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16 June 2021

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

Re: GUI-0074: Process validation: Terminal sterilization processes for drugs

Dear Madam or Sir:

PDA appreciates the opportunity to comment on Health Canada's draft guidance GUI-0074 *Process validation: Terminal sterilization processes for drugs*. PDA supports Health Canada's efforts to update and combine the existing guidances on process validation for sterilization procedures. In the attached comment table, PDA offers specific suggestions to strengthen technical content through alignment with best practices for sterilization and to improve clarity.

PDA strongly recommends that Health Canada review the document for alignment with current internationally recognized standards. Inconsistency between this regulatory guidance and current global standards and practices can not only create confusion for global users, but also can lead entities to use methods that are no longer recognized as contemporary practice.

- The more comprehensive ISO 14937 approach would be a better choice for this document than the three-phase validation lifecycle approach that is currently described. The ISO 14937 approach is widely adaptable to current and future sterilization modalities and includes sterilizing agent characterization, process and equipment characterization, product definition, process definition, validation, routine monitoring, maintenance of process effectiveness.
- PDA recommends that Health Canada revise the document to refer to current and internationally recognized terms and definitions wherever possible to avoid confusion (e.g., ISO 11139:2018) and update citations to refer to the most current versions of documents or to refer to the "current version."
- PDA is especially concerned that the draft guidance references sterilization design/development/qualification approaches that lack sufficient scientific support and are no longer recognized by international standards such as ISO 11137, including the 25 kGy overkill approach and the use of a biological indicator (BI) approach with radiation sterilization.
- Since the development and validation approaches are significantly different between radiation (bioburden-based process design without BIs) and moist heat/EO (overkill/combined BI bioburden process with BIs), we believe that additional

efficiency and clarity could be gained by providing separate standards for radiation and moist heat/EO.

PDA also recommends that Health Canada review the document carefully for terms that could lead to confusion. For example, while the term “dose” has been consistently and exclusively applied to sterilization with radiation, this document utilizes this term broadly for moist heat and ethylene oxide sterilization modalities as well.

PDA is concerned that the document as written will limit the potential for many drugs to utilize terminal sterilization in the future, especially with its focus on the use of overkill validation methods. PDA strongly recommends that Health Canada consider collaboration with sterilization experts from PDA and other industry organizations in the continued development of this guidance. For instance, PDA can assemble teams of experts on specific topics and can raise topics through workshops, webinars, and conferences. Like you, we are committed to advancing science to support product quality and patient safety, and the topics covered by this guidance are of special interest throughout our organization.

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 global experts in sterilization for parenteral products on behalf of PDA’s Science 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: Glenn Wright, PDA; Janie Miller, PDA

Health Canada Santé Canada

May 3, 2021

SUBJECT: Consultation Comment Form

Dear Stakeholder,

Health Canada is conducting a consultation on the following draft guidance document. The consultation will be open for 30 days from May 3, 2021 to June 2, 2021.

- GUI-0074: Process validation: Terminal sterilization processes for drugs

Please email your comments to HPIL-Consultation-IPSOP@hc-sc.gc.ca, using this form. All comments will be considered in the finalization of the document. The 30-day consultation period is from May 3, 2021 to June 2, 2021, 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	
Title	
Organization/Company	Parenteral Drug Association
Address	4350 East West Hwy, Suite 600
City	Bethesda
Province	MD
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.

GUI-0074: Process validation: Terminal sterilization processes for drugs

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
General Comments			**We recommend the use of current and internationally recognized terms/definitions wherever possible to avoid confusion (e.g., ISO 11139:2018). Similarly, some terms are misused which could also lead to confusion. For example, the term "dose" has been consistently and exclusively applied to sterilization with radiation, while this document utilizes this term broadly for moist heat and ethylene oxide (EO) sterilization modalities as well.** **Several of the citations in the in the body and Appendix B of the document include references to documents and associated practices that are out of date. For example, the current ISO revision for establishing the sterilization dose is ISO 11137-2:2015. If possible, Health Canada might replace the issue dates/version numbers with "current version" to maintain currency even as the referenced documents are revised (e.g., "ISO 11137-2 current version").** **Additionally, the document continues to recognize sterilization design/development/qualification approaches such as the 25 kGy overkill approach and the use of a biological indicator approach with radiation which lack sufficient scientific support and are no longer recognized by international standards such as ISO 11137.**	
			The document specifies a three-phase lifecycle approach which is not consistent with the more comprehensive ISO 14937 approach which is widely adaptable to current and future sterilization modalities and includes: sterilizing agent characterization, process and equipment	

