operating procedures."
Chapter 5 Sections 5.1 -5.3 and 5.6	Comment: These sections simply restate aspects of the Directive which should be transposed into National law, and as such are superfluous in guidance. Proposed change: Delete sections 5.1, 5.2, 5.3, and 5.6.
Chapter 6 Section 5.7 (i)	Comment: Reputation and reliability are different and both are important Proposed change:…suppliers reputation AND reliability…
Chapter 5 Section 5.7	Comment: Due diligence is seen as an important part of any activity when combating the entry of falsified medicines into the supply chain, but this Section does seem to go some way beyond any requirements in the Directive. Proposed change: "Due-diligence is an important activity, and should be carried out by the distributor when obtaining stocks of medicinal products or entering into a new contract with a supplier. A wholesale distribution authorisation holder should make an

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Chapter/section	UK Comment
	assessment of the suitability, competence and reliability of another party involved in the supply of medicinal products. A risk based approach should be used for this purpose, considering amongst other things: i) what is known about the new supplier, for example their reputation, reliability, and authorised activities; ii) that certain medicinal products are more likely to be the target of falsification; iii) the quantities of products on offer, when compared to quantities normally in circulation; iv) any unusual discount or reduced price for a particular product, which do not reflect those typical in the market."
Chapter 5 Section 5.10	Comment: Again, something which goes a little beyond the requirements of the Directive, and could benefit from a little revision. Proposed change: "The diversion of certain products, such as products containing narcotics or psychotropic substances at risk of misuse, is a particular problem. Wholesale distributors should monitor transactions of products identified on a risk-assessment basis, and challenge any irregularity in sale patterns so as to avoid diversion of medicinal products. Wholesale dealers should also ensure that they fulfil any public service obligation imposed upon them."
Chapter 5 Section 5.11	Comment: Not sure what the basis for this obligation is, the closest is probably Articles 76(3) and 76(4). In any circumstances it is extremely unlikely the wholesale distributor will have any access to the content of a Marketing Authorisation held by another company.
Chapter 5 Section 5.11	Comment: This section requires: 'Wholesale distributors wishing to distribute or distributing medicinal products in Member State(s) other than the Member State in which the marketing authorisation was granted should, on request, make available a copy of the marketing authorisation to the national competent authority'. It is not clear which NCA the copy of the MA should be made available to.
Chapter 5 Section 5.13	Comment: Products requiring special storage or security conditions should be transferred at the earliest opportunity, rather than after appropriate checks as this could place the product at risk. Areas of special storage may require their own quarantine areas to permit this. Proposed change: "Where medicinal products require special storage or security

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	measures, they should be transferred to appropriate quarantined storage facilities at the earliest opportunity."
Chapter 5 Section 5.15	Comment: Article 51 places an exemption from the need for a manufacturer to re-control batches of product imported from another Member State, if the batch is accompanied by the control reports of the importing manufacturer. The obligations under Article 51 do not apply to wholesale dealers, and so this section should be deleted.
Chapter 5 Section 5.15	Comment: The responsibility for certification and release to market rests with the manufacturer. Wholesalers should only be trading in stock certified and released to the market by a QP.
Chapter 5 Section 5.16	Comment: Wholesale distribution authorisations do not permit holders to import medicinal products from a third country, and so they should not be receiving medicinal products from a third country. This is a Directive requirement (in the same way as sections 5.1 etc) rather than guidance and should be deleted.
Chapter 5 Section 5.17 & 5.24	Comment: These two sections state the same requirements Proposed change: Rationalisation of the text
Chapter 5 Section 5.19 & 5.25	Comment: These two sections state the same requirements Proposed change: Rationalisation of the text
Chapter 5 Section 5.22	Comment: There is a risk that out of date stock may enter the supply chain, so it should be removed from saleable stock at the earliest opportunity. Proposed change: "Medicinal products beyond their expiry date or shelf life should be withdrawn immediately from saleable stock Physical removal of unsuitable stock should be performed at the earliest opportunity."
Chapter 5 Section 5.23	Comment: What should happen after "Irregularities should be investigated and documented"?
Chapter 5 Section 5.30	Comment: Products should be packed in such a way as to maintain the quality of the product, and show evidence of tampering during transit. Proposed change: "Products should be packed in a way to avoid breakage, contamination and theft. The packing should be adequate to maintain the quality of the product during transport, and reflect the approved storage conditions for the product. The containers in which medicinal products are shipped should be securely sealed. For products at particular risk of falsification or diversion the package seal should indicate any tampering during transit."

