PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

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

September 7, 2017

China Food and Drug Administration
Beijing, China
eMail：gmp-cfdi@cfdi.org.cn
RE: Guidance on simulation testing of sterile processes (sterile products)(for comments)无菌工艺模拟试验指南（无菌制剂）(征求意见稿)

Dear Sirs:

PDA greatly values the opportunity to review this draft document and provide suggestions to improve clarity and harmonization. In general, PDA recommends looking into the terminology used throughout the guidance and harmonising with the terms commonly used in other similar globally recognized documents such as PIC/s and WHO guidelines.

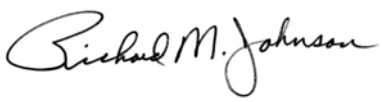
PDA has noted several instances where this new draft guidance diverts from currently accepted industry practice in aseptic process simulation such as: volume of filled containers, personnel designated to participate, and amount of environmental monitoring sampling. PDA encourages harmonization of requirements wherever possible and the current industry practices noted have been accepted by inspectors representing health authorities across the world.

In support of this response, PDA has referenced three current technical publications which discuss the best science and practices for aseptic processing: *Technical Report No. 22, Points to Consider for Aseptic Processing: Part 1, and Part 2.* These publications are available from PDA. Please see the detailed comments for further explanation.

The Parenteral Drug Association (PDA) is a non-profit international professional association of more than 10,000 individual member scientists from industry and regulatory agencies. Many of our members have deep technical expertise in injectable, sterile products and work closely with global standards in this area.

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

Sincerely,



Richard Johnson
President and CEO, PDA

CC: Richard Levy, PDA; Denyse Baker, PDA

CFDA Draft Guidance
Guidance on simulation testing of sterile processes (sterile products)(for comments)无菌工艺模拟试验指南（无菌制剂）(征求意见稿)
2017

总评　General Comments

总评 **General Comments**	理由 **Rationale**	关键性 是/否 **Critical Comment? Y/N**
In general, PDA recommends looking into the terminology used throughout the guidance and harmonising with the terms commonly used in other similar globally recognized documents such as PIC/S and WHO guidelines.	Adopting commonly understood terminology will improve the understanding among manufacturers worldwide and facilitate their compliance with the desired requirements.	N
总体上，PDA 建议检查指南中使用的术语，使术语与在全世界范围内受到广泛认可的类似文件如 PIC/S 及 WHO 指南保持一致	采用公认的术语可以增加世界范围内生产商的理解，也有助于促进其符合预期要求。	否
PDA has noted several instances below where this new draft guidance diverts from currently accepted industry practice in aseptic process simulation. Three examples are: volume of filled containers (section 6.5), personnel designated to participate in the simulation (section 6.13, 6.8.4), and amount of environmental monitoring sampling (section 6.7.4, 6.12.1). Please see additional comments and details below.	PDA has documented recommendations with rationale for Aseptic Processing in several publications most notably PDA Technical Report 22, *Process Simulation for Aseptically Filled Products,* and *PDA Points Consider for Aseptic Processing*, Part1 and Part 2. (see References)	Y
PDA 注意到这个新的草案指南有几处与当前行业接受的在无菌工艺模拟方面的惯例有所偏离。3 个实例包括：6.5 小节：容器装量；6.13 及 6.8.4 小节：参与无菌工艺模拟的人员；6.7.4 及 6.12.1 小节：环境监控取样设计。其他建议及详情请参见如下。	PDA 在多个出版物中描述了关于无菌工艺的建议及理由，特别是 PDA 的第 22 号技术报告《无菌灌装产品的无菌工艺模拟》及 PDA 无菌工艺关注要点第 1 部分和第 2 部分。（参见参考文献）	是

对文本的具体评论 Specific Comments to the Text

章节号 **Section No.**	当前文本 **Current Text**	拟议变更 **Proposed Change**	理由 **Rationale**	关键性 是/否 **Critical Comment? Y/N**
6.5:	The volume of filling during APS is only expected to be 1/3 to 1/2 of the container volume.	PDA recommends no limitation should be required.	PDA Technical Report 22 recommends two criteria to determine fill volume. There must be enough medium in the container: to contact all the container-closure seal surfaces when the container is inverted and swirled; and enough medium to allow for detection of microbial growth. The PDA Points to Consider for Aseptic Processing part 2 (rationale) also mentions “Aseptic process simulation should as closely as possible simulate the actual production in order to capture any potential inherent risks or variables that could negatively impact the process (e.g., foaming, splash up).”	Y

6.5:	容器中培养基灌装量通常应能达到容器体积的 1/3～1/2。	PDA 意见不需要设限制。	PDA 第 22 号技术报告推荐了确定灌装量的两个标准。 容器中必须有足够培养基：可保证产品通过倒置和旋转接触到所有包装系统的内表面；以及有足够的培养基来检测微生物生长。 PDA 无菌工艺关注要点第 2 部分（理由）还提到“无菌工艺模拟应尽可能模拟实际生产，以捕获可能对无菌工艺产生负面影响的任何潜在的内在风险或变量（例如起泡，向上飞溅）。”	是

