Application & Validation of Single-Use Technology in Biopharm

一次性技术在生物制品中的应用及验证解析

Lynn Liu 刘秋琳

+86 186 2111 7553 lynn.liu@merckgroup.com

Field Marketing GPP, Merck Millipore

2015.3 Haikou

Agenda

1 Single-Use Technology Application 一次性技术的应用

2 Regulation & Guidelines for Single-Use Systems 一次性系统法规与指南

3 Validation for Single-Use Systems 一次性系统验证

Agenda

1 **Single-Use Technology Application 一次性技术的应用**

2 Regulation & Guidelines for Single-Use Systems 一次性系统法规与指南

3 Validation for Single-Use Systems 一次性系统验证

Disposable Technology in Aseptic Processing: Drivers
一次性技术在无菌工艺中的驱动力

New Facility Design 新厂设计

Design, construction, and validation of a GMP biomanufacturing facility设计、建造和验证一个符合GMP要求的工厂

- reducing capital expenditures缩短项目时间
- minimizing the project timeline减少固定资产投资
- increasing operational flexibility增加操作的灵活性
- *"minimizing operational cost"减少运行花费*

-Wei Huang, GEN, 2005

Retrofitting Existing Operations 更新改造现有的设备

- Ease of Use易用
- Flexibility灵活
- Reduce Capital expenditure减少固定资产投资
- Changes in process or transfer of new process into facility工艺变更或者将新工艺转移到原工厂设施
  - New buffer , New media, Process hold volumes increase, etc例如：新的缓冲液,新的介质,工艺处理的液体体积增加等

Growing spectrum of applications emerge 出现了越来越多具体应用的案例

- Mixing, sampling, filtration, bioreactors, transfers, containers etc搅拌混合,取样,过滤,生物反应器,转移,容器等
- In parallel a growing spectrum of components emerge与一次性技术的应用并行的功能模块组件形成
- Engineered solution are evolving from applications and components涉及的工程方案有一次性技术的应用和实现某种功能的组件

What are your key drivers?关键的驱动力是什么?

You are a Biotherapeutic Manufacturer 如果您是 生物制药企业

- Eliminate cleaning requirements减少清洁必须的环节/操作
- Reduce time & labor cost减少时间&人力的花费

You are motivated by lower operating& maintenance costs

您的驱动力来自较低的运行和维护花费

You are a Contract Manufacturer 如果您是 订单生产企业

- Eliminate cleaning requirements减少清洁必须的环节/操作
- Reduce time & labor cost减少时间&人力的花费

You are motivated to get a fast & flexible up and running process您会被这种快速和灵活，安装上就可以使用的特点驱动

MAb Process Template by Disposable
使用一次性系统的单抗工艺模板

Bioreactor

CLARIFICATION

AFFINITY CHROMATOGRAPHY

CEX CHROMATOGRAPHY

AEX CHROMA-TOGRAPHY

VIRUS REMOVAL

ULTRAFILTRATION

STERILE FILTRATION

Bulk Drug Substance

Martillac BioDevelopment – Single-Use Facility
法国Martillac生物制品中心 – 一次性系统工厂实物图

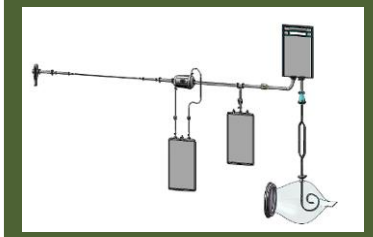
Mobius Single-Use Products　　Mobius一次性产品

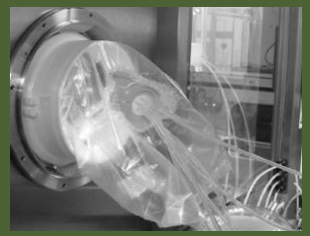
Sterile Connectors and Disconnectors

Mixers, Sampling Solutions and Assemblies

Mobius CellReady & FlexReady Systems

Final Formulation and Filling Solutions





Agenda

1 Single-Use Technology Application 一次性技术的应用

2 Regulation & Guidelines for Single-Use Systems 一次性系统法规与指南

3 Validation for Single-Use Systems 一次性系统验证

FDA/EU General GMP Guidelines
FDA/EU 通用 GMP 指南

FDA

FDA, Code of Federal Regulations, Part 211, "Current Good Manufacturing Practice for Finished Pharmaceuticals", Part 211.65, "Equipment Construction", 2005

