Bethesda Towers
4350 East West Highway, Ste. 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
www.pda.org

PDA Europe gGmbH
Am Borsigturm 60
13507 Berlin
Germany

October 3, 2016

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

Reference: FDA Draft Guidance: Insanitary Conditions at Compounding Facilities
Docket ID: FDA-2016-D-2268

Dear Sir/Madam:

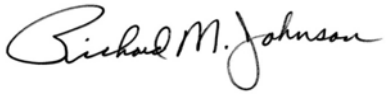
The Guidance for Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug and Cosmetic Act, Issued July 2014, cites section 501(a)(2)(B) as not applicable to compounded product under Section 503A, but according to the Guidance for Industry Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B, does apply. This draft guidance identifies section 501(a)(2)(A) as being applicable, and provides the FDA's current thinking on the topic. Further, Guidance for Industry Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B is focused on those aspects that relate to sterility assurance of sterile drug products. The FDA Guidance for Industry, Insanitary Conditions at Compounding Facilities, Draft Guidance does not contain a similar statement that narrows the focus, however the majority of the content of the Guidance is drawn from FDA experience with sterile compounded products.

The inference from the flow of the document is that the only section which would be applicable to non-sterile compounding would be Section III., A., 1, Insanitary Conditions Applicable to the Production of Sterile and/or Non-Sterile Drugs. PDA recommends that FDA clarify scope to ensure that other products requiring sterile preparation such as ophthalmic products and wound care products are clearly included. Some comments are identified as "critical" in the attachment because these recommended changes to the text would specifically address and prevent conditions noted in recent FDA Warning Letters to compounding facilities.

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 pharmaceutical and biological manufacturing, as well as training in compounding and pharmacy practices including members representing the Regulatory Affairs and Quality Advisory Board and Board of Directors.

If there are any questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson

Cc: Denyse Baker, PDA; Richard Levy, PDA

Food and Drug Administration Draft Guidance
Insanitary Conditions at Compounding Facilities
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General Comments

General Comments	Rationale	Critical Comment
The Guidance for Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug and Cosmetic Act, Issued July 2014, cites section 501(a)(2)(B) as not applicable to compounded product under Section 503A, but according to the Guidance for Industry Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B, does apply. This draft guidance identifies section 501(a)(2)(A) as being applicable, and provides the FDA's current thinking on the topic. Further, Guidance for Industry Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B is focused on those aspects that relate to sterility assurance of sterile drug products. The FDA Guidance for Industry, Insanitary Conditions at Compounding Facilities, Draft Guidance does not contain a similar statement that narrows the focus, however the majority of the content of the Guidance is drawn from FDA experience with sterile compounded products. **The inference from the flow of the document is that the only section which would be applicable to non-sterile compounding would be Section III., A., 1, Insanitary Conditions Applicable to the Production of Sterile and/or Non-Sterile Drugs. PDA recommends that FDA clarify scope to ensure that other products which should be produced under sterile conditions such as ophthalmic and wound care products are clearly included not just injectable products.** PDA further recommends the guidance should be aligned with the "2004 FDA Guidance for Industry: Sterile Drug Product Produced by Aseptic Processing-Current		Y, Critical portion is bolded.

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General Comments	Rationale	Critical Comment
Good Manufacturing Practice" because both Sterile and non-Sterile products are in the scope.		
PDA recommends the title be clarified as follows: **Avoiding** Insanitary Conditions **and Contamination** at Compounding Facilities	This draft includes several suggestions that are important to good manufacturing practices which are not technically insanitary conditions but issues of cross contamination. (e.g. lines 109, 117)Rather than create a separate guidance document, PDA recommends clarification of the title and scope to include these concerns as well.	Y

