Regulatory Aspects of BFS Production inlcuding Environmental Monitoring

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Overview概要

1. Regulatory Aspects法规方面

1A. FDA/USP

1B. EG-GMP Guide指导

2. Environmental Controls环境控制

3. Comparison of sterility assurance between BFS- and traditional aseptic filling

BFS Technology is described in:

- **Europe:** EU-GMP Guide Annex 1, Chapter 26-27, since 1996

- **USA:** FDA Guidance for Industry - Aseptic Processing 2004
  Appendix 2: Blow-Fill-Seal Technology
  USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environment

- **China:** China GMP Annex 1 Chapter 16 BFS
- **PDA** Technical Report No 77: The Manufacture of Sterile Pharmaceutical Products Using Blow–Fill-Seal Technology

- **Japan:** Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing 2005 Chapter 20.2 BFS

- **World Wide**: WHO good manufacturing practices for sterile pharmaceutical products
  WHO Technical Report Series, No. 961, 2011 Annex 6 Chapter 9 BFS

PDA Parenteral Drug Association

Technical Report No. 77

The Manufacture of Sterile Pharmaceutical Products Using Blow-Fill-Seal Technology

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1. Regulatory Aspects法规方面

Europe: 欧洲

EU-GMP Guideline Annex 1, Chapter 26 / Valid from

01.03.2009欧盟GMP方针附件1，26章/2009年3月1日生效

USA: 美国

FDA Guidance for Industry - Aseptic Processing

Appendix 2: Blow-Fill-Seal Technology / 2004 2004USP专论

USP Monograph chapter < 1116>FDA工业指导-无菌处理附件2：吹瓶-灌装-封口三合一技术/

1A. EU-GMP Guide Annex 1 Manufacture of Sterile Medicinal Products (chapter 26/27) 欧盟GMP规则附件1 无菌医药产品的生产（章26/27）

Blow/Fill/Seal units are purpose built machines in which, in one continuous operation, Containers are formed…filled and then sealed…. Blow/Fill/Seal equipment used for aseptic production… is fitted with an effective grade A air shower….installed in at least a grade C environment, provided that grade A/B clothing is used…... Products which are terminally sterilised…. should be installed in a Grade D area. …Environment should comply with the viable and non viable limits at rest and the viable limit only when in operation

吹-灌-封设备是容器成型，药液灌装，容器封口连续完成的全自动的专用设备。

用来无菌药品生产的设备带有百级层流罩，需安装至少C级环境区域里，使用A/B级洁净衣服。产品须最终灭菌的，设备应放在D级环境区域里。环境应满足静态和生产状态下繁殖度和非繁殖度限制要

1B. FDA

FDA Guideline Sterile Drug Products FDA无菌产品指导规范

Produced by Aseptic Processing — Current Good Manufacturing Practice由无菌工艺生产---现行GMP规范

APPENDIX 2: BLOW-FILL- SEAL TECHNOLOGY

Blow-fill-seal (BFS) technology is an automated process by which containers are formed, filled, and sealed in a continuous operation. **This manufacturing technology includes economies in container closure processing and reduced human intervention** and is often used for filling and packaging ophthalmics, respiratory care products, and, less frequently, injectables….environment surrounding BFS machinery should….meet Class 100.000 (ISO 8)…Air in the critical area should meet Class 100 (ISO 5) microbiological standards

附件2：BFS吹瓶-灌装-封口三合一技术

BFS技术是指容器成型、灌装、封口在一台设备上连续完成的自动化工艺过程。它有容器的经济性生产，而且减少人为的干扰。它常用来生产包装眼药，呼吸护理产品。并有时用于生产注射类产品。 BFS设备的环境要求满足10万级。重点区域的空气质量要求应满足微生物性百级标准

USA: USP < 1116>

MICROBIOLOGICAL CONTROL AND MONITORING OF ASEPTIC PROCESSING ENVIRONMENTS

- **ADVANCED ASEPTIC TECHNOLOGIES**
- Advanced aseptic technologies can be defined as those that do not rely on the direct intervention of human operators during Processing.
- **At present, technologies** such as isolators, **blow/fill/seal**, and closed RABS (designs that are never opened during setup or operation) **may be considered advanced aseptic technologies, provided that direct intervention by gowned personnel is disallowed during processing**.