6.6.1	The duration of the simulation testing will be equivalent to [that of actual] production;	PDA recommends deleting this statement.	PDA aseptic process PtC Part 2 does not necessarily recommend the use of full or extended duration media fills without evaluation – "*Where there are no risk-based duration-related effects, and/or where longer duration does not add any scientific merit, then it should not be necessary for a process simulation to equal or be longer than the maximum production duration*	
6.6.1	无菌工艺模拟试验的持续时间和实际生产相当。	PDA 建议删除此句。	PDA 无菌工艺 PtC 第 2 部分并不推荐在没有评估的情况下，培养基灌装采用与实际生产一致的持续时间或延长的持续时间。- "如果没有基于风险的持续时间相关的效应，和/或更长持续时间不增加任何科学价值的话，那么无菌工艺模拟不需要等于或长于最大生产持续时间。	

6.6.4	Simulation after the end of manufacturing After the manufacture of a batch of products, filling of the culture media is directly undertaken without disassembling, cleaning, disinfecting, sterilizing or other activities.	PDA recommends deleting this requirement.	PDA believes this approach should not be recommended, as it does <u>not</u> include the set up and start of the filling line (arguably the most critical and risky time). Actually it does the opposite by not including the inherent interventions in beginning a product batch. PDA defines this in Technical Report 22. Again this approach can lead to a false sense of security.	
6.6.4	生产结束后模拟 在一批产品生产结束后，不经拆卸、清洁、消毒、灭菌等工作，直接进行培养基灌装	PDA 建议删除这一要求。	PDA 认为不应推荐这种方式，因为没有包含灌装线的连接和启用（可认为是最关键和最高风险）。实际上恰恰相反，因没有包含产品生产开始时的固有常规干预。PDA 在技术报告 TR22 中有此规定。同时，这种方法也会导致一种错误的安全感。	

6.7.4	Environment The poorest environment poses a challenge for simulation testing. In such an environment, one should consider taking a single batch of products at the end of the sterile manufacturing cycle. The longest time interval is after the intermittently-produced air conditioning system has been repeatedly started, or after periodic sterilization during continuous production	~~In such an environment, one should consider taking a single batch of products at the end of the sterile manufacturing cycle~~. **Environmental Monitoring data should be used to confirm suitability of the environmental conditions with media fill as a back up to catch any unforeseen variable.**	PDA disagrees with the premise. Media fill is not the way to ensure that the environment is suitable for aseptic processing.	
6.7.4	环境 最差环境为模拟试验提供了挑战。在这种环境下，应考虑选择无菌生产周期末端单批产品。最长的时间间隔是间歇式生产的空调系统重复重新开启后或连续生产期间周期性灭菌。	环境监测数据应该用来确认环境条件的适宜性，并以模拟灌装作为支持以捕捉任何不可预见的变量。	PDA 不同意该前提。不能通过培养基灌装来确保环境对无菌工艺的适宜性。	

6.13	Personnel Factors All personnel who are authorized to enter the sterile filling areas, including observers and maintenance personnel, should take part in at least one successful simulation test of sterile processes each year. Only if this is done can they participate in sterile operations in normal manufacturing.	PDA recommends this addition for clarification. **Participation in simulation test may not be required prior to initial entry to sterile operations if other means of qualification is conducted and documented.**	In Technical Report 22, PDA recommends there is not a requirement for participation in a successful media fill prior to first entry into a sterile operation. The language in the draft as proposed is consistent with periodic qualification but should not be interpreted as a requirement prior to initial personnel entry to a sterile filling area.	
6.13	人员因素 所有被授权进入无菌灌装区域的人员，包括观察人员和维修人员，都应当每年至少参加一次成功的无菌工艺模拟灌装实验。只有完成此项，他们才可参与正常生产的无菌操作。	**PDA 建议增加澄清。如果已经实施并记录了其他方式的确认，可以不要求在初始参与无菌操作之前要参加模拟实验。**	PDA 在第 22 号技术报告中建议，在首次参与无菌操作之前参加一次成功的培养基模拟灌装不是必须的。正如所提议的，草案中的说法和定期确认一致，但不应被理解为是人员首次进入无菌灌装区域的一个必要条件。	

6.8.4	Personnel Inherent interventions that are standardized and simple can be implemented by some operating personnel and evaluated by others. Highly complex operations, such as those of assembly filling machines, etc., and all personnel who engage in such operations should participate in the operations in simulation testing of sterile processes, and the operating conditions should not be superior to the operating conditions of daily production.	**Personnel who do interventions** in *Highly complex operations, such as those of assembly filling machines, etc.,* **should be trained and certified to perform these specific interventions** *and ~~all personnel who engage in such operations~~ should participate in the operations in simulation testing of sterile processes, and the operating conditions should not be superior to the operating conditions of daily production."*	It is suggested to rephrase to the last sentence. The intention must be to ensure that all persons are certified to perform aseptic interventions/connections, and that the APS includes the relevant interventions, not that all personnel should participate during the APS.	Y
6.8.4	人员 标准化的、简单的固有干预可以由一些操作人员实施并据此评估其余人员。对于高度复杂的操作，比如装配灌装设备等，参与此类操作的所有人员都应该参加无菌工艺模拟实验的操作，且操作条件不应优于日常生产的操作条件	执行高度复杂操作（如装配灌装设备等）的干预人员应就这些特定干预的实施予以培训和确认，并应当参无加菌工艺模拟实验操作，且操作条件不应优于日常生产的操作条件。	建议修改最后一句。应确保所有人员有资质实施无菌干预/连接，并确保无菌工艺模拟包括所有的相关干预，而不是所有人员应参与无菌工艺模拟。	是

