PDA®
Parenteral Drug Association

Connecting People, Science and Regulation®

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May 1, 2017

Health Canada
RE: Consultation on draft GUI-0001

Dear Madam/Sir:

PDA is pleased to provide comments on *GUI-0001: Good manufacturing practices guide for drug products.* In general, the implementation of plain language principles improves readability and comprehension of the regulations. PDA has provided comments where we believe further clarity will help achieve this objective. The use of symbols to highlight significant information is also considered an improvement and definition of their meaning and consistency of use will further enhance readability of the document.

In addition, PDA would like to congratulate Health Canada on taking a significant step forward on international harmonization with its proposal to replace its own regulations in favor of adopting the PIC/S standards for aseptic processes.

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 response was prepared by the volunteer members with expertise in pharmaceutical and biopharmaceutical manufacturing on behalf of the Regulatory and Quality Advisory Board and Board of Directors.

If there are any questions, please do not hesitate to contact me. (Johnson@pda.org)

Sincerely,

Richard Johnson
President and CEO, PDA

CC: Rich Levy, PDA; Denyse Baker, PDA

Health Canada Santé Canada

January 18, 2017

SUBJECT: Consultation Comment Form

Dear Stakeholder,

Health Canada is conducting a consultation on the following draft guidance documents. The consultation will be open for 90 days from January 18, 2017 to April 18, 2017.

- GUI-0001: Good manufacturing practices guide for drug products
- GUI-0023: Risk classification guide for drug good manufacturing practices observations
- GUI-0031: Good manufacturing practices for medical gases
- GUI-0080: How to demonstrate foreign building compliance with drug good manufacturing practices
- GUI-0119: Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs

Please email your comments to HPIL-Consultation-IPSOP@hc-sc.gc.ca, using one copy of this form for each guidance document. All comments will be considered in the finalization of the documents. The 90-day consultation period is from January 18, 2017 to April 18, 2017, 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	Director, Science and Regulatory Affairs
Organization/Company	Parenteral Drug Association
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Step 1 Enter the title and number of the guidance document for which you are providing comments.

GUI-0001: Good manufacturing practices guide for drug products

Step 2: If your comments pertain to *GUI-0119: Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs*, proceed to Step 3. For comments pertaining to other documents proceed to Step 4.

Step 3: Question: Do you agree with a proposal by Health Canada to adopt guidance for the manufacture of sterile drugs published by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as proposed in GUI-0119: Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs?

Considerations: The PIC/S documents to be adopted are "Guide to Good Manufacturing Practice for Medicinal Products Annexes - Annex 1 -Manufacture of sterile medicinal products"(PE 009-12 - 1 October 2015) and "GMP Annex 1 Revision 2008,Interpretation of Most Important Changes For The Manufacture of Sterile Medicinal Products"(PI 032-2 – 8 January 2010). The proposed adoption of these PIC/S documents for the manufacture of sterile drugs is intended to facilitate increased international harmonization. These PIC/S documents are currently being revised with a consultation opportunity expected in the first half of 2017.

Response

PDA agrees with Health Canada's proposal to adopt the stated internationally recognized guidance for aseptic processing.

Note: If you agree with the proposed adoption, you may submit your comments now. If you disagree with the proposal, proceed to Step 4.

Step 4: 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	Criticality
N/A	N/A	N/A	As part of PDA's commenting process, we identify comments we define as critical. Any of the following factors could make a comment "critical" for purposes of this analysis. Critical is defined as: • Comment has a major impact on patient safety or product quality • Not adopting the comment will have a large/major impact on the industry or process (i.e. greater than 1 year to become compliant; financially greater than $1M Euros to implement;) • Not adopting the comment will lead to difficult or complex to implement changes that may impact multiple quality and/or operating systems Note: comment criticality is based on the most important aspects of the specific document or text concerned. Criticality of the draft document relative to other guidance is not a factor considered when assessing comments.	N/A	
N/A	N/A	The use of symbols throughout the document.	Provide definitions for each symbol or the purpose of each symbol used in the document and then revise to ensure each has been used consistent with its definition.	This guidance uses a variety of symbols, presumably to highlight certain types of information. However, there is no apparent consistency to the use of symbols throughout the document. It's therefore	

