PDA Global Headquarters
Bethesda Towers
4350 East West Highway
Suite 200
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
www.pda.org

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Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Reference: Draft Guidance for Industry on Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes; Federal Dockets Management System Docket FDA-2008-D-0391

Dear Sir/Madam,

PDA is pleased to offer comments on the FDA Draft "Guidance for Industry on Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat 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 comments were prepared by a committee of experts with experience in parametric release of terminally sterilized moist heat drug products including members representing our Regulatory Affairs and Quality Committee and our Science Advisory Board. PDA appreciates the opportunity to offer comments on this Draft Guidance and wishes to thank FDA for the opportunity to do so.

PDA endorses the need to maintain regulatory guidance documents in a state that emphasizes current technology, science and best practices. We also acknowledge the effort made by FDA in the publication for comments of FDA's Draft "Guidance for Industry on Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes". PDA strongly supports the inclusion of a risk assessment of the potential for the production and release of non-sterile products as one of the primary criteria in the support of a parametric release program.

With regard to the draft guidance document on parametric release, we have provided detailed comments identified by line number and have included a supporting rationale in the accompanying table. The following is a brief overview of the major points that PDA believes are most important to highlight to strengthen this guidance document:

- Chemical, biological, and/or physical indicators which may be used as load monitors lack the sensitivity to confirm that all critical sterilization cycle parameters have been met. An appropriately designed, correctly executed and effectively monitored sterilization process should be sufficient to mitigate the necessity for a laboratory test to confirm sterility, including laboratory testing of chemical and/or biological load monitors.

- Inasmuch as load monitors only demonstrate that a sterilization cycle occurred and do not have the sensitivity to demonstrate that all critical parameters have been met, classification of indirect monitors as defined in ISO 11140 provides no risk mitigation and should not be recommended.
- With regard to the content of submissions for parametric release, the Draft Guidance seems to focus primarily on existing products and seems to exclude new products from parametric release. We believe that with a properly executed assessment to identify and mitigate the risk of producing a non-sterile unit, new products (those for which there is no prior history of release via the sterility test) should also be eligible for approval using parametric release.

Again, PDA appreciates the opportunity to comment on this draft guidance document and provides these recommendations for your consideration. PDA believes that these comments will clarify and strengthen the guidance document to better serve the needs of both regulators and industry.

We would be pleased to offer our expertise in a public discussion and/or meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,

Robert B. Myers
President, PDA

Enc: Detailed Comment Spreadsheet; v 4, 9-28-08

PDA Comments; Draft Guidance for Industry on Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes

September 2008

Line No.	Current Text	Proposed Change	Rationale
37 -40	However, you may find information relating to such topics in the Agency's guidance for industry on *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. [6, 7]	However, you may find information relating to such topics in the Agency's guidance for industry on *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, [6, 7] and in moist heat sterilization technical reports available from pharmaceutical industry professional associations, such as PDA Technical Report #1: *Validation of moist heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control*.	The reference provided is incomplete since it does not provide adequate detail regarding approaches for moist heat sterilization efficacy studies and qualifiction/validation practices. We recommend that moist heat sterilization technical reports developed by industry and regulators such as PDA Technical Report #1: *Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control* be referenced to provide detail regarding state of the art approaches and practices for moist heat sterilization programs.
75 - 82	The *sterilization load monitor*,[8] either in the form of a chemical indicator[9] or biological indicator, is included with each load to demonstrate that the sterilization cycle has occurred and the criteria for critical parameters have been met.	The *sterilization load monitor*[8.], in the form of a physical, chemical or biological indicator is included with each load to demonstrate that the validated sterilization cycle has occurred. The sterilization load monitor is placed in an appropriate position in the load, based on the evaluation of development and qualification data. The use of the sterilization load monitor only satisfies the CGMP requirement for a laboratory test when used in combination with a sterility assurance program that is in a demonstrated state of control.	Load monitors do not have the sensitivity to confirm that all critical sterilization cycle parameters have been met. They typically change color or BIs may be rendered sterile long before the validated sterilization process has been delivered. At best, they are qualitative measures that indicate some portion of the process has been delivered. Physical indicators may be used to demonstrate the achievement of one or more critical sterilization cycle parameters. The PDA appreciates the demonstrated

