Technical Report No. 61

Steam In Place

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PDA
Parenteral Drug Association

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致蒲公英论坛蒲友：

本书（TR61 SIP）翻译工作由蒲公英制药技术论坛www.ouryao.com 布克_41 提供原文并发起主持。对各位的利用业余时间进行翻译工作表示至真至诚的感谢！！

在此特别感谢以下参与翻译工作人员！

翻译及校对人员名单

序号	章节	页码	认领情况	认领人	完成情况
1	1.0-2.0	1-6	已认领	观沧海	已完成
2	3.0	7-10	已认领	张正言	已完成
3	4.0	11-18	已认领	开羽	已完成
4	5.0	19-25	已认领	wj1914	已完成
5	6.0	26-36	已认领	一沙一叶	已完成
6	7.0	37-39	已认领	weiguizhang0326	已完成
7	8.0-8.3	40-44	已认领	334352444	已完成
8	8.4	45-47	已认领	wmx2046	已完成
9	8.5-8.5.7	47-48	已认领	wj1914	已完成
10	8.5.8-8.5.12	49-51	已认领	molly	已完成
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The Steam in Place Task Force would like to dedicate this technical report in memory of Lance Morien.

The content and views expressed in this Technical Report are the result of a consensus achieved by the authorizing Task Force and are not necessarily views of the organizations they represent.

Steam In Place

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Table of Contents

FIGURES AND TABLES INDEX

Introduction
引言

PDA Technical Report No. 1, Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control, updated in 2007, focuses on the microbiology and engineering concepts of moist heat sterilization and the general approach to sterilization science in batch sterilizers (autoclaves) (1). This technical report is intended to complement PDA Technical Report No. 1 and will focus on steam in place (SIP) processes.
于 2007 年更新的 PDA 技术报告 1 号，湿热灭菌工艺的验证：周期设计、开发、确认和持续控制，侧重于湿热灭菌的微生物学和工程学方面的概念以及以批次灭菌的灭菌器（高压灭菌器）（1）的一般灭菌方法。该技术报告是 PDA 技术报告 1 号的补充，侧重于在线蒸汽灭菌（SIP）工艺。

The primary objective of the task force responsible for this technical report was to develop a scientific technical report on SIP processes that provides recommendations for use by industry and regulators. References to appropriate and up-to-date scientific publications, international regulatory documents, journal articles, technical papers, and books are used to provide more detail and supportive data can be found.
本报告特别工作组的主要目的是提供一份推荐给企业和监管部门使用的在线蒸汽灭菌科学技术报告。本报告参考了最新的科技出版物、国际法规文件、期刊文章、技术论文和书籍，从中可查得更多详细并有说服力的数据和资料。

Steam in Place was chosen as the title because this document focuses on the various applications of steam for in situ sterilization for “sterile” applications and for in situ sanitization and other bioburden control applications widely used for systems that do not claim to be “sterilized” via steam. We also differentiate “steam in place” from the more generic term “sterilize in place” used to describe in situ sterilization using various types of gaseous or liquid sterilizing agents including steam (1).
选择 SIP 作为标题是因为本报告侧重于采用蒸汽进行原位灭菌、原位消毒和其他控制微生物限度等，而不仅限于通过蒸汽灭菌。同时还应区别于使用各种其他物质如气体或液体混合在蒸汽中进行在线灭菌的方法。

The task force was composed of European, North American, and South American industry professionals to ensure the methods, terminology, and practices of SIP reflect sound science and can be applied globally. This technical report was disseminated for public review and comment prior to publication, to provide the widest possible review and ensure its suitability as a guide to industry.
特别工作组由欧洲、北美和南美的业内专家组成，确保 SIP 使用的方法、专业术语和做法具有良好的科学性并可以在全球范围内使用。本报告在正式出版之前曾公开征求意见，以确保本报告作为业内的一个指南的适应性。

SIP is often a pivotal step of aseptic processing for sterile product manufacture, and as such, may benefit from the application of risk management methodologies. The characterization, evaluation, and assessment of risk are useful to direct overall efforts for cycle development and subsequent validation. After development of a risk assessment, more resources can be focused on mitigating risk for systems, equipment, or processes that have the highest potential for product contamination. The management of risk may be employed throughout the lifecycle of SIP equipment and processes to efficiently focus and allocate resources commensurate with the probability of impacting final product purity and safety. Descriptions of the specific steps and tools for risk management are available from a variety of sources (2,3).
对于无菌产品的生产，SIP 经常是无菌处理的关键环节，因此，可以从风险管理方法的应用中受益。风险的鉴定、评估和评价对于指导循环开发和随后的验证都非常有价值。经过风险评估后，更多的资源可集中

于降低那些对产品具有高的潜在污染的系统、设备或过程的风险。风险管理可以应用于 SIP 设备和工艺的整个生命周期，对于可能影响产品纯度和安全的隐患按照严重程度进行控制。风险管理的具体步骤和使用的工具在其他地方说明（2,3）。

1.1 Scope
范围

The scope of this technical report is limited to discussion of SIP processes that provide moist heat sterilization and/or sanitization of equipment and systems supporting the manufacture of medicinal products. The principles discussed in this report may also be applied to those systems where portable equipment is steamed at a fixed station (steam out of place).
本技术报告只讨论使用湿热对医药生产设备和系统进行灭菌和或消毒的 SIP 工艺，其原理也适用于便携式设备离线灭菌。

Application of the concepts presented in this technical report to laboratories or other non-CGMP applications, including hospitals, is not intended.
本技术报告使用的概念对实验室或非 CGMP 范围，包括医院不作要求。

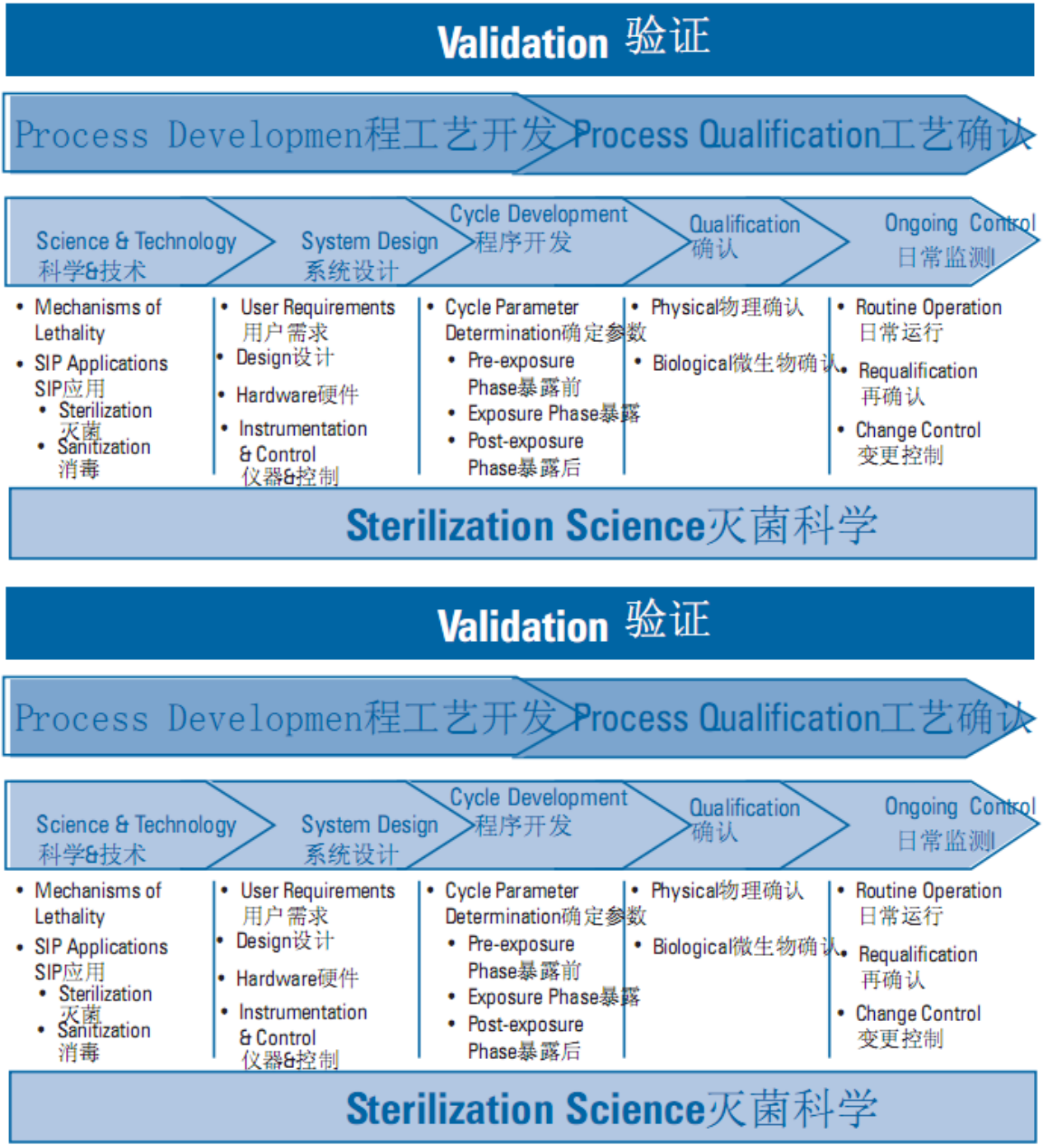
The following concepts are out of scope:
以下概念超出范围

- Clean-in-Place (except where related to SIP)
  在线清洁（除非涉及到 SIP）
- In situ media sterilization
  生产用介质灭菌
- Product Sterilization
  产品灭菌
- Design and qualification of utilities
  公用系统的设计和确认

This technical report is organized in a logical progression from the essential elements of SIP system design through SIP cycle development, qualification, and ongoing operation.
本技术报告自 SIP 系统设计的必要元素，贯穿程序开发、系统确认和日常运行具有严密的逻辑性。

In the interest of clarity, the report provides a glossary of technical terms, and begins with a discussion of the SIP Life Cycle as depicted in Figure 1.1-1.
为清楚起见，报告提供的技术术语词汇表，从谈论 SIP 生命周期开始，如图 1.1-所示。的讨论。

Figure 1.1-1 Steam in Place Life Cycle 图 1.1-1 SIP 的生命周期



Validation 验证
Process Developmen程工艺开发
Process Qualification工艺确认
Science & Technology 科学&技术
System Design 系统设计
Cycle Development 程序开发
Qualification 确认
Ongoing Control 日常监测
• Mechanisms of Lethality
• SIP Applications SIP应用
• Sterilization 灭菌
• Sanitization 消毒
• User Requirements 用户需求
• Design设计
• Hardware硬件
• Instrumentation & Control 仪器&控制
• Cycle Parameter Determination确定参数
• Pre-exposure Phase暴露前
• Exposure Phase暴露
• Post-exposure Phase暴露后
• Physical物理确认
• Biological微生物确认
• Routine Operation 日常运行
• Requalification 再确认
• Change Control 变更控制
Sterilization Science灭菌科学

Sterilization science for SIP systems will be discussed to expand on the concepts developed in PDA Technical Report No. 1. The System Design section will cover the design considerations for an SIP process including hardware (e.g., pipes, tanks, filters, valves) and controls (e.g., monitoring and control instruments). Example process parameter tables for SIP cycles are provided to support assessment of risk associated with different cycle phases. The Cycle Development section applies theoretical concepts that are developed into the practical application of a comprehensive SIP process.

在 PDA TR1 的基础上对 SIP 系统的灭菌科学进行扩展探讨。SIP 系统设计部分将涵盖设计方面的考虑，包括硬件（例如，管道，储罐，过滤器，阀门）和控制（例如，监测和控制仪器）。SIP 的实例程序数值表能够提供对不同周期的风险评估提供支持。系统的开发部分提供 SIP 程序能够发展为实践应用的理论概念。

The Performance Qualification section focuses on the application of physical and biological approaches used to demonstrate the efficacy of particular SIP processes as they relate to intended use.
在性能确认部分的重点是采用物理和生物挑战试剂的方法来证明一个特定的 SIP 工艺能达到他预期的使用目的。

Finally, the Ongoing Process Control section discusses ways to establish and maintain a continuous state of control after the SIP process is implemented. This section includes recommendations for procedural controls, records management, change control, requalification, and maintenance practices
最后，日常监测部分讨论在 SIP 工艺执行后建立和维持一个持续的状态。本节包括对控制程序的建议，记录管理，变更控制，再确认，和维护保养的建议。

1.0 Glossary of Terms
术语

Term usage may differ from company to company, and some terms may be subject to change in the future. However, the terms used in a sterilization program must be clearly defined and well understood within the company. Regulatory guidelines may offer other definitions that should be considered. This technical report uses the following terms, listed here with their definitions and synonyms where applicable.
每个公司对术语的使用不尽相同，有一些术语将来可能会发生变化。然而，在一个公司内，灭菌方案中所采用的术语必须清晰、明确，易于理解。还应结合考虑监管部门的指南提供的术语定义。本报告用到了以下术语，并同时附上相应的定义及必要的同义词。

Bioburden 微生物负荷
Viable microorganisms on or in a pharmaceutical product or in the manufacturing environment.
在医药产品或生产环境中活的微生物数量。

Biological Indicator (BI) Challenge System 生物指示剂挑战系统
A test system containing viable microorganisms of a pure specified strain providing a defined resistance to a specified sterilization process (4). [Synonyms: BI challenge system, microbial challenge, microbiological challenge system.]
一个含有纯的特定的菌株的活的微生物测试系统，此系统对某一灭菌程序具有规定的耐受性。(1) [同义词：生物指示剂挑战系统，微生物挑战，微生物挑战系统]

Biological Qualification 生物指示剂确认
A component of performance qualification that demonstrates, by use of biological indicators, that the required lethality (F_{BIO}) or spore log reduction (SLR) is achieved consistently throughout the sterilized or sanitized portion of the SIP system.
采用生物指示剂来证明整 SIP 系统始终能达到所规定生物杀死率（F_{BIO} 值）或孢子降低的对数的试验。它是性能确认的组成部分。

Bracketing Approach 分组法
A scientific approach for defining characteristics (e.g., Tank sizes, system configurations filter sizes and types) that are tested (in a qualification study or validation study) at upper and/or lower limits.
在（确认和验证研究中的）上限和或下限进行测试的科学方法。

Calibration 校准
The demonstration that an instrument or device produces results within specified limits when compared to those produced by a reference standard or a standard that is traceable to national or international standards, over an appropriate range of measurements.
采用与相关标准或者源于国内或国际的标准进行比较， 以证明一项仪器或设备所得结果符合规定限度标准的活动。

Cold Spot 冷点
The location within an SIP system that achieves the lowest process lethality (F_0) during a SIP process. Note: When lethality values are not available or not applicable (e.g., a sanitization process operating at less than 100 ℃) the cold spot is the location with the lowest temperature profile during the SIP cycle.

在 SIP 系统中，杀灭力最低的位置（F_0 最小的位置）。注意：如果在 SIP 过程中不用 F_0（或不适用）表示灭菌结果，此时指的是 SIP 过程中的温度最低点。

Cool-down Phase 冷却阶段

The phase of an SIP cycle that occurs after completion of the exposure phase. Parameters (e.g., time, temperature, pressure) of a cool-down phase are typically defined in order to meet applicable user requirements for system cooling and drying.

指 SIP 灭菌循环完成之后的阶段。应设定冷却阶段的参数（如：时间、温度、压力）以满足用户对冷却和干燥的要求。

Critical Control Point 关键控制点

A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level (3).

一个用来保护或消除药品质量风险或将风险降低到可接受的水平的步骤，对这些步骤的控制是必不可少的。

Cycle Development 程序的开发

A series of activities performed for the purpose of defining or confirming the cycle parameters (e.g., time, temperature, pressure) necessary to ensure sanitization or sterilization.

为保证消毒或灭菌的效果而进行确认参数（如：时间、温度、压力）的一系列活动。

Deadlegs 死角

An area of entrapment in the vessel or piping run that could lead to contamination of the product due to insufficient exposure to moist heat (5).

容器或管道运行中不能被湿热蒸汽有效灭菌从而导致产品受到污染的区域。

D_T Value D_T 值

The time in minutes required for a one-logarithm, or 90%, reduction of the population of microorganisms used as a biological indicator under specified lethal conditions. For steam sterilization, the D-value should always be specified with a reference temperature, D_T. For example, a BI system with a D121˚C of 1.4 minutes requires 1.4 minutes at 121 ℃ to reduce the population by one logarithm. [Synonym: D-value]

在规定的灭菌条件下，使所用生物指示剂的数量下降一个对数单位，或杀灭 90%所需的时间。在湿热灭菌中，D 值总需注明参照温度，即以 DT 表示。例如，一个 D121℃=1.4 分钟的生物指示剂系统，表示在 121℃下，杀灭 90%的芽孢需要 1.4 分钟。（即：D 值）

Exposure Phase 灭菌阶段（暴露阶段）

The phase of the SIP cycle in which the appropriate parameters (e.g., time, temperature, pressure) are maintained within defined ranges for the time (exposure time or dwell period) determined to be necessary to achieve the desired lethality.

系指 SIP 灭菌程序中，为获得设定杀灭效果，保持设定灭菌参数温（如：时间、温度、压力）持续时间。

F-Value (Lethality Factor) F 值（累计杀灭时间）

A measurement of sterilization effectiveness, the F-value is the calculated equivalent lethality (using a specified z-value), in terms of minutes at a reference temperature (T_{ref}), delivered by a sterilization cycle.

灭菌效力的度量值。F 值是在规定的 Z 值下，一灭菌程序赋予被灭菌物品在参照温度（T 参照）下的等效灭菌时间。

F_0 F_0值

A term used when the specific reference conditions of T_{ref}= 121.1℃ and z = 10℃ are used to calculate the equivalent lethality. For example, when the z-value of the BI is 10℃, a cycle with an F(T=121.1℃, z=10℃), or F_0, equal to 8 minutes is equivalent (in terms of delivered lethality) to a square wave cycle of 8 minutes at 121.1℃. A square wave cycle that provided an exposure of 25.9 minutes at 116℃ would also yield an F_0 of 8 minutes.

是指 Z 取 10℃时，一个湿热灭菌程序赋予被灭菌品 121.1℃下灭菌的等效灭菌时间。例如，当生物指示剂的 z 取 10℃，F（T=121.1℃，z=10℃）赋予产品 8 分钟的程序，或 F0 为 8 分钟，与一个 116℃灭菌 25.9 分钟是等效的，F0 均为 8。

Note: The reference temperature used in calculating F_0 is 121.1℃, which is the approximate mathematical equivalent of 250℉. The reference temperature of 121℃ for F_0 will be used throughout this report for brevity.

注意：用于计算 F_0 值得参考温度是 121.1℃，其近似于 250℉ ，本报告为了方便 F_0 使用的参考温度都指 121.1℃。

$F_{Biological}$ (F_{BIO}) 灭菌程序的生物杀灭时间（F_{BIO}值）

A term used to describe the empirically derived lethality of microorganisms on or in a BI challenge system. The F_{BIO}-value is calculated as $D_T \times LR$, where D_T is the D-value of the BI system at the reference temperature (T) and LR is the actual logarithmic reduction ($\log N_0 - \log N_F$) of the BI population achieved during the cycle. Where N_0 is the initial population of the BI and N_F is the remaining population after the sanitization/sterilization cycle.