*"Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be **reactive, additive, or absorptive** so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."*

"接触组分、中间产物或者药品的设备表面必须不和药物反应、不添加成分、不吸附药物，若改变药物的安全性、一致性、浓度、质量或纯度，则不能满足官方或者其他既定要求。"

EU

European Commission, EUDRALEX Volume 4, "Good Manufacturing Practices, Medicinal Products for Human and Veterinary Use", Chapter 3, "Premise and Equipment", 2003

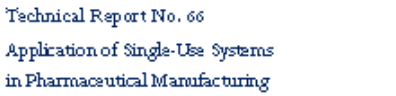
*"Production equipment shall not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be **reactive, additive or absorptive** to such an extent that it will affect the quality of the product and thus present any hazard."*

"生产设备不能对产品有任何危害。接触产品的生产设备必须不起反应、不添加成分或吸附药物而影响到产品的质量并产生危害。"

More reference on SUS is being updated by regulatory
法规机构将正在更新关于一次性系统的法规要求和指南

- PDA Technical Report No. 66th: Released on Oct. 2014
  PDA 66号技术报告：2014.10已发布
- USP Material Safety revisions: USP关于材料安全性方面的更新
  New mandatory chapter for processing materials; 工艺过程材料
  New voluntary chapter for E&L E&L章节
- BPSA Guidance on best practices Particulate Control;
  BPSA指南关于颗粒物的控制；
- BPOG / BPSA E&L Standard Protocol Effort;
  BPOG/BPSA标准化E&L测试方案；
- PQRI: Tech reports & Guidelines from Parenteral and ophthalmic drug products leachables and extractables group

Table of Contents of PDA TR66
PDA 66号技术报告内容



1. Introduction
2. Glossary of Terms
3. Points to Consider for Single-Use System Manufacturing Strategy
4. **Single-Use Technologies and System Integration**
5. **Qualification and Verification of Suppliers, Materials, Components and Completed Assemblies**
6. **Business Drivers for the Adoption of Single-Use Systems**
7. **Implementation of a Single-Use System**
8. **Appendix I: Overall User Requirement Specification Example**
9. **Appendix II: Project Execution Plan Example**
10. **Appendix III: Training Requirements Example**
11. References

Priority / Relevancy
High
Medium
Low

Qualification and Verification of SUS – PDA TR66
验证与确认– PDA 66号技术报告

The end user must identify that the SUS supplier's approach to the design and selection of materials of construction includes components and materials such as:

终端用户必须认识到SUS供应商设计和选择结构材料的方法包括组件和材料，例如:

- Filters　过滤器
- Sensors　传感器
- Polymers　聚合物
- Lubricants　润滑剂
- Slip Agents　助滑剂

Qualification and Verification of SUS – PDA TR66
验证与确认– PDA 66号技术报告

It is important for the end user to have access to controlled documentation of the qualification studies.

对于终端用户，获得SUS材料和组件的确认测试受控文档很重要。

- Batch Numbers traceable to the raw materials　可追溯到原材料的批号
- Product shelf life　产品效期
- Certificate of quality　质量证书
- Certificate of integrity　完整性证书
- Endotoxin certification (to required and specific endotoxin level)　内毒素认证（所需的具体内毒素含量）
- Animal-free certification　无动物来源认证
- Sterilization certification (if sterility is claimed)　灭菌认证（若有无菌保证）

More Cooperation with Supplier; Higher Requirement for Supplier.

Qualification and Verification of SUS – PDA TR66
验证与确认– PDA 66号技术报告

Risks Associated with SUS 一次性系统相关风险

Table 5.2-1 Risk Complexities of SUS Items and Applications

		System Complexity				
		Low	Moderate	High		
Impact to Process	Low	Buffer/Storage	UF*/DF†/ Concentration	Clarification/ Recovery	Low	Impact to Process
	Moderate	Transport/ Shipping	Connectors/Mixing/ Medium Storage	Cell Culture/ Fermentation	Moderate	
	High	Freeze/Thaw	Purification/ Product Storage	Fill and Finish	High	