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			willingness of the agency to support the development of technology and sound scientific principals by proposing that some indication of appropriate processing (load monitor) satisfies the requirement in 21CFR211.167 for a "Laboratory Test". However, PDA believes that an appropriate, properly designed, correctly executed and effectively monitored sterilization process, as required for "parametric release" approval, in and of itself, should mitigate the necessity for a superfluous "laboratory test" including the sterilization load monitor. The evidence of sterility, provided by appropriate monitoring of the identified "critical" parameters in the sterilization process is superior to and obviates the need for a load monitor. PDA believes that the only potential use for sterilization load monitors might be as an enhancement to processed/non-processed product segregation which may not be required in a correctly designed and executed process. A requirement for sterilization load monitors, especially high level integrating systems (still less sensitive than the monitoring of all critical parameters) also would represent a significant additional cost in production without any enhancement in the quality of the sterile product and could lead to a reduced interest from industry regarding parametric release

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86	FDA conducts scientific evaluation of the parametric release program as part of a cooperative effort between the review staff, compliance staff, and field investigators to ensure the overall state of control of sterile processing of human and veterinary drug products.	FDA conducts scientific evaluation of the parametric release program as part of a cooperative effort between the review staff, compliance staff, and field investigators to ensure the overall state of control of **sterilization programs for** human and veterinary drug products.	The term "sterile processing" is typically used to describe aseptic processing. "**Sterilization programs**" is a more accurate term in this statement.
90	FDA has accepted the practice of parametric release for products terminally sterilized by moist heat since 1985.	FDA has accepted the practice of parametric release for **drug** products terminally sterilized by moist heat since 1985.	Devices have been approved by FDA prior to 1985.
108 - 111	A statement that describes how the risk assessment includes current control strategies for the terminal sterilization cycle, the risk that these strategies might fail to ensure sterility, and how prior manufacturing experience and knowledge were incorporated into the risk assessment should be provided in the application	A statement that describes how the risk assessment, prepared consistent with the principles of ICH Q9, includes current control strategies for the terminal sterilization **program**, the risk that these strategies might fail to ensure sterility, and how prior manufacturing experience and knowledge were incorporated into the risk assessment should be provided in the application.	Control strategy used as defined as ICH Q10. First use of the phrase control strategy should reference ICH Q10 in Section V. Reference to ICH Q9 provided to ensure clarity for risk assessment.
113	Control Strategy for the Terminal Sterilization Cycle	Control Strategy for the Terminal Sterilization Program	Inconsistent use of terms. Bullets in this section are broad programmatic requirements and not exclusively terminal sterilization cycle requirements.
133 - 136	A description of the microbiological monitoring plan for the product and components prior to terminal sterilization with emphasis on spore detection and heat resistance of bioburden in the product, or a statement that the plan has not changed since last approved and validated.	A description of the microbiological monitoring plan for the product and components prior to terminal sterilization with emphasis on spore detection and heat resistance of bioburden in the product (for only product-specific or bioburden based sterilization processes), or a statement that the plan has not changed since last approved and validated.	The draft as written does not address overkill cycles. For validated overkill sterilization processes, the microbiological monitoring plan does not need to have an "emphasis on spore detection and heat resistance of bioburden in the product."