它是生物指示剂挑战试验系统中微生物实际杀灭效果的量度。生物杀灭时间可以 $D_T \times$ LR 计算获得，这里，D_T是生物指示剂系统以 T 度为参照温度下的 D 值， LR 是灭菌过程中生物指示剂实际的对数单位下降值（$\log N_0 - \log N_F$）。N_0 是指 BI 开始的数量，N_F 是指在消毒/灭菌后存活的 BI 数量。

$F_{Physical}$ (F_{PHYS}) 灭菌程序的物理杀灭时间（F_{PHYS}值）

A term used to describe the delivered equivalent lethality that is calculated based on the physical parameters of the cycle. The F_{PHYS} value is calculated for a reference temperature (T_{ref}) and z value using the equation:

F_{PHYS} 系指以灭菌程序的物理参数计算的等效杀灭时间。F_{PHYS} 值根据参考温度(T_{ref})和 z 值通过以下公式求得：

Where, 式中，

i = time interval between readings, i 等于读数间隔

Ti = temperature reading for that interval, Ti 等于第 i 次读的温度

Tref = reference temperature Tref 为参考温度

z = temperature change required to change the D-value by a factor of 10

z 为使 D 值变更一个对数单位温度需调节的度数。

Flash Steam 闪蒸蒸汽

A mixture of steam and water that occurs when hot water under pressure moves to a region of lower pressure.

当高压热水下移动到较低的压力区域时产生的蒸汽和水的混合物。

Gravity Displacement Process 重力置换程序

A sterilization process based on the principle that air within the system is more dense than steam entering the system. As steam enters the system, air is pushed out the bottom drain/vent/trap and exits with the condensate.
以冷空气比进入腔室的蒸汽重而沉降在腔室底部的原理而运行的灭菌程序。 当蒸汽进入腔室时，将冷空气及冷凝水通过疏水器从底部排出。

Hazard 危险
The potential source of harm (3).
潜在的危害源（3）。

Heat-up Phase 加热阶段
The phase of an SIP cycle that occurs prior to the exposure phase. Process parameters (e.g., air removal, preheating, uniform temperature distribution)are developed for this phase in order to meet applicable user requirements for system conditioning. [Synonym: come-up time, heat-up time.]
是 SIP 程序达到灭菌温度前的阶段。工艺参数（如：排除空气、预热、均温）从此阶段开始发展达到用户对系统环境的要求。（同义词：准备时间，预热时间）

Installation Qualification (IQ) 安装确认
Documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations, and/or user requirements (6).
对设备或系统的安装或改造进行形成文件的确认，以证明达到了经批准的设计，制造商的建议，和/或用户的要求（6）。

Leak Test 泄漏测试
See System Integrity Test
参考系统完整性测试。

Minimum Acceptable Cycle (MAC) 最低可接受程序
The minimum cycle conditions (in terms of delivered minimum lethality or minimum time and temperature) that would be considered acceptable.
最低程序参数（最短的灭菌时间或最短时间和温度的结合）至少能达到可接受的范围。

Operating Parameters 运行参数
Values (e.g., time, temperature, pressure) that are controlled and/or measured that collectively define each phase of an SIP cycle (e.g., heat-up, exposure, and cool-down).
加以控制和/测量的值（如：时间、温度、压力），其在 SIP 程序的各个阶段都有定义。

Critical Parameters 关键参数
Values (e.g., time, temperature, and pressure) that are controlled and/or measured to ensure the efficacy of a steam in place cycle. Failure to meet a critical parameter should result in rejection of the cycle.
需要控制和/测量的参数（如：时间、温度和压力）以确保 SIP 程序的有效性。关键参数的不合格将会导致程序被拒绝。

Key Parameters 重要参数
Values that are controlled and/or measured and are used to assure the ongoing "state of control" of steam in place cycles. Failure to meet a key process parameter should result in an investigation.
需控制/和测试以保证 SIP 在"受控状态"正常运行的参数。重要参数不合格时，需进行调查。

Operational Qualification (OQ)运行确认

Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges (7).

对已安装或改造完成的设备或系统在预先定好的运行范围进行形成文件的确认以证明他符合要求。

Overkill Design Approach 过度杀灭程序设计法

A sterilization method where the steam in place cycle is capable of meeting or exceeding both an F_{BIO} and F_{PHYS} of 12 minutes and worst case bioburden assumptions are made to demonstrate an SAL of 10^{-6}. (Note: For typical SIP systems, the F_{PHYS} will need to be greater than the F_{BIO} .)

对于一个 SIP 程序能够保证 F_{BIO} 和 F_{PHYS} 都达到或超过 12 分钟或能证明可使微生物负荷降低到 10^{-6}（注意：对于 SIP 系统，F_{PHYS} 值需大于 F_{BIO} 值）的无菌保障水平的设计方法。

Partial-Cycle Qualification 非完整程序确认

A qualification method that uses less than the full exposure time to demonstrate sterilization or sanitization cycle efficacy. [Synonym: fractional cycle.]

通过运行部分程序证明灭菌或消毒的有效性的一种确认方法。[近义词：部分循环]

Performance Qualification 性能确认

Documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications (7).

指形成文件的确认，以证明设备和其连接在一起的辅助系统，根据经过批准的工艺方法和技术标准能有效并始终如一地完成相应活动。

Pre-Vacuum Process 预真空程序

A process in which air is removed by applying a vacuum (i.e., negative pressure) or pulses of vacuum to precondition the system prior to the exposure phase.

采用真空（如：负压）或脉冲真空除空气后才开始灭菌的程序。

Pure Steam 纯蒸汽

Steam in which the condensate complies with the Compendial monograph, Water for Injection (WFI) (8,9). [Synonyms: clean steam, high quality steam]

其冷凝水符合美国药典专论“注射用水”（WFI）（8，9）要求的蒸汽。[近义词：洁净蒸气、高质量蒸气]

Routine Operational Cycle 常规运行程序

Parameters that are specified for ongoing SIP operations used in production. The operational cycle is typically controlled to produce additional lethality over the qualified minimum acceptable cycle in order to provide increased sterility assurance.

指日常 SIP 运行的各种参数。为了获得更高的无菌保证水平，日常运行的灭菌程序的灭菌时间要大于最低可接受的灭菌程序。

Sanitization 消毒

A process that reduces the number of viable microorganisms to a defined level.

将活的微生物数量降低到一个预定水平的过程。

Saturated Steam 饱和蒸汽

Steam that is at a temperature and pressure that corresponds to the vaporization curve of water. It is in a state of equilibrium between being a liquid and a gas with no entrained liquid water.
指处于水蒸发曲线对应点压力及温度的蒸汽。它是蒸汽中不夹带液态水，处于汽液平衡状态的蒸汽。

Spore Log Reduction (SLR) 孢子降低的对数

The number of log reductions (10-fold changes) of spores from the initial population. For the overkill sterilization method, one targets a spore log reduction of 12 to achieve 1×10^{-6} probability of a survivor when using a biological indicator having a population of 1×10^{6}.
从最开始的孢子数降低了的对数（以 10 的倍数变化）。对于过度灭菌方法，其中一个目标是使孢子降低 12 个对数，当使用的生物指示剂的浓度为 1×10^{6} 时灭菌后微生物的存活率为 1×10^{-6}。

Steam in Place Cycle 在线蒸汽灭菌程序

A sequence of defined steps and operating parameters (e.g., time, temperature, and pressure) performed in situ on equipment and/or systems to provide a given sterility assurance level (SAL) or defined sanitization level.
对设备和/或系统在原位运行一个由一系列的步骤和运行参数（如：时间、温度和压力）组成的程序以达到某个特定的无菌保障水平（SAL）或卫生级别。

Steam Orifice 蒸汽孔板

A specifically sized hole (e.g., 1/32 or 1/16 inch diameter) to allow condensate or steam to pass through. [Synonyms: flow orifice, steam bleed.]
一个特定大小的孔（例如，1 / 32 或 1 / 16 英寸直径）允许冷凝水或蒸汽通过。[同义词：流量孔板，蒸汽排放。]

Steam Trap 蒸汽疏水阀

A self-actuating, automatic device that removes condensate and air from the system.
一个自动从系统中排出冷凝水和空气的自动装置。

Sterile Boundary 无菌分界线

The sterile boundary is the demarcation in a system between the portion of the system that requires sterile contact surfaces (e.g., sterile side of filters and downstream piping) and the rest of the system (e.g., upstream side of filters, condensate drain lines).
无菌分界线的划分，指系统中要求接触表面是无菌的部分（如：过滤器的无菌段和下游管道）和系统的其他部分（如：过滤器的上游侧，排水管道）

Sterility Assurance Level (SAL) 无菌保障水平

Probability of a single viable microorganism remaining after SIP.
在进行 SIP 后单个微生物可存活的概率。

Note: The term SAL uses an assumed quantitative value, generally 10^{-6} or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value but provides a greater assurance of sterility than an SAL of 10^{-3} (10).
注意：SAL 一般使用像 10^{-6} 或 10^{-3} 这样的假设值来描述灭菌保障水平，10^{-6} 虽然比 10^{-3} 小，但其所提供的无菌保障水平高于 10^{-3} 提供的无菌保障水平（10）。

Sterilization 灭菌

A process used to render a system free of viable microorganisms with a specified probability.
指用以使一个产品达到规定微生物存活概率的工艺过程。

Superheated Steam 过热蒸汽

Steam that is at a higher temperature than that indicated by the equilibration curve for the vaporization of water (at a given pressure).

在一定压力下，其温度高于水蒸发曲线所指示温度的蒸汽。

Survivor Curve 存活曲线

Graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbiocidal agent under stated conditions (11).

在设定的条件下，随暴露于灭菌剂时间的增加，微生物失活数量变化的曲线图。（11）

System Integrity Test 系统完整性测试

Any test designed to detect leaks or other breaches in system integrity that might **compromise** operator safety or system sterility (or sanitary status). [Synonym: leak test.]

系统完整性测试中的检漏或破坏性检测，可能会对员工的人身安全或系统的无菌状态（或卫生状态）有影响。[近义词：泄露测试]

Mass Flow Integrity Test 大流量完整性测试

A system integrity test that measures the mass flow needed to maintain a given pressure.

，通过测试维持规定压力所需的最大流量的一种系统完整性测试方法。

System Pressure Hold Test 系统保压测试

A system integrity test in which the system is pressurized to a predetermined level with filter sterilized compressed air or other compressed gas, after which the system is isolated and the amount of pressure loss over time is measured.

，使用无菌的压缩空气或其他压缩气体将系统加压到预定水平后，密闭该系统，随着时间的推移测定压力损失量的一种系统完整性测试方法。

System Vacuum Hold Test 系统真空度测试

A system integrity test in which the system under test is evacuated to a predetermined setpoint and the system is isolated from the external environment. The decay in vacuum level over time is measured.

将系统抽真空至一个预先设定点并且系统相对于外部环境是独立的，随着时间的推移测量其真空度衰减的一种系统完整性测试方法。

Temperature Probe 温度探头

A sensor (e.g., thermocouple or resistance temperature detector (RTD)) that has been specifically designed to measure temperature. Temperature probes may be control, resident, surface mounted, validation, mapping, or permanent.

一个经过特制的用于测量温度的传感器（如：热电偶，标准温度探头）。温度探头应被控制、固定、表面安装、验证、图示或位置不变。

Validation 验证

A documented program that provides a high level of scientific assurance that a manufacturing process will reliably produce acceptable product. The proof of validation is obtained through rational experimental design and the evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase.

一个能够科学地确保生产工艺生产出合格产品的有文件和记录证明的程序。验证的证据应通过验证方案的

合理设计并对数据资料进行科学、全面评估获得，这些数据资料最好始于工艺的开发阶段，直至商业化生产。

z-value z 值

The number of degrees of temperature change necessary to change the D-value by a factor of 10. The z-value allows integration of the lethal effects of heat over time (i.e., calculation of F0) as the temperature changes in a cycle.

使 D 值变更一个对数单位温度需调节的度数。它可用于累计一个灭菌程序在加热和冷却阶段随温度变化的杀灭时间。

2.0 Steam in place Science and Technology
在线灭菌科学与技术

Whereas PDA Technical Report No. 1 focuses on essential scientific tools used for the design, development, and qualification of batch (i.e., autoclave) sterilization cycles, this report addresses areas specific to the in situ application of steam for sterilization purposes as well as various types of sanitization processes ***(1).***

鉴于 PDA 1 号技术报告集中介绍了用于设计、提高和确认批灭菌循环（例如，高压灭菌柜）使用的基本的科学工具，这份报告在 PDA 1 号报告的基础上将针对于在位蒸汽灭菌目的的应用，关注各种形式的消毒处理过程*（1）*。

2.1 SIP Applications
SIP 的应用

The overkill design approach is the most common method used for systems that are sterilized by SIP since there is usually not the concern for degradation of product. When claiming sterilization using the overkill approach, bioburden monitoring is reduced or is not required (see below) since a worst case bioburden assumption is used to determine the delivered lethality needed to achieve a sterility assurance level (SAL) of 10-6 on or in the system being sterilized. When using this approach, the qualification program must demonstrate that both the *F*BIO and *F*PHYS are equal to or greater than 12minutes. Examples of calculating an overkill cycle are provided in **Section 6.3.1.**

由于在系统做 SIP 的过程中通常不用考虑产品的降解问题，因此过度杀灭的设计是最常见的用于系统 SIP 的方法。当灭菌使用过度杀灭的方法时，需要使用一个经过假设的最差条件的生物负载水平来证明这种灭菌方法的致死率可以达到 10^{-6} 的无菌保证水平（SAL）或者这种灭菌方法可以使系统达到无菌状态。当使用这种灭菌方法时，确认过程必须证明 *F*BIO 和 *F*PHYS 大于等于 12 分钟。6.3.1 部分提供了一个计算过度杀灭程序的例子。

When the process does not require sterility, the SIP approach is commonly referred to as “sanitization.” Depending on the requirements of process control, the sanitization process would typically not have an established SAL requirement. Sanitization processes may also be used for reducing bioburden levels in systems that show higher than accepted microbial counts or as a prophylactic measure to keep microbial counts “under control”. In these cases, temperature is typically monitored at the worst-case location and cycle time is decided based on temperature readings at this location. Cycle end-point is either bioburden removal or reduction, and success is demonstrated by bioburden measurement after each cycle is performed.

当某个过程不需要无菌时，SIP 这种方法一般被称作“消毒”。根据过程控制的要求，消毒过程没有一个具有代表性的无菌保证水平的要求。消毒过程也可以用来减少系统的微生物负载水平，消毒过程的微生物水平高于生物总数的可接受标准，或者把消毒过程作为预防性措施“控制”微生物的数量。灭菌循环的终点是生物负载的移除或者减少，每次灭菌循环结束后都要检测生物负载来证明灭菌成功。

Table 3.1-1 Includes some example applications of SIP processes, cycle development considerations, and potential validation approaches.
表格 3.1-1 包括 SIP 应用过程，程序开发的考虑和潜在验证方法的一些例子，

Purpose 目的	Application 应用	Cycle Development Considerations 程序开发的考虑	Validation Considerations 验证的考虑
Sterilization Process 灭菌过程			
	SIP process where sterilization is claimed. (Example: Aseptic filler piping for a sterile drug product) 要求灭菌的 SIP 过程（例如，无菌药品的除菌过滤）	■ Time 时间 ■ Temperature 温度 ■ Pressure 压力 ■ System and filter integrity 系统和滤芯的完整性 ■ Positive pressure maintenance 正压维持 ■ Temperature/pressure correlation 温度/压力关联 ■ Cold spot determination 冷点的判断 ■ Temperature mapping 温度测绘 ■ Air and condensate removal 空气和冷凝物的祛除	■ BIs are used 使用 BI ■ Temperature probes meet defined limits 温度探头达到要求的限度 ■ Demonstrate total kill 证明总杀死量 ■ Monitor temperature at worst case locations 探测最差点的温度 ■ FBIO ≥ 12 minutes (Overkill) at each BI location 每一个 BI 布点位置的 FBIO ≥ 12 分钟（过度杀灭） ■ FPHYS ≥ 12 minutes (Overkill)* FPHYS ≥ 12 分钟（过度杀灭）* ■ Sterile hold time 灭菌保持时间
Sanitization Process 消毒过程			
	SIP process that inactivates bioburden (examples:WFI system that is steam sanitized, vessels used in biopharmaceutical manufacturing to control bioburden prior to use for pooling, etc.) 生物负载失去活性的 SIP 过程（例如，WFI 系统的蒸汽消毒，用于生物制药的容器合并使用前的生物负载控制）	■ Time 时间 ■ Temperature 温度 ■ Pressure 压力	■ No BIs/FBIO/FPHYS required 没有 BIs/FBIO/FPHYS 的要求 ■ Monitor temperature at worst case locations 探测最差点的温度 ■ Monitor bioburden level before and after sanitization 消毒前后检测微生物负载的水平 ■ Demonstrate bioburden removal 证明生物负载的去除量

* For typical SIP systems, the FPHYS will need to be greater than the F_{BIO}
*对于典型的 SIP 系统，FPHYS 值应该大于 F_{BIO} 值

Because SIP processes can be used for such a wide range of applications, it is very important for the user to define the purpose and the desired outcome of the SIP process before the system is designed. Risk assessments made prior to the design of the system can be used to help define if a sanitization or sterilization process is required.
因为 SIP 过程有非常广的应用范围，对于使用者来说最重要的是在系统设计之前，明确使用 SIP 过程的目的和渴望得到的结果。如果某个系统要求消毒或者灭菌，那么在系统设计之前进行风险评估来定义这个过程。

2.2 Mechanisms of Lethality
致死率的机理

The mechanism of microbiological lethality for steam in place systems is the thermal destruction of microorganisms by direct contact with the sterilizing medium (steam). The mechanism of heat transfer is conduction where the transfer of energy occurs from latent heat. As with other saturated steam sterilization methods, the rate of microbial destruction under conditions of constant temperature progresses logarithmically over time.
SIP 系统微生物致死率的机理是通过直接接触的灭菌媒介（蒸汽）的热力来摧毁微生物，热传递的机理是热传导，传递的热量来自于潜热。与其它的饱和水蒸气的灭菌原理一样，生物致死率在恒温的过程中随着时间的延长呈对数级下降。

The kinetics for these complex reactions are best represented as a First Order chemical reaction. This means that there is a linear relationship between the logarithm of the number of surviving microorganisms and the time of exposure (see **Figure 3.2-1).**
这些复杂的动力学反应最好被描述为一级化学反应，这意味着在存活微生物的数量和暴露时间之间存在着线性关系（见曲线 3.2-1）

[Equation 1]【方程式 1】

$$\text{Log } N_F = -F_{(T,z)} / D_T + \text{Log } N_0$$

where,
其中，

N_F = Number of microorganisms after exposure of F equivalent minutes
NF =暴露 F 分钟等效时间后的微生物数量

$F_{(T,z)}$ = Equivalent lethality of a cycle calculated as minutes at a reference temperature (T), using a defined temperature coefficient (z)
$F_{(T,z)}$ =以定义的温度系数（Z），参考温度为（T）并以以分钟为单位来计算的一个程序的等效致死率。

D_T = Thermal resistance value, in minutes, of the microorganism at a specific temperature (T).
D_T =在特定的温度（T）时微生物的耐热值（以分钟计）

Note: This specific temperature must be the same as the reference temperature used for calculating F-value.
备注：这个特殊的温度必须跟用来计算 F 值的参考温度一致