*UF – ultrafiltration †DF – diafiltration

Agenda

1 Single-Use Technology Application 一次性技术的应用

2 Regulation & Guidelines for Single-Use Systems 一次性系统法规与指南

3 Validation for Single-Use Systems 一次性系统验证

Testing Requirements for Single-Use Assemblies
一次性系统的测试要求

Regulatory Requirements 法规要求	Associated Studies 相关研究
Additive 添加	Particulate 颗粒物
	Extractables & Leachables 可提取物和浸出物
Adsorptive (removal) 吸附	Interaction Studies (Compatibility…) 相互作用研究（兼容性…）
Efficacy, Performance 药品功效/性能	Drug Performance 药品性能
Reactive 反应	Drug Stability 药品稳定性

Compatibility
兼容性

- Compatibility assessment as early as possible
  尽早进行兼容性评估
- Proper evaluation of the design space limits
  对系统的限度进行恰当的评估
- Reconsider compatibility at each process change (scale up, filter change…)
  当工艺变更时（放大、过滤器更改等），需要对兼容性进行再评估

Compatibility Data Collection
兼容性数据收集

Collect supplier's Information
收集供应商的信息

- Manufacturer's compatibility tables
  供应商的兼容性列表
- Manufacturer's Validation Guides
  供应商的验证指南

	Guanidine Thiocyanate, 5M salt, aqueous solution	Helium gas	Hexane HC, aliphatic	Hydrochloric Acid, 1 N (HCl) acid, inorganic	Hydrochloric Acid, 6N (HCl acid, inorganic	Hydrochloric Acid, conc. (HCl) acid, inorganic	Hydrofluoric Acid acid, inorganic	Hydrogen gas	Hydrogen Peroxide, 3% peroxide	Hydrogen Peroxide, 30% peroxide	Hydrogen Peroxide, 90% peroxide
Housing materials											
HDPE high density polyethylene	GR	R	LTD	R	R	R	R	R	R	R	NR
PP polypropylene	ND	R	NR	GR	TST	NR	NR	R	R	TST	R
PS polystyrene	ND	ND	NR	R	TST	NR	NR	ND	R	R	R
PVC polyvinyl chloride	ND	ND	NR	GR	TST	NR	NR	R	R	TST	R
MMA acrylic based copolymer	GR	ND	GR	GR	ND	ND	GNR	ND	ND	ND	ND
ABS acrylonitrile-butadiene-styrene polymer	ND	ND	GNR	GR	ND	ND	GNR	ND	ND	ND	ND
SAN styrene-acrylonitrile polymer	ND	ND	GR	ND	ND	ND	ND	ND	ND	ND	ND
PC polycarbonate	ND	R	NR	GR	TST	NR	NR	R	R	R	R
PET polyethylene terephthalate	ND	ND	R	GR	R	R	NR	R	R	R	R
EASTAR copolyester	ND	ND	R	ND	ND	ND	ND	ND	ND	ND	ND
Filter materials											
PP polypropylene	ND	R	NR	GR	TST	NR	NR	R	R	TST	R
PVC polyvinyl chloride	ND	ND	NR	GR	TST	NR	NR	R	R	TST	R
PC polycarbonate	R	R	R	R	R	R	TST	R	R	R	R
PTFE polytetrafluoroethylene	GR	R	R	R	R	R	R	R	R	R	R
PVDF polyvinylidene fluoride	ND	TST	R	R	TST	NR	NR	R	R	R	R
MCE mixed cellulose esters	ND	R	GR	GR	NR	GNR	NR	R	NR	NR	NR
PES polyether sulfone	ND	ND	G								
NYL nylon	ND	R	R								

Collect drug manufacturer's information
收集药企的信息

- Device fluid pathway
  溶液流向
- Drug product solvents
  药品组成
- Key process parameters : Temperature, contact time
  关键参数：温度、接触时间

