22 February 2019

Health Product Inspection and Licensing Division
Health Product Compliance Directorate
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via email

Dear Sir or Madam

The International Society for Pharmaceutical Engineering (ISPE) would like to submit comments on the Cleaning Validation Guide (GUI-0028).

ISPE is an individual membership Society of more than 18,500 professionals in 90-plus countries involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE membership. These comments were developed by a global ISPE team of subject matter experts.

We appreciate the opportunity to submit these comments for your consideration.

Sincerely,

John E. Bournas
CEO & President, ISPE

Health Canada Santé Canada

Comment Form

Optional Contact Information:

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

Cleaning Validation Guide GUI-0028

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

Name:
email:
Table 1: Comments – GUI-0028 : Cleaning Validation Guide

Section	Page Number	Current Text	Proposed Revision or Comments	Rationale
Section 5.2	8	Technical Measures Include, vii: Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools.	vii. harder to clean (e.g. filters or polymers) add new line "viii – Reducing the number of harder to clean surfaces such as polymers"	Polymers also are not easy to clean or not to validate their surface due to their rough surface structure
Section 5.2	8	Suggested addition	Add "xiv. Prevent surface damage during storage or cleaning mechanical actions."	Damaged surfaces can`t be cleaned to a validated cleaning limit
Section 7	11	Step 3 On going monitoring	In addition to monitoring the cleaning process, ongoing monitoring should also consider equipment condition monitoring such as surface qualities and damage	Polymers and stainless-steel surfaces age after a period of time or damaged during processing or cleaning. Older and damaged surfaces do have an impact of the cleanability.
Section 7	11	Cleaning verification refers to the actual assessment of equipment cleanliness and is used throughout the cleaning lifecycle approach.	Cleaning verification refers to the actual assessment of equipment cleanliness and is used throughout the cleaning lifecycle approach. However, cleaning verification is not a substitute for cleaning process qualification. If cleaning verification is to be pursued long-term without an appropriate cleaning process qualification, an appropriate scientific rationale should be available.	Cleaning verification is commonly misused where cleaning is "checked" before equipment is used, but where systemic failures in the cleaning process are not addressed holistically. This can result in a process that is not well controlled and is counter to the principle of building quality into the process. Additional language or a precaution is appropriate at this point.

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Section 7	11	Cleaning verification	…scientifically set MACO or for non-product contact surfaces according table 1 of the PDA Letter "Isolator Surfaces and Contamination Risk to Personnel" for GMP and Occupational Safety (attached).	Cleaning verification Non-product contact surfaces can have an impact on product quality especially in aseptic Fill & finish as those are close to open containers and surface contamination close to open containers can contaminate the final dose in the container like vial or syringe
Section 7	11	Cleaning validation refers to the overall validation program, from the development stage all the way through the ongoing monitoring stage.	Is it correct to say that cleaning verification and cleaning qualification process are part of cleaning validation? If so, adding this statement would be useful for the readers and provides better clarity.	Cleaning verification process is enough to support the data during development stage of the product.
Section 7.1.1	12-13	NA	One verification run is recommended to confirm expected results for new product family.	Guards against a mistake in rationale, recipe configuration, etc.
Section 7.1.2	13	a. Having adequately detailed instructions and establishing range/value of the critical process parameters: i. sequence of the cleaning steps ii. cleaning agent to be used and its concentration iii. cleaning agent application means (e.g. soaking or scrubbing) iv. contact time v. temperature of the cleaning solutions and rinses vi. rinsing techniques (soaking, flushing, times and pressures)	New: Vii Recovery rates based on the sampling method	Clarification The recovery rate should be better than 70% and based on the PDE even higher to demonstrate effectiveness of cleaning. Reference attached PDA letter.