			characterization, product definition, process definition, validation, routine monitoring, maintenance of process effectiveness. However, sterilizing agent characterization would not be applicable to the three processes described as these are well understood and have a long history of successful use.	
Section 4. First Information Box	8	Terminal Sterilization Definition:	Although the definition may be correct according to PICS, is there an opportunity to utilize an SAL different than 10^-6?	See ISO 19930:2017, *Guidance on aspects of a risk-based approach to assuring sterility of terminally sterilized, single-use health care product that is unable to withstand processing to achieve maximally a sterility assurance level of 10-6*
Section 4. Second Information Box	8	It is important to track the resistance as well as the number of organisms to assure that the terminal sterilization parameters continue to provide the required sterility assurance level (SAL).	For bioburden-based processes, it is important to monitor and assess the resistance as well as the number of organisms to assure that the terminal sterilization parameters continue to provide the required sterility assurance level (SAL).	Overkill processes are not based on product bioburden and utilize BI population and resistance levels that significantly exceed that for the product bioburden which obviates the need for product bioburden with these process types. Bioburden population monitoring and assessment should be performed.
Title, General considerations	9		This section attempts to consider the content of sections dealing with process and product definition (6.7 and 8) in the ISO 14937 standards but it does not consider all critical aspects.	See broad comment above with recommendation for use of ISO 14937 framework including product definition section.
Section 6. Information box	9	The goal, when manufacturing sterile drugs, is to control the pre-sterilization bioburden to an appropriate level. It is important…	A section to address product definition should be added.	This is an essential component of overall process development but is not typically considered a component of sterilization process validation. Sterilization process validation assumes that the bioburden is controlled and understood at an earlier stage. Without knowing the bioburden the sterilization process cannot be designed, developed, and validated.
Item 2.	10	Conduct studies to determine bioburden in the materials to be sterilized. These studies should also	This content should be moved to the new product definition section that we recommend adding, and updated as follows: Conduct studies to determine bioburden in the materials to be sterilized. For products	This content should be moved to the recommended product definition section. Process hold times and partial or interrupted sterilization cycles will not

		include evaluation of the impact of hold times as well as partial or interrupted cycles on the bioburden.	that promote the growth of microorganisms, these studies should include the impact of process hold times as well as partial or interrupted sterilization cycles on the bioburden.	have unfavorable impact on product bioburden for products that do not support the growth of microorganisms.
Item 1. at bottom of page	10	The overkill method is used when the product/material can withstand prolonged exposure to the sterilization process without adversely affecting the quality of the product/material.	The overkill method may be used when the product/material can withstand prolonged exposure to the sterilization process without adversely affecting the quality of the product/material over the life of the product.	The current language implies that an overkill cycle is required when possible. However, other validation approaches (e.g., bioburden based) may be more applicable depending on the sterilization process selected and the potential for impact on the product/material over the life of the product.
Item 1. at bottom of page	10	A cycle designed with the overkill approach can be defined as a process that is sufficient to provide at least a 12 log reduction of microorganisms having a minimum D-value of 1 minute.	A moist heat or EO cycle designed with the overkill approach can be defined as a process that is sufficient to provide at least a 12 log reduction of microorganisms having a minimum specified D-value.	This section fails to indicate specific and exclusive applicability to moist heat and EO sterilization which, unlike radiation, includes the use the overkill approach and use of the term "cycle". As initially written, the description of overkill is specific to moist heat and is not applicable to EO sterilization where the BI D-value used for overkill is typically greater than 1 minute and is determined based on exposure to critical sterilization process conditions (e.g., gas concentration, temperature and/or and RH).
Item 2.	11	The probability of survival approach is used…	The product specific or combined BI bioburden approach…	All sterilization cycle design approaches are based on probability of survival. The recommended revision includes terms for this design approach that are well recognized in ISO and PDA *Technical Report 1: Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control.*
Item 2.a.	11	The probability of survival is determined…	Update in consideration of Rationale provided in next column.	The use of a BI is not indicated in this section. Due to lack of applicability and use by the industry, it is recommended that this section be modified to cover the commonly used Product