Line No.	Current Text	Proposed Change	Rationale
145 - 146	We recommend that your risk assessment focus on the risk of failure to achieve sterility for each unit of every batch.	We recommend that your risk assessment focus on the risk of failure to achieve the minimum required Probability of a Non-sterile Unit (PNSU) for each unit of every batch.	Sterility is based on probability and is not an absolute term as reflected in the revised recommendation.
166 - 167	The application/supplement number(s), including approval date(s), of the submission(s) that provides for the current terminal sterilization cycle, as applicable.	The application/supplement number(s), including **a complete and detailed citation to any current terminal sterilization cycle, as applicable.**	The goal is to identify precisely where to find information referred to. In eCTD format, such descriptions of volumes and page numbers (as historically submitted) may not be relevant because documents submitted electronically and are searchable electronically by topic or key word.
179 - 180	…. there is a provision for resterilization. In such cases, issues of stability and container closure integrity also become relevant.	… there is a provision for reprocessing. In such cases, it should be demonstrated that reprocessing does not adversely affect product stability or container closure integrity	Product may not be sterile after initial processing; use of the term "reprocessing" is recommended. PDA believes that the intention of this statement regarding the relevance of stability and container closure integrity is properly reflected in the revised wording.
187 - 192	A description of the sterilization load monitor including indication of: 1) the type of monitor being proposed, 2) how the load monitor will be used and analyzed, 3) what functions are being measured by the monitor, and 4) the rationale for the location of the load monitor.. Additionally, for indirect monitors, we recommend that you include a statement justifying the classification for the indirect indicators that you are using as defined in International Standards Organization (ISO) document 11140 (see section V reference 2).	A description of the sterilization load monitor including: 1) the type of monitor being proposed, 2) how the load monitor will be used and analyzed, 3) what functions are being monitored, 4) the rationale for the location of the load monitor. Additionally, indirect load monitors should be designed to react to one or more critical process variables and be capable of distinguishing between processed and unprocessed product.	Since sterilization load monitors can only demonstrate that a sterilization cycle occurred, and do not have the sensitivity to demonstrate that all critical parameters have been met, classification of indirect monitors as defined in ISO 11140 provides no risk mitigation and should not be recommended. However, the recommended rewrite includes detail taken from ISO11140 for Class 1: Process Indicators to provide adequate guidance regarding criteria for selection of a sterilization load monitor for use with parametric release
101 – 105; 129 – 131; 133 – 136;	The document primarily addresses submission requirements for existing products released with the sterility test and	Recommend removal references on lines indicated to "same as those already approved" and rely on the results of the risk assessment during	Additional clarity is needed around submission requirements for completely new products (those not previously

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150 – 155; 169 - 173	inadequately addresses requirements for new products not previously approved for either sterility test or parametric release. .	submission review for products that are currently released using the sterility test and for new products that are similar to products that are currently released with parametric release	approved with the sterility test release) and previously approved products (those approved with the sterility test release). There are a several statements that indicate that specific elements of the existing sterilization program "should be the same" as those in previously approved submissions that were approved. These considerations appear to apply only to existing products and seem to exclude new products from consideration for parametric release. Lines 108-111 indicate that "A statement that describes how the risk assessment includes current control strategies for the terminal sterilization cycle, the risk that these strategies might fail to assure sterility, and how prior manufacturing experience and knowledge were incorporated into the risk assessment should be provided in the application. In regards to the contents of the risk assessment, Lines 156-157 state "Experience with the proposed or similar product (and container closure system), the overall risks to sterility, and the steps you have taken to assess and control these risks. PDA believes that the ability of the risk assessment process to identify and mitigate risks of manufacturing and releasing a non-sterile product unit can be effectively applied to both scenarios and should serve as the basis for submission approval. History and experience with an existing

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			product, not yet approved for parametric release, can be successfully leveraged in assessment of risk in this effort. Accordingly, history and experience with an existing product that is similar to a new proposed product may also be successfully leveraged using risk assessment.
210 - 215	… then you can meet the filing requirements with a special report (21 CFR 314.81(b)(3)(ii)) or annual report (21 CFR 514.8(b)(4)**).**	… then you can meet the filing requirements with a special report (21 CFR 314.81(b)(3)(ii)) **in the case of a human drug product, or an** annual report (21 CFR 514.8(b)(4)**) for a veterinary drug.**	The intent of this section is not clear regarding the application of this provision. Examples of the application of this provision would be helpful. Additionally, please provide guidance on the filing category of changes to a biologic when a company has previous experience using parametric release.