Compatibility
兼容性

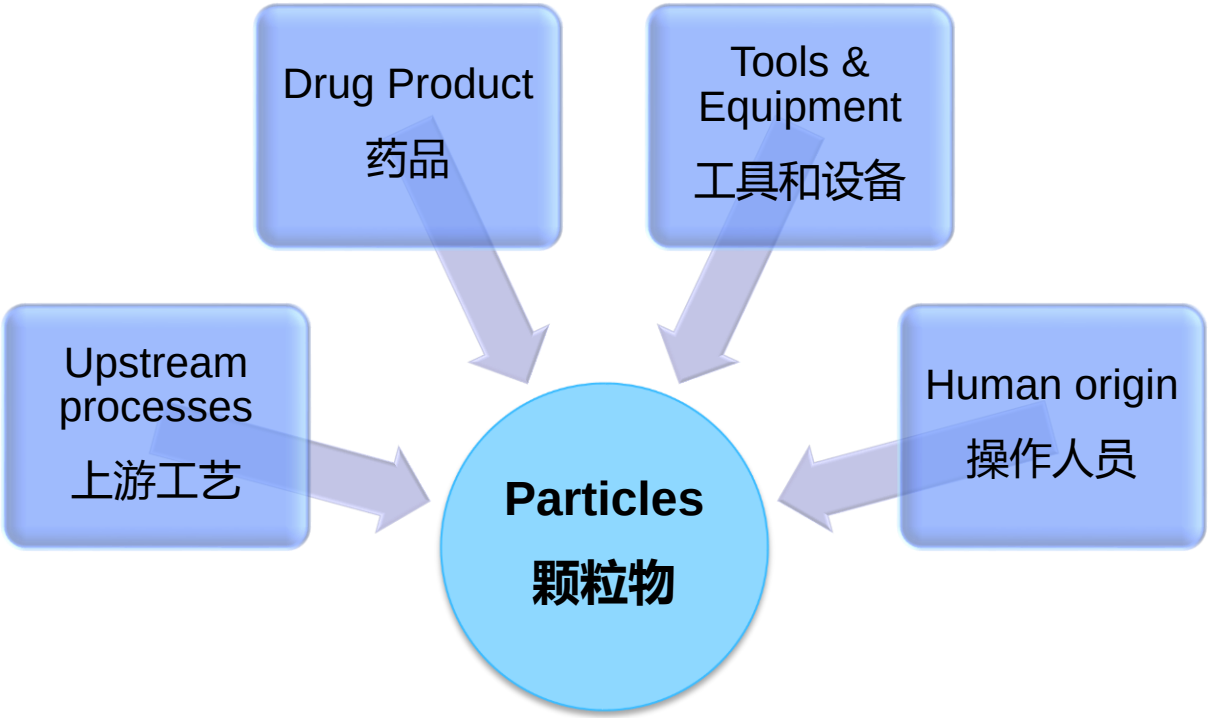
Certification
兼容性证书

- Any possible interaction between the selected components and the Drug Product formulation is assessed using **qualification docs, compatibility charts and literature**.
- 通过**验证报告、兼容性列表和文献**来评估组件与药品之间的相互作用

Testing with Drug Product
用产品测试

- Test results assessment: **Comparison before and after exposure;** Acceptance criteria review; Visual examination
- 测试结果评估：**比较接触前后的结果**；审核接受标准；目测