				Specific/Combined BI Bioburden. It is not clear if this is meant to be a purely bioburden-based cycle design approach. Please consult ISO 14937 for general detail on the combined biological indicator/bioburden method or PDA TR No. 1, section 4.1.1.2, which can be used to provide details on the use of the product specific/combined BI bioburden approach with moist heat sterilization.
Item 4.	12	Complete the validation of analytical methods…		Need to clarify the specific analytical methods including meaning and application.
Exclamation box	12	… you can use physical/chemical indicators to distinguish sterile from non-sterile goods. These devices indicate adequacy of the sterilization conditions by a visible change, but do not indicate that the load is sterile.	…you can use physical/chemical indicators or validated track and trace systems to distinguish processed and unprocessed goods. These devices indicate exposure to certain sterilization conditions by a visible change, but do not indicate that the load is sterile.	Validated product tracking and control systems are also capable of distinguishing between processed and unprocessed product. Additionally, chemical indicators are only capably of providing indication of exposure to a thermal process and are not capable of reliably distinguishing between sterile and non-sterile goods or providing indication of adequacy of sterilization cycle conditions.
Item 1.	12	Calibrate sterilization indicators used in validation studies…	Confirm achievement of certified performance criteria from the approved supplier's certificate prior to use in validation studies…	It is only possible to calibrate or determine the performance of chemical indicators in resistometers. This is performed by chemical indicator suppliers and not by users.
Item 2. at bottom of page.	12	Test physical and chemical indicators to demonstrate adequate pre-determined response to both time and exposure.	Delete	Performance certification, including response to both time and exposure, is performed by chemical indicator suppliers and not users—see previous comment.
Item 3. at bottom of page.	12	Test biological indicators for viability and quantification of the challenge organism as well as for the time and exposure response. This applies to	Test biological and chemical indicators for viability and quantification of the challenge organisms for indicators obtained commercially. Biological indicators prepared in-house must also be tested for D-value, z-value (moist heat only) and survival/kill time.	BI suppliers provide a performance certificate for BI which obviates the need to test for D-value, z-value (moist heat only) and survival/kill time if population and purity have been confirmed by the user—see

		indicators either prepared in-house or obtained commercially.		previous comment. BIs prepared in-house require full performance testing by the user.
Microbiological performance qualification (MPQ) – biological challenge reduction studies	13	General Comment to Entire MPQ Section	This entire MPQ section needs to be rewritten for clarity. Many of these details are provided for each method later in this document; a significant portion of this section's content could be eliminated with reference to the MPQ sections discussed later.	This information is covered for each specific process and this summary information is confusing and not appropriate for all three methods discussed. For example, with radiation, neither the BI challenge specified in Table 1 nor the use of a microorganism as determined by sampling the environment is used to determine the sterilization process.
Item 5.	13	When qualifying commercial or in-house biological indicators, ensure the choice of media (pH, electrolytes, carbohydrates, etc.) and sample carriers (suspension in ampoules, paper strips, inoculated products and inoculation on solid carriers) are consistent with the materials used in the validation of the terminal sterilization process.	When qualifying commercial or in-house biological indicators, ensure the choice of media (pH, electrolytes, carbohydrates, etc.) and sample carriers (suspension in ampoules, paper strips, inoculated products and inoculation on solid carriers) are based on the BI supplier's recommendations and consistent with the materials used in the validation of the terminal sterilization process.	The choice of media would be that recommended by the manufacturer or known to be conducive to the growth of the microorganism used, not necessarily only consistent with materials used in the validation of the terminal sterilization process.
Item 2.	13	You may use a worst-case bioburden challenge using an appropriate organism as described in the table below. In all other cases, you should use the microorganism with the highest D-value occurring in the natural population (as determined by sampling the environment). You should have proper scientific justification available to support the use of the chosen organism.	You may use a worst-case bioburden challenge using an appropriate organism as described in the table below. You may also use an alternate BI organism that demonstrates a greater D-value than the product bioburden. In all other cases, you should use the microorganism with the highest D-value occurring in the natural bioburden population. You should have proper scientific justification available to support the use of the chosen organism.	The use of product bioburden could allow manufacturers to justify the use very low Fo cycles if the "natural population" has an inherently low D-value. It's also not clear if "sampling the environment" refers to product samples, samples obtained from the manufacturing environment, or both. The use of an alternate BI with resistance level that is greater than the product bioburden is also a valid approach and more conservative approach than using product bioburden. Additionally, resistant organisms to be used to challenge the sterilization process should be chosen