N_0 = Number of microorganisms prior to exposure
N_0 =暴露之前的微生物数量

In **Figure 3.2-1,** *DT* is a measure (the negative reciprocal) of the slope of the semilogarithmic survivor curve; therefore, it describes the relationship between the number of survivors versus equivalent (F-value) exposure time. F-value is a term used in the model to characterize exposure time to moist heat. By definition, the F-value is expressed by a reference temperature so that it truly represents the equivalent exposure time at that reference temperature in terms of lethality. Since routine operational cycles are not square wave cycles (i.e., the system does

not come up to temperature instantaneously,remain at the precise set point throughout the exposure phase, and then cool down instantaneously),the z-value, or temperature coefficient, is used in the model to calculate the equivalent lethality at different temperatures. Examples of lethality rates are shown in **Table 3.2-1.**

在图 3.2-1 中，*DT* 是半对数存活曲线的斜率（负倒数），因此，D_T 描述了微生物的存活量和等效（F 值）暴露时间的关系。F 值是一个表示湿热暴露时间特征的模型的术语。根据定义,F 值是以一个参考温度来表示，因此 F 值,真正代表了在等效的曝露时间内参考温度的杀灭力。由于常规操作周期不是方波周期(例如，系统不能瞬间达到设定温度，在整个暴露阶段都精确的留在温度设置点，然后瞬间降温),z 值或温度系数，在这个模型中用来计算在不同温度下的等效杀灭力。致死率的例子如**图 3.2-1** 所示。

Figure 3.2-1 Microbial Survivor Curve

图 3.2-1 存活的微生物曲线

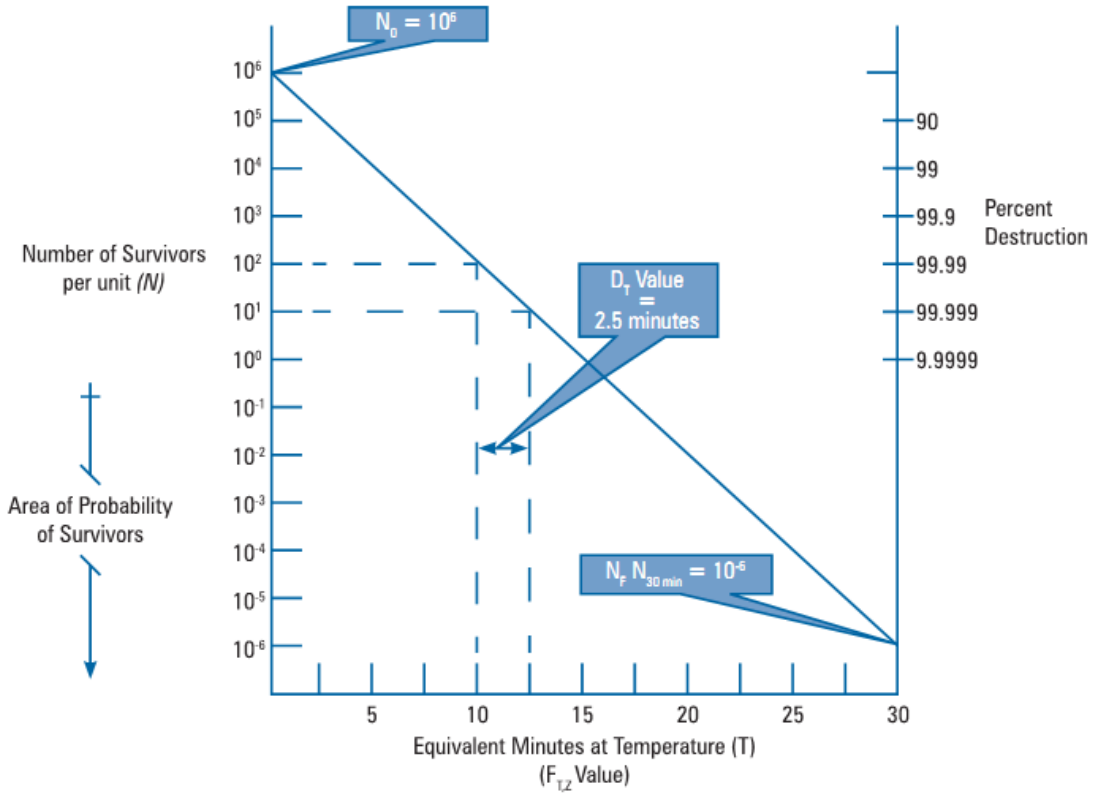


Table 3.2-1 Example Lethality Rates (F0 per Minute) at Various Process Temperatures

图 3.2-1 在各种工艺温度下的的致死率（F0 每分钟）的例子

°C	F_0 Per Minute
100.0	0.008
105.0	0.025
110.0	0.078
115.0	0.245
120.0	0.776
121.1	1.000
125.0	2.455
130.0	7.762
135.0	24.547

Steam generation and distribution infrastructure should be qualified to demonstrate that the steam is suitable for

its intended use (e.g., Pure Steam for product contact surfaces). The semi-logarithmic model of inactivation of microorganisms for saturated steam processes assumes steam is saturated(does not exhibit superheat) and is free from non-condensable gases. Wet steam, superheated steam and steam containing non-condensable gases have the potential to adversely affect the lethality rate in the sterilization/sanitization processes. The quantities of residual air and condensate that may be present in SIP processes is likely to be in excess of those that could be found in the steam supply. For this reason, point-of-use steam quality testing (e.g.,superheat, non-condensable gases, and dryness) is typically performed on the main steam header branch to the equipment that is being steamed. A risk based assessment should be used to determine the number of point-of-use locations to test in order to best represent the steam supply system.
蒸汽发生器和分配系统应该通过验证来证明蒸汽能够达到预期的用途（例如，与产品表面接触的纯蒸汽），饱和蒸汽的微生物失活半对数模型是假设蒸汽是饱和的（不是过热蒸汽）以及不凝性气体是合格的。湿饱和蒸汽、过热蒸汽和干饱和蒸汽会潜在的影响灭菌或者消毒过程的致死率。SIP 过程中可能出现残留气体和冷凝物的量超过蒸汽供应系统中的残留气体和冷凝物的情况。基于这种原因，使用点的蒸汽质量检测（例如，过热度、不凝性气体、干度）可以典型的证明从蒸汽分配器到设备分支的输送情况。为了更好的展现蒸汽供应系统的性能，应该在风险评估的基础上决定蒸汽使用点检测数量。

Figure 3.2-2 illustrates saturated steam conditions (pressure and temperature), which maximize the heat transfer during steaming. Deviation from the saturation line due to air and condensate in the system or superheat in the supplied steam will limit the steam's effectiveness. **Figure 3.2-3** depicts the impact of air trapped inside equipment being steamed in relation to Dalton's Law of Partial Pressure.
图 3.2-2 说明饱和蒸汽（一定的压力和温度）在汽化过程中最大化热传递的情况，蒸汽输送系统中的气体和凝结物或者蒸汽供应系统的过热度都会降低蒸汽的效率，从而偏离蒸汽的饱和线。图 3.2-3 说明了蒸汽系统中的残留空气对蒸汽质量的影响符合道尔顿分压原理。

Figure 3.2-2 Optimal Heat Transfer Curve
图 3.2-2 最佳的热传递曲线

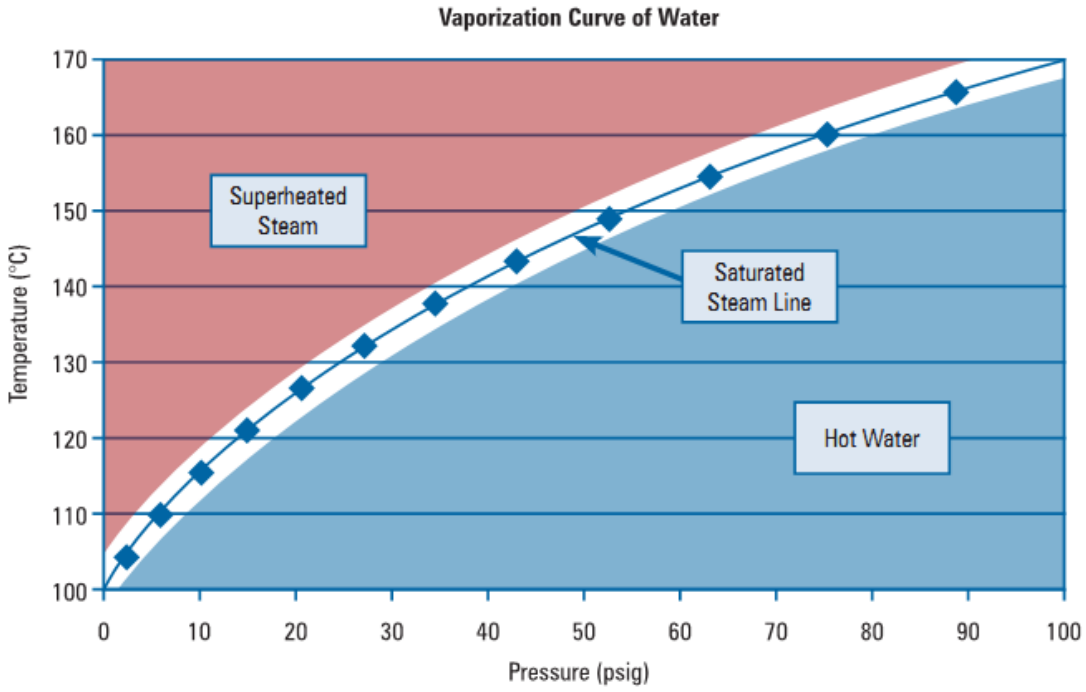
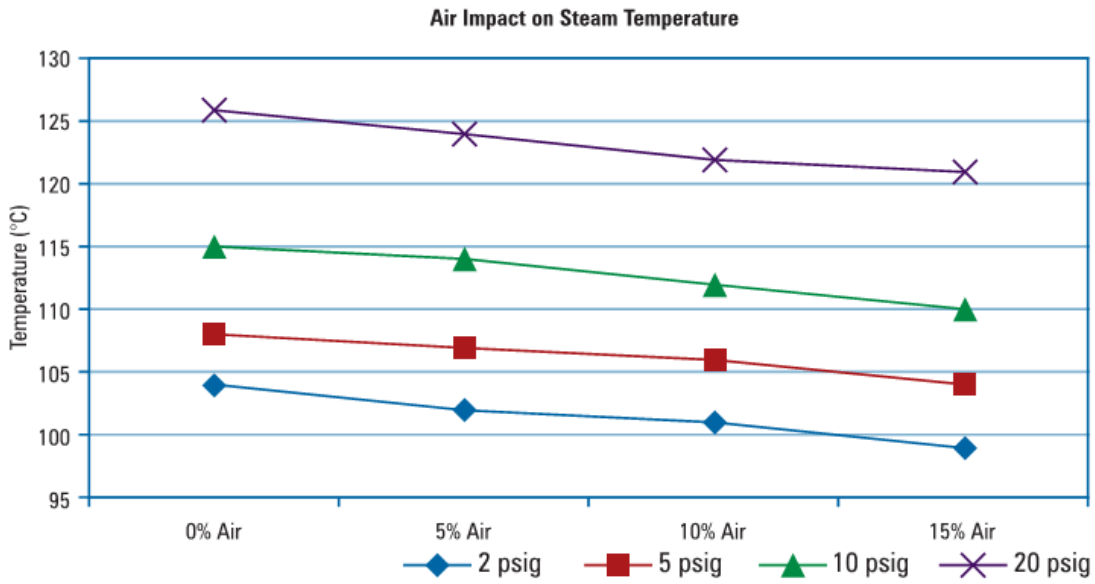


Figure 3.2-3 Effect of Trapped Air on Steam Temperature
图 3.2-3 残留空气对蒸汽温度的影响



3.0 System Design
系统设计

The design of equipment should take into account SIP to ensure that the system can be steamed effectively and efficiently. This section provides guidance by offering information on what to consider (e.g., equipment design, level of automation, ongoing monitoring) prior to designing an SIP process. A risk assessment may direct effective use of resources during system design.
设备的设计应当考虑 SIP 以确保系统可以进行有效且高效的灭菌。本章节在设计 SIP 工艺之前先通过提供需要考虑的信息来提供指南（例如：设备设计、自动化水平、持续监测）。在系统设计时，进行一个风险评估可以使资源的利用直接、有效。

Overall system SIP sanitization/sterilization can be achieved via two methods. Simple systems inclusive of every possible attachment are typically steamed as a whole in one SIP cycle. Complex systems are frequently steamed via separate SIP cycles. This multi-cycle method can also include the attachment of previously autoclaved equipment to a sterile system.
整体系统 SIP 清洁/灭菌可以通过两种方式实现。简单系统通常在一次 SIP 灭菌中连带其包含的所有可能的附件进行整体蒸汽灭菌。复杂系统则经常进行单独的 SIP 灭菌。这种多次灭菌的方法也可应用于无菌系统中的需提前热压处理的设备附件。

3.1 Planning for Design of SIP Cycle
SIP 程序设计计划

The boundary of the system(s) to be steamed (e.g., process equipment, feed and transfer lines) should be defined and documented (such as through process and instrument drawings) to ensure a successful cycle. Consider the following points after establishing the steaming boundary:
进行蒸汽灭菌的系统的范围（例如：工艺设备、供应和输送线路）应当进行定义和记录（例如通过工艺和仪器图纸）以确保程序成功运行。在建立蒸汽灭菌系统范围后要考虑以下几点：

- An SIP cycle design must be capable of steaming all internal surfaces of the system within the boundary for a defined temperature and time. It must also be able to cool down the system within a timeframe which meets the system owners' business needs.
  一个 SIP 循环的设计必须能够按照定义的温度和时间对范围内系统的全部内表面进行蒸汽灭菌。该设计也必须能够按照该系统所有者的需求在一定时间内对系统进行冷却。

- The SIP cycle must provide delivery and penetration of saturated steam at predefined temperatures to all internal surfaces. This requirement incorporates design aspects associated with heat transfer, steam supply, and air and condensate removal.
  SIP 循环必须在预先定义的温度下对所有的内表面提供饱和蒸汽的交换和穿透。这一需求由热传递、蒸汽供应、以及空气和冷凝水的去除各相关方面的设计组成。

- The system should be designed to ensure adequate heat transfer to the system so the heat delivered by steam to the system's internal surfaces (conduction) is greater than the heat lost from the system to the environment (convection). Steam system delivery capacity must match or exceed the system requirement for attaining and maintaining sterilization conditions.
  系统设计应使系统得到足够的热交换以确保蒸汽传递到系统内表面的热量（热传导）大于系统传递到外界环境的热损失（热对流）。蒸汽系统的输送能力必须符合或超过系统实现及保持灭菌条件的需求。

- The system should be designed so air and condensate is not trapped in any location where steam is intended to penetrate. Saturated steam must be in contact with the targeted surface for the duration of the exposure phase, or the efficacy of the cycle will be compromised. Ideally, piping systems and vessels are designed so air and condensate is easily purged out of areas such as deadlegs and filter housings through bleed valves or steam traps. Manually operated SIP cycles will need detailed instructions within procedures to ensure this is accomplished each time in a repeatable manner.
  系统设计应使空气和冷凝水不会在任何需要进行蒸汽渗透的位置累积。饱和蒸汽必须在接触阶段期间与目标表面持续接触，否则灭菌的效果会受到影响。理想情况下，管道系统和容器应被设计为空气和冷凝水在一些区域，如管道分支和过滤器等处通过排气阀和疏水阀可以很容易的去除。人工操作的 SIP 循环需要详细的程序指令，以确保每次的操作具备可重现性。

- The SIP cycle must provide measurement, control, and monitoring of system temperature and pressure during the cycle hot phases (heat-up and exposure), and of pressure during the cool-down and hold phases. To enhance condensate removal, pipe slopes should be maximized wherever possible. A typical piping design specification would reference a minimum slope of a 1/8” per foot of pipe.
  SIP 程序必须提供测量、控制、供热阶段（升温和灭菌）系统温度和压力的监测，以及冷却和保持阶段期间压力的监测。为了加强去除冷凝水，管路的坡度应尽可能最大化。典型的管路设计参考参数为每英尺管路最小坡度为 1/8”。

- Appropriate instrumentation, controls, and monitoring systems must be installed to enable and ensure the delivery and control of saturated steam. Instrumentation should be of the appropriate range and sensitivity to monitor and control temperature and pressure within the targeted value ranges. Critical locations within the sterile boundary should be monitored during each phase of the SIP cycle.
  必须安装适当的仪表、控制和检测系统以确保能够供应和控制饱和蒸汽。仪器仪表应有适当的检测范围和灵敏度以保证在目标值范围对温度和压力进行监视和控制。无菌范围内的关键位置在 SIP 期间的每一个阶段均应进行监控。

- SIP cycle design should ensure that temperature and/or pressure limitations of the process are not exceeded (such as for filters or elastomers).
  SIP 循环的设计应确保温度和/或压力不超过工艺限度（例如对于过滤器或弹性部件）

- Access points should be provided for insertion of validation biological indicators and temperature sensors at potential worst-case locations (e.g. low points, high points, filter housings).
  应在潜在的最差位置为生物指示剂和温度传感器提供验证接口。（例如：低点、高点、过滤器外壳。）

3.2 Equipment Design Considerations
设备设计注意事项

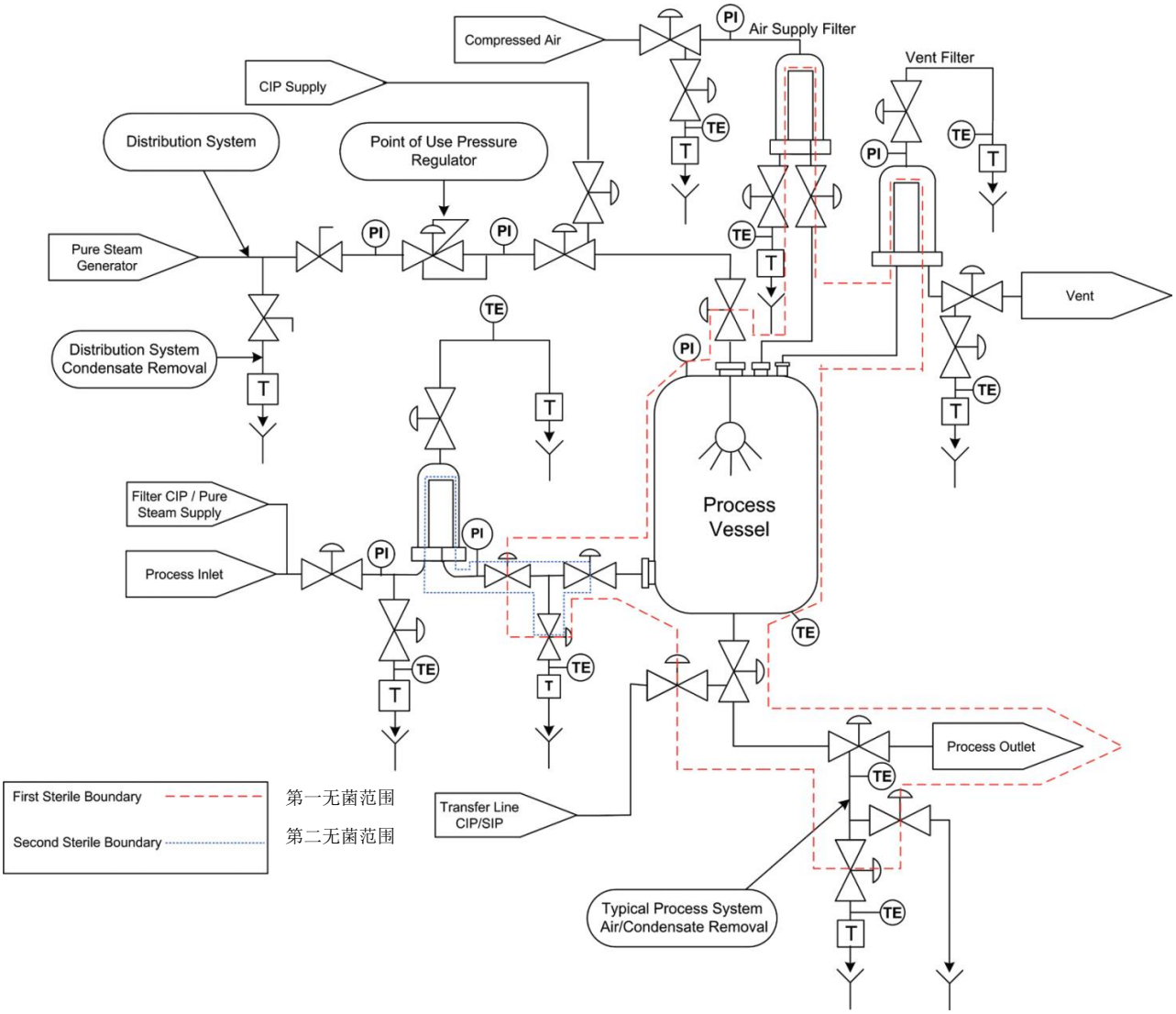
Similar to other processes, such as clean in place (CIP), SIP equipment design should be integrated into the manufacturing process design and operations (12). Material used for construction and surface finish should be defined and documented for all product contact parts. Accordingly, the surface finish should be specified based on cleaning performance requirements to minimize product or microorganism adhesion.
与其他工艺如在线清洁（CIP）类似，SIP 设备设计应与生产工艺设计和操作结合（12）。所有与产品接触的部分其建造材质和表面光洁度均应定义并有文件记录。相应的，表面光洁度应基于清洁性能需求以使产品或微生物的粘附最小化。

The system shown in **Figure 4.2-1** is an example of a process tank with a single feed that is delivered aseptically via a sterilizing-grade filter. Two sterile boundaries have been identified in the drawing below as an example. The two boundaries can be steamed separately, or as one SIP circuit. The tank and the filters (feed and vent) are equipped with steam traps to ensure efficient and effective condensate removal during heat up and exposure. The tank trap should be sized to handle the large condensate load as well as temperature control during exposure to ensure a consistent SIP cycle. Temperature elements are placed at SIP boundaries and potential cold spots. The temperature elements provide real time confirmation that the SIP is successful every time it is run.