Particles
颗粒物



Particles 颗粒物

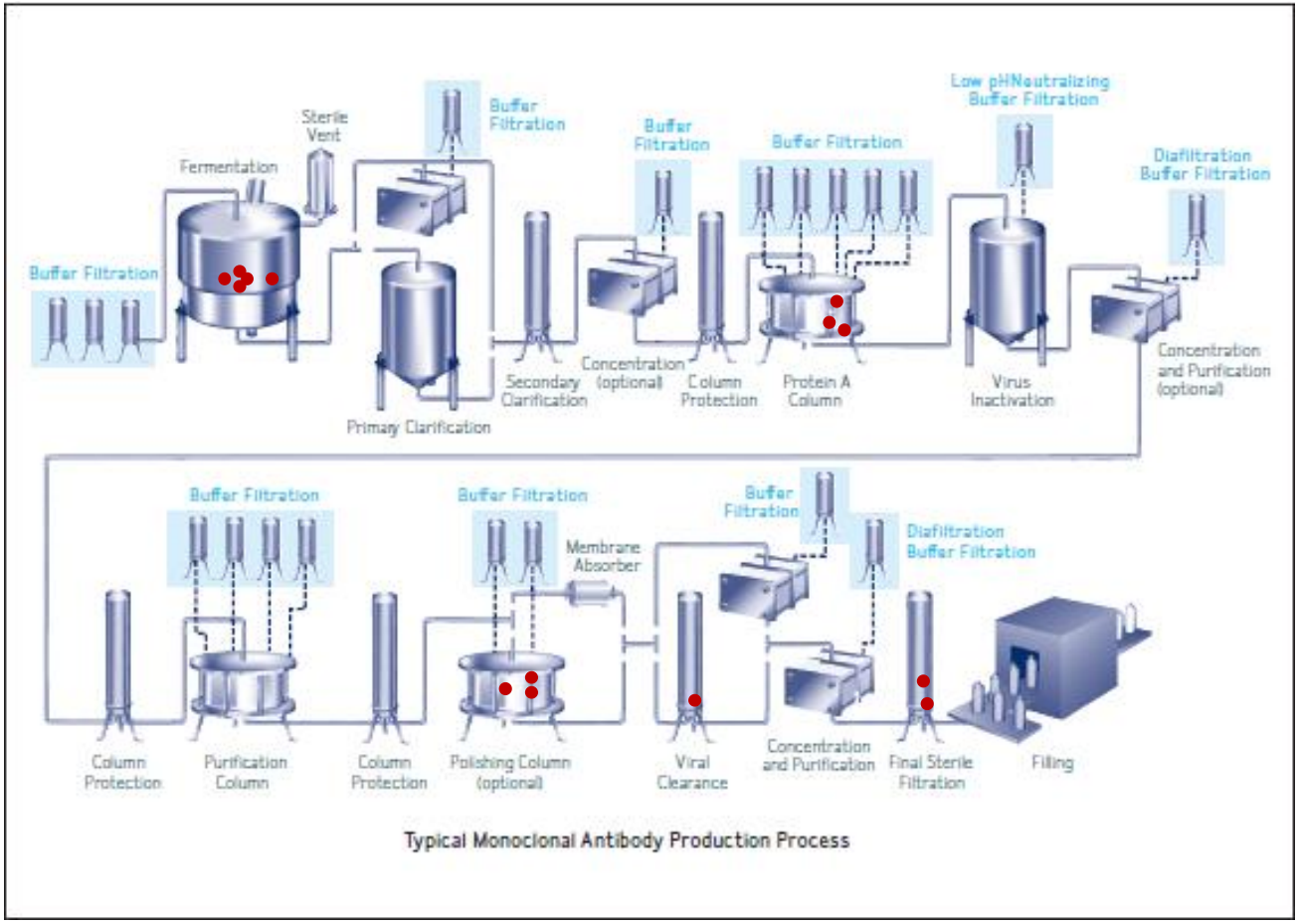
Organization 法规机构	Standards 标准
USP – National Formulary 美国药典	<1> Injections; <787> Subvisible Particulate Matter in Therapeutic Protein Injections; <788> Particulate Matter in Injections; <790> Visible Particulates in Injections; <1788> Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions
EP 欧洲药典	2.9.19 Subvisible; 2.9.20 Visible
JP 日本药典	6.06 Visible; 6.07 Subvisible

Particle limitations for both light-obscuration and microscopic particle-count methods
USP <788>中光透法和显微镜计数法的颗粒物限度

USP <788> Large-Volume Parenterals (>100 mL)	Particle Limits 颗粒物限度
Light obscuration method 光透法	≤25 particles/mL that are ≥10 µm, and ≤3 particles/mL that are ≥25 µm
Microscopic particle count method 显微镜计数法	≤12 particles/mL that are ≥10 µm, and ≤2 particles/mL that are ≥25 µm
USP <788> Small-Volume Parenterals (≤100 mL)	**Particle Limits 颗粒物限度**
Light obscuration method 光透法	≤6,000 particles/mL that are ≥10 µm, and ≤600 particles/mL that are ≥25 µm
Microscopic particle count method 显微镜计数法	≤3,000 particles/mL that are ≥10 µm, and ≤300 particles/mL that are ≥25 µm