Overview Clean room limits (in operation)
洁净房间的总体要求（生产过程中）

US	ISO	EU 欧盟	≥ 0.5 µm Particles/m³	Active air cfu/m³ 实际空气Cfu/立方米	Settling plates in cfu/Plate 沉淀物盘	Contact plates in cfu/Plate 接触盘	Glove in cfu/plate 手套
100	5	A	**EU at rest and operation (US) 3,520**	US: 1 EU: <1	1 <1	<1	<1
10,000	7	B	**At rest EU: 3,520** **In operation EU/US: 352,000**	US: 10 EU: 10	5 5	5	5
100,000	8	C	**At rest EU: 352,000** **In operation EU/US: 3,520,000**	US: 100 EU: 100	50 50	25	
-----	9	D	**Not defined** 未定义	EU: 200	100	50	

Definition Annex 1 EG-GMP/FDA Guidance Sterile Drug Products produced by aseptic processing:

定义附件1欧盟GMP/FDA规则

无菌工艺生产的无菌医药药品

Clean room classification of BFS-installations:

三合一设备安装的洁净房间洁净度要求

无菌生产: Air shower : A/100

室内环境: C/100.000

Only for Annex 1 EU GMP

终端灭菌产品 without Air shower

室内环境: D (仅欧盟GMP规则定义)

- Microbiologicals and Particle limits must be fullfilled “at rest” for the clean rooms
- 必须满足静态下洁净房间的微生物和粒子数限制要求。

- Microbiologicals limits must be fullfilled also „at operation“ Status (Particles limits are not valid)
- 必须满足运行状态下微生物数的限制要求

  （粒子数限制要求是无效的)

Gowning for Blow/Fill/Seal Installation

三合一设备生产着装要求

EU

A/B clothingA/B衣服:
Full suit, face mask, hood,
boots, sterile gloves
Sterile or sanitised suit
No formal requirement for goggles
No watches make up or jewellery

全身衣服，面具，帽子，鞋靴，无菌手套
无菌或消毒衣服，护目镜无正式要求
不佩戴手表、珠饰、不化妆

US

Aseptic, class 10,000:
Full suit, face mask, hood, goggles, boots/shoe over covers, gloves
Suit should be sterile
无菌，万级
全身衣服，面具，帽子，护目镜，靴子/鞋套，手套
衣服需无菌

Conclusion: Very similar requirements
结论：非常相似的要求

Qualification / Validation Aspects of BFS-Technology – What is different between FDA and EU?

EU-GMP ANNEX 1 CHAPTER 27: BLOW / FILL / SEAL TECHNOLOGY

… Because of this special technology particular attention should be paid to, at least the following:

- **equipment design and qualification**
- **validation and reproducibility of cleaning-in-place and sterilization-in-place**
- **background clean room environment in which the equipment is located**
- operator training and clothing, and
- **interventions in the critical zone of the equipment including**

FDA Guidance for Industry
"Sterile Drug Products Produced by Aseptic Processing"
Annex 2 Chapter B:

Advantages of BFS processing are known to include rapid container closure processing and minimized aseptic interventions. However, only **a properly functioning process** can realize these advantages. We recommend affording special attention to setup, troubleshooting of equipment, and related aseptic personnel procedures. **Equipment sterilization, media fills, polymer extrusion/sterilization**, **product-plastic compatibility**, **forming and sealing integrity**, and **unit weight variation are among the key issues to address in validation and qualification studies…**