				based on the product bioburden and not the manufacturing environment as the latter is not directly representative of the product bioburden.
Item 3.	13	Assess the sterilization cycle by introducing a known quantity of specific microorganisms with established D-values…	For moist heat and EO processes, assess the sterilization cycle with a known quantity of challenge microorganisms (e.g., BI or product bioburden)…	In radiation sterilization, a known quantity of specific organisms are not introduced to assess the sterilization cycle—see ISO 11137 series of standards.
Table 1	14	Ionizing irradiation *Bacillus pumilus*	There is no recognized BI with Ionizing irradiation. ~~*Bacillus pumilus*~~ Use data derived from the inactivation of the microbial population in its natural state on product.	Radiation processes are validated based on product bioburden or on a standard distribution of resistant microorganisms. *Bacillus pumilus is not a valid BI and* has not been used as an indicator for radiation sterilization for a number of years, as it is not the most resistant organism to the sterilization method. It has also been removed from pharmacopeias.
Item 4.	14	Run positive controls for each lot of biological indicator tested with every load to verify the viability of the challenge organism.	Run positive controls for each lot of biological indicator tested with every load to verify the viability of the challenge organism and to ensure the recovery method is capable of detecting viable microorganisms.	Positive controls also confirm the detection capability of the recovery medium.
Item 1.	15	…allowed for an interruption.	…allowed for an interruption. Additionally, the effect of the process interruption should be assessed to evaluate the potential impact on sterilization cycle efficacy and product/packaging functionality.	The potential impact on cycle efficacy must also be considered with an interruption of the sterilization process.
Section 8	15	Whole section	See comments	The detail in this section seems to apply to liquid products only, but with requirements for physical steam quality which is applicable to porous hard goods. Consider inclusion of separate sections to address the unique sterilization aspects of porous hard goods and liquid loads since the considerations for these are much different. Is there another document to cover porous hard goods items that can be referenced?

Item 1. a., b. and c. top of page	16	a. requirements for purity and quality of steam b. Requirements for dryness, superheat, saturation and non-condensable gasses c. additives,…	a. Requirements for purity and quality (saturated steam processes only) steam. b. requirements for dryness, superheat, saturation and non-condensable gasses (saturated steam processes only) c. contaminants (including from additives),	Steam quality physical requirements are only applicable to saturated steam process and are not applicable to superheated waterspray air overpressure processes. Also, contaminants in steam are usually inorganic or organic in nature and can arise from the carryover of feedwater in the steam generator or from the surfaces of steam distribution systems. Inorganic contaminants such as cations and anions should be controlled and particular attention should be paid to possibility of heavy metal ions being present. Organic contaminants such as endotoxins can give rise to adverse reactions in patients.
Item 1.i.	16	The maximum quantity of each contaminant present in any liquid, gas, steam admitted to sterilizer chamber.	The maximum quantity of each contaminant present in any liquid, gas, steam admitted to the sterilizer chamber for product configurations that are unsealed or where there is potential contact with the product formulation or product fluid path.	This requirement is not applicable to sealed containers where there is no risk of exposure to the product formulation or fluid path.
Item 1.o.	17	the location and acceptance criteria for biological indicators (BIs) and chemical indicators (CIs)	If used, the location and acceptance criteria for biological indicators (BIs) and chemical indicators (CIs)	BIs would not be used for parametric release. It is not common to use BIs for liquid loads or porous hard good loads with the exception of development and qualification studies. If this section is referring to these study types, heat penetration and temperature distribution probes should be included.
Info box	17	Wrap your dry item to be sterilized (other than products in sealed containers) in a material that allows removal of air and penetration of steam, and prevents recontamination after sterilization. … All loaded items should be dry	Wrap your dry porous hard goods items to be sterilized (other than products in sealed containers) in a material that allows removal of air and penetration of steam, and prevents recontamination after sterilization. … All loaded items should be dry upon removal from the sterilizer. Load dryness should be confirmed by visual inspection (where possible) and with gravimetric analysis as a part of the sterilization process qualification and/or acceptance.	Additional clarification is needed regarding the process and requirements for visual inspection of components that may be wrapped in opaque materials. Visual inspection of the load may involve removing the sterile barrier to visually observe the sterilized materials, thus negating the steam sterilization process. It's also not clear if this applies