				unclear what meaning or significance should be ascribed to the statement associated with the symbol.	
249	19	Take appropriate steps to minimize risk associated with building design and location,…	Take appropriate steps to minimize risk associated with building design and location in those buildings where drugs are fabricated or packaged,…	Some campuses have buildings with no fabrication of drugs occurs. Added wording clarifies that these activities are directed at drug fabrication buildings.	
269-270	19	Segregate mechanical areas such as boiler rooms and generators from products areas.	Segregate mechanical areas such as boiler rooms, ~~and~~ generators, and other engineering areas from production areas.	Improved clarity.	
283	20	…areas), and checking and replacing air filters periodically.	…areas), and performing periodic verification ~~checking~~ and replacing air filters periodically.	Improved clarity.	
297-298	20	Where electronic inventory control is used…	Where electronic inventory control for quarantined materials is used…	Maintains consistency with previous sentence.	
311	20	…compressed air, and nitrogen.	…compressed air, ~~and~~ nitrogen, etc.	Add account for other utilities and types of water systems (deionized water, distilled water, RO water, etc.)	
314	21	Clearly identify the content of distribution systems for liquids and gases at their outlets.	Clearly identify the content of distribution systems for liquids and gases used in the production of drugs at their outlets.	Some campuses have buildings where no fabrication of drugs occurs. Added wording clarifies that these activities are directed at drug fabrication buildings.	
370	23	Arranging your equipment in an orderly way makes cleaning nearby areas easier…	Arranging your equipment in an orderly way makes cleaning ~~nearby~~ adjacent areas easier…	The term “nearby” was used in the 2009 guidance. The terms “nearby” and “adjacent” are not interchangeable and have different meaning.	
376-377	23	Ensure equipment parts that come in contact with raw materials, in-process intermediates or drugs are cleanable.	Ensure equipment parts that come in contact with raw materials, in-process intermediates or drugs are cleanable or can be removed for cleaning.	Added text provides flexibility while maintaining intent of the interpretation.	
396-397	23	(use metal detectors where there is a risk of metal contamination from the manufacturing process, such as with tableting)	Provide appropriate controls where there is a risk of metal contamination from the manufacturing process, such as with tableting.	This new language should be a separate bullet and not a parenthetical statement. Additionally, new language should allow for other means of control other than solely metal detectors.	
416-417	24	Ensure that equipment surfaces are free from cracks, peeling paint and other	Ensure that equipment surfaces are free from cracks, peeling paint and other defects where the potential for	Clarifies that the focus of the requirement is on process-related equipment.	

		defects.	contamination during drug fabrication or packaging exists.		
426-472	24	Calibrate this equipment on a scheduled basis and keep records.	Calibrate this equipment on a scheduled basis and keep calibration records.	The reader may assume the records that are to be kept are the range, precision and accuracy of the measuring device, not records of calibration.	
441	25	Identify equipment used for major processing or testing operations…	Recommend using a single qualifier or defining the intended difference between equipment sets to which each qualifier refers. (see also lines 1008 and 1011)	These regulations use the qualifiers principal (1008), critical (1011), and major (948) for equipment but provides no definitions. It is therefore unclear if the requirements are talking about the same or different classes of equipment. Similarly, it is unclear how "major" processing or testing operations would be defined.	Critical
445-446	25	It is essential that only qualified staff supervise the fabrication of drugs, as the operations involved are highly technical in nature. They require constant vigilance, attention to detail,…	It is essential that only qualified staff supervise the fabrication of drugs. These ~~, as the~~ operations involved are highly technical in nature, and ~~. They~~ require constant vigilance, attention to detail,…	The modification made has changed the meaning of the original text.	
465	26	…or accreditation body…	…or Canadian accreditation body…	The current text is unclear whether the qualifier "Canadian" applies to just university or to accreditation body as well. Proposed text clarifies the expectation.	
473-474	26	…may delegate duties and responsibilities (for example, to cover all shifts) to a qualified person…	…may delegate duties and responsibilities (for example, to cover all shifts) to a person qualified by ~~person~~…	The term "qualified person" is new to this revision and has not been defined within the guidance. Additionally, use of this term may cause confusion with the "qualified person" defined in the EU.	
516-517	27	…(including technical, maintenance, and cleaning staff).	…(including personnel involved in the fabrication of the drug and technical, maintenance, and cleaning staff).	Add additional text for clarification and consistency with the 2009 version	
531-532	28	Sanitation in a pharmaceutical plant influences the quality of drugs products, as well as employee attitude.	Sanitation in a pharmaceutical plant, as well as employee attitude, influences the quality of drugs products.~~, as well as employee attitude.~~	Reworded for clarity – "sanitation" does not influence employee attitude	