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Section 7.2	14	You may begin a cleaning process qualification study once you have a fully defined cleaning process. This can be before the start of commercial production if equipment, batch sizes, and formulation/operating parameters are not subject to change.	It would be helpful if the guideline were to laydown certain rules for choosing a product for cleaning validation. Very often it is expected of the manufacturer to validate the cleaning of each and every product manufactured in the facility which very often is not feasible. We propose to identify the worst-case product for cleaning validation based on its solubility in the cleaning solvent and its toxicity (i.e. the PDE). The product which is least soluble in the cleaning solvent and which has the least PDE should be chosen for cleaning validation. We propose such explanation be included in the guideline.	It may not be always possible to perform cleaning qualification on all products produced in a facility. Choosing a worst-case product based on, for example, its solubility, strength as a part of risk assessment could be essential.
Section 7.2.3	14	none	New J. Hard to reach sampling points	Hard to reach sampling points can be hidden purveyors of residuals or contamination. Especially, if the vessels are not dedicated to a singular product.
Section 7.2.b	15	a. You may also incorporate worst case condition challenge testing (e.g. minimum detergent contact time, minimum or maximum temperatures and minimum rinse time/volume/pressure). Worst case challenge testing is of particular importance when manual cleaning systems are employed.	Worst case challenge testing should be executed as part of CV stage 1 – cleaning process design.	If a reduction in detergent concentration is used during CV runs, you are not proving you can effectively rinse / remove the regular quantity of detergent. Also, mistakes can be made in re-configuring recipes and you would not be validating the actual recipe used for routine cleaning.
Section 7.3	16	b. highly potent and toxic products	Include a definition for potent and toxic products	Defining a potent and toxic product could become a subjective interpretation.
Section 7.3.1	17	2. Changes that may potentially impact cleaning processes include:	New i. Surface quality changes likes scratches or damages.	Surface quality have an important impact for the cleaning results.

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Section 8.2	18	Companies should also ensure that the selectivity of the analytical method has been established in relation to potential degradants formed during the cleaning process.	When using a specific method, companies should also ensure that the selectivity of the analytical method has been established in relation to potential degradants formed during the cleaning process, and where required, appropriate limits are established for those degradants (see Section 10).	This sentence does not apply to non-specific methods. Further, the establishment of selectivity is only the beginning of what needs to be done if there are known degradants.
Section 8.3	18	3. Conduct recovery studies for all cleaning analytical and sampling methods:	3. Conduct recovery studies for all cleaning analytical and all sampling methods:	Suggest that the modifier "ALL" is added before sampling methods so that the expectation for recovery studies for both swab and rinse is clear.
Section 8.3	18	- Conduct recovery studies for all applicable product contact surfaces.	- Conduct recovery studies for all applicable product contact materials ~~surfaces~~, grouping materials of construction with appropriate rationales, where necessary.	It is neither practical nor possible to conduct recovery studies on all materials of construction. Grouping for this purpose has been in use by the industry for decades, with supporting data. Worst case recovery for the group is then used for all members of the group. Furthermore, labelling them as "surfaces" adds a complicating factor of surface finish not just materials.
Section 8.3	18	- Establish recovery correlation coefficients for each product contacting surfaces	- Establish recovery factors ~~correlation coefficients~~ for each product contacting material ~~surfaces~~	"Correlation coefficients" have a meaning in statistics that is not intended here. Please change to "factor" or "correction factor". Also change from "surface" to "material" in accordance with the prior comment.
Section 8.3 Info Box	19	Informational Box: Note: It is recommended that investigations into failures quantify the exact amount of the analyte under question and attempt to quantify any other sources of potential contamination.	Note: It is recommended that investigations into failures quantify the exact amount of the analyte under question and attempt to identify and quantify any other sources of potential contamination in order to assess their safety as potential carry-over.	The statement as written was not clarified as to whether it was intended for specific or non-specific methods. The first half of the sentence could apply equally to both, however the end of the sentence with "quantify" only, is inappropriate to non-specific methods and for specific methods, as is the case with "unknown peaks" the identity of the material is critical to being able to assess whether the quantity of material identified is appropriate or not.