		upon removal from the sterilizer. Load dryness should be confirmed by visual inspection as a part of the sterilization process acceptance.		to terminally sterilized dry product or the sterilization of porous load equipment, materials, or container-closure components.
Item 1.e.	17	The purity and quality of steam (especially any requirements for dryness, superheat, saturation and non-condensable gases)	For saturated steam sterilization processes, the purity and quality of steam (especially any requirements for dryness, superheat, saturation and non-condensable gases)	Steam Quality testing is not applicable to superheated waterspray processes with air overpressure.
Top of page	18	You must include an evaluation of both the empty chamber and the loaded chamber in these studies.	You can include an evaluation of both the empty chamber and the loaded chamber in these studies, supported by a risk assessment.	The risk assessment could include an evaluation for the necessity of empty chamber temperature distribution vs. loaded chamber based on historical data or if one study type gives more useful information over the other.
Item 3.	18	This should consist of runs using the maximum and minimum cycle times and temperatures specified for the equipment.	Delete	It is not necessary to include the maximum and minimum cycle times and temperatures for empty chamber studies (if performed). The use of nominal cycle times and temperatures is acceptable for empty chamber studies.
Items 5. and 6.	20	5. Monitor heat delivered to the slowest heating unit of the load. Use this data to calculate the minimum lethality (F_0 value) of the sterilization process. See Appendix C for more information regarding D-value and F_0 value. 6. Once you have identified the slowest heating units of the load, perform replicate runs to verify that the desired minimum process F_0 value can be achieved consistently throughout the load. Determine the number of required runs using a	5. Monitor heat delivered to the load including the slowest to heat items if these are present. Use this data to evaluate the achievement of minimum lethality (F_0 value) requirements. See Appendix C for more information regarding D-value and F_0 value. 6. ~~Once you have identified the slowest heating units of the load,~~ Perform replicate runs to verify that the desired minimum process F_0 value can be achieved consistently throughout the load. Determine the number of required runs using a quality risk management approach. The process is considered acceptable once such consistency in the achievement of minimum lethality has been adequately established.	Not all sterilizers and loading configurations have a consistent reproducible cold spot or a slowest to heat item within a load.