567-568	29	Ensure removal of cleaning residues (such as detergents and solvents) from equipment.	Ensure residues from the ~~removal of~~ cleaning process ~~residues~~ (such as detergents and solvents, etc.) are removed from equipment.	Revised wording for clarity	
596-598	30	Ensure staff…have a thorough health exam before starting work. Staff should be periodically re-examined based on their job requirements.	Ensure staff…have a thorough health exam before starting their employment ~~work~~. Staff should receive periodic medical examinations ~~be periodically re-examined~~ based on their job requirements.	Revised wording for clarity. Current wording implies a health screening must be conducted before starting each day/shift/etc. Clarified that a "re-examination" is a medical re-examination, and not an informal re-examination by someone outside the medical profession.	
602-603	31	…may adversely affect the quality of drugs from handling exposed materials and drugs.	…may adversely affect the quality of drugs from handling exposed raw material, primary packaging materials, in-process drugs, and drugs.	Revised wording for clarity.	
End section 2	31		Personal hygiene procedures, including the use of protective clothing, apply to anyone entering the production areas.	Add wording from 2009 guidance that personal hygiene procedures and the use of protective clothing applies to anyone entering the production areas of a facility.	
779-782	37	Text added on selection of Vendors "Identifying and choosing raw material vendors is an important operation. You should involve staff who have a particular and thorough knowledge of the materials and suppliers. Their knowledge of materials should include an understanding of risk and certification where required (e.g. BSE/TSE risks)"	Amend text to "Identifying and choosing raw material vendors is an important operation. You should involve staff who have sufficient knowledge of the materials and suppliers. Their knowledge of materials should include an understanding of risk and certification where required (e.g. BSE/TSE risks)"	Text amended for clarity. E.g., "particular" and "thorough" are subjective terms – intent is important here so suggest revising the language.	Critical
882-883	42	Defined, monitored, and systematically reviewed.	Systematically reviewed in light of experience.	Added phrase from 2009. This phrase clarifies the intent of and basis for the review.	
936	43	(within the validated clean hold time)	(including within the validated clean hold time)	Clean hold time is not the only important characteristic that defines "clean".	
967	44	The rationale for disposition,…	The rationale for disposition of any associated product or material lots.	Clarify that disposition refers to product.	

976	45	Follow validation protocols approved in marketing authorization submission at pre-market stage.	Where applicable, follow validation protocols approved in marketing authorization submissions …	Not all validation protocols are approved in marketing authorization submissions at the pre-market stage. Most aren't even included. Further, it's unclear what is meant by pre-market stage. Recommend deleting or modifying as suggested.	**Critical**
981	45	Validate changes… before implementing them.	Validate changes to production processes, systems, equipment, materials or suppliers that may affect product quality and/or process reproducibility. Validating before implementation, while not always possible, is preferred. Concurrent validation should be justified.	While preferable, it is not always be possible to validate prospectively. The current text appears to preclude concurrent validation as a viable option.	**Critical**
987	45	The master formulae should be in accordance with the marketing authorization.	The master formulae should be consistent with the marketing authorization.	Proposed language captures the same intent.	
1008	45	Identification of the principal equipment to be used	Recommend using a single qualifier or defining the intended difference between equipment sets to which each qualifier refers. (see also lines 441 and 1011)	These regulations use the qualifiers principal (1008), critical (1011), and major (948) for equipment but provide no definitions. It is therefore unclear if the requirements are talking about the same or different classes of equipment. Either provide definitions for each term if they are intended to refer to different classes of equipment, or chose a single term and use consistently throughout the regulations.	**Critical**
1011	46	The procedures (or referent to the procedures) to be used for preparing the critical equipment…	Either provide definitions for each term if they are intended to refer to different classes of equipment, or chose a single term and use consistently throughout the regulations. (see also lines 441 and 1008)	These regulations use the qualifiers principal (1008), critical (1011), and major (948) for equipment but provides no definitions. It is therefore unclear if the requirements are talking about the same or different classes of equipment.	**Critical**

