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

RE: Draft Guidance entitled "Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs"; Docket No. FDA-2011-D-0691

Dear Sir/Madam:

PDA is pleased to offer comments on the draft guidance entitled "Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs". 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 the manufacture of Positron Emission Tomography Drugs, as well as manufacturing and validation of aseptically processed drug substance and drug products. The committee included members representing our Regulatory Affairs and Quality and Science Advisory Boards. PDA appreciates the opportunity to offer comments and wishes to thank FDA for the opportunity to do so.

In general, our reviewers found this to be a document which will have utility for the manufacturers of PET Drugs and will provide needed guidance to them in the conduct of aseptic processing simulation studies. PDA believes that the principles contained in this draft guidance should be consistent with other FDA documents which address the conduct of aseptic processing simulation studies, as well as other industry documents and practices addressing the subject To that end, we have made some suggestions in the accompanying table which we believe will further strengthen the draft guidance, bring it into alignment with these other documents and practices and increase the utility to the manufacturers of PET drug products.

We would be pleased to offer our expertise in a 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,

Richard V. Levy, Ph.D.
Senior Vice President, Scientific & Regulatory Affairs, PDA

CC: Richard M. Johnson, PDA
Robert L. Dana, PDA

PDA Consolidated Comments; Media Fills for PET Products
Version 5; 12/16/11

Line No.	Current Text	Proposed Change	Rationale
19	The goal of aseptic processing is to make a product that is free of microorganisms and toxic microbial byproducts, most notably bacterial endotoxins.	Remove "…most notably bacterial endotoxin…" Should read: "The goal of aseptic processing is to make a product that is free of microorganisms and toxic microbial byproducts, such as bacterial endotoxins"	The goal of "parenteral product" aseptic process includes being free from endotoxin, but that is not necessarily the case with all aseptic processing
64	(sterile)	Add words 'product contact'	These reflect a more specific description and will be helpful to those performing the simulations.
64	The media fill should evaluate the aseptic assembly and operation of the critical (sterile) equipment, qualify the operator, and demonstrate that the environmental controls are adequate to meet the basic requirements necessary to produce a sterile drug by aseptic processing	The media fill should evaluate the aseptic assembly and operation of the critical (sterile) equipment, operator technique, and demonstrate that the environmental controls are adequate to meet the basic requirements necessary to produce a sterile drug by aseptic processing	Media fills alone do not "qualify" the operator
65	Environmental controls	Insert word 'contamination' between them	Insertion reflects a more specific description

Line No.	Current Text	Proposed Change	Rationale
76	'packaging'	Replace with the word 'filling'	More appropriate term
79	Microbiologically contaminated containers are expected to become visibly turbid due to growth of the organisms after suitable incubation.	Microbiologically contaminated containers are expected to exhibit observable evidence of microbiological contamination after suitable incubation	Some contaminants will exhibit other types of visible contamination such as fibrous or globules. Some media is designed to change colors if contaminated.
83	Media fills should be conducted in the same locations where the production occurs and employ the broadest scope of possible manipulations that could occur during production.	Media fills should be conducted in the same locations where the production occurs and employ the broadest scope of possible manipulations and interventions that could occur during production.	Industry standard language is "interventions".
85	be sampled	Insert the word 'aseptically' between those words	More specific instruction
89	A minimum number ($\leq 10^2$)	Delete words and parentheses so that it reads: with $\leq 10^2$ of each microorganism	In the context of this document growth promotion (GP) and positive controls are the same; GP is always conducted with less than 100 CFU
89 and 225	New sentence	The positive control inoculation should occur in the QC laboratory, not in the manufacturing equipment.	Clarification
101-102	involved in the manufacture	involved in the aseptic manufacture	Clarification

Line No.	Current Text	Proposed Change	Rationale
102	should participate in the media fills	should participate in at least one media fill per year	More instructive and consistent with 2004 Guidance; consistent with line 167
102 & 103	None	Add the following sentence: All processing steps that he or she normally performs during aseptic manufacturing of a PET product should be simulated	Additional instruction
106-108	A connection to the container of sterile medium may be substituted in place of the filter. Alternatively, a filter may be included during media fills, but the filter should not be used to sterilize the growth medium.	If the sterilizing filter hinders the flow of the growth medium, a filter of the same configuration with a larger pore size may be substituted. The filter should not be used to sterilize the growth medium.	It is important to include the filter and its housing to ensure the sterilization process for this equipment is effective.
111 & 112	The temperature of the medium should be the same temperature as the drug solution would be during manufacture	Propose deleting this sentence	It's not clear how the reader could perform an in-process temperature measurement aseptically
122	examined every 2 or 3 days	examined at appropriate intervals	less prescriptive
140-141	validated steam autoclave process	validated process such as steam autoclaving	There may be other sterilization processes that are appropriate.
149	membrane, in the event you choose to include a filter in the simulation.	membrane.	See the rationale for suggested revision to lines 106-108.

Line No.	Current Text	Proposed Change	Rationale
173-174	These tests should include visible inspection, pH, sterility, and growth promotion.	These tests should include visual inspection and growth promotion.	Consistent with common industry practices for media preparation
212	Growth promotion testing is commonly done before using the medium in an experiment	Propose deleting this sentence, because it isn't accurate	This is true for Environmental Monitoring plate media, but NOT for media fills or container/closure integrity tests
223-225	It is also permissible to perform a positive control at the end (after incubation) of a media fill by inoculating an uncontaminated media fill test container and returning for additional incubation	Replace 'It is also permissible' with the words 'It is desirable'	The 'positive control' is really a growth promotion test which is best performed as described in lines 223-225. One wants to know that the media used for the process simulation would support growth of microorganisms over the whole incubation period.