2. ENVIRONMENTAL CONTROLS
环境控制

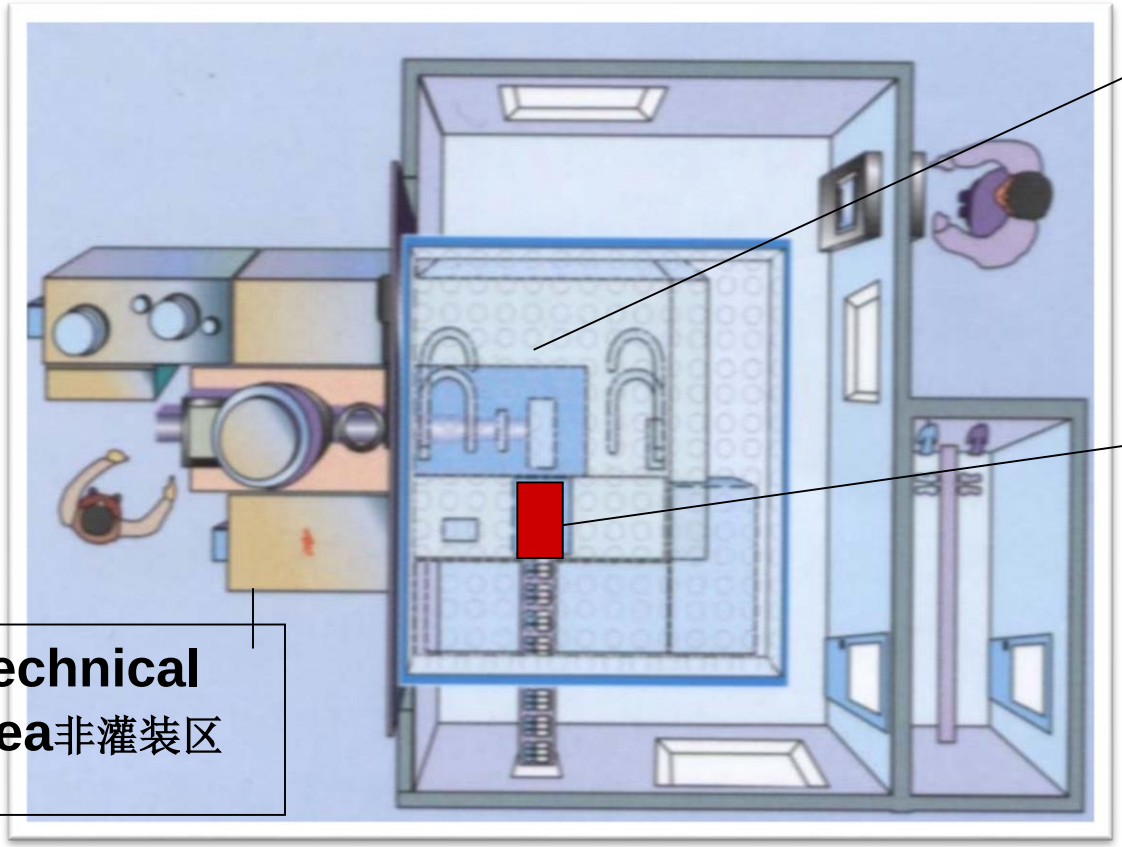
Methods of „Monitoring“:监测方法

- Measure of air velocity空气速度的测量
- Measure of airborne contamination (active sampling)空气传播污染（实样采集）
- Sedimentation plates沉淀盘
- Contact plates for surfaces and personnel

  用于表面和人员的接触盘
- Particle counting颗粒计数

Clean room – Monitoring洁净室监测

Clean room concept for BFS-Systems: shuttling BFS系统洁净室概念



Cleanroom class C Area under the HEPA filter
层罩下的C级洁净区

Air shower
Air quality-class A Area
Fill area
空气冲淋
A级洁净区

Technical Area非灌装区

BFS-Technology Type 460 ***located in clean room class C***

Parison head for Manufacturing Endless-Tube/Parison Dosing needles are located in the Parison