如**图 4.2-1** 所示的系统是一个通过除菌过滤来无菌投料的单管路工艺罐示例。举例来讲，在下图中已经确定了两个无菌范围界限。这两个范围区域可以单独进行蒸汽灭菌，或作为一个 SIP 循环。罐和过滤器（进和出）装备有疏水阀以确保能够有效和高效的去除升温和灭菌阶段的冷凝水。罐的装置应有足够的规格保证在灭菌期间能够处理大量的冷凝水负荷以及温度控制，从而确保 SIP 程序的正常运行。温度传感器置于 SIP 范围内以及潜在的冷点。温度传感器提供实时数据来证明在 SIP 的整个运行时间内，灭菌是成功的。

Figure 4.2-1 Example of Steam Distribution and Process Tank Layout

图 4.2-1 蒸汽分配和工艺罐设计举例



Legend for Drawing: T = steam trap, TE = Temperature Element, PI= Pressure Indicator

图片说明：T = 疏水阀，TE = 温度传感器，PI = 压力指示器

Pure Steam Generator = 纯蒸汽发生器

Distribution System = 分配系统

Distribution System Condensate Removal = 分配系统除冷凝水

Point Of Use Pressure Regulator =压力调节点

CIP Supply = CIP 供应

Compressed Air = 压缩空气

Air Supply Filter = 空气过滤器

Process Vessel = 工艺容器

Vent Filter = 排气过滤器

Vent = 排放口

Filter CIP/Pure Steam Supply = CIP 过滤器/纯蒸汽供应

Process Inlet = 工艺进口

Transfer Line CIP/SIP = CIP/SIP 输送管路

Typical Process System Air/Condensate Removal = 典型工艺系统除空气/冷凝水

Process Outlet = 工艺出口

Since systems requiring SIP are often the same as those cleaned via CIP, materials of construction should be selected by considering not only temperature limitations, but potential chemical interactions encountered in both processes. Examples requiring temperature consideration include: process equipment, instruments, and connection gaskets that are in contact with steam. Alternative materials of construction (e.g., high performance alloys, glass, and titanium) may be considered if stainless steel is incompatible with the process.
通常系统要进行 SIP 时也需要 CIP 进行清洁，安装材质的选择不仅要考虑温度限制，还要考虑两个工艺中潜在的化学相互作用。举例来说，需要考虑温度的包括：工艺设备、仪表、与蒸汽接触的连接垫圈。如果不锈钢材质对于工艺不适用，也可以考虑替换的安装材料（例如：高性能合金、玻璃、钛合金）。

Equipment design considerations are typically recorded in the user requirements documentation. Risk management tools may be used to facilitate design criteria ***(3,6,13,14)***. Consider the following points when designing an SIP system:
设备设计注意事项通常记录在用户需求文件中。可以采用风险管理工具来帮助制定设计标准（***3.6.13.14***）。在设计一个 SIP 系统时考虑如下几点：

Steam Consumption
蒸汽消耗量
The steam supply capacity should be designed/evaluated to ensure adequate steam supply for the SIP system(s), with the maximum peak demand during the free-steam heat-up phase. Consideration should also be given to steam supply load to ensure adequate capacity for all uses (e.g., SIP, autoclave, and humidification).
应设计/评估蒸汽的供应能力以确保在蒸汽自由升温阶段中最大峰值期间为 SIP 系统提供足够的蒸汽来满足其需求。同样应考虑蒸汽供应的负载以确保有足够的能力供应所有使用点（例如:SIP、高压灭菌柜、加湿）。

Good engineering practices for steam system design must be followed when selecting the pressure reduction valve. Pressure control should be sufficiently robust to minimize fluctuations in steam pressure delivered to the target SIP system(s).
当选择减压阀时必须遵循蒸汽系统设计的良好工程规范（GEP）。应有足够的压力控制能力使蒸汽压力传递到目标 SIP 系统时波动最小化。

Note: Steam equipment manufacturers should be consulted for piping design and sizing for steam and condensate requirements as each type of equipment may require different configurations.
注意：不同类型的设备有可能对蒸汽和冷凝水的配置需求不同，因此管道设计和规格制定应咨询蒸汽设备制造商。

Gas Consumption
气消耗
The gas flow capacity piped to the system should be sufficient to dry and pressurize the system post - SIP to maintain system integrity. Insufficient gas flow may also result in extended cool-down time.
输送到系统的气体应有足够的干燥度和压力保证系统在 SIP 后维持系统的完整性。气体流量不足也会导致冷却时间延长。

Filter Considerations
过滤器考虑要点

Filter and filter housing sizes and materials of construction should be suitable for the intended use and able to withstand SIP (15). The peak airflow demand for air filters usually occurs during the SIP cooling phase.
过滤器及过滤器外壳的尺寸和材质应适用于预期用途并能经受 SIP（15）。对空气过滤器的峰值需求通常发生在 SIP 的冷却阶段。

Filter housing configurations and bleed valves should allow the filter core and housing to drain condensate. Housing options include single or multiple cartridge designs in T- or inline-styles. Vent filter housings may be heated (e.g., via steam jacket or electric blanket) to minimize condensation during use (16).
过滤器外壳的结构和排气阀应使过滤器滤芯和外壳能够排除冷凝水。外壳的选择包括单个或多个套筒设计为 T 型或内联的形式。可以对呼吸器过滤器外壳进行加热（例如：通过蒸汽套管或电加热装置）以保证工作期间的冷凝水量最小化。

To ensure condensate and air removal, filter housings frequently have high point vents and should have low point drains and be positioned with the core opening down. Careful consideration should be given to materials of construction for disposable filter capsules, since most capsule shells are not compatible with SIP operating conditions. Consideration should also be given to the selection of filter housings that comply with applicable pressure vessel codes.
为确保排除空气和冷凝水，过滤器外壳通常在高点有排气点，在低点有排水点并定位滤芯开口是向下的。由于大部分一次性过滤器的材质不能经受 SIP 条件，因此一次性过滤器的材质选择必须经过深思熟虑。选择过滤器外壳时也应考虑适用的压力容器规范的符合性。

Steaming conditions should be reviewed to ensure they are within the filter vendor’s recommended parameters. The permissible pressure drop across the filter under SIP temperatures is significantly lower than under ambient temperature conditions and less in the reverse rather than the forward direction. Differential pressure limits are temperature dependent and should be considered when determining the steam path. The pressure differential should be monitored and/or controlled during SIP. Post-SIP filter integrity testing provides assurance that the filter has not been damaged during the SIP cycle, but there are some disadvantages to performing pre-use, post-SIP integrity testing. Potential pros and cons of conducting pre-use integrity tests before or after the SIP process are shown in **Table 4.2-1**.
应回顾蒸汽灭菌情况以确保处于过滤器供应商推荐的参数范围内。在 SIP 温度条件下允许的穿过过滤器的压力降远低于环境温度条件下允许的压力降，当蒸汽反向穿过过滤器时的允许值更低。压差限度取决于温度，当决定蒸汽管道通路时应考虑这一点。SIP 期间应对压差进行监测和/或控制。SIP 后过滤器完整性测试提供了过滤器在 SIP 过程没有损坏的保证，但在执行 SIP 后完整性测试、使用前完整性测试时有一些缺点。在 SIP 之前或之后进行使用前完整性测试的潜在利弊列于**表 4.2-1** 中。

The timing and use of filter integrity tests should be conducted according to applicable regulatory requirements and through the use of risk assessment tools (17).
过滤器完整性测试的时间选择和应用应根据适用的法规要求并通过使用风险评估工具来进行管理（17）。

Table 4.2-1 Comparison of Pros and Cons for When to Perform the Pre-Use Filter Integrity Test
表 4.2-1 执行过滤器使用前完整性测试的优劣比较

Pre-SIP/Pre-Use Integrity Test (with filter element installed in the housing to be used for the process) SIP 前/使用前完整性测试（滤芯安装在用于该工艺的过滤器外壳内）		**Post–SIP/Pre-use Integrity Test SIP 后/使用前完整性测试**	
PRO 优点	**CON 缺点**	**PRO 优点**	**CON 缺点**
Confirms the filter is installed properly and without any damage, for example to the O-ring seal 确认过滤器安装正确并且完好无损，如密封圈。	Filters that may be damaged during SIP would not be detected until the post use integrity test 过滤器如在 SIP 过程中损坏有可能直到进行使用后完整性测试时才会发现。	Reduced business risk for production lot/batch as filter integrity is confirmed after SIP 由于完整性测试是在 SIP 后进行的，因此降低了当批产品的风险。	Typically requires system positive pressure to be relieved to conduct the integrity test (could lead to media and/or sterility failures and extended production down times) 通常进行完整性测试需要系统提供正压。(可能导致培养基灌装和/或无菌失败，并延长生产时间。
Confirms the filter with the right pore size has been installed 确认安装的过滤器孔径正确。	Test is time consuming and redundant to the filter manufacturer’s release test 测试耗费时间，并且与过滤器供应商的出厂检验重复。	Confirms the right filter has been installed correctly 确认过滤器及其安装正确无误。	Significant process down time to do testing and drying of the filter before use to avoid product dilution 在关键工艺之前停机做测试，并且要将过滤器干燥防止稀释产品。
Can be performed offline reducing down time of process and it may be easier to test serial filter configurations 可以离线进行测试减少工艺停机时间，而且对于串联的过滤器结构进行测试更容易。	Wetting fluid should have low bioburden to avoid additional endotoxin release after steam sterilization 在蒸汽灭菌后，为避免额外的内毒素污染，润湿液应控制在较低的微生物负荷。	Performed online 在线进行。	Requires downstream manipulation and redesign due to wetting agent removal and venting needs (increase of complexity and ingress points), unless product wet integrity parameters are used 由于需要进行润湿剂去除和气吹扫，需要对下游进行处理和重新设计（增加了进口，更加复杂），除非使用润湿产品的参数进行完整性测试。

Pre-SIP/Pre-Use Integrity Test (with filter element installed in the housing to be used for the process) SIP 前/使用前完整性测试（滤芯安装在用于该工艺的过滤器外壳内）		Post–SIP/Pre-use Integrity Test SIP 后/使用前完整性测试	
PRO 优点	**CON 缺点**	**PRO 优点**	**CON 缺点**
The filter wetting process removes filter extractables 过滤器的润湿过程去除了过滤器的可溶性成分。	Serial filter integrity testing is complex and requires sufficient user training 串联式过滤器完整性测试较复杂，需要对操作人员进行充分的培训。	The filter wetting process removes any remaining filter extractables 过滤器的润湿过程去除了过滤器所有的残余可溶性成分。	Can require integrity testing equipment to be introduced into classified areas (e.g., aseptic filling isolator) 需要在洁净区安装完整性测试仪（例如：无菌灌装隔离器区域）
Filter can be dried to avoid damage during steam sterilization 在灭菌期间过滤器可以进行干燥以避免损伤。	Requires specific test area 需要特殊的测试区域。		Serial filter designs may require additional engineering to ensure that sterility between filters is not compromised e.g., sterile gas is required, a valve installed between filters, and a sterile vent on the second housing 串联式过滤器需要额外的工程设计以确保过滤器之间的无菌保障，例如：必须使用无菌气体、过滤器之间安装阀门，在第二级过滤器外壳安装无菌排气口。
Does not infringe on the sterile barrier (does not compromise sterility) 不破坏无菌范围（不影响无菌）	May not meet specific regional regulatory expectations 可能不能满足某些特殊区域的管理预期。		Does not add to drug safety, since the filter is tested post-use, but potentially increases risks to the sterile filtrate side 由于过滤器在使用前也会进行完整性测试，因此不会增加产品的安全性，但是有可能增加无菌滤液的风险。

In some cases, filters will be wet prior to the SIP cycle but this should be avoided if possible. To prevent excessive pressure differentials when steaming wet filters, the steam may be introduced into both sides of the filter or slowly increased with vent and drain valves fully opened until steam flow is established. This approach may also be used to accommodate very large systems where the filter restricts steam passage to the extent that the system cannot be adequately steamed. An isolation valve downstream of the liquid service filter housing will allow a second steam

supply to operate independently if it remains closed until the pressure on the tank side of the valve equals the pressure on the filter side. There are several other approaches including steaming through the vent filter.
某些情况下，在 SIP 之前，过滤器是湿的，应当尽力避免这种情况。当湿的过滤器被蒸汽灭菌时为了防止压差过大，在过滤器两侧同时引入蒸汽或者在排气阀和排水阀全开的状态下缓慢的增加蒸汽量直至形成蒸汽流。这种方法也可以用于适应非常庞大的系统中过滤器限制了通道中蒸汽通过量从而不能充分进行蒸汽灭菌的区域。液体过滤器外壳下游的隔离阀可以提供另外一个独立操作的蒸汽供应，该阀门只有在罐的一侧压力与过滤器一侧的压力相等时才打开。还有其他的几个方法例如将蒸汽先通过排气过滤器等。

The use of serial sterilizing grade filters may require additional engineering to ensure that the sterility in between the filters is not compromised by:
串联除菌级过滤器的使用需要以下的额外工程来确保过滤器之间的无菌环境不被破坏：

a) Preventing negative pressure from forming in between the filters, especially if the filters are subjected to SIP in a wetted state, during post SIP cool-down.
防止过滤器之间形成负压，特别是当过滤器在湿的状态下 SIP 或 SIP 后冷却的时候。

b) Maintaining sterile conditions if the filters are to be integrity tested post-SIP, prior to use.
如果过滤器完整性测试在 SIP 后、使用前进行，其无菌条件需要维持。

Condensate Removal via Steam Trap and Flow Orifice Selection *(18-22)*
通过蒸汽疏水阀和孔板疏水阀去除冷凝水选择（18-22）
During the SIP process, it is critical to remove condensate from the system in order to maintain the system temperature. Steam trap and/or flow orifice locations should be designed to facilitate condensate removal during the process. Steam traps may also include the capability of discharging air to reduce system heat up times. **Table 4.2-2** may aid in determining adequate air removal in the SIP system and piping systems. The ideal condition is to remove all the air, as shown in the column marked 0% (percentage of air in steam). For example, if the steam pressure is 15 psig, the temperature would be 121 ℃ if all the air is removed.
SIP 过程期间，为了保持系统温度，系统中的冷凝水去除是至关重要的。应设计蒸汽疏水阀和/或孔板疏水阀的位置以便于 SIP 过程期间冷凝水的去除。蒸汽疏水阀还应包括排除空气的能力以减少系统升温时间。**表 4.2-2** 可以帮助确定 SIP 系统和管道分配系统中适当的空气去除设置。理想情况下是去除所有的空气，在下图中 0%这一列中显示（蒸汽中空气的百分比）。例如，如果蒸汽压力（表压）是 15 磅/平方英寸，在其中没有空气的情况下，温度应为 121℃。

Table 4.2-2 Temperature Reduction Caused by Air
表 4.2-2 空气对温度下降的影响

Pressure bar (psig)	Temp. of Steam Mixed w/ Various Percentages of Air (by volume) °C (°F)			
	0%	10%	20%	30%
0.71 (10.3)	115.6 (240.1)	112.3 (234.3)	108.9 (228.0)	104.9 (220.9)
1.03 (15.0)	121.0 (249.8)	117.7 (243.8)	114.1 (237.3)	110.0 (230.0)
1.74 (25.3)	130.7 (267.3)	127.2 (261.0)	123.4 (254.1)	119.1 (246.4)
2.41 (35.0)	139.9 (283.8)	136.4 (277.5)	132.6 (270.6)	128.3 (262.9)
3.47 (50.3)	147.8 (298.0)	143.9 (291.0)	139.7 (283.5)	135.1 (275.1)

Pressure bar (psig)	Temp. of Steam Mixed w/ Various Percentages of Air (by volume) ℃(℉)
压力 bar（磅/平方英寸）	蒸汽与不同比例空气混合（按体积计）的温度℃（℉）

Values derived using Dalton's Law of Partial Pressure
使用道尔顿分压定律推导出的值。

Types of steam trap (as defined by International Standard ISO 6704:1982) (23)
蒸汽疏水阀的类型（按照国际标准 **ISO 6704:1982** 定义**) (23)**

There are three primary types of steam traps:
蒸汽疏水阀有三个基本类型：

- Mechanical (operated by changes in fluid density) — This range of steam trap operates by sensing the difference in density between steam and condensate. These include 'ball float traps' and 'inverted bucket traps'. In the 'ball float trap', the ball rises in the presence of condensate, opening a valve which allows the denser condensate to pass. With the 'inverted bucket trap', the inverted bucket floats when steam reaches the trap and it rises to shut the valve. Both are essentially 'mechanical' in their method of operation.
- 机械式疏水阀（由流体密度的变化控制动作）—这类疏水阀通过感应蒸汽和冷凝水之间的密度差异来控制动作。其中包括“浮球式疏水阀”和“倒吊桶式疏水阀”。浮球式疏水阀，当其中存在冷凝水时，浮球浮起将阀打开排出冷凝水。倒吊桶式疏水阀，当蒸汽进入阀体内时，倒扣的桶浮起关闭阀门，两种疏水阀的操作方式本质上都是“机械性的”。