		quality risk management approach. The process is considered acceptable once such consistency in lethality has been adequately established.		
Item 2.	21	It is important that your initial product/material qualification tests the product/material using widely separated radiation doses.	It is important that your product/material qualification tests the product/material using the DmaxT considered to be worst case with respect to product functionality. The worst case product/material qualification dose may not always be the highest dose (e.g., complex cross-linking effects).	This section is too prescriptive with the requirement for widely separated radiation doses. It is most efficient and valid to qualify the DmaxT based on MSD/DminP and upper level of dose range. Due to some unique material properties such as cross-linking of polymers which may be a favorable condition for some products, the highest dose may not always be the worst case dose.
Info Box	22	Electron beam generators can deliver the same dose in a fraction of a second to a very small volume of product.	Electron beam generators (including the application of X-rays) can deliver the same dose in a fraction of a second to a very small volume of product.	Include reference to X-rays
Bottom of page	22	As a result, you must validate each source of radiation separately for a product/material.	As a result, you must evaluate the potential product/material effects (and any microbiological effects) prior to adopting an alternate radiation source, you must:	It is possible to transfer products from one radiation source to another without running a complete validation, depending on radiation modality and ability of the irradiator to deliver a dose equal to or greater than the established minimum sterilization dose without exceeding the maximum dose.
Item 1.	23	Overkill Method	Delete this paragraph.	There is no valid overkill approach for radiation and 25 kGy is not always capable of providing a 10^{-6} SAL to all products.
Item 2.	23	The result is a treatment dose that is tailored to the actual need (bioburden), which is less than the very high 25 kGY.	The result is a treatment dose that is tailored to the actual need (bioburden), which may be less than the very high 25 kGY.	Depending upon bioburden population, some minimum radiation sterilization doses may exceed 25 kGy—see previous comment.
Item 3.	23	The species-specific bioburden approach relates the radiation dose delivered to the most resistant	The species-specific bioburden approach relates the radiation dose delivered to the most resistant organism in the bioburden population ~~found in the manufacturing area and~~ on the product/material.	The radiation dose is based on product bioburden, not manufacturing area environmental monitoring.

		organism in the bioburden population found in the manufacturing area and on the product/material.		
Info Box	24	ISO 11137-1:2006, ISO 11137-2:2013, ISO 11137-3:2017	Change date/year reference to current version	Listing of year is not the current revision including amendments and reaffirmations.
Bullets at bottom of page	24	Examples of instruments: …	Add bullet: • calorimeters	Aluminum calorimeters can be used to measure radiation energy deposition in the delivery of dose in E-Beam processing and these are also calibrated.
Item 5.	25	Perform dose distribution studies for each product/material-loading configuration and each product/material size.	Perform dose distribution studies for each product/material-loading configuration and each product/material size. Products can also be placed into processing categories, where the dose distribution studies would be performed for the processing category.	Dose distribution studies should be performed for processing categories and not necessarily each product.
Section 10	26	… moisture or heat sensitive and cannot be sterilized by steam sterilization.	… moisture, heat, or radiation sensitive and cannot be sterilized by moist heat or ionizing radiation sterilization	Besides heat and moisture, some products/materials are also sensitive to radiation where EO should always be considered the last option for terminal sterilization.
Item 3.a.	27	using non-porous materials	using non-permeable materials/configurations	Porosity is not necessarily a consideration for delivery of EO sterilization efficacy whereas permeability of the item or packaging should be considered.
Item 3.e.	27	Using pressure relief valves, stopcocks, manifolds or cotton plugs that restrict EO penetration	Using pressure relief valves, stopcocks, manifolds, cotton plugs or occluded spaces including closed containers (e.g., vials, ampules) that restrict or prevent EO penetration.	Closed containers represent occluded areas where penetration of EO is prevented.
Item 4.c.	28	… and ethylene glycol (EG) …	Remove reference to EG	EG has been removed from ISO 10993-7, because if EO residues are acceptable, EG levels are acceptable – EO is the limiting reagent in the by product formation of EG.