Outlet and Punching Device

Moulds are mounted on rotating chain, therefore continuous process

Overview Table: Example Clean room Monitoring

一览表：洁净室监测举例

Location位置	Method方法	Frequency频率	Limit要求
Air shower 空气冲淋 ***Air quality A/ 100***	Air velocity风速	Batch related End of Production/ Weekly生产的最后一批次/每周	To be defined/Over-pressure should be present需定义/必须是过压
For shuttling machine only Rotary machines have no air shower class A!	Air borne microorganism (Sedimentation plate not possible)空气传播微生物（不能用沉降盘）	Shiftwise/End of the batch每一批次结尾的那班	< 1 cfu/cbm
	Particle counting (non viable) 颗粒计数（不可繁殖颗粒）	Continuous/End of the Batch 连续/批次结束	max 3500/cbm in operation
	Contact/Swab plates接触/抹拭盘	End of Batch批次结束	< 1 cfu/25 cm^2

Overview Table: Example Clean room Monitoring

一览表：洁净室监测举例

Location位置	Method方法	Frequency频率	Limit要求
Cabin or under HEPA Filter C/100.000 箱柜或者位于HEPA过滤器下面的C/100,000级关键区域	Air velocity 空气流速	Monthly 每月	To be defined/Overpressure must be present to areas with lower/non clean room level (10 – 15 Pascal)需定义/必须是过压（10-15帕，非洁净室水平）
	Air borne micro-organism空气传播微生物	Shiftwise/End of Batch每一批次 结尾的那班	< 100 cfu/cbm active air sampling or 50 cfu/settling plate 90mm /4 hours < 100 cfu/立方米或者50cfu/90毫米盘/4小时
	Non viable Particle-count颗粒计数（不可繁殖颗粒）	End of Batch 批次结束	No limits for operation EU-GMP/ 352.000/cbm at rest 动态无要求，静态要求3500每立方
Inner area Machine cover/ Air shower outer surface设备内部/空气冲淋室外表面	Contact plates 接触盘	End of Batch 批次结束	To be defined 4 – 30 cfu/cm^2 需定义4-30cfu/cm^2

Overview Table: Example Clean room Monitoring

一览表：洁净室监测举例

Location位置	Method方法	Frequency频率	Limit要求
Personnel Clean room C/100.000 人员 C级/100,000洁净区	Contact plates / Gloves 接触盘/手套	After each Intervention in the critical area (C) under HEPA Filter including clean room monitoring 帘内关键区域的每一次干预之后，包括洁净室监测	Max.: 10 cfu/25 cm^2 最大值： 10 cfu/25 cm^2
	Contact plates Overall 全面接触盘	After each Intervention in the critical area (C)under HEPA FIlter including clean room monitoring 帘内关键区域的每一次干预之后，包括洁净室监测	Max 40 cfu/25 cm^2 最大值： 40 cfu/25 cm^2

2. Comparison of sterility assurance between BFS and traditional aseptic filling

Advanced Aseptic Processing Definition

"An advanced aseptic process is one in which direct intervention with open product containers or exposed product contact surfaces by operators wearing conventional cleanroom garments is not required and never permitted."

Agalloco, Akers & Madsen, "What is Advanced Aseptic Processing?",Pharmaceutical Manufacturing, 2006.