- Thermostatic (operated by changes in fluid temperature) — The temperature of saturated steam is determined by its pressure. In the steam space, steam gives up its enthalpy of evaporation (heat), producing condensate at steam temperature. As a result of any further heat loss, the temperature of the condensate will fall. A thermostatic trap will pass condensate when this lower temperature is sensed. As steam reaches the trap, the temperature increases and the trap closes (e.g. bimetallic).
  温控式疏水阀（注：即热静力式疏水阀）（由流体温度的变化控制动作）—饱和蒸汽的温度由它的压力决定。在蒸汽空间内，蒸汽放弃其蒸发焓（热量），在蒸汽温度生成冷凝水。任何进一步的热损耗都会造成冷凝水温度下降。当温控式疏水阀感觉其中的温度降低时，就会打开阀门，排除冷凝水。当蒸汽进入阀内，温度上升，阀门关闭(如：双金属)。

- Thermodynamic (operated by changes in fluid dynamics) — Thermodynamic steam traps rely partly on the formation of flash steam from condensate, e.g. thermodynamic disc.
  热力式疏水阀（注：即热动力式疏水阀）（由流体动力的变化控制动作）—热力式疏水阀依赖于冷凝水生成闪蒸蒸汽来控制开闭。例如：热力阀盘式疏水阀。

Table 4.2-3 An example of considerations for steam trap selection
表 4.2-3 蒸汽疏水阀注意事项举例

Feature 特性	Mechanical 机械式		Thermodynamic 热力式	Thermostatic 温控式
	Inverted Bucket 倒桶式	Ball or Float w/ without Thermostatic Disc 浮球式/无热力阀盘	Disc 圆盘式	Balanced Pressure Disc / Bimetallic 压力平衡式/双金属式
Sanitary Application 洁净型应用	No 否	No 否	Yes 是	Yes 是
Method of Operation 运行方式	Intermittent 间歇	Continuous 连续	Intermittent 间歇	Intermittent 间歇
Energy Conservation (Time in service) 能力保持（检修时间间隔）	Excellent 优秀	Good 好	Poor 差	Fair 一般
Resistance to Wear 抗磨强度	Excellent 优秀	Good 好	Poor 差	Fair 一般
Corrosion Resistance 抗腐蚀性	Excellent 优秀	Good 好	Excellent 优秀	Good 好
Resistance to Hydraulic Shock 抗液压冲击	Excellent 优秀	Poor 差	Excellent 优秀	Fair 一般
Vents Air and CO_2 at Steam 蒸汽温度下排除空气和 CO_2	Yes 是	No 否	No 否	No 否
Ability to Vent Air at Very Low Pressure 低压下排除空气能力	Poor 差	Excellent 优秀	N/R	Good 好
Ability to Handle Startup Air Loads 初始空气负荷处理能力	Fair 一般	Excellent 优秀	Poor 差	Excellent 优秀
Operation Against Back Pressure 抗压运行	Excellent 优秀	Excellent 优秀	Poor 差	Excellent 优秀
Resistance to Damage from Freezing 抗冻结损害	Good 好	Poor 差	Good 好	Good 好
Ability to Purge System 净化系统能力	Excellent 优秀	Fair 一般	Excellent 优秀	Good 好
Performance on Very Light Loads 极轻量负载下工作性能	Excellent 优秀	Excellent 优秀	Poor 差	Excellent 优秀
Responsiveness to Pools of Condensate 对集中的冷凝水的反应能力	Immediate 即时	Immediate 即时	Immediate 延迟	Immediate 延迟
Ability to Handle Dirt 处理污垢能力	Excellent 优秀	Poor 差	Poor 差	Fair 一般

Feature 特性	Mechanical 机械式		Thermodynamic 热力式	Thermostatic 温控式
	Inverted Bucket 倒桶式	Ball or Float w/ without Thermostatic Disc 浮球式/无热力阀盘	Disc 圆盘式	Balanced Pressure Disc / Bimetallic 压力平衡式/双金属式
Comparative Physical Size 外形尺寸比较	Large 大	Large 大	Small 小	Small 小
Ability to Handle “Flash Steam” 闪蒸蒸汽处理能力	Fair 一般	Poor 差	Poor 差	Poor 差
Mechanical Failure (Open-Closed) 机械故障（开-关）	Open 开	Closed 关	Open 开	Open or Closed 开或关

3.3 SIP System Control and Monitoring
SIP 系统控制和监测

3.3.1 Automation
自动系统

Effective SIP operations may be conducted irrespective of the extent of process automation. The degree of automation for control and monitoring is a decision that should be made based on the criticality of the application and the resources available for commitment to control and monitor tasks. With thoughtful and proper implementation, increased levels of automation can benefit more complex SIP processes. However, if the required SIP operations are not operationally intensive, greater economies may be realized with reduced levels of automation. Organizations should evaluate the level of automation desired while considering the intent, complexity, and scope of the SIP process. Determination of the level of automation desired may be facilitated through the use of risk assessment tools.

对于有效的 SIP 运行，可以不考虑过程自动化管理。控制和监测的自动化程度应基于程序的关键程度和用于保证控制和监测任务的可用资源来决定。经过仔细考虑和适当的实施，提高自动化水平有利于更加复杂的 SIP 流程。但是，如果所需的 SIP 程序运行其操作并不复杂，采用较低的自动化水平可能更加经济。组织机构应评估所需的自动化水平并同时考虑 SIP 流程的目的、复杂性和范围。通过使用风险评估工具可能会帮助确定所需的自动化的水平。

A high level of automation allows less operator oversight, repeatable compliance to procedures, less variability post-implementation and may also facilitate use of process analytical technologies (PAT). Fully automated systems involve more work initially to assure that sterilization or sanitization is being performed correctly and as intended each and every time it is run in terms of system design, software development, and qualification. Conversely, with lesser degrees of automation, process monitoring becomes more dependent on operator training, documentation, and procedures which are well known to lead to possible errors.

高自动化水平可以减少操作人员的失误、使每次运行均可重复地按程序设定进行、使用后可变性更少、还可以协助过程分析技术（PAT）的使用。全自动化系统涉及到更多的前期工作以确信灭菌或清洁得到正确的处理，并且每次运行均符合系统设计、软件开发和验证的预期。反之，对于自动化程度较低的系统，工艺过程的监控更加依赖于操作者的培训、文件系统、以及对容易产生错误的工艺步骤的充分理解。

The implications of three different levels of automation are described in **Table 4.3-1**.
表 4.3-1 中描述了三种不同自动化水平的影响

Table 4.3-1 Examples of Levels of Automation
表 4.3-1 自动化水平举例

Level 水平	Software Development 软件开发	Qualification 验证	Process Variability 工艺过程可变性	Resource Requirements 资源需求
Automated 自动化	Extensive 广泛	Extensive 广泛	Repeatable 可重复	Automation 自动化
Semi-automated 半自动化	Variable 变量	Variable 变量	Variable 变量	Automation and Operations 自动化和操作
Manual 手工	None 无	Minimal 极少	Operator dependent 依赖操作者	Operations 操作

3.3.2 Controlling the SIP Cycle
过程控制

The SIP cycle may be controlled using either a time and temperature strategy, or a calculated *F*0 value as the process variable. The time and temperature approach relies on durations empirically determined during cycle development, and usually depends upon the successful, uninterrupted exposure of the system to a relatively constant temperature. Should the temperature (monitored at critical locations throughout the system) drop below the designated minimum cycle temperature, the timer may be stopped or reset. Alternatively, controlling based on *F*0 allows for determination of an SIP cycle endpoint by taking into account equivalent physical lethality across multiple temperatures.
SIP 过程即可采用时间和温度作为工艺参数的控制策略也可采用计算 F_0 值做为工艺参数的控制策略。采用时间和温度的方式来控制依赖于过程开发期间积累的经验决定，通常依赖于系统成功的、不间断的在一个相对恒定的温度下的灭菌。当温度（在整个系统的关键位置监控）低于规定的最小过程温度时，计时器应当停止或重新计时。当使用 F_0 值控制时，可以根据计算不同温度下的等效物理杀灭能力确定一个 SIP 过程的终点。

For saturated steam, there is a direct correlation between temperature and pressure. Either variable can be used for feedback control, but in practice, this information is used to control introduction of steam either through dedicated pressure control valves or through the use of existing diaphragm valves as described in **Section 4.2.**
对于饱和蒸汽来说，温度和压力直接相关。任一变量都可用于反馈控制。但是在实际运用中，压力参数通常用于通过专用的压力控制阀或使用既有的隔膜阀控制蒸汽通入量，如 **4.2 节**所述。

Two keys to successful control are 1) proper selection and sizing of the steam supply and 2) fixing the pressure via a locked regulator immediately upstream of the equipment. The pressure is typically set slightly above the expected operating pressure to account for systemic pressure losses. Maintenance of steam pressure should be ensured once the cycle is developed.
成功控制的两个关键是： 1)蒸汽供应选择合理并符合标准。2)设备的上游通过一个锁定的稳压器保证压力稳定。设定压力通常略高于预期所需的工作压力以抵消系统压力损失。一旦 SIP 过程开始应确保蒸汽压力得到维持。

Another effective method of SIP control is modulating pressure or temperature control valves to control steam during SIP. Depending on the design, either the valve toggle method or control valve method can have economic advantages. If vessel piping and valve placement are designed properly, most or all of the piping associated with the vessel may be steamed along with the vessel, rather than having separate cycles for the piping.
另一个有效的 SIP 控制方法是在 SIP 过程中通过调节压力或温度控制阀来控制蒸汽。根据设计，无论是采用阀切换的方法或是采用控制阀的方法均有一定的经济优势。如果容器管道和阀门的位置设计正确，与容器相关的大多数或全部的管道可与容器一同进行蒸汽灭菌，而不需为分配管路单独进行 SIP。

3.3.3 SIP for Portable Vessels
可拆卸容器的 SIP

Similar methodologies may be applied to SIP of portable vessels by designing a CIP/SIP station with automatic sanitary diaphragm valves in the CIP/steam supply. A single station can service tanks of various sizes via individual recipes that operate the valves for each tank size or design. Correct timing for each tank is determined during cycle development.
通过相似的在 CIP/蒸汽供应源设计一个有自动卫生型隔膜阀的 CIP / SIP 站的方法，可用于可拆卸容器的 SIP 过程。一个 CIP / SIP 站通过针对不同罐的尺寸或设计来对阀门操作采用不同的方法，能够进行多种尺寸的罐的处理。每个罐的正确的处理时间在 SIP 过程的开发阶段决定。

3.3.4 Semi-Manual and Manual SIP Operations
半手工和手工 SIP 运行

While increasing the level of automation is recommended for enhanced control and cycle reproducibility, it is not uncommon to encounter manually operated systems. The prerequisites and design principles considered for automated systems also apply to manual SIP systems. Reducing the extent of automation ranges from semi-automated systems that are manually initiated but automatically controlled, to manually operated systems controlled through hand operated valves and pressure and temperature indicators, to those with limited to no instrumentation. In such cases, through the use of appropriate documentation and well defined operating procedures, manually operated SIP processes can be conducted with a reasonable level of reliability.
建议通过提高自动化水平来加强控制和 SIP 过程的重现性的同时，也常常遇到手工操作系统。自动系统需考虑的先决条件和设计原则也适用于手工操作系统。在手工启动但自动控制的半自动化系统的基础上，再减少自动化的程度和范围，即为手工操作系统，其通过手动阀门和温度、压力指示器这些有限的仪器仪表进行控制。这种情况下，通过使用适当的文件、明确的操作规程，手工操作的 SIP 流程也能在一个合理的可靠度水平下运行。

Manually operated SIP cycles require many of the same safety, risk assessment, and validation considerations expected of automated systems. Process monitoring logistics, the physical limitations of operators, and increased process variability should be taken into consideration if a manually operated system and SIP cycle are to be designed and operated. Without automation, process interlocks must be proceduralized through SOPs, signage, and highly visible warnings.
手工操作 SIP 过程需要许多与自动化系统预期相同的安全、风险评估和验证方面的考虑。若设计和运行一个手工操作系统和 SIP 过程，应考虑工艺监测的数理逻辑、操作者的体力限制以及增加的工艺过程可变性。没有自动化系统的情况下，通过 SOPs、标识和明显可见的警告标志来实现工艺过程互锁。

At a minimum, systems should be designed with appropriate isolation valves, pressure regulators at the steam source, and a means of monitoring the pressure within close proximity to the associated manual valves. As with any system, steam traps should be installed at the low points to remove condensate. If internal temperature indicators are not installed, surface mounted probes, melt sticks, or sensors can be used to confirm that the

external temperature is greater than the specified minimum. Using a combination of both pressure and temperature measurement in close proximity to each other ensures that saturated steam conditions exist (refer to **Figure 3.2-2).**
系统最低限度应设计适当的隔膜阀、蒸汽源的稳压器以及在靠近相应的手动阀的位置的压力监测手段。为排除冷凝水，任何系统的蒸汽疏水阀均应安装在低点。如未安装内部的温度指示器，可用明装的温度探头、感温棒或温度传感器来确认表面温度高于规定的最低温度。要采用对压力和温度的组合测量，在两者的结果极为对应的条件下，以确保饱和蒸汽状态，（参见**图 3.2-2**）。

For validation of the cycle, supplemental temperature measurement techniques are recommended. Further, since the potential for greater process variability exists with a manually controlled SIP cycle, an overkill sterilization approach is preferred.
对 SIP 过程的验证，推荐采用温度补偿测量技术。进一步说，由于手工控制 SIP 过程存在更大的潜在工艺过程可变性，应首选过度杀灭的灭菌方式。

4.0 Cycle Development Considerations
周期开发考虑

The SIP cycle development objective is a robust process that is repeatable and consistently meets user requirement specifications.
SIP 周期开发的目标开是开发出一个稳健的、可重现的、能持续满足客户需求的程序。

The user should assess the intended application and purpose of the system and consider regulatory expectations for systems when claiming sterilization versus sanitization. The overkill method (F_{BIO} and F_{PHYS} ≥12 min) is not required when claiming sanitization of a system.
当声明被开发的程序是灭菌还是消毒时，用户应该评估预期的应用和系统的目的，并且考虑监管的预期要求。如果声明是用于消毒，则不需要用过度杀灭法（F_{BIO} 和 F_{PHYS} ≥12 min）。

Operational parameters and their classification (e.g., “critical” or “key”) are determined during cycle development. A risk assessment based on intended use may be useful in determining these parameters.
在周期开发时就确定操作参数，并将它们分类（例如：“重要的”或“关键的”）。基于使用的风险评估在确定这些参数时会有帮助。

Risk assessments of SIP processes can be implemented at identified control points through a review of the unit operations and various phases of the process. Operations where the opportunity and likelihood of product contamination is low may be focused on the equipment, instrumentation, and procedures supporting microbial control through sanitization.
通过审查单元操作和过程的各个阶段，SIP 流程的风险评估可以在确定控制点实现。当产品受污染的机会和可能性很低时，操作可集中在消毒过程中支持微生物控制的设备、仪器仪表及程序上。

Each SIP cycle can be divided into a series of steps or phases, depending on the intended use and risk assessment of the SIP cycle. The phases of a typical SIP cycle may include:
根据 SIP 循环使用目的和风险评估，每个 SIP 循环可以分为一系列步骤或阶段。典型的 SIP 循环可包括以下阶段：

- Pre-SIP system integrity test
  SIP 前完整性检测
- Heat up/Air displacement
  加热/空气置换
- Exposure/Dwell time
  灭菌/保压时间
- Cooldown/Steam removal/Drying
  冷却/去除蒸汽/干燥
- Post-SIP system integrity test SIP\
  SIP 后完整性检测

Each phase has its own intended objective. **Table 5.0-1** lists the phases of a typical SIP cycle, and briefly describes the objectives of each phase. This table is intended to provide a brief illustration of phases that could be encountered during a typical SIP cycle and is not all-inclusive. Specific parameters that are controlled during each phase are discussed further in **Table 5.2-1. Figure 5.0-1** provides an illustration of the phases of a typical SIP

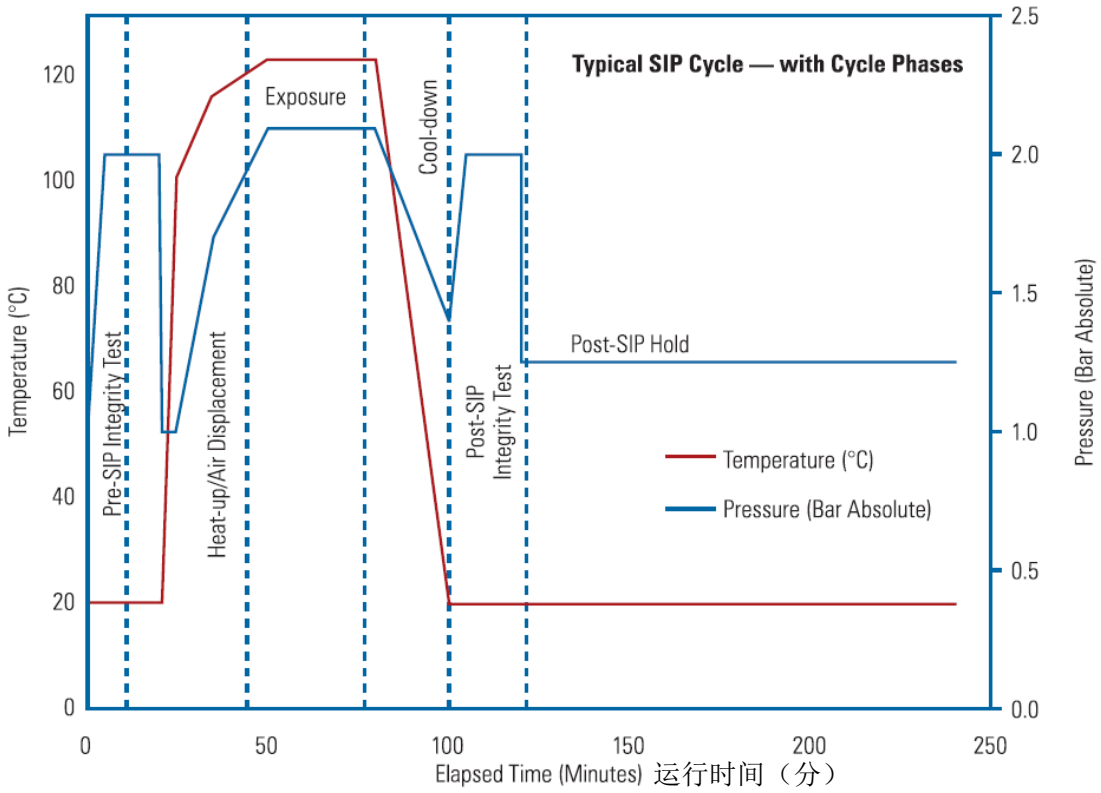
cycle.
每个阶段都有它自己的预期目标。表 5.0 - 1 列出了典型的 SIP 周期各个阶段,并且简要描述了每个阶段的目标。这个表的目的是对典型的 SIP 周期各阶段提供一个简要的说明,并不是包括了所有的阶段。每个阶段特定控制参数在表 5.2 - 1 进行进一步的讨论。图 5.0 - 1 提供了一个典型的 SIP 周期每个阶段的说明。