Item 1.	28	• air washes and air flow	• Air/nitrogen washes ~~and air flow~~	From ISO 11135: Recirculation velocity should be specified when assessing product residual levels. Recirculation velocity is not the same as air flow.
3rd bullet in second Info Box	29	Gas concentration: At higher ethylene oxide (EO) levels, the sterilization process is more effective and requires a shorter dwell time. As the EO gas concentration increases from e.g. 50 to 500 mg/L, the inactivation rate increases.	Remove "e.g., 50 to 500 mg/L"	Remove "e.g., 50 to 500 mg/L" unless a formal reference can be cited. Some caution about this statement is needed, due the industry effort to reduce EO gas concentrations and thus emissions. Some contract sterilizers are requiring cycles to run at <400mg/L wherever possible and these processes have been supported by successful validation activities.
Item 1.	30	The exposure time is then doubled to provide the overkill sterilization process.	The exposure time that has demonstrated to deliver complete BI inactivation is doubled to provide the overkill sterilization process.	Provided clarification details for EO half cycle. Also, is the EO cycle calculation approach not recognized by Health Canada? If it is recognized, this approach should be included in this document as its use has increased across the globe in the effort to reduce the amount of EO gas used.
Item 2.	30	Biological indicator (BI) cycle is only used in cases where the product's/material's bioburden before ethylene oxide (EO) treatment can be proven to be consistent.	Biological indicator (BI)/bioburden cycle is ~~only~~ used in cases where the product's/material's bioburden before ethylene oxide (EO) treatment ~~can be proven to be~~ is relatively consistent over time and less resistant than the biological indicator.	This refers to the BI/bioburden based cycle (see ISO 11135 Annex A), and the statement that the bioburden can be proven to be consistent should be clarified. ISO 11135 states: "relatively consistent over time."
Item 3.	30	Absolute bioburden cycle: This cycle is used when the product bioburden resistance to the ethylene oxide (EO) process is very high….	This cycle can be used when the product bioburden resistance to the ethylene oxide (EO) process is very high…. <u>It also can be used when the bioburden is very low in resistance and relatively consistent, allowing an optimized sterilization cycle.</u>	This approach can also be used when the bioburden is very low in resistance, thus allowing the use of a more optimized sterilization cycle.
Item 3.	31	The more resistant organisms are isolated and used in ethylene oxide (EO) cycle development studies, and an inactivation curve is established.	~~The more resistant organisms are isolated and~~ Representative product is used in ethylene oxide (EO) cycle development studies, and an inactivation curve is established for the product bioburden to project the exposure time required to achieve the desired SAL. ~~The~~	The absolute bioburden approach can be performed using product samples, not necessarily isolating organisms and inoculating them onto product. In fact, it is not desirable to use liquid inoculum as this

		The inoculums should consist of the bioburden average plus three standard deviations (3σ).	~~inoculums should consist of the bioburden average plus three standard deviations (3σ).~~	may change the natural bioburden resistance and with gaseous sterilization processes artifacts (e.g., stacking of spores) may be generated that can overestimate the actual/natural resistance.
Info Box	32	VHP discussion	Delete this info box.	This section is entitled EO Sterilization and the limited mention of the VHP modality without further information could create confusion with users. There are also other gaseous terminal sterilization modalities (e.g., NO_2, ClO_2, ozone, etc.) that are currently in use for terminal sterilization.
Item 5.	33	Document biological challenges when performed in routine process monitoring procedures.	Document biological challenges (unless parametric release is utilized) when performed in routine processing monitoring procedures.	Parametric release does not require the use of biological challenges nor the Test for Sterility.
Item 6.	33	Obtain samples from each batch of a drug for ongoing bioburden testing…	Bioburden testing requirements should be based on risk assessment including raw materials, manufacturing process controls and the sterilization cycle design/development approach.	The bioburden testing program should be risk-based where bioburden testing for each batch may not always be required (e.g., some overkill processes).
Item 1.	33	Re-validate the process at scheduled intervals, at least annually to ensure there has not been an undetected change in the product or process. Requalification should be performed using the same operational parameters and acceptance criteria as the original qualification runs.	~~Re-validate~~ Review the performance of the process (including product) and change control history at scheduled intervals, at least annually to ensure there has not been an undetected change in the product or process and determine the extent of requalification that is necessary. The outcome of the periodic review of the sterilization process, including the rationale for the decisions reached and the extent of changes made to the sterilization process, product or requalification requirements (if applicable), shall be documented.	Changed to align with ISO 11135 and 17655. "Requalification" will vary depending on the sterilization modality; radiation sterilization which is based on dose audits, do not technically follow the same parameters and acceptance criteria as the original qualification runs. For other modes of sterilization, changes may have been made that change the requalification requirements.
Middle of page	37	D_{121} – D-value of the BI at an exposure temperature of 121°C (Sterilization by Moist Heat)	D_{121} – D-value of a microorganism at an exposure temperature of 121°C (Sterilization by Moist Heat)	D_{121} value is also applicable to product bioburden.
Terms	35-42			Info Box at the bottom of Page 35 indicates that "These definitions explain how terms are used in this document." Accordingly, terms that are not

				utilized or referenced in this document should be removed from this section.