1021	46	Where applicable, the master formulae should be in accordance with the marketing authorization.	The master formulae should be consistent with the marketing authorization	Terminology is more commonly used and understood.	
1022	46	- And subject to independent checks by -	Ensure packaging operations are covered by master formulae. Where applicable, the master formulae should be in accordance with the marketing authorization. These master formulae must be prepared by—and subject to approval by— packaging/labelling and quality control personnel	This current text is more consistent with checks done during manufacturing and packaging operations, not approval of the master batch record. The phrase most commonly understood is that master formula (master batch records) are approved by Production and QC personnel.	
1169	51	Conduct annual quality reviews of all drug products…	Regular periodic or rolling quality reviews of all drugs, should be conducted with the objective of verifying the consistency of the existing process … Ordinarily, such reviews should be conducted annually. Longer frequencies are acceptable if suitably justified.	This current text is more restrictive than 2009 text which allows for regular periodic or rolling quality reviews. Further, annual doesn't make sense for some products such as orphan drugs.	
1209	52	Presents a risk to consumer health	Presents an unacceptable and avoidable risk to consumer health.	Every drug presents some level of risk which would be generally recognized as unavoidable (adverse events that are inherent to product use). Assumption of risk is accepted when outweighed by the benefits of the treatment. Recalls are a mechanism to protect consumers from avoidable risks. Proposed wording is consistent with this idea.	
1303-1304	55	You must provide the contract acceptor with all information needed to carry out contracted operations correctly, according to the marketing authorization and any other legal requirements.	You must provide the contract acceptor with all product-related information needed to carry out contracted operations correctly, according to the marketing authorization and any other legal requirements. This includes information from other contract acceptors performing work associated with the product.	Additional text clarifies that the information to share is limited to product quality and the manufacturing process, and excludes commercial information. The additional sentence clarifies a situation where the contract giver is a virtual company having more than one contract acceptor. The information from these other contractual arrangements should be shared.	
1320-1324	56	Do not subcontract to a third party any of the work entrusted to you under contract without the contract giver's prior evaluation and written approval.	Work entrusted to you under contract may be subcontracted to a third party provided the contract giver provides an evaluation and written approval prior to any	Contract manufacturers work with many contract givers. Some of the contract givers require the contract acceptor to use certain suppliers. Many of	

		Arrangements made between you and any third party should ensure that information and knowledge—including from assessments of the suitability of the third party—are made available to the original contract giver.	work being performed by the subcontractor. Arrangements made between you and any third party prior to the contract agreement should be disclosed to the contract giver. The contract acceptor should ensure that information and knowledge—including from assessments of the suitability of the third party—are made available to the contract giver.	these arrangements might be in place before a new contract giver requests services. This new language would provide that contract acceptors disclose any subcontracting arrangements with the new contract giver.	
1325-1326	56	Do not make unauthorized changes (outside the terms of the contract) that may adversely affect the quality of the outsourced activities for the contract giver.	Ensure you have agreement with the contract giver(s) before implementing any changes (outside the terms of the contract) that may adversely affect the quality of the outsourced activities for the contract giver.	The contract acceptor should be able to make changes to their facility but these changes should be agreed to with the contract provider(s) and a determination made before the changes are made that there will be no adverse affect to any products.	
1358-1359	57	vi. a description of how complaints and information about potentially defective products received by the contract giver are (when applicable) handled and investigated by the contract acceptor (with results sent to the contract giver for review).	….(when applicable) handled and investigated by the contract acceptor (with results sent to the contract giver for review). The contract giver should inform the contract acceptor when the complaint investigation is complete.	The contract giver should formally acknowledge to the contract provider that their part of the investigation is complete. This will ensure that the complaint process is a closed loop between the contract provider and giver.	
1751	71	Text is missing from new version	Add in “The use of recycled or reprocessed primary packaging components is permitted only after a full evaluation of the risks involved, including any possible deleterious effects on product integrity. Specific provision is made for such a situation in the specifications.”	Provides manufacturing flexibility yet retains control of process. It’s unclear whether the intent is to eliminate the controls or to now preclude the use of recycled components.	
1765-1770	71-72	Identifying and choosing primary and printed packaging material vendors is an important operation. You should entrust this activity only to staff who have a particular and thorough knowledge of the materials and suppliers. Staff knowledge of materials should include an understanding of risk and the need to	Identifying and choosing primary and printed packaging material vendors is an important operation. You should entrust this activity only to staff with sufficient knowledge of the materials and suppliers. Staff knowledge of materials should be based on appropriate risk assessments and the need to avoid potential leachables (e.g. 2-mercaptobenzotiazole (MBT) in rubber stoppers for injectables, or methylbenzophenone and derivatives in label	Text amended for clarity. E.g., “particular” and “thorough” are subjective terms – intent is important here so suggest revising the language.	

		avoid potential leachables (e.g. 2- Good manufacturing practices guide for drug products (GUI-0001) Page 72 of 151 mercaptobenzotiazole (MBT) in rubber stoppers for injectables, or methylbenzophenone and derivatives in label adhesives).	adhesives).		
2041-2042	86	This includes information from all stages of the product lifecycle, and all records related to the quality of drug products.	This includes information from all stages of the product lifecycle, for all records related to the GMP quality of drug products.	Revised wording does not inadvertently draw early-stage R&D records into scope of GMPs.	