Table 5.0-1 Typical Steps and Phases of an SIP Cycle with Relevant Objectives
带相关目标的一个 SIP 周期的典型的步骤和阶段

Phase Objectives 阶段目标	Objectives 目的
Pre-SIP System Integrity Test (optional) SIP 前系统完整性检测（可选）	Determine if the system will meet user-defined requirements for operator safety and system integrity. 确定系统将满足用户定义的操作者安全和系统的完整性要求
Heat Up/Air Displacement Phase 加热/空气置换阶段	Displace air and heat up the system via introduction of steam at high points in the system, forcing air out through low points in the system (gravity displacement) or by single or repeated evacuation of the system followed by introduction of steam to a predetermined pressure set point (vacuum/steam pulses). 通过在系统的高位置点引入蒸汽置换空气并加热系统, 迫使空气通过系统低位置点（重力位移）排出系统，或通过单一或多次抽真空随后引入蒸汽到预定压力设置点(真空/蒸汽脉冲)。 Condensate removal 除去冷凝水 Keep filter differential pressures within defined limits 保持过滤器的压差在规定范围内
Exposure/Dwell Time Phase 暴露（灭菌）/保压时间	Maintain the system at a predefined temperature and pressure for the time required to achieve the desired minimum lethality. 暴露(灭菌)/保压阶段 使系统温度和压力保持在一个规定的的时间，以获得期望的最小的致死率 Condensate removal 除去冷凝水 Keep filter differential pressures within defined limits 保持过滤器的压差在规定范围内
Cool-down/Steam Removal/Drying Phase 冷却/蒸汽去除/干燥阶段	Cool and dry the system to user-defined levels; typically uses filtered gases (e.g., compressed air or nitrogen) to cool, dry, and maintain pressure on the system. 冷却并干燥达到用户定义的水平；通常用过滤后的空气（例如压缩空气或氮气）进行冷却、干燥并使系统维持在一定的压力 Keep filter differential pressures within defined limits 保持过滤器的压差在规定范围内
Post-SIP System Integrity Test (optional) SIP 后完整性检测（可选）	Determine if the system will meet user-defined requirements for operator safety and system integrity. 确定系统将满足用户定义的操作者安全和系统的完整性要求
Post-SIP Hold (optional) SIP 后保持（可选）	Maintains the system integrity between completion of SIP and use of the system.Post-SIP Hold usually uses compressed gases to pressurize the system. This phase is recommended for critical/ sterile applications. 维护系统在完成 SIP 后和使用系统这段时间的完整性。 后 sip 保持

	通常使用压缩气体增压来实现。这是关键/无菌的应用阶段。

Figure 5.0-1 Example of SIP Cycle Phases
图 5.0-1 实例：SIP 程序过程



4.1 Use of Risk Management during Development
开发过程中风险管理的应用

Risk management techniques may be used in cycle development to ensure that product risks are appropriately minimized and that a risk-based level of cycle development is performed. Appendix A provides more details on the application of a risk based approach for SIP systems.
风险管理技术可以用于程序开发,以确保产品的风险降至最低，以及程序开发是在风险评估的基础上执行的。附录 A 为 SIP 系统提供基于风险应用方法的更多细节。

4.1.1 Risk Assessment
风险评估

Risk assessment should look at the overall risk to the product and, if appropriate, provide a detailed risk review of the system to determine potential points of failure and mitigation methods. The detailed risk review, if needed, should build upon the engineering design review. Items to consider as part of the risk assessment may include:
风险评估应该看产品的整体风险，如果合适的话，提供一个详细的系统的风险审查以确定潜在的故障点和解决方法。如果需要,详细的风险审查应建立于工程设计审查的基础上的。需要考虑的风险评估可能包括:

- The processing step in which the system being steamed in place is involved. For example, a system used to prepare buffers or reagents for early manufacturing steps for an API may present a relatively low risk, whereas a system involved in final fill and finish of an aseptically filled product may present a very high risk
涉及到 SIP 的工艺步骤。例如,生产 API 初始阶段准备缓冲液或试剂工艺可能是相对较低的风险,而对于最终产品的无菌灌装工艺是非常高的风险。

- The potential for product impact based on the degree of product contact (non-contact, indirect contact, or direct contact) with the system being steamed-in-place
  SIP 系统与产品接触程度(非接触、间接接触,或直接接触)对产品的潜在影响
- The complexity of the system undergoing SIP
  系统 SIP 的复杂程度
- The severity of failure and probability of detection of an SIP failure. These two factors are related to their location in the processing stream, degree of product contact, and system complexity. The severity of failure should always be considered at the highest value for an aseptically filled product (see PDA Technical Report No. 44) ***(3)***.
  SIP 失败的严重性和可检测概率。这两个因素都与他们的位置, 与产品接触程度,和系统的复杂性有关。对于无菌灌装产品，失败的严重性应该一直打最高分数。（见 PDA 技术报告 44）***(3)***

4.1.2 Risk Mitigation
风险降低

Risk mitigation should be based on the level of risk tolerance determined during the risk assessment. Depending on the level of risk tolerance, mitigation efforts may include:
风险降低应基于在风险评估中确定的风险容忍度水平。根据不同的级别的风险容忍度,缓解措施可能包括：

- Pre-SIP and pre-use system integrity tests
  SIP 前和系统使用前完整性检测
- Additional monitoring points and biological indicators (if any) used during cycle development
  程序开发期间额外监控点和使用的生物指示剂
- Additional safety factors built into the SIP cycle
  SIP 程序的额外安全系数
- Additional alarm points and/or control limits for temperature and pressure.
  温度和压力的额外报警点和/或控制限

4.1.3 Cycle Development Data
周期开发数据

The amount of cycle development data needed to determine the key and critical parameter levels should be commensurate with the overall system risk. A high-risk system should have extensive data before proceeding to qualification; Other than routine commissioning tests, a low-risk system may need little or no cycle development data to proceed to qualification.
为确定关键和重要参数水平所需要的程序开发数据应该与整个系统的风险相称。在进行程序确认之前，高风险的系统应该有大量的数据来确定参数;除了常规调试测试,一个低风险的系统可能需要很少或没有程序开发数据就可以进行确认工作。

4.1.4 Testing
测试

Some routine tests that might be performed during cycle development:
在程序开发期间可进行一些常规测试

- Perform temperature mapping to determine cold and hot spots in the system.
  进行温度分布测试以确定系统的冷点和热点
- Verify that excessive condensate is not building up at any points (e.g., low point drains, filter housings) in the system. The use of thermal imaging instruments can be used for this. Adjust/modify steam traps and system bleeds as necessary.
  确认系统在任何点(如。排水口,过滤器外壳点)都不存在过度冷凝。使用热成像仪器可以用于此检测。

必要时调整/修改疏水阀和系统抽气装置。

- Verify that valve timing and sequence of operations are as described in the automation control systems' detailed design specification.
  确认阀定时和操作顺序与自动化控制系统详细设计规范所述一致
- Determine time and temperature required to achieve an appropriate F_{PHYS} value.
  确定获得 F_{PHYS} 值所需的时间和温度
- Biological challenge, to ensure that an adequate F_{BIO} is achieved before proceeding to qualification of high-risk systems.
  在对高风险系统进行确认前进行生物挑战测试，确保能获得足够的 F_{BIO}

4.2 Cycle Parameter Determination
程序参数确定

Critical operating parameters for SIP cycles include time, temperature, and pressure. These parameters are manipulated to achieve the desired degree of sterilization or sanitization. Time, temperature, and pressure parameters should be determined for each phase of the SIP cycle (see **Table 5.0-1** for typical cycle phases). **Table 5.2-1** provides the operating procedure for each phase, as well as a brief description of the time, temperature, and pressure set points.

SIP 程序的关键操作参数包括时间、温度和压力。通过操纵这些参数来实现所需程度的灭菌或消毒。应该确定 SIP 周期每个阶段的时间、温度、和压力参数 (见表 5.0 - 1 典型的周期阶段)。表 5.2 - 1 提供了操作过程的每个阶段,以及一个简短的描述的时间,温度和压力设置点。

Table 5.2-1 also describes time, temperature, and pressure parameters for the optional System Integrity Test that may be performed before and/or after SIP of a system. Although there are several System Integrity Test methods (e.g., Pressure Hold, Mass Flow, and Tracer Gas), **Table 5.2-1** only includes the most common System Integrity Test: the Pressure Hold Test.

表 5.2 - 1 还描述了可选系统 SIP 前和/后完整性检测的时间、温度、压力参数。虽然有几个系统完整性测试方法(如压力保持、质量流量,示踪气体),表 5.2 - 1 只包括最常见的系统完整性测试:压力保持测试。

Table 5.2-1 Example of Typical SIP Cycle Operational Parameters
表 5.2-1 典型 SIP 循环操作参数

SIP Step SIP 步骤	Parameters 参数	Considerations 注意事项
Pre-SIP System Integrity Test (optional) SIP 前完整性检测（可选）		
Pressure Hold Test 保压测试	Procedure 程序	The system pressure is brought to a predetermined set point. All valves are shut off and the system is held for a predetermined amount of time. Pressure drop over that time is measured. 使系统压力达到预定的值。所有阀门都关闭,保压至一段时间。测量压力下降至一定水平所需要的时间
	Time 时间	There are typically three time periods defined for a pressure hold test: pressurization time, stabilization time, and hold time. Each time period during a pressure hold test should be monitored and controlled. 通常有三个时间段定义压力保持测试:增压时间、稳定时间和保持时间。每个时间段都应该进行监控。 Pressurization Time is the time required to pressurize the system to the operating pressure for the pressure hold test. It is dependent on the volume of the system and the capacity (liters per minute at a given pressure drop) of the compressed gas supply. Most procedures set an upper limit for pressurization time, as extended pressurization time may indicate a significant loss of system integrity. 增压时间是压力保持测试时对系统进行增压达到操作压力所需的时间。它是依赖于系统压缩气体供应的体积和容量(给定的压降下：升/分钟)。大多数程序设置一个上限增压时间，因为延长加压时间可能表明系统完整性已遭到明显破坏。 Stabilization Time is a brief period—typically around 5 minutes—allowing the pressure within the system to equilibrate and any temperature increases due to pressurization of the system to stabilize. 稳定时间是一个短暂的时间，通常约 5 分钟，为系统内压力平衡时间，及由于系统增压后稳定系统引起温度上升。 Hold Time is defined by system size, system pressure, and the size of leak to be detected. Hold times should be minimized to avoid excessive temperature fluctuations. 保持时间是由系统大小、系统压力、检测到泄漏的大小决定的。保持时间应该最小化,以避免过度的温度波动
	Temperature 温度	The system temperature is monitored (typically at ambient temperature) throughout the test to minimize false positives (“virtual leaks”) or false negatives caused by temperature fluctuations. 系统温度在整个测试过程中进行监测(通常在环境温度)以减少温度波动引起的假阳性(“虚拟泄漏”)或假阴性。 **NOTE:** Gay-Lussac’s Law: The pressure of a fixed amount of gas at a fixed volume is directly proportional to its temperature in degrees Kelvin. ($P_1/T_1 = P_2/T_2$). 注意：盖•吕萨克定律: 在固定的体积下，固定量的气体压力与开尔文温度成正比。($P_1 / T_1 = P_2 / T_2$)。 When specifying the temperature for a pressure hold test, system characteristics such as jacketing, insulation, measuring instrument accuracy and ambient temperature of the surrounding area and the compressed gas supply should be considered. 当指定了压力保持测试的温度,应考虑系统特性如夹套、绝缘、测量仪器精度和环境温度和压缩气体供应。
	Pressure 压力	The system is typically pressurized to a pressure less than or equal to the system pressure during the SIP cycle. 该系统通常是加压到压力小于或等于 SIP 期间系统压力。 The pressure hold period begins after pressurization and the system pressure is allowed to stabilize for a few minutes. 系统压力加压后开始压力保持期，允许压力稳定几分钟。 The allowable pressure loss during the pressure hold period is based on several factors including system volume, system design, and system criticality. 在压力保持期允许的压力损失是基于几个因素,包括系统体积、系统设计和系统重要程度。 Except during initial pressurization, system pressure is monitored, but not controlled. 除了在初始增压阶段外，其他时间应监测系统压力,而不用控制系统压力。

SIP Step SIP 步骤	Parameters 参数	Considerations 注意事项
Heat-Up/Air Displacement (Gravity Displacement or Vacuum/Steam Pulses) 加热/空气置换（重力置换或真空/蒸汽脉冲）		
Gravity Displacement Method (typical Method used) 重力置换方法（典型方法）	Procedure 程序	Steam is introduced into the high points of the system. Density differences cause the heated steam to displace trapped air in the system downward. Steam traps and constant bleeds at low points in the system allow the trapped air and condensate to exit. 蒸汽引入系统的高点。密度差异导致热蒸汽置换下面系统内的空气。系统下面的疏水阀和恒定流量装置允许空气和冷凝水排出。
	Time 时间	In large systems, gravity displacement may occur as a two-phase process: 在较大的系统，重力置换可有两个阶段 Phase 1: Valves in the system (system low points and farthest points from steam inputs) may be opened to allow for a rapid displacement of air and heat-up of the system. This phase typically operates at or near atmospheric pressure. 阶段1：系统阀门 (系统低的点，离蒸汽输入最远的点)可被打开,允许快速置换空气和加热系统。这一阶段通常是或接近大气压力。 Phase 2: Valves allowing for a rapid steam purge are closed, forcing the steam to exit from the traps and/or constant bleeds. This allows the system to pressurize and heat to the final system temperature and pressure. 阶段2：将允许蒸汽快速吹扫的阀门关闭,迫使蒸汽通过疏水阀和/或恒定流量装置排出。这允许系统增压和加热到最终的温度和压力 Time is typically monitored. 通常对时间进行监测。
	Temperature 温度	The time required for gravity displacement is determined empirically by temperature mapping (see section 5.4). The endpoint of gravity displacement may be determined by temperature at one or more low points in the system. 重力置换需要的时间很大程度上由温度分布决定(见5.4节)。系统中低位置一个或多个点的温度可决定重力置换的终点。 Temperature should be monitored during the displacement process. The end point of gravity displacement is typically determined by comparing the temperature at the control probe to the pressure at the same point. 置换过程应监控温度。将同一点温度与压力比较来决定重力置换是否结束。
	Pressure 压力	Pressure should be regulated and monitored during the heat-up air displacement phase. 应规定并监控加热空气置换阶段的压力。 By the end of the gravity displacement phase, the system pressure should be approximately equivalent (within predetermined limits) to the pressure of saturated steam at the operating temperature of the system (see **Table 4.2.2).** The accuracy of system instrumentation and the location of the pressure and temperature measurements should be taken into account when setting limits for the system temperature/pressure relationship. 到重力置换结束阶段,系统压力要基本与操作温度下饱和蒸汽压力相同(在预先确定的范围) (见表4.2.2章)。当设定温度/压力关系的时候，要考虑系统检测仪表的准确性、压力和温度检测仪器的位置。

SIP Step SIP 步骤	Parameters 参数	Considerations 注意事项
Vacuum/Steam Pulse Method 真空/蒸汽脉动方法	Procedure 程序	Air is mechanically evacuated from the system to a predetermined vacuum setpoint. Steam is then injected to a predetermined setpoint to heat the system. The evacuation or series of evacuations (vacuum pulses) followed by steam injections (steam pulses) are used to remove air and heat up the system. Steam traps and trap bypass valves are used to remove condensate from the system. 通过机械手段将系统抽真空至预定真空度。然后注入预定量蒸汽加热系统。一次抽真空或多次抽真空(真空脉冲)，然后通蒸汽(蒸汽脉冲)，去除空气并加热系统。疏水阀和疏水旁路阀用来从系统去除冷凝水。 **Note:** trap and bypass valves should only be opened when the system is under positive pressure. 注意：当系统处于正压状态下时，疏水阀和疏水旁路阀应保持开启。
	Time 时间	Time may be monitored or controlled to assure air displacement. The following parameters should be documented: 监控时间确保空气置换完全。记录下列参数： • Pulse times 脉冲次数 • Proportional valve settings 定量阀设定 • Multiple vacuum/steam pulses as required 按要求进行的多次抽真空/蒸汽脉冲
	Temperature 温度	Temperature should be monitored during air displacement and used during cycle development to determine the number of vacuum/steam pulses required. 空气置换期间要监控温度，程序开发期间也要监控温度以确定需要的抽真空/蒸汽脉冲次数。
	Pressure 压力	Pressure is typically controlled during a vacuum/steam pulse cycle. The depth and number of vacuum pulses, steam pulse pressure, and number of steam pulses correlate directly to the amount of air removed during a vacuum/steam pulse air displacement cycle. See PDA Technical Report No. 1, **Section 4.3.1.1** for further discussion of vacuum/steam pulses ***(1).*** 抽真空/蒸汽脉冲周期通常要控制压力。抽真空程度和次数、蒸汽脉冲压力、蒸汽脉冲次数置换空气量直接相关。抽真空/蒸汽脉冲(1)进一步讨论见PDA技术报告1号，章节4 3 1 1。

SIP Step SIP 步骤	Parameters 参数	Considerations 注意事项
Exposure 灭菌	Procedure 程序	The system temperature is brought to a predetermined temperature set point after completion of the heat-up/air displacement phase. Exposure timing begins once the predetermined temperature set point is reached. Exposure timing continues until the minimum required time is reached. 在完成加热/空气置换阶段后，系统温度达到预定的温度，此时开始灭菌阶段计时。计时持续至达到最低要求的时间。
	Time 时间	Time is monitored and controlled. Exposure time set point should be sufficient to achieve the desired degree of sterilization or sanitization.灭菌时间应监测和控制，应设置足够的灭菌时间确保达到期望的灭菌或消毒效果。 **Note:** some systems may use *F*0 control, in which the exposure period is terminated once a predetermined *F*0 is achieved. Time to achieve the desired *F*0 should be monitored for *F*0 control cycles. **注意：**某些系统控制F0，一旦达到一定F0，系统即终止SIP。对于通过控制F0来监控SIP的系统同样要监控SIP时间。
	Temperature 温度	Temperature is monitored and controlled. Exposure temperature is typically ≥121 ℃, but may be different based on system and cycle design parameters. System time and temperature should be adjusted as necessary to achieve the minimum desired level of sanitization or sterilization. 温度应检测和控制。灭菌温度通常≥121°C,但基于系统和循环设计参数也可以是不同的。系统时间和温度应该根据需要进行调整,以达到最小的期望水平的卫生处理或消毒。
	Pressure 压力	Pressure should be monitored to evaluate the temperature/pressure relationship related to saturated steam. The accuracy of system instrumentation and the location of the pressure and temperature measurements should be taken into account when setting limits for the system temperature/pressure relationship. See **Table 4.2-2** for more information. 应该监测压力以用于控评估温度/压力与饱和蒸汽的关系。当设定温度/压力关系的时候，要考虑系统检测仪表的准确性、压力和温度检测仪器的位置。见表4.2 - 2获得更多信息。
Steam Removal/ Cool-Down/Drying 蒸汽去除/冷却/干燥	Procedure 程序	Steam supply to the system is shut off and compressed gas is supplied to the system to cool down and dry the system. Positive pressure is maintained in the system during cool-down and drying. For a description of an alternate method for a system drying under vacuum, see **Section 8.5.11.** 系统蒸汽供应关闭、通压缩气体给冷却并干燥系统。冷却干燥过程中保持正压。章节8 5 11描述了一个真空干燥系统的替代方法。
	Time 时间	Time may be monitored and controlled to determine the length of this phase. 测试和控制时间以确定该阶段的时长
	Temperature 温度	Temperature is monitored to ensure system is cooled to a predetermined temperature before use. 监控温度确保整个系统在使用前冷却至预定的温度
	Pressure 压力	Pressure should be monitored to ensure system pressure remains within predefined limits. 监控压力确保压力保持在预定的限度
Post SIP System Integrity Test (optional) SIP后完整性检测（可选）	See Pre-SIP System Integrity Test 见SIP前完整性检测	