Section	Page Number	Current Text	Proposed Revision or Comments	Rationale
Section 9.1	19	Omission on surface anomalies	Rouge is the most common type of surface anomaly discovered during visual inspection and should be treated separately than cleaning and should be investigated.	Use of caustic solution can cause rouging after time. An acidic rinse step is sometimes recommended to remediate this. Rouge is generally considered a preventive maintenance problem. PDA Technical report No.49.
Section 9.1	19	Visual inspection is a qualitative method to determine equipment cleanliness and involves the inspection of equipment for the absence of visible residue and foreign material. This is an important element of any cleaning program	Visual inspection is a non-qualitative and non- quantitative method…	Visual clean is better than 4ug/cm2 and for high potent or toxic substances not suitable. The whole chapter should be new defined as visual cleaning is not appropriate for a lot of products and if surfaces are damaged an uncontrolled risk occur.
9.1.1	19	Conduct spiking studies to determine the concentration at which most active ingredients are visible. This is an important consideration as visual inspection alone may not be adequate if the product is not visible at concentration levels that may pose a risk to patient safety (e.g. below the calculated MACO value).	Conduct spiking studies to determine the concentration at which most active ingredients are visible when relying on visual inspection as a primary method to demonstrate cleanliness..(e.g. below the calculated MACO value).	Spiking studies are only needed when no analytical methods are used. The statement as written would appear to mandate these studies for all materials and all materials of construction which is not required nor practical, especially in cases where visual inspection is only a secondary technique. The industry has typically only required this when the visual inspection was intended to be a critical method in their approach.

Section	Page Number	Current Text	Proposed Revision or Comments	Rationale
Section 9.2.2 and 9.2.3	20 and 21	None – Missing content	9.2.2 → Specify the rinse solution to be used and the quantity per unit area in order to properly quantify rinse results 9.2.3 → Specify the placebo material to be used and the quantity per unit area in order to properly quantify analytical results	Similar statement appears under swab 9.2.1.b. however it was missing under rinse and placebo. The dilution that is applied when large volumes are used for rinsing the equipment can quickly make residues fall below the limit of quantitation unless the rinse or placebo to surface area are strictly known and controlled.
Section 10 Important Box	21	None – Missing content	Add text to the Important to Know Box as follows: Non-specific test methods still require the use of a toxicologically appropriate limit.	The proliferation in the belief of adequate "safety" when using limits such as 500 ppb or conductivity values associated with compendial methods for water require that this statement be present.
Section 10.3	21	In addition, companies should consider employing traditional measures of cleaning (1/1000th of a dose and 10 ppm) as alert limits. Cleaning procedures have traditionally been established as being able to meet such limits.	Please consider deleting this paragraph	Generally, regulators across the world have stopped accepting the 1/1000th dose and 10 PPM criteria.
Section 10.4.a	21	a. recommended that residue limits be set for each individual piece of equipment.	Please delete statement or include examples of where the limits would be different for pieces of equipment in the same train.	This is a difficult concept to understand without examples of where a full batch does not all proceed to the next piece of equipment at the same time.
Section 11	22	3. Areas of special concern for microbiological considerations include: a. Clean hold times: Establish a maximum period of time that cleaned equipment can sit after storage before use without re-cleaning or re-sanitization. Demonstrate that the maximum allowable clean hold time storage does not result in microbial proliferation. b. Ensure that microbiological assessments are considered (per risk management	Additional e. Ensure that surfaces are not damaged or provide hidden areas where microbiological growth is possible	Surfaces damage like scratches can be an area of microbiological growth.

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		principles) when assessing maximum campaign lengths. c. Ensure that stagnant water is not allowed to remain in equipment after cleaning or use. Equipment should be dried before use or storage. d. Ensure that procedures are established for the appropriate handling of hoses. Hoses (e.g. purified water hoses) are a known area of potential microbial contamination. 4. Ensure that microbiological limits are scientifically justified.		
Section 12	22	For long transfer lines, consider removable sections to evaluate the efficacy…	For long transfer lines, design to flood the pipes and to obtain turbulent flow rate should be evaluated to guarantee cleaning efficacy…	Having removal sections for a sterile transfer line will increase the number of connections in the sterile boundary which increases risk of leaks and reduces the sterility assurance level Designing the cleaning cycle to guarantee fluid contact to all the surfaces to clean with turbulent flow rate is the best practice. For same cleaning cycles parameter with higher turbulence (more mechanical action) for the transfer pipe conditions, compared to other surfaces which are visibly inspected or swabbed for cleanliness (tank surfaces), the obtained results allow to demonstrate the cleaning efficacy for the pipe.
Section 12.1 Info Box	23	You may use purified water as the last rinse for product-contact equipment used to	You may use purified water as the last rinse for product-contact equipment used to manufacture non-sterile	While sterile ophthalmic products *may* use Purified Water in their formulation this presupposes that there are no products that might be produced with WFI.

