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29 March 2019

Health Product Inspection and Licensing Division
Health Canada
13th Floor, Jeanne Mance Building
200 Eglantine Driveway, Tunney's Pasture
Ottawa Ontario K1A 0K9
Canada

Reference: Good manufacturing practices for active pharmaceutical ingredients (GUI-0104)

Dear Madam or Sir:

PDA appreciates the opportunity to comment on the revised draft guidance on good manufacturing practices for active pharmaceutical ingredients (GUI-0104). We present our comments in Table 1, attached.

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 have been prepared by a committee of PDA members with expertise in pharmaceutical and biopharmaceutical manufacturing on behalf of PDA's Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,

Richard Johnson
President and CEO

cc: Tina Morris, PDA; Ruth Miller, PDA

Health Canada Santé Canada

December 31, 2018

SUBJECT: Consultation Comment Form

Dear Stakeholder,

Health Canada is conducting a consultation on the following draft guidance document. The consultation will be open for 90 days from December 31, 2018 to March 31, 2019.

- GUI-0104: Good manufacturing practices for active pharmaceutical ingredients

Please email your comments to hc.api.questions-ipa.sc@canada.ca, using this form. All comments will be considered in the finalization of the document. The 90-day consultation period is from December 31, 2018 to March 31, 2019, inclusive.

Comments can also be mailed to:

Health Product Inspection and Licensing Division
Health Product Compliance Directorate
13th Floor, Jeanne Mance Building
200 Eglantine Driveway, Tunney's Pasture
Address Locator # 1913D
Ottawa Ontario K1A 0K9

Sincerely,

Health Product Inspection and Licensing Division

Canada

Health Canada Santé Canada

Comment Form

Optional Contact Information:

Name	Richard Johnson
Title	President and CEO
Organization/Company	Parenteral Drug Association
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City	Bethesda
Province	MD, USA
Postal Code	20814
Email Address	johnson@pda.org

Step 1 Enter the title and number of the guidance document for which you are providing comments.

Good manufacturing practices for active pharmaceutical ingredients (GUI-0104)

Step 2: Complete Table 1 which can be found on the next page by indicating the line number, page number, current text, proposed revision or comments, and a rationale. You may add additional lines as required.

Health Canada Santé Canada

Table 1: Comments

Line Number	Page Number	Current Text	Proposed Revision or Comments	Rationale
126	8	The guidance in this document has been written with a view to harmonize with GMP standards from: • the International Conference on Harmonisation (ICH) • the Veterinary International Conference on Harmonisation (VICH) • the Pharmaceutical Inspection Cooperation/Scheme (PIC/S) • other international regulatory agencies	PDA agrees with this objective, but suggests that Health Canada's efforts at harmonization with ICH and PIC/S would be clearer if the agency were to update the prior version of GUI-0104 without completely rewriting it as proposed. While in many cases PDA supports the use of plain language in regulatory documents, such language should be adopted carefully and discretely when referencing globally harmonized language. We highlight below some specific and meaningful differences in wording between this revision and ICH Q7, but have not attempted to comprehensively identify all potential issues that may arise as regulated entities work through this document. As an alternative, Health Canada might consider adopting ICH Q7 verbatim, then editing GUI-0104 to describe only Canada-specific topics such as site licensing for biologics and narcotics.	ICH Q7 and the PIC/S Guide to Good Manufacturing Practices for Medicinal Products Part II are harmonized. This draft guidance's departure from the language of those harmonized documents presents challenges for companies that operate globally, which is particularly significant in the area of API. This revision could inadvertently bring about disharmonization due to the differences in the language used in this revised document.
126	9	This version reflects recent regulatory amendments, clarifies existing requirements...	PDA suggests that Health Canada's intentions would be clearer if the agency were to update the prior version of GUI-0104 but not completely rewrite it as Health Canada has proposed.	By attempting to provide clarity through the use of plain language, Health Canada may instead raise confusion about the GMP requirements for APIs under Canadian law vs. the requirements of other

			As one specific example, PDA suggests that Health Canada clarify its intention in omitting two appendices that appear in the current version of GUI-0104 and that reflect ICH Q7 content (Appendix D on APIs for Use in Clinical Trials, and Appendix C on Specific Guidance for APIs Manufactured by Cell Culture/Fermentation). With these omissions, does Health Canada intend any change to the status of that Q7 language in Canada?	countries that also have adopted ICH Q7 and the PIC/S GMP Guide. With this rewrite--and its divergence from the language used in ICH Q7 and the PIC/S guidance--it is unclear which previous guidance statements Health Canada intends to change. PDA believes that, for the most part, Health Canada probably intends to maintain consistency with the ICH document, but this revision makes it more difficult for industry to understand whether that is always the case.
261	16	Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process and should be documented.	PDA suggests that Health Canada include at least some of the seven examples of product quality review that are articulated in ICH Q7 section 2.50 and the PIC/S guidance: A review of critical in-process control and critical API test results; A review of all batches that failed to meet established specification(s); A review of all critical deviations or non-conformances and related investigations; A review of any changes carried out to the processes or analytical methods; A review of results of the stability monitoring program; A review of all quality-related returns, complaints and recalls; and A review of adequacy of corrective actions.	The examples provided in ICH Q7 are useful in helping regulated industry understand what may be included in product quality review.
319	21	Provide good ventilation, air filtration and exhaust systems.	Provide adequate ventilation, air filtration and exhaust systems.	ICH Q7 section 4.21 uses the term "adequate," which has more meaning than "good."

320	21	... to avoid contamination and cross- contamination ...	to minimize contamination and cross-contamination	In line 288, this document refers to the need to minimize contamination. ICH Q7 section 4.21 also uses the term "minimize" rather than "avoid."
105	7	The manufacturer should state and document their rationale for the point at which the API production begins since this is the point when GMP requirements will apply. For synthetic processes, this is usually the point when the API starting material is introduced into the process, but for other processes (fermentation, extraction, etc.) a rationale should be established on a case-by-case basis. Chart 2.0 below provides more guidance on where GMPs outlined in this guide start to apply.	Delete this text from the blue box "The scope of this document does not include...."	This text appears in two locations on this page. It appears to belong only in the blue box at line 106, and not in the blue box at line 105.
1091	50	Your packaging orders should include ... whether your line monitors are working properly.	[Delete]	PDA does not believe that this documentation adds value.