Particles
颗粒物

Filters will retain the vast majority of particles…
过滤器能截留住大多数颗粒物



Typical Monoclonal Antibody Production Process

Particles
颗粒物

Particle contribution 颗粒物来源

- Coming from any plastic material after a filter
- 来源于过滤器后的某些塑料

Final particle QC 最终产品中颗粒物检测

- In the final container 在终端容器中
- Under worst case conditions 在最差条件下

Determination of the flush volume 确定冲洗体积

- Needed to decrease the amount of particles
- 降低颗粒物数量

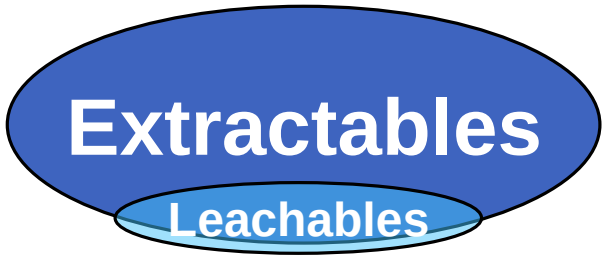
Focus on Extractables and Leachables
关注可提取物与浸出物

Extractables 可提取物

- Extracted from plastic or elastomeric materials in solvents under aggressive conditions.
- Determined under “worst-case” conditions (Model Stream approach) 最差条件（模拟溶剂）

Leachables 浸出物

- Compounds that leach from the plastic or elastomeric materials into actual drug product under normal use conditions.
- Determined with the product under normal processing/storage conditions 实际产品真实工艺/储存条件



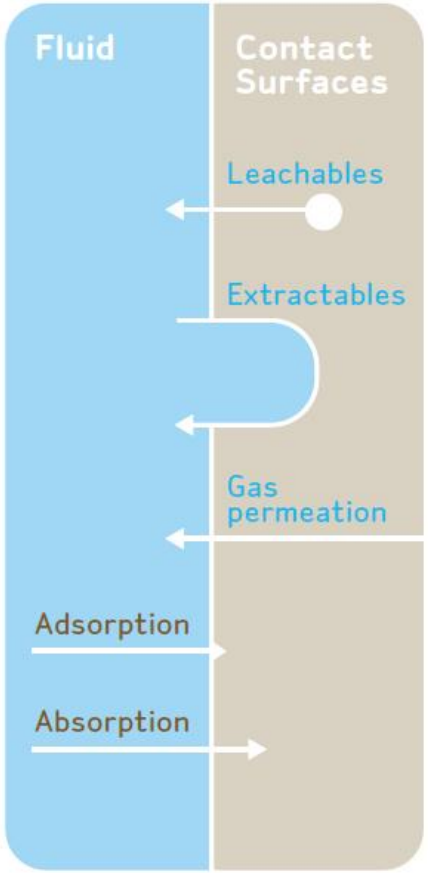


Figure 1. Possible interactions between fluid and its contact surfaces

Regulatory Expectations Summary
法规期望总结

Incorporate Qbd by selecting well qualified and safe materials

选用良好质量和安全性的药品接触材料

Generate Extractables information in model solvents under worst-case conditions

在模拟溶剂和最差条件下得到可提取物信息

Perform risk assessment

进行风险评估

Conduct Leachables studies as necessary

必要时进行浸出物实验

Perform toxicity evaluation and demonstrate safety

进行毒理评估，并证明其安全性

EMA, “Guideline on Plastic Immediate Packaging Materials”, 2005
BPSA, “Recommendation of Extractables and leachables Testing”, Revised 2010
PDA, Technical Report No. 26 Revised 2008, *Sterilizing Filtration of Liquids*

How to deal with the E&L data?
如何评估得到的可提取物和浸出物数据？

- No Official Acceptance Criteria established for Extractables and Leachables
  可提取物和浸出物没有建立接受标准
  - ✓Compound Specificity 成分专属性
  - ✓Toxicological Data on Compounds 物质的毒理学数据
  - ✓Concentration in final dosage 最终剂型中的浓度
  - ✓Dose Size, Regimen, Dose Delivery 剂量大小、给药时间、给药途径
  - ✓Patient Population 个体差异

- Concept of Threshold of Toxicological Concern (TTC) has its roots in the concept that 'safe levels of exposure' can be identified for individual chemicals with known toxicological profiles.