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Chapter/section	UK Comment
Chapter 5 Section 5.33	Comment: This section simply restates aspects of the Directive which should be transposed into National law, and as such is superfluous in guidance. Proposed change: The title of the subsection should be “Export to a third country”, as it does not relate to export to another Member State.
Chapter 5 Section 5.33	Comment: Need to include customs warehouses as well as free zones. Also typo change operation to operating. Proposed change : ”…is operating from a customs free zone or customs warehouse”
Chapter 5 Section 5.34	Comment: It needs to be made clear that Export here means direct from the wholesale dealer in the UK to a third country. Proposed change: “the rules for wholesale distribution apply in their entirety in the case of export of medicinal products to a third country, with the following exceptions.”
Chapter 5 Section 5.34	Comment: The third country customer may not need to hold a distribution authorisation, but they should be authorised to receive the products concerned. The exporter should confirm the bona fides of supply to the same degree as a customer in another Member State. Proposed change: “b. The customer should be authorised to receive the products in the third country. The exporter should confirm the authority of the customer to receive the product in the same manner as if supplying to another Member State.”
Chapter 5 Section 5.34c	Comment: Current text - ‘Moreover, where the medicinal product intended for exportation has been obtained directly from another third country, without the product being prior to that placed on the market (i.e. without prior import), the supplier does not have to bear a wholesale distribution authorisation’. Proposed change: “Where the medicinal product intended for export has been supplied directly from another third country and prior to export from the EU has not been placed on the market (i.e. not been imported), the third country supplier does not need to hold a wholesale distribution authorisation.
Chapter 5 Export to a third country	General comment: The WHO guidelines for charitable donations of medicines to third countries provides sound guidance to exporters. http://www.who.int/selection_medicines/emergencies/guidelines_medicine_donations/en/ Should a reference to the document be considered, for such donations from authorised wholesale dealers?

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Chapter/section	UK Comment
Chapter 6 Section 6.4	Comment: Product distribution complaints should also be documented, in the same manner as product defects/falsified products. Proposed change: "Any product distribution complaint should be documented and thoroughly investigated."
Chapter 6 Section 6.10	Comment: Should line 1 read "Medicinal products requiring temperature controlled storage conditions…."?
Chapter 8 Section 8.2	Comment: Can a self inspection be performed in an independent and detailed way by designated competent person(s) from the company? Proposed change (if any): "Self-inspections should be conducted by suitably trained and competent person(s) from the company".

Chapter 10	Comment: Brokers must comply with certain requirements applicable to holders of a wholesale distribution authorisations set out in Article 80 (d) to (i) of Directive 2001/83/EC. Brokers must:
	
	- have an emergency plan which ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or marketing authorization holder for the medicinal product concerned; (Article 80(d) of Directive 2001/83/EC)
	- keep records either in the form of purchase/sales invoices or on computer, or in any other form, giving for any transaction in medicinal products [received, dispatched or] brokered at least the following information:
	  - date,
	  - name of the medicinal product,
	  - quantity [received, supplied or] brokered,
	  - name and address of the supplier or consignee, as appropriate,
	  - batch number of the medicinal products at least for products bearing the safety features referred to in point (o) of Article 54; (Article 80(e) of Directive 2001/83/EC)
	- keep the records referred to under (e) available to the competent authorities, for inspection purposes, for a period of five years; (Article 80(f) of Directive 2001/83/EC)
	- comply with the principles and guidelines of good distribution practice for medicinal products as laid down in Article 84. (Article 80(g) of Directive 2001/83/EC).
	- maintain a quality system setting out responsibilities, processes and risk management measures in relation to their activities; (Article 80(h) of Directive 2001/83/EC)
	- immediately inform the competent authority and, [where applicable,] the marketing authorisation holder, of medicinal products they [receive or] are offered which they identify as falsified or suspect to be falsified. (Article 80(d) of Directive 2001/83/EC).

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Chapter/section	UK Comment
	It needs to be clear that the section on broker captures all of the above or cross reference is made e.g. keeping records for 5 years.