6.9	Ordinarily a transparent container will be used instead of an opaque or brown container.	Add the following text to the end of the sentence: **As long as the transparent container does not perform better than the opaque or brown version.**	Clarification of when the selection of transparent container is appropriate.	
6.9	通常使用透明容器代替不透明或棕色的容器。	给最后一句增加如下文字：只要透明容器不会比不透明或棕色容器更好操作。	澄清何时选择透明容器是恰当的。	

6.10.3	Post Culture Testing After the culturing has finished, all products undergoing filling simulation will be subject to sterility testing . Ordinarily visual observations will be made with the products at suitable temperatures.	After the culturing has finished, all products undergoing filling simulation will be subject to ~~sterility testing .~~ ordinarily visual observations **for evidence of contamination** ~~will be made~~ with the products at suitable temperatures. Any vials visibly contaminated are subject to further culturing and analysis.	Clarification: The use of the term "sterility testing" may be interpreted as compendial sterility testing such as filtration and further culturing. PDA believes the intent is to subject these vials to visual check for turbidity.	
6.10.3	培养后检查 培养结束后，应对所有模拟灌装的产品进行无菌检查。在适宜的温度下对产品进行常规目视观察。	培养结束后，在适宜的温度下对所有模拟灌装产品进行常规目视观察, 发现其是否存在污染。任何目视污染的瓶子应被进一步培养和分析。	澄清：无菌检查可能被理解为药典无菌测试，例如过滤和进一步培养。PDA 认为术语含义是对这些瓶子的浑浊度进行目视检查。	
6.10.3	Post Culture Testing When opaque containers are being filled, consideration should be given to making the observations on filled transparent containers	Add this text: **Alternatively contents of the incubated opaque containers can be transferred to a transparent container for visual check for turbidity.**	In PDA's experience transparent containers even of similar design, may actually run better on a filling line and therefore not truly simulating the opaque or brown counterpart conditions in the media fill.	
6.10.3	培养后检测 若使用不透明容器进行灌装，则可考虑灌装在透明容器中进行观察	增加此文：此外，可将在不透明容器中培养的物质转移至透明容器中目视检查浊度。	根据 PDA 的经验，即使是简单设计的透明容器，在灌装线上也可能（比不透明容器）运行的更顺畅；因此，在培养基灌装中（使用透明容器）并不能真实的模拟不透明或棕色容器的条件。	

6.12.1	….environmental monitoring that takes place during simulation testing should include extra monitoring results.	If this requirement will be kept PDA suggests to focus on personnel sampling in order to have a better data material to define routes of contamination in cases of failed APS – (personnel being the biggest risk of contamination)	This appears to be an unnecessary increase in EM, if there is no indication that the sterile processes are not under control. Justification: - EM sample locations are defined by risk assessments and concentrated on locations critical to product. - EM sample locations are determined after an extensive monitoring during process qualification with extensive activities and worst case s scenarios - Particle monitoring in critical grade A is continuous, i.e. sampling already takes place for the full duration of the aseptic processing	Y
6.12.1	……在培养基灌装时的环境监控应包括额外的监控结果	如果保留该要求，PDA 建议重点关注人员取样，以便于有更好的数据解释无菌工艺模拟失败的污染途径（人员是最大的污染风险）	如果没有证据显示无菌工艺处于不受控状态，这似乎是一个不必要的环境监控增加。理由如下： - 环境监控位点基于风险评估确定，并重点关注产品相关的关键位点。 - 工艺确认时，对大范围的活动和可能出现的最坏情况进行了大量监控之后，确定了环境监控取样位点。 - A 级区的关键区域不间断进行粒子监控，即：在无菌工艺全程已经进行了取样。	是

These references are available from the PDA Bookstore (store.pda.org)
这些参考资料可从 PDA 书店获得（Store.pda.org）

1. *Technical Report No. 22 (Revised 2011), Process Simulation for Aseptically Filled Products,* originally published in 1996.
Date of Publication: December 2011
ISBN Number: 9780939459353
*22 号技术报告（2011 年修订版）无菌灌装产品的无菌工艺模拟，*1996 年首次发布。发布日期：2011 年 12 月
ISBN Number: 9780939459353

2. Points to Consider for Aseptic Processing: Part 1, January 2015
Date of Publication: March 2015
ISBN Number: 9780939459759
无菌工艺关注要点：2015 年 1 月，第一部分
发布日期：2015 年三月
ISBN 号：9780939459759
3. Points to Consider for Aseptic Processing: Part 2, May 2016
Date of Publication: May 2016
ISBN Number: 9780939459896
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