  毒理学关注阈值（TTC）概念起源于可确定具有已知毒理学档案的单个化合物的“安全暴露水平”这一概念中。

Case Study -- Blank Run on Complete Process
案例分析 -- 完全工艺下的空白实验

200L SU Bioreactor batched with Cell Culture Media **细胞培养基-200L一次性反应器**	▪ No inoculation ▪ 13 days at process temperature & agitation, with feeds ▪ Sampled at t=0, t=13 days ▪ Day 13 harvest followed by full DSP
Downstream Processing **下游工艺**	▪ Full-scale operations with all devices/resins ▪ All unit operations utilized single-use systems & flowpaths ▪ All process buffers prepped & stored in SU bags ▪ Sampling from each buffer bag/process intermediate pool
Sample Analysis Methods **取样分析方法**	▪ GC-MS (VOC and sVOC) ▪ LC-MS (non VOC) ▪ ICP (Metals)

Fully Single-Use MAb Process
完全一次性单抗工艺

Analysis Samples

t=0 Culture Fluid

Bioreactor

Mobius® CellReady 200 L Bioreactor

13-day Culture Fluid

Depth Filtration

Millistak+® D0HC + X0HC Pod filters

Clarified Harvest Pool

Capture Step

ProSep® Ultra Plus resin

Post Capture Pool

Virus Inactivation

Mobius® Mix system with Millipore Express® SHC filter

Post VI Pool

Bulk Drug Substance

t=0
t=7
days

Express® SHC filter

UF/DF

Pellicon® 3 Ultracel 30kD cassette

Post VF Pool

Viral Filtration

Viresolve® Pro+ solution

Post AEX pool

AEX Step

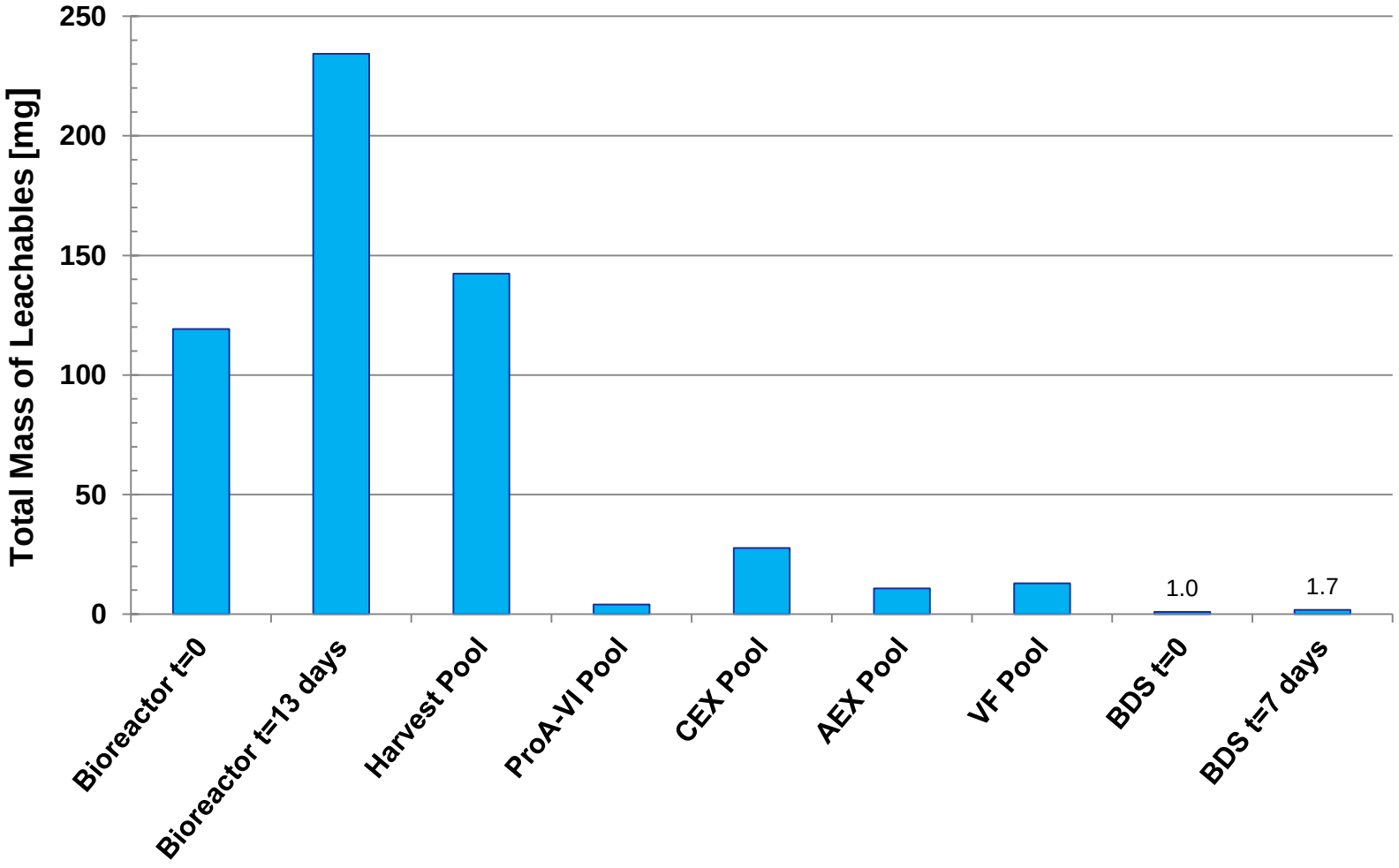
Membrane adsorber

Post CEX pool

CEX Step

Fractogel® SO_3 resin

Total Mass of Leachables through Process
工艺过程中浸出物总量



Patient Exposure to Leachable in BDS
患者接触原液中的浸出物含量

Based on mAb high-dosing regimen of 1050 mg API/2 weeks 高剂量

- Case 1: Assume BDS API concentration = 100 g/L

LEA Concentration (µg/mL)	Dosage (mL)	Frequency (days)	Leachables	
			Total µg/dose	Daily Average µg/person/day
0.9	10.5	14	9.2	0.65

- Case 2: Assume BDS API concentration = 10 g/L

LEA Concentration (µg/mL)	Dosage (mL)	Frequency (days)	Leachables	
			Total µg/dose	Daily Average µg/person/day
0.9	105.0	14	91.6	6.54

Assess Risk / Patient Safety
风险评估/病人安全性

	Daily Average µg/person/day	Risk
Case 1	0.65	Low
Case 2	6.54	High

PQRI	Threshold Concentration (µg/person/day)
Genotoxic Compound	1.5