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		manufacture non-sterile products or sterile products for ophthalmic use.	products or sterile products for ophthalmic use that use Purified Water for their formulation.	Since these are simply illustrations of the prior point that the grade of water should match the formulation, it would be appropriate to clarify this should also match.
Section 12.3	23	Dedicated equipment may be required for the production of some products. Examples of reasons you may decide to dedicate equipment include potent/toxic products, the potential for allergic reactions and/or sensitization and products which are extremely difficult to clean. Product dedication may also be appropriate, in some instances, for Cleaning validation guide (GUI-0028) Page 24 of 31 Equipment parts which are either difficult to clean, sample or visually inspect (especially for higher risk products). Use QRM	Additionally:…… the potential for allergic reactions and/or sensitization and products which are extremely difficult to clean or for materials e.g. silicon where the surface quality can make validation very difficult.	Rough surfaces from Polymers, Silicon or other materials cannot be validated for cleaning.
Section 12.3	23/24	Product dedication may also be appropriate, in some instances, for equipment parts which are either difficult to clean, sample or visually inspect (especially for higher risk products). Use QRM principles to determine cleaning validation requirements and MACO values. Areas of concern with dedicated equipment include: a. microbiological considerations b. cleaning agent removal c. potential product degradants and process impurities	Please delete bullet point or clarify the requirements for visual inspection when using dedicated equipment.	The current text contains a contradiction: the first paragraph states, that dedicated equipment may be appropriate if equipment parts are difficult to visually inspect and bullet point d of the areas of concern with dedicated equipment states, that the effectiveness of the visual inspection should be considered (when using dedicated equipment).

Section	Page Number	Current Text	Proposed Revision or Comments	Rationale
		d. the effectiveness of visual inspection		
Section 12.3	24	Dedication equipment Use QRM principles to determine cleaning validation requirements and MACO values.	Dedication equipment Use QRM principles to determine cleaning validation requirements and MACO values for detergent.	MACO limit cannot be calculated on API but for detergent since only a sole drug is running the equipment.
Section 14.8	27	Calculations may also be based on toxicity values. In such cases, the relevant toxicity data is not the toxicity of the protein in question, but of the degraded fragments, which is often assumed to be less of a safety concern (but such studies are normally not performed).	Calculations may also be based on toxicity values. In such cases, the relevant toxicity data is not the toxicity of the protein in question, but of the degraded fragments, which is often assumed to be less of a safety concern (but such studies are normally not performed). Rationales for a given approach to limits and any risk-based assumptions made must be defined.	This statement has no conclusion about what guidance you would offer to be compliant in this situation. Suggest closing this loop with this or an analogous statement of intent.
Section 14	27 Line 8	Omission on TOC limits in biotechnology manufacturing	TOC limits upstream are typically less stringent	Product cleaned from the equipment surfaces has more extraneous materials (such as cellular materials), PDA Technical report No.49.
Section 13 and 14	24, 25, 26 and 27	All text	See Comment	There is a lack of parallelism in this section that could lead to misunderstandings of the intended approach. For example: 1. biologics calls out the grouping of equipment and products (without anything new from the front of the document other than examples) and API is silent on this, potentially leading to the conclusion that it is not permitted in API. 2. Biologics under point 7 describes degradation; API does not refer to synthetic changes in the molecule or any degradants that might be residual to its purification process 3. Biologics calls out upstream (bulk manufacture) vs. downstream (purification) in terms of limits

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				and residue identification; API also has these same issues across the synthesis. 4. API calls out specific equipment (i.e., overhead condensers) and cleaning challenges but there are no equivalents in biologics section for items such as resin, filtration membranes and such which intersect with process validation issues like lifetime studies The suggestion is to look at what is and is not addressed and make these sections more parallel in terms of topics.
Section 14.2	25	basses	bases	Bases is spelled incorrectly.
1 Section 4.5 Info Box	26	closed	closely	Incorrect word
Appendix B	30	References Laws and regulations	Parenteral Drug Association PDA Letter November 6 2017, "Isolator Surfaces and Contamination Risk to Personnel"	Covers cleaning limits for non- product contact surfaces for GMP and Occupational Safety