Specific Comments to the Text

Line No.	Current Text	Proposed Change	Rationale	Critical Comment
Section I. Intro; lines 30-35	The policies described in this guidance document specifically address pharmacies, Federal facilities, physicians' offices (including veterinarians' offices), and outsourcing facilities that compound or repackage human or animal drugs (including radiopharmaceuticals); or that mix, dilute, or repackage biological products.	Move this statement to be part of a scope statement at beginning of the section.	As noted in the general comments above, PDA recommends more clarity about purpose and scope the guidance document including placing this explanation about topic of guidance at the beginning of this section as part of a scope statement.	
Lines 113-114 and lines	Vermin (e.g., insects, rodents) observed in	… observed in production areas or	Replace 'adjacent' with 'accessible'. An area which is adjacent but completely sealed off from the production area	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment
279-280	production areas or areas immediately adjacent to production.	areas immediately ~~adjacent~~ **accessible** to production."	may not pose a risk as one that is accessible.	
Lines 217-229	d. Cleaning and Disinfecting	• **Special attention must be given to difficult to clean areas**	PDA recommends adding additional criteria for cleaning especially in cases where compounding areas may not have proper aseptic design features for cleanability. See also comments to lines 170	Y
Lines 113-121	The following are examples of insanitary conditions that are applicable to both sterile and non-sterile drug production.	Add a new bullet, **Standing water or evidence of water leakage**	Similarly to sinks and drains, the presence of standing or leaking water can lead to contamination.	Y
Line 123	Insanitary Conditions in a Sterile Operation	Add an explanatory paragraph **Products that should be produced in a sterile operation are any products that are intended to be administered through the routes other than orally, rectally or to intact skin. Sterile products include products beyond just those intended for**	PDA recommends providing additional guidance as to which products this section applies to. It states 'Sterile Operation' which could be interpreted to mean parenterals, but there is a much broader range of products which should be produced under sterile conditions. Rather than listing all types of sterile products, PDA recommends an explanation of which products should be produced in a Sterile Operation. PDA also recommends reference to the USP <797> list of products for which the route of administration is typically considered sterile.	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment
		injection such as: opthalmics, inhalation products, and wound dressings. This is not an all-inclusive list.		
Line 131-134	• Failing to disinfect or change gloves frequently enough given the nature of the operations to prevent contamination. • Engaging in aseptic processing wearing non-sterile gloves. This could contaminate the critical area.	Switch the order of these two statements.	Changing the order of the statements having the bullet about use of non-sterile gloves before discussing changing or disinfecting gloves is a more logical flow.	
Lines 146-149	Moving quickly in the vicinity of open containers or instruments (e.g., needles). While conducting aseptic manipulations, ISO 5 airflow must be unidirectional to protect the product from contaminating particles. Quick movement of personnel disrupts the airflow and increases the risk of bringing lesser	Add the following: **Dynamic smoke studies should be used to illustrate what is an inappropriate quick movement by a visual demonstration of what would disrupt first air.**	PDA observes that this section should provide guidance as to what constitutes 'Move quickly.' There is an objective to balance exposure of open product with disruption and movement needs to be understood in a way that most readers will strike the right balance. PDA recommends the use of dynamic smoke studies to help the compounding organization define what is an inappropriate quick activity. Smoke studies provide a visual demonstration of what would disrupt first air. (See also comments noted in line 253)	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment
	quality air into the ISO 5 area			
Line 163:	Storing open sterile vials within the critical area without protective cover longer than needed for the process of filling drug product.	~~Storing~~ **Staging** open sterile vials within the critical area …	The term "storing" seems inappropriate. It connotes a long term situation not related to filling drug product. PDA recommends the term "Staging." Sterile vials should never be "stored" uncovered but covered as soon as possible to prevent microbial ingress or other contamination.	
Lines 168 "a. Aseptic Practices"	New Bullet Added	**Operators with topical or respiratory infections or with open wounds**	PDA recommends adding a statement regarding personnel readiness and hygiene required for those working in this type of operation to be consistent with the FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing —Current Good Manufacturing Practice.	Y
Line 169 and Line 215	– Under "b. Equipment/ Facilities," but also applicable to "d. Cleaning and Disinfecting"	Add Opening Statement: **Materials of construction should be appropriate for processing, cleaning, and sterilization. Materials such as cardboard, wood or paper are inappropriate. Stainless steel, glass, medical grade silicone and similar materials are appropriate for**	The guidance should speak to the appropriate materials of construction and design criteria per current GMP requirements and be consistent with the FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing —Current Good Manufacturing Practice.	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment
		product contact. Preference should be given to using pre-sterilized disposables. Design of equipment and facilities should ensure ease in cleaning and drying.		
Lines 176 – 177		"Classified areas … (e.g. utility pipes or ~~ledges~~ **horizontal surfaces**, such as windowsills".	PDA recommends adding the phrase "horizontal surfaces" and deleting the term "ledges" so this bullet will be more comprehensive of all possible dust collecting surfaces not just overhangs.	Y
Lines 195 – 196:	A lack of HEPA-filtered air, or inadequate HEPA filter coverage or airflow, over the area to which sterile product is exposed.	… over the area ~~to which~~ **where** sterile product is exposed.	PDA recommends this change to improve clarity and readability.	
Line 200	The presence of sinks or drains in the cleanroom where the ISO 5 area is located.	The presence of sinks**,** ~~or~~ drains **or water sources (taps)** in the cleanroom where the ISO 5 area is located.	Water taps are also a source of microbial contamination and should not be positioned within ISO 5 areas.	Y
Line 230 "d. Cleaning and Disinfecting"	Add a new bullet to the list of things to avoid.	**Do not use sterile agents kept in the clean area without replacement past the expiry date or "discard after**	PDA recommends adding this criterion because expired disinfecting or cleaning agents are not effective.	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment
		opening" date.		
Lines 253-255	Conducting smoke studies under dynamic conditions with personnel present helps to ensure that unidirectional airflow is maintained while personnel are working in the ISO 5 area.	Add the following text: **This type of study can illustrate the impact and risk of moving too quickly in an aseptic area as noted earlier in section A.2.a.**	PDA recommends it would be helpful to link this section on dynamic conditions testing to the section on moving quickly at lines 146-149.	
Line 260-262	4. Conduct media fill studies to closely simulate… and conditions that provide a challenge to aseptic operations.	Add the following **A media fill program should be established with rationale for justified frequency.**	PDA notes media fills should be tailored to both the type of product and nature of operations in order to be representative of risk to products produced and not be one time occurrences.	Y
Line 308	… it should undertake a comprehensive assessment of its operations, … to conduct this comprehensive evaluation and to assist in implementing appropriate corrective actions.	….conduct this comprehensive ~~evaluation~~ **assessment**	For clarity and consistency, PDA recommends the same term be used in both parts of the sentence.	