Neurotoxic Organophosphate Compound	18
Cramer Class III	90
Cramer Class II	540
Cramer Class I	1800

A Look at Individual Compounds
考察单个化合物

- The leached compound identified in the greatest concentration within the BDS after 7 days storage was Hexanal (CAS 66-25-1) 浓度最高的化合物为己醛

LEA Concentration (µg/mL)	Dosage (mL)	Frequency (days)	Leachables	
			Total µg/dose	Daily Average µg/person/day
0.1	105.0	14	11.6	0.83

- The concentration of any individual leachate would fall below a worst-case threshold exposure limit of 1.5 ug/day 任何单个组分的浸出物浓度在最差条件下都低于接触阈值1.5ug/day
- Toxicity of individual compounds can be further evaluated and would likely demonstrate orders of magnitude below safety thresholds 进一步评估各化合物的毒性，其数量可能都低于安全阈值
- Ex. An ADE for Butanal/Pentanal was established at 3.75 mg/person丁醛/戊醛的ADE，被定为3.75 mg/人

Conclusions 结论

1. Complete Leachables Blank Run demonstrates that the downstream purification unit operations provide a level of removal of leachables throughout the process
浸出物在下游纯化工艺过程中能大量去除

2. Study confirms and supports direction of industry to focus on evaluating E&L from the bioreactor and from BDS storage through to drug product
对可提取物和浸出物的关注从上游到下游

3. Study brings confidence in patient safety in regard to leachables from single-use processes as demonstrated by toxicological threshold analysis
一次性工艺所带来的浸出物从毒性阈值分析中表明对病人的风险较低

4. Final filling operations utilize primarily the same MoC's as evaluated here, providing confidence that leachables should not pose a safety hazard
最终灌装操作使用的同样的操作和评估方法，为降低最终产品中浸出物的风险提供了信心

Summary 总结

1. Key industry drivers lead to single-use processing solutions.
   关键驱动因素领导着一次性技术的发展和趋势。

2. Regulation & Guidelines drive the need of validation for single-use system.
   法规驱动着一次性系统的验证需求。

3. What kind of validation should be performed? Compatibility, Particles, E&L, Adsorption…
   需要做哪些验证？兼容性，颗粒物，可提取物和浸出物，吸附……

4. Your SUS supplier should be able to provide insight and value to the entirety of the related validation evaluation.
   一次性使用系统（SUS）供应商应能提供对相关验证评估的建议和能力。

Thank you!

谢谢大家！