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January 15, 2016

European Medicines Agency
Canary Wharf London, UK
QWP@ema.europa.eu

Ref: Guideline on manufacture of the finished dosage form
EMA/CHMP/QWP/245074/2015

Dear Sir/Madam,

PDA welcomes the opportunity to provide comments on this new guideline and understands it does not introduce new requirements on authorised medicinal products for human use. PDA comments are attached to this letter and consist primarily of requests for additional clarification to enhance ease of use for all parties.

For example, PDA recommends that the scope and wording of the guideline should be precise in order to avoid any misinterpretation. The wording as chosen in the draft ("chemical and herbal medicinal products") does not include all medicinal products that are regulated by Dir 2001/83/EC, e.g. drug products containing semi-synthetic active substances. . Also the conditional language "does not generally apply to radiopharmaceuticals; however the principles may be applied where relevant" can also lead to misunderstanding and confusion. PDA believes that having a clear scope for this guideline consistent with EU Directives is important for ease of use and has provided specific suggestions in the attached comments.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of pharmaceutical manufacturing experts representing our Regulatory and Quality Advisory Board and Board of Directors.

If you have further questions, please do not hesitate to contact me.

With very best regards,

Georg Roessling, Ph.D., Senior VP, PDA Europe
Cc: Richard Johnson, PDA; Denyse Baker, PDA

January 15 2016

3 February 2015 2 EMA/CHMP/QWP/245074/2015 3 Committee for Human Medicinal Products (CHMP) Guideline on manufacture of the finished dosage form

Comments from:

Name of organisation or individual
PDA (The Parenteral Drug Association)

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).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
Name	Comment	Decision to Submit/ withdraw comment
	Throughout the guidance document reference is made to the "bulk product". It appears to be used differently in different sections. (See Line 223-225: any isolated material waiting forward processing and line 83: a drug product batch sub divided for final packaging.) In order to avoid any misunderstanding, definitions should be provided in the "Definitions" (see also comment to line 257).	
	PDA recommends that the scope and wording of the guidance should be precise in order to avoid any misinterpretation. The wording as chosen in the draft ("chemical and herbal medicinal products") does not include all medicinal products that are regulated by Dir 2001/83/EC, (e.g. drug products containing semi-synthetic active substances). Also the conditional language "does not generally apply to radiopharmaceuticals; however the principles may be applied where relevant" can also lead to misunderstanding and confusion. PDA believes that having a clear scope for this guideline consistent with EU Directives is important for ease of use. See also specific comment to lines 49-56.	

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)*
29-30		Comment: Wording that requires clarification. Proposed change (if any): The note for guidance has been updated to reflect **the requirements as laid down in the current legislation (Directive 2001/83/EC, ref 1)** ~~changes~~ **and to follow** ~~to~~ the format and content of the Common Technical Document (CTD) Module 3 dossier.	Decision to Submit/ withdraw comment
34 & 60		Comment: Clarify that reference is made to the marketing authorisation, not to the manufacturing authorisation. Proposed change (if any): However as stated in article 23 of Directive 2001/83/EC (ref 2) after a **marketing** authorisation has been issued …	
49-56		Comment: PDA recommends the following modification to the scope and wording in order to fully align with Dir 2001/83/EC and in order to avoid any misinterpretation. Proposed change (if any): ”This guideline is applicable to the manufacture of the finished dosage form of ~~chemical and herbal~~ medicinal products for human use **as are regulated by the provisions laid down in Directive 2001/83/EC apart from advanced therapy medicinal products (ATMPs)**. ~~The principles described are in general also applicable to biological medicinal products.~~ Due to the nature of ~~advanced therapy medicinal products (~~ATMPs~~)~~, the guideline is not applicable to these. ~~This guideline does generally not apply to radiopharmaceuticals; however, the principles of this guideline may be applied where relevant.~~	

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)*
88-89		Comment: The link between sufficient batch size to demonstrate process capability and the stated 100,000 units in the example is unclear. Please consider clarifying the process or consideration for determining process capability such as the use of statistical process capability indices.	
126-127		Comment: A validation protocol is generally not submitted as part of a dossier and should therefore be deleted in the sentence below. Proposed change (if any): To make the process fully understandable and to allow assessment of the validity of the process validation studies~~/ validation protocol~~ to support the claimed manufacturing process, (…).	
154-156		Comment : This text in line 154-156 "*The same requirements apply to the level of detail in the manufacturing process description irrespective of the development approach, i.e. if the product has been developed by the traditional or enhanced approach"* seems to contradict the examples given at lines 351 and 355. Please consider a single example at line 351 that accounts for criticality. Proposed Change: PDA suggests that no distinction between QbD and non-QbD should be made as is stated in line 154.	
195		Comment: Editorial (avoid repetition). Proposed change (if any): Where relevant, the justified technical adaptations in various~~ manufacturing~~ steps in the manufacturing process	
205		Comment: Unclear wording. What is a "truly" alternative manufacturing process? Suggestion to delete the word. Proposed change (if any): … ~~truly~~ alternative manufacturing processes, which use different principles …	

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)*
219 -257		Comment: Include a definition for "bulk product" that explains the use in both lines 83 and lines 223 or provide an alternate term and definition where the meaning is different. Proposed Change: The definition from Eudralex Volume 4 seems applicable for the use in line 83 but perhaps a modified definition is needed for the use in lines 223 – 225 such as: Bulk product: A product which has complete all processing stages up to but not including **final formulation** or final packaging.	
228-230		Comment: PDA is concerned that the example provided will be viewed as an implied requirement to challenge the maximum hold time during process validation runs. In PDA's opinion that would be too prescriptive and not aligned with current PV thinking. Companies should be able to provide whatever evidence and data is appropriate to support their specific product and proposed process hold times for evaluation by the regulators to judge whether that evidence adequately supports the claim. Proposed Change: *"… maximum holding times of bulk product should be stated and appropriately supported by data ~~(e.g. challenging the maximum hold time in process validation studies or by providing dedicated stability studies for the bulk storage~~).*	
351 and 355		Comment: Please consider a single example that includes criticality. Previous documents such as *Guideline on process validation for finished products and data to be provided in regulatory submissions* of 27 Feb 2014 suggests that process validation address critical steps (and presumably critical parameters) of the manufacturing operation. There is no provision in any other document to ignore criticality. (see also comment to lines 154-156)	

Please add more rows if needed.