3. Comparison of sterility assurance between BFS- and traditional aseptic filling

- Media-Fill as confirmation for the suitability of aseptic filling
- BFS Association Questionnaire 2003 in cooperation with PDA
- Questionnaire is comparable to PQRI Question., which was made after launch of FDA Draft „ Guideline on Aseptic Processing“

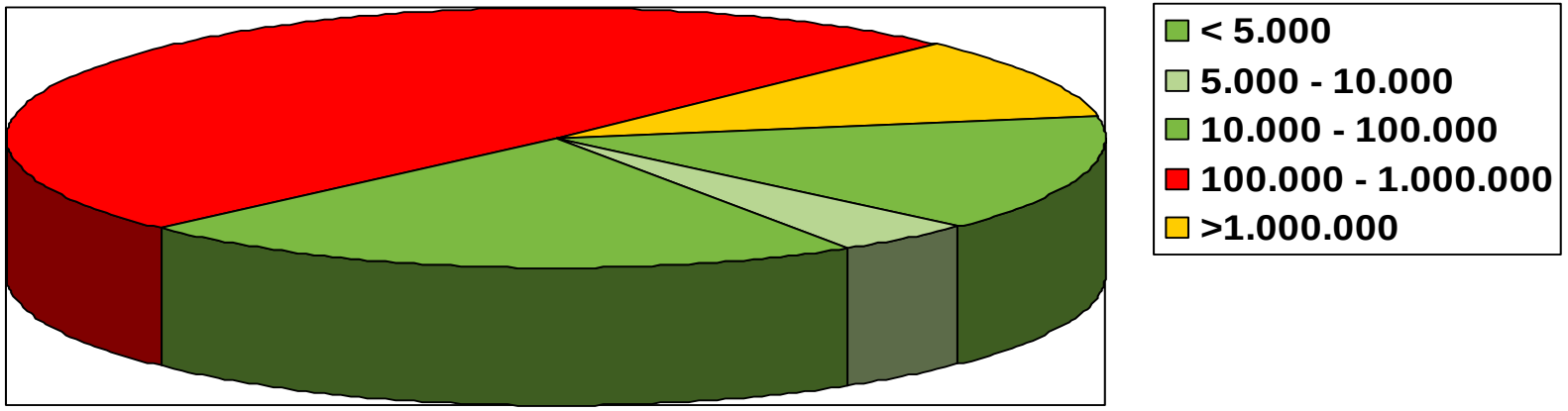
3. Comparison of sterility assurance between BFS- and traditional aseptic filling

Table 1 Batchsize of Media Fills

	PQRI	BFS IOA
Amount of Media Fills	606	208
Amount of filled units/ Media Fill		
< 10.000	61%	42%
> 10.000	39%	38%
> 50.000	-	19%
> 100.000	-	1%

3. Comparison of sterility assurance between BFS- and traditional aseptic filling

Diagramm 1 Ansatzgröße der Chargen auf BFS-Anlagen



3.Comparison of sterility assurance between BFS- and traditional aseptic filling

Table 2 Contaminated Media Fills

	PQRI	BFS IOA
Amount of Media-fills	606	208
% contaminated Media-fills	55 = 9%	2 = 0,9%
Amount contaminated units		
1	36 = 66%	2 = 100%
2	3 = 6%	-
3 – 5	14 = 26%	-
> 5	1 = 2%	-

3.Comparison of sterility assurance between BFS- and traditional aseptic filling

Definition Amount contaminated units:

„An isolated incident (no trend) in which one contaminated unit beyond the 5.000 unit level may be considered a random event“

PQRI Aseptic Processing Work Group, Final Report March 2003

Contaminated Media Fills	
PQRI	34% with more than 1 contaminated Unit
BFS IOA	0% with more than 1 contaminated Unit

3. Comparison of sterility assurance between BFS- and traditional aseptic filling

Summary:

- No Interventions in class A/B areas for BFS Technology during production and at rest
- Equipment runs with a lot of Interventions out of the Clean room for Dark/White separated machines (Remote Control)
- Integrated SIP / CIP / DIP Processes for high security during equipment preparation
- Running of long filling times/big batches with BFS-Technology (up to one week is possible)
- Questionnaire shows shows low contamination rates 1/10 in comparison with conventionell aseptic filling lines (like Isolators)

Literature

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Thank you very much for your Attendance!

非常感谢您的参与！