4.3 Filter Cycle Development Considerations
过滤器循环开发考虑

It is important to control temperature and differential pressure as well as minimize condensate buildup during SIP to maintain filter integrity. It is crucial to ensure that filters are used in accordance with the manufacturers' technical specifications and recommendations.
控制温度和压差以及减少 SIP 期间冷凝以维持过滤器完整性是很重要的。确保按照制造商的技术规范和建议使用过滤器是至关重要的。

4.3.1 Wet Filters
润湿过滤器

Maintaining low differential pressure across the filters will be largely dependent on whether the membrane is wet or dry. Wet membranes hold liquid in the pores by capillary forces. Liquid in the pores is a barrier to gas flow. Steam introduced on one side of the filter cannot easily penetrate and pressurize the opposite side of the filter if a membrane is wet, resulting in buildup of differential pressure. A filter may be wetted prior to SIP due to:
保持过滤器两端低差压在将很大程度上取决于膜是湿的或干的。湿的膜在毛细管力作用下保持孔内有液体。孔内液体阻止气体流动。如果膜是湿的过滤器一侧的蒸汽无法轻易透过膜并对另一侧增压,导致过滤器两端形成压力差。一个过滤器 SIP 之前润湿有以下理由：

- Performance of a pre-use integrity test on the filter, which requires the filter to be completely wetted
  使用前需要进行完整性检测，需要膜被完全润湿
- Filter type (some require wetting prior to heat sterilization)
  过滤器类型（一些在热灭菌前需要润湿）

There are three strategies to avoid differential pressure across a filter that has been wetted prior to the SIP cycle:
在 SIP 前有三种方法避免过滤器两端产生压差

- Blow-down—Filter drying may be accomplished by applying air pressure in the forward direction above the filter bubble point to establish bulk flow through the filter. Sufficient time for bulk gas flow must be allowed to ensure that the filter is dry enough to readily allow steam passage without excessive pressure differential.
  吹扫-过滤器干燥可以用压力大于泡点值的空气进行顺方向吹扫，使空气能够吹通过滤器。必须使空气吹足够的时间，使过滤器充分干燥便于蒸汽通过时压差不要太大。
- Controlled introduction of steam to the system—Steam is introduced slowly from the upstream side of the filter during the heat up phase until a rise in pressure is observed downstream of the filter. The time required to heat the liquid in the pores is dependent on steam flow over the surface of the filter. Steam flow over the surface is facilitated by opening vents and drains during steam introduction.
  控制引入蒸汽到系统-过滤器在升温阶段蒸汽缓慢从上游进入，直到观察到下游有压力上升。加热过滤器孔内液体需要的时间依赖于过滤器表面的蒸汽流速。通过打开过滤器的通气口及排水口有助于增加蒸汽流速。
- Use of dual steam sources (upstream/downstream)—Careful consideration should be given to sequencing of valve openings and closings to ensure air displacement/steam penetration of the filter membrane and prevention of vacuum conditions post-SIP.
  使用双蒸汽来源（上游/下游）-仔细考虑阀门的开关顺序，以确保空气置换/蒸汽透过过滤膜，预防 SIP 后出现真空环境。

If steam is introduced to the core side of the wet filter (reverse SIP), steam flow over the surface is greatly reduced because it is not possible to vent the high point of the cartridge core. The system is essentially dead-ended. Under

these conditions it can take a long time to heat and vaporize the liquid in the pores. High differential pressure conditions may result during this time. While the reverse SIP of wet filters is not recommended, the reverse steaming of dry, hydrophobic filters is an acceptable practice, as long as the filter manufacturer's maximum differential pressure rating is not exceeded.
如果蒸汽从滤芯内部即湿的一侧进入(反向 SIP)，表面蒸汽流将大大减少，因为滤芯的高点不可能疏通。系统实质上是到这为止了。 在这种情况下需要很长时间来加热和蒸发过滤器孔内的液体。这段时间过滤器上下游会形成高压差。尽管不推荐反向 SIP，但是对于干燥疏水性滤芯进行反向 SIP 是可以接受的，只要不超过过滤器制造商的最大压差。

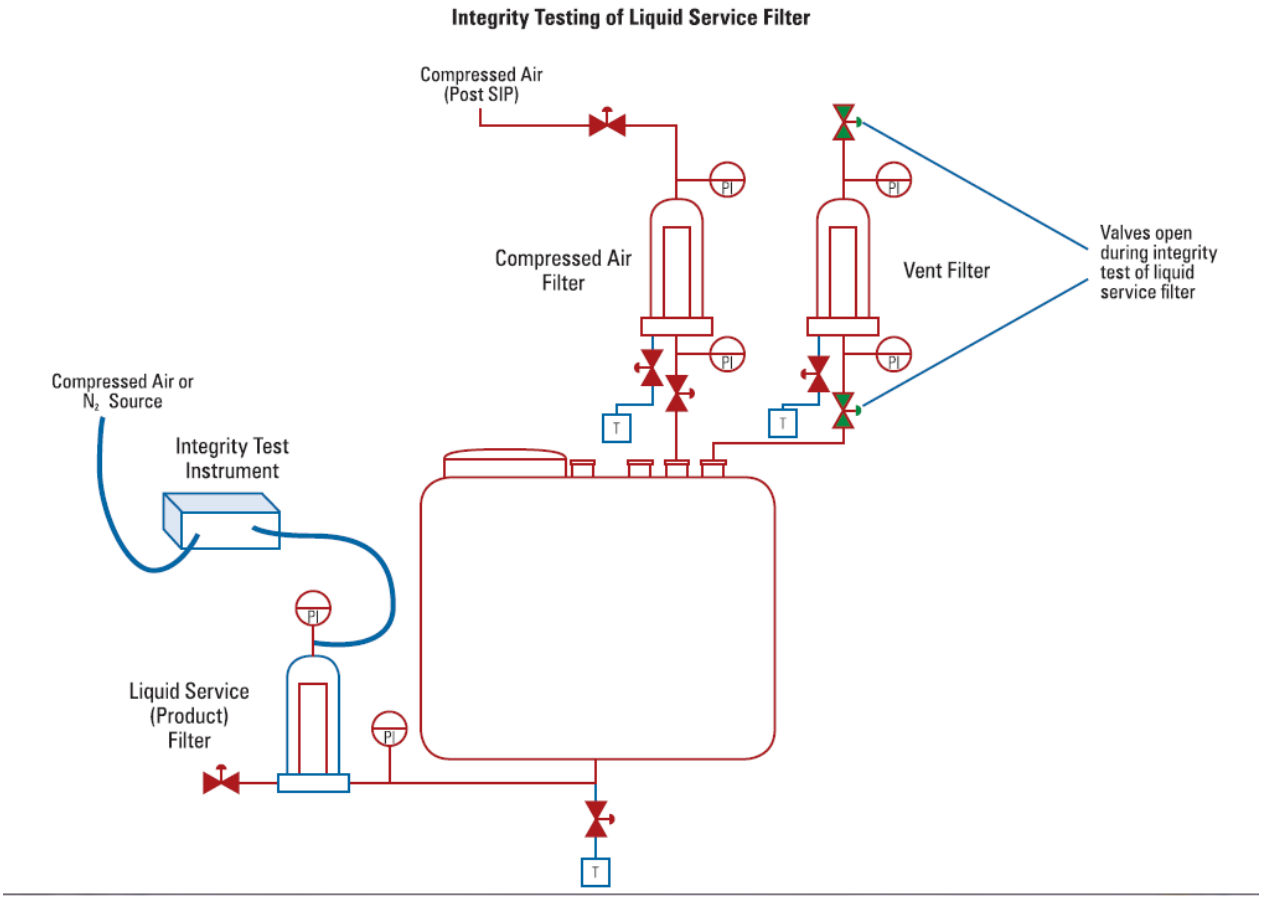
Correct valve sequencing and properly located low-point condensate drains can ensure the filter does not become wet unintentionally during SIP. Isolating the filter and heating the piping prior to introducing steam to the filter assembly is an effective strategy for avoiding excess condensate introduction to the filter during the heat up phase.
正确的阀顺序和低点排冷凝水点位置正确可以确保过滤器在 SIP 过程中不会无意中被弄湿。 在引入蒸汽前，隔离过滤器，给管道预先加热是一个有效的策略来避免加热阶段带入过多冷凝水。

Filters wet with alcohol solutions should be dried via blow-down or oven prior to SIP to avoid potential chemical compatibility issues from hot alcohol exposure and to minimize ingression of alcohol vapor into the SIP system.
如果使用酒精润湿的过滤器，在 SIP 之前应将酒精吹或烘干干，以避免过滤器暴露在热酒精中发生化学相容性问题，并减少酒精蒸汽进入 SIP 系统。

4.3.2 Filter Integrity Tests *(16,17)*
过滤器完整性测试

Suitable integrity test of the filter cartridge may be performed pre-use and must be performed post-use for sterile applications. Regional expectations vary on the application of pre-use integrity tests. Downstream sterility must be maintained post sterilization. The downstream side of the filters tested by Bubble Point or Forward/Diffusive Flow in situ on a tank or system should be vented to atmosphere through a sterilized vent filter as depicted in **Figure 5.3.2-1.** Off-line integrity testing of filters pre-SIP and post-use is acceptable, however, the installation integrity check is lost unless the housing with the filter is removed and tested. Refer to **Section 4.2** for more details related to filters and filter integrity testing considerations.
对于无菌应用来讲，在使用之前可以对过滤器进行合适的完整性测试,而使用后必须进行完整性测试。不同地区对使用前的完整性测试要求不同。灭菌后必须保持下游的无菌性。储罐或系统上过滤器用泡点或前进流/扩散流测完整性时，下游必须通过一个已灭菌的滤芯与大气接通，如图 5. 3. 2- 1，SIP 前和 SIP 后进行离线过滤器完整性测试都是可以的，然而，这样或导致安装完整性遭到破坏，除非滤壳随着滤芯一起拆下来进行完整性测试。4.2 节对过滤器及过滤器完整性有更详细的描述。

Figure 5.3.2-1 Example of In Situ Filter Integrity Test
图 5.3.2-1 在位过滤器完整性测试的实例



4.4 Temperature Mapping
温度分布

Temperature mapping is an iterative process with physical adjustments to the system or changes in SIP process sequences to optimize temperature distribution. These studies can identify locations for permanent monitoring devices and validation probes in areas of the SIP system that are the most difficult to heat and/or displace air. They are performed by placing temporary probes throughout the SIP system boundary to ensure the control probes effectively capture thermal behavior of the SIP system. Probe locations and the rationale for selecting each location should be documented. The number of temporary probes needed varies according to the complexity, criticality, and size of the system.
温度分布测量是一个反复过程，对系统进行物理调整或改变 SIP 流程序列以优化温度分布。这些研究可以确定永久监控设备的位置和 SIP 系统验证探头布点位置，验证探头应布在系统中最难加热和/或空气最难置换的位置。通过将探头布在 SIP 系统边界,确保控制探头有效地捕获 SIP 系统热性能。探头位置以及每个位置的选择理由应该被记录。探头数量取决于系统的复杂程度、重要程度、尺寸。

Ideally, temperature mapping should not be performed until after the system has been insulated, as applicable. Thermal imaging instruments may be used to identify slower-to-heat surfaces that could benefit from the installation of additional insulation. However, many systems have components such as filter housings or aseptic filling parts that cannot be insulated due to use of the system and or components.
理想情况下，在系统未被隔热之前，不能进行温度分布测试。热成像仪器可以用来识别加热较慢的的表面，加热慢的区域可以从安装额外的绝缘获益。然而，许多系统由于安装有如过滤器外壳或无菌灌装部件,不能被隔热。

5.0 Performance Qualification
性能确认

Performance qualification (PQ) is the documented verification that the equipment and ancillary systems, as assembled, can perform effectively and reproducibly based on the approved process method and specifications. When or where these activities (OQ or PQ) are performed is up to the end user.
性能确认(PQ)是当设备和辅助系统安装完成,依据经批准的产品工艺和质量标准能够有效并可重复运行的文件证明。何时何地执行 OQ 或 PQ 取决最终用户。

Performance qualification may include the following:
性能确认包括以下内容：

- Physical qualification: will include temperature mapping runs to confirm that the temperature range requirements are met and that the minimum *F*0, or time and temperature, is consistently achieved in the system.
  物理确认：将包括温度测绘以确认符合温度范围要求,以及最小 F_0、时间或温度在系统中一致性实现。
- Biological qualification: conducted with appropriate microbiological challenges to confirm that the minimum F_{BIO} is consistently achieved in the system ***(24)*.**
  生物确认：用适当的微生物挑战实验以确认最小 F_{Bio} 始终在系统中一致性实现
- Bioburden control or sterile hold time studies onducted as required to demonstrate that the sanitized or sterilized system can be maintained in that condition for the desired length of time before use.
  按要求进行的生物负载控制或无菌保存时间研究表明消毒或灭菌系统可在使用前在所需条件保持期望的时间
- Documented assessment and rationale for the selection of locations for the following:
  经书面评估和原理阐述对以下位置进行选择：
  - Permanent temperature monitoring locations
    永久性温度监测点
  - Validation temperature monitoring locations
    验证温度监测点
  - Biological indicator locations
    生物指示剂点

Measurements of time, temperature, and pressure may be sufficient for SIP sanitization qualification. For SIP sterilization qualification, measurements of time, temperature, pressure, and biological indicator destruction are required to demonstrate consistency between physical and microbiological results. A safety margin of higher temperatures and/or extended exposure times may be built in for routine operational cycles to account for process, biological, and instrument variability. Temperature and time considerations should be included for heat labile items (e.g., filters, gaskets, tubing).
测量的时间,温度和压力需满足在线灭菌的消毒确认。对于在线灭菌的灭菌确认，测量的时间、温度、压力和生物指示剂的破坏需要证明物理和微生物结果之间的一致性。建立高温和/或延长的曝露时间的安全临界范围用于常规操作周期来说明工艺的、生物的和仪器的可变性。温度和时间应该包括对热不稳定的项目(如：过滤器、垫圈、管道)。

Multiple runs (typically 3) should be conducted to confirm reproducibility of the steam in place process for initial qualification.
多次运行(通常 3 次)应在初始确认时确认过程中蒸汽的重现性。

The following activities should be completed and documented in accordance with company policy and current

regulatory expectations prior to performance qualification:
以下活动应优先于性能确认按照公司政策和现行法规预期完成并以文件形式记录:

- Procedures for the operation of the system(s) being qualified
  系统(s)操作规程是合格的
- Qualification of utilities as needed for the steam in place process (e.g., steam and compressed gases with appropriate quality and capacity testing)
  公用工程的确认同样需要工艺中的蒸汽(如具有合适质量与容量测试的蒸汽与压缩空气)
- Qualification of the system (e.g., design qualification, commissioning and/or installation qualification, and operational qualification) and calibration of critical instrumentation (e.g., control systems, monitoring devices, and alarms)
  系统确认（例如，设计确认，调试和安装确认，运行确认）以及关键仪器的校准（例如，控制系统，监控设备，和报警设备）
- Development of the SIP cycle parameters, including preliminary temperature mapping
  在线灭菌循环参数的制定，包括初始温度绘图
- Training of personnel involved in performance qualification
  包含在性能确认中的人员培训

5.1 Use of Risk Management during Qualification
确认过程中风险管理的应用

Risk management tools can be used to determine the level of qualification required, develop specific acceptance criteria, and tactical considerations such as placement of temperature sensors and BIs. The level of qualification required typically parallels the amount of cycle development required. Qualification efforts can generally be divided into System/Equipment Qualification and Cycle Qualification.
风险管理工具可以用来确定确认需求的级别,制定具体的验收标准,和战术考虑，例如温度传感器和生物指示剂的布点等。通常确认需求的级别与开发周期需求量相平行。确认通常可以分为系统/设备确认和周期性确认。

5.1.1 System/Equipment Qualification
系统/设备确认

Depending on system/equipment risk level, qualification may range from documented factory and site acceptance tests (FAT/SAT) to detailed qualification protocols and test scripts. Typical items considered during system/equipment qualification include:
根据系统/设备的风险级别，确认可以从文件规定到现场验收测试来细化确认方案及测试脚本。系统/设备确认中包括的典型项目有:

- Operation of traps and steam bleeds
  疏水阀和蒸汽排放阀的操作
- Operation of manual and automated valves
  手动和自动阀的操作
- Verification of valve sequencing
  阀门动作程序的确认
- Verification of defined system pipe slopes / system drainability
  已确定的系统管路的斜率/系统排水能力的验证
- Verification of calibration for critical instruments
  关键设备的校准确认
- Verification of temperature within the system (the number of points to be verified depends on system risk)

系统内温度的验证（根据系统风险确定需验证的点的数量）

- Verification of operation of controls, interlocks, and interfaces
  控制操作、连锁操作和接口操作的验证

Additional testing to consider for high-risk systems includes:
高风险系统需考虑的额外测试：

- Detailed temperature mapping throughout the system
  详细的系统温度分布图
- Execution of test scripts to ensure that the control system will maintain key and critical parameters under expected conditions
  执行测试脚本,以确保控制系统将保持在预期条件下的关键和重要参数
- Detailed verification of critical alarms
  详细的关键报警确认
- Verification of system integrity, including filter integrity, after operating at time and temperature extremes (within a predefined operating range determined during cycle development)
  系统完整性的验证,包括在操作时和经受极端温度(在开发过程中确定的一个预定的操作范围)后过滤器的完整性

5.1.2 Cycle Qualification
周期性确认

The level of qualification required for an SIP cycle should be based on the level of risk presented by the system being steamed in place. Items affected by system risk include:
在线灭菌周期所需的确认级别应根据现场蒸汽系统的风险水平确定。影响系统风险的项目包括:

- Use of grouping or bracketing for systems being steamed in place. Low-risk, low-complexity systems may use a bracketing approach, while high-risk, high-complexity systems may require each system to be qualified ***(25)***.
  现场可使用分组或托架系统提供蒸汽。低风险,低复杂性系统可使用托架系统的方法,而高风险、高复杂性的系统则需要确认每个系统
- Temperature probes: High-risk systems will typically use more temperature probes during qualification than low-risk systems
  高温探头：高风险系统相比低风险系统通常在确认中使用更高温度的探头
- Biological indicators: High-risk systems will typically use more biological indicators at a higher challenge level than low-risk systems, which may even have no biological indicators.
  生物指示剂：高风险系统相比低风险系统通常在更高的挑战级别上使用更多的生物指示剂，而低风险系统甚至不需要使用生物指示剂

5.2 Physical Qualification
物理确认

The primary objective of the physical qualification component of SIP qualification is to obtain physical data confirming that the developed cycle consistently delivers the desired minimum lethality throughout the SIP system. The minimum lethality depends on the kind of SIP cycle used and on the desired degree of sanitization or sterility assurance.
在线灭菌确认中的物理确认部分的主要目标是获取物理数据以确认开发周期持续在在线灭菌系统中提供所需的最低杀伤力。最低杀伤力取决于在线灭菌的循环使用种类和期望的消毒灭菌保证。

5.2.1 Sanitization vs. Sterilization

消毒和灭菌

The extent of qualification depends on the intent of the SIP cycle. SIP performed for the purpose of system sanitization may only require physical qualification. For systems that are sanitized, bioburden testing (via applicable sampling methods such as rinse water samples and swab sampling) should be performed as part of the physical qualification of the SIP process as applicable.
确认的程度取决于在线灭菌的周期的目的。若在线灭菌操作只为进行系统消毒，那么只需物理确认。对于需要进行消毒和生物负载监测(通过适用的取样方法如冲淋水取样和擦拭取样)的系统，物理确认是在线灭菌过程中的一部分。

SIP performed for the purpose of system sterilization will require both physical and biological qualification. Physical and biological qualification should be performed simultaneously. The destruction of a biological challenge alone is not sufficient evidence of the suitability of a cycle. The biological challenge data should support the physical data and vice versa.
若在线灭菌的目的是进行系统灭菌，则同时需要物理确认和生物确认。 物理确认和生物确认应同时进行。破坏生物的挑战本身并不足以证明循环的适用性。生物挑战数据应当支持的物理数据,反之亦然。

Initial qualification runs are typically performed in triplicate to ensure consistency. Fewer runs may be performed if a technical rationale is provided.
初始确认通常运行三次,以确保一致性。如果有技术依据支持，可进行更少的运行次数.

5.2.2 Temperature Mapping
温度分布

The primary purpose of temperature mapping is to verify steam distribution throughout the system. Significant variation of temperatures during this study could indicate the presence of air or condensate at an insufficient temperature.
温度分布的主要目的是验证整个系统的蒸汽分配。在此项研究中充足的温度变化可能表明在温度不足时有空气或冷凝水存在。

Temperature probes should be positioned in the cold spots identified during cycle development. The number and location of the temperature sensors depend on the size, layout, and complexity of the SIP system (e.g., a simple SIP system, such as a transfer line, may only have temperature mapping probes adjacent to the controlling temperature device) ***(26)***. Placement of the temperature probes and rationale should be documented.
温度探头在冷点的位置在周期开发中确定。温度传感器的数量和位置取决于 SIP 系统大小,布局,和复杂性(如,一个简单的 SIP 系统,如输送管线,可能只有温度探头邻近温度控制设备)(26)。温度探头的布置位置和原理应以文件形式记录。

Probe insertion should be performed in a manner that does not impact the SIP process or impair any of the safety equipment/features of the process. For example, care should be taken to ensure that introduction of the probes into the system does not hinder steam flow or removal of condensate nor facilitate air removal. Typical temperature probe locations for an SIP system include:
探头的插入方式不应影响 SIP 流程或损害任过程中的任何安全设备或安全性能。例如,应该小心以确保探头的插入不妨碍蒸汽流或阻碍冷凝水或空气的去除。SIP 系统中典型的温度探头位置包括:

- Downstream and/or within filter core
  下游和/或内部的过滤器
- Possible condensate accumulation locations (e.g., low points and the upstream side of filter housings)

冷凝水可能聚集的位置。(例如,低点和过滤器外壳上游侧

- Upstream of steam traps
  上游的蒸汽疏水阀
- Nozzles and high points where air may be difficult to displace
  喷嘴和高点,这些位置空气可能难以置换
- Surfaces of large mass items (e.g., lyophilization shelves)
  大体积物体表面（如冻干机装架）
- Surfaces of uninsulated portions of the system being steamed
  蒸汽经过的不保温部分的表面
- System boundaries
  系统的边缘
- Deadlegs (condensate/air entrapment)
  盲管（冷凝水/空气冷井）
- Adjacent to temperature and/or pressure instruments
  邻近温度或压力设备的位置

Care should be taken to ensure that the measurements accurately represent the system being measured when installing thermocouples. One consideration is that probe tips should be oriented to avoid erroneous measurements due to condensate droplet accumulation at the tip of the probe. **Figure 6.2.1-1** shows two adjacent probes with different orientations. The figure shows that condensate does not accumulate on the tip of TC 1 but does accumulate on the tip of TC 2. This insulates the probe and affects the temperature readings. **Figure 6.2.2-2** depicts data resulting from installing thermocouples oriented as illustrated in **Figure 6.2.2-1.**
应小心,以确保测量值准确反映在安装热电偶时系统中被测到的情况。其中一个考虑因素是,应调整探头的位置以避免由于冷凝水在探头的聚集而导致的错误测量。图 6.2.1-1 显示两个不同位置的相邻探针。表明,冷凝水不聚集在探头 TC1 上但是聚集在探头 TC2 上。隔离探头发现影响温度读数。图 6.2.2-2 描述了如图 6.2.2-1 所示安装热电偶时的数据结果。

Figure 6.2.2-1 Example of Probe Orientation

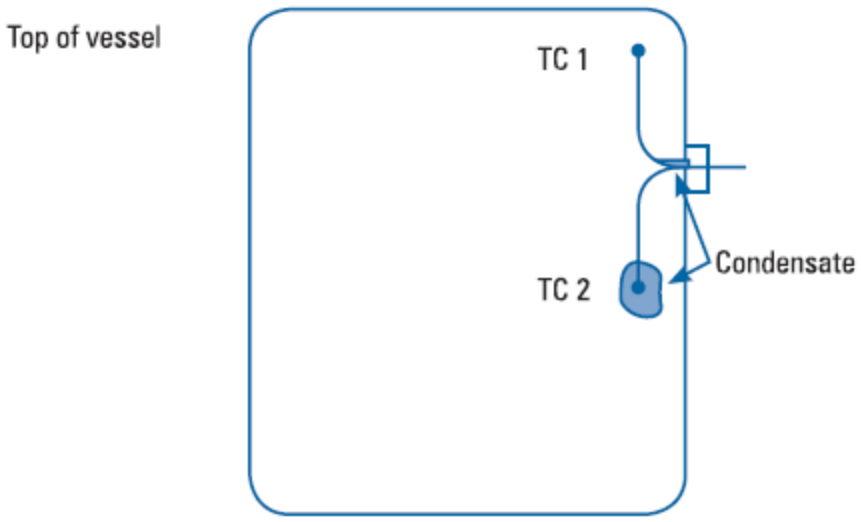
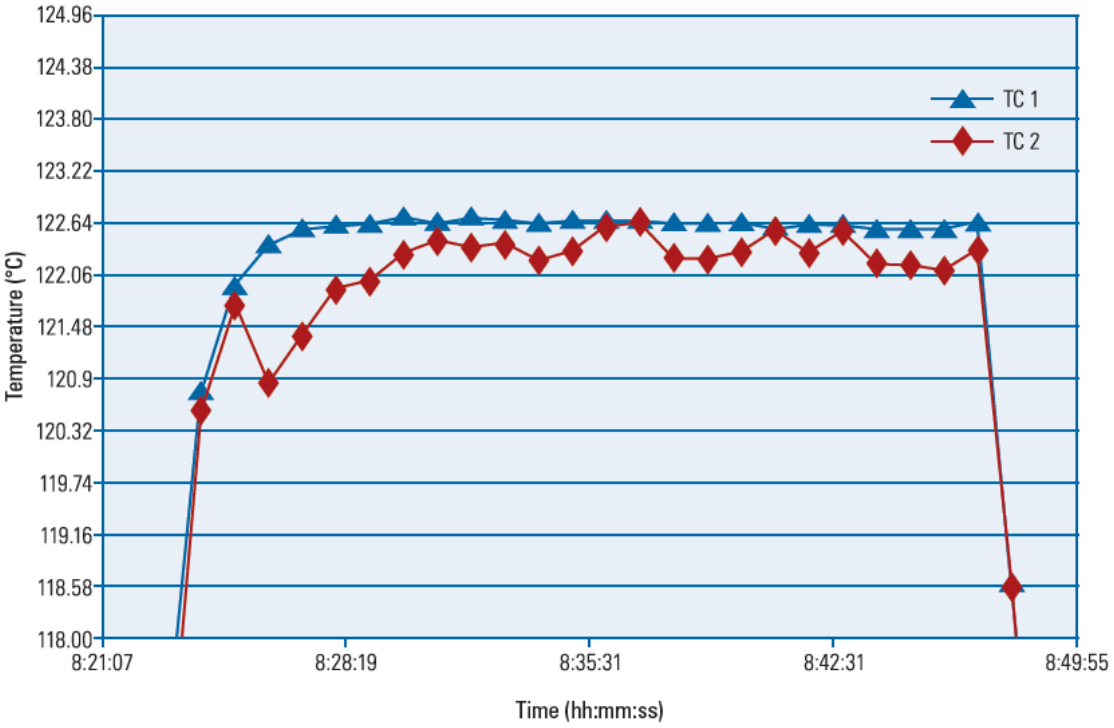


Figure 6.2.2-2 TC 1 vs. TC 2 Temperature Profile



Depending on the system being steamed and the intent of the SIP cycle, the study may require that the temperature locations reach the minimum desired temperature at the end of the heat-up phase. The temperature achieved at the end of the heat-up phase, as measured by a permanent probe, may be used as a routine check (automated or manual) to confirm satisfactory heat up for routine production cycles.
根据产生蒸汽的系统和 SIP 循环的目的,这项研究要求在升温阶段结束时温度位点达到所需的最低温度。在升温阶段结束时,可用一个永久的探头作为例行检查(自动或手动)来确认日常生产周期的令人满意的升温效果。

Temperature data should also be collected from permanent temperature probes that are designed into the system to control and/or monitor temperature during the SIP process. This data should be compared to the data from the temperature probes installed during validation to provide a link between the routine production monitoring and the validation study.
温度数据也应收集从永久温度探针设计到系统的控制和/或监测 SIP 过程中温度。这个数据应该比温度探测器安装在验证的数据提供一个联系日常生产监控和验证研究。

5.3 Biological Qualification
生物学确认

The objective of the biological component of cycle qualification is to obtain microbiological data confirming that the developed cycle achieves lethality requirements established during cycle design. Not all SIP systems require biological qualification. If sterility of the SIP system is not claimed, biological qualification may not be required.
灭菌确认的生物学部分的目的是获得微生物数据来确认灭菌方法达到了设计时确立的致死率要求。不是所有 SIP 系统都需要生物学确认。如果 SIP 不要求无菌性，则不要求生物学确认。

5.3.1 Microbial Challenge
微生物挑战

In order to assess whether the cycle delivers sufficient lethality to meet design requirements, an appropriate microbiological challenge should be selected to give meaningful results. The microbiological challenge system

should have a resistance and challenge level appropriate for its purpose. The biological qualification data is used to calculate the F_{BIO} for the cycle.
为了评估灭菌过程实现的致死率满足设计要求，需要采用合适的微生物挑战来给出有意义的结果。微生物挑战系统应该具有适合其目的的抵抗性和挑战性。生物学确认数据用于计算灭菌过程的 F_{BIO}。

Biological qualification using microbiological challenges follows a straightforward sequence:
采用微生物挑战的生物学确认采用以下顺序：

- An appropriate microbiological challenge system is devised based on the desired lethality (F-value) determined during the design process.
  根据设计工艺确认的 F 值来设计微生物挑战系统。

- The SIP system is exposed to minimum acceptable cycle (MAC) conditions (or less depending on the D-value and population of the microbiological system).
  SIP 系统采用可接受的最差条件（MAC）（或更差，这取决于 D 值和微生物系统的数量。
- After completion of the cycle, the microbiological challenge systems are retrieved.
  灭菌完成后，回收微生物挑战 系统。

- Each microbiological challenge system is individually incubated in appropriate media and conditions for growth of survivors. Directions for use, including data about conditions to be used for recovery of test organisms after exposure to the sterilization process should be obtained from the Biological Indicator manufacturer ***(27)***. The length of time that the exposed Biological Indicator is held before incubation should be validated ***(28)***.
  每个挑战系统但与培养在适合存活微生物生长的培养基和条件下。需要生物指示剂供应商提供使用说明，包括有关经过灭菌工艺的测试微生物的回收的条件的数据（27）。需要验证培养前灭菌后的生物指示剂的存放时间。（28）

- The results are evaluated to ensure that the spore log reductions (SLRs) achieved for the microbiological challenge systems meet predetermined acceptance criteria.
  要评估结果确认微生物挑战系统得到的孢子减少指数符合预定的标准。

- For typical SIP validation runs, all exposed Biological Indicators should show total kill.
  对于通常的 SIP 验证，所有使用过的生物指示剂要全部杀灭。

- Growth of the microbiological challenge organism is required in positive controls.
  微生物挑战用的微生物的生长要有阳性对照。

When using the overkill approach for “sterile” SIP applications, there are various methods that can be used to demonstrate an F_{BIO} of at least 12 minutes. Following are three qualification examples to demonstrate various methods for obtaining an F_{BIO} of 12 minutes with various BI D-values.
当使用过度杀灭的方法来进行 SIP 时，有很多方法证明至少 12min 的 FBIO。以下三个确认例子可以证明采用不同 D 值得生物指示剂来实现 12min 的 Fbio 的不同方法。

Example 1
实例 1
For the overkill design approach, the desired lethality, F_{PHYS} and F_{BIO}, is greater than or equal to 12 minutes. If a

BI with a resistance of 2.0 minutes and a population of 1.0 x 106 is used in the qualification study, then the F_{BIO} is calculated as follows:
对于过度杀灭的设计方法，预期的致死率，Fphys 和 Fbio 要大于或等于 12min。如果确认研究采用抗力 2min 和数量 1.0×10^6 的指示剂，那么 Fbio 的计算方法如下:

$F_{BIO} = D_T \times$ SLR (spore log reduction(孢子减少指数))
$F_{BIO} = 2.0 \times 6.0$
$F_{BIO} = 12.0$

Therefore, a minimum acceptable cycle (MAC) that inactivates a BI challenge with an $N0 = 1.0 \times 10^6$ and a D-value of 2.0 minutes has been biologically qualified as an overkill cycle (F_{BIO} = 12.0 minutes).
这样，一个能灭活 $N0 = 1.0 \times 10^6$ 和 D 值 2.0 minutes 的生物指示剂的 MAC 程序就通过过度杀灭程序来生物学确认了。

Example 2
实例 2
If the design requirement is an *FBIO* of 12 minutes and the BI has a starting population (*N*0) of $1 \times 10^6$and a D-value of 1.5 minutes, then the exposure time has to be reduced. The exposure time factor can be calculated by the following:
如果设计要求 Fbio12min，并且 BI 起始总数量 1.0×10^6 D1.5 值 min，那么灭菌时间要减少。灭菌时间因子可以通过以下计算：

Exposure Time Factor = ($D_T \times$ SLR) / Desired F_{BIO}
灭菌时间因子= (DT ×SLR) / 期望的 F_{BIO}

Exposure Time Factor = (1.5 × 6.0) / 12.0
灭菌时间因子=(1.5 × 6.0) / 12.0

Exposure Time Factor = 0.75
灭菌时间因子=0.75

Therefore, an SIP cycle that is operated at 75% of the minimum production cycle exposure time conditions that inactivates a BI challenge with an $N_0 = 1.0 \times 10^6$ and a D–value of 1.5 minutes has been biologically qualified as an overkill cycle (F_{BIO} = 12.0 minutes). In order to calculate the Full Cycle F_{BIO}, the Partial Cycle F_{BIO} ($D_T \times$ SLR) is multiplied by the reciprocal of the Exposure Time Factor:
这样，一个能灭活 $N_0 = 1.0 \times 10^6$ 和 D 值 1.5 minutes 的生物指示剂的 75%MAC 程序灭菌时间的灭菌程序就通过过度杀灭程序来生物学确认了。为了计算总的灭菌 F_{BIO}，部分灭菌 F_{BIO} ($D_T \times$SLR)要乘以灭菌时间因子的倒数：

Full Cycle F_{BIO} = 1/Exposure Time Factor × ($D_T \times$SLR)
总的灭菌 F_{BIO} = 1/灭菌时间因子 ×(DT ×SLR)
Full Cycle F_{BIO} = 1/0.75 × (1.5 minutes×6)
总的灭菌 F_{BIO} = 1/0.75 ×(1.5 minutes ×6)
Full Cycle F_{BIO} = 12.0 minutes
总的灭菌 F_{BIO} = 12.0 minutes

Example 3

实例 3

If the design requirement is an F_{BIO} of 12 minutes and the BI has a starting population (N_0) of 1×10^6 and a D-value of 1.0 minutes, then the exposure time has to be reduced. The exposure time factor can be calculated by the following:

如果设计要求 F_{BIO}12min，并且 BI 起始总数量 1.0 x 10^6，D 值 1.0min，那么灭菌时间要减少。灭菌时间因子可以通过以下计算：

Exposure Time Factor = (D_T × SLR) / Desired F_{BIO}

灭菌时间因子 = (D_T × SLR) /期望的 F_{BIO}

Exposure Time Factor = (1.0×6.0) / 12.0

灭菌时间因子= (1.5×6.0) / 12.0

Exposure Time Factor = 0.5

灭菌时间因子 = 0.5

Therefore, an SIP cycle that is operated at 50% of the minimum production cycle exposure time that inactivates a BI challenge with an N_0 = 1.0 × 10^6 and a D-value of 1.0 minutes has been biologically qualified as an overkill cycle (F_{BIO} = 12.0 minutes). In order to calculate the Full Cycle F_{BIO}, the 50% Cycle F_{BIO} (D_T × SLR) is multiplied by the reciprocal of the Exposure Time Factor:

这样，一个能灭活 N_0 = 1.0 ×10^6 和 D 值 1.0 minutes 的生物指示剂的 50%MAC 程序灭菌时间的灭菌程序就通过过度杀灭程序来生物学确认了。为了计算总的灭菌 F_{BIO}，部分灭菌 F_{BIO} (D_T × SLR)要乘以灭菌时间因子的倒数：

F_{BIO} = 1/Exposure Time Factor × (D_T × SLR)

F_{BIO} = 1/灭菌时间因子 ×(DT ×SLR)

F_{BIO} = 1/0.5 × (1.0 minutes × 6)

F_{BIO} = 1/0.5 ×(1.0 minutes ×6)

F_{BIO} = 12.0 minutes

F_{BIO} = 12.0 minutes

Note: The approach used for example 3 is often called the Half-Cycle Qualification approach.

备注：实例 3 被称作半周期确认方法。

5.3.2 Use and Placement of Biological Indicators
生物指示剂的使用和替换

Biological indicators are typically obtained from commercial sources. The BI challenge system is typically spores of *Geobacillus stearothermophilus;* however, other certified BIs may be used. The use of the semi-logarithmic model to determine the inactivation characteristics of the BI challenge system may also be used to calculate the appropriate challenge to biologically qualify a cycle, regardless of the resistance of the challenge organism selected. (See Section 6.3.1 for examples.)

生物指示剂一般都是购买的。生物指示剂挑战系统一般是嗜热脂肪芽孢杆菌的孢子，然而也可用其它合格的生物指示剂。用于确定生物指示剂挑战系统失活性质的半对数模型也可用于生物学角度确认灭菌周期，不考虑选择的菌种。

There are several types of biological indicator challenge systems. The different types of BI systems appropriate for SIP validation are discussed in **Table 6.3.2-1.** The table gives the description of the different BI types and the

pros and cons of using them to qualify an SIP cycle.
有几种 BI 挑战系统。表格 6.3.2-1 讨论了适合 SIP 验证的集中 BI。表格中给出了 BI 种类的描述，和使用它们来确认 SIP 灭菌的优缺点。

Table 6.3.2-1 Types of Biological Indicators
表 6.3.2-1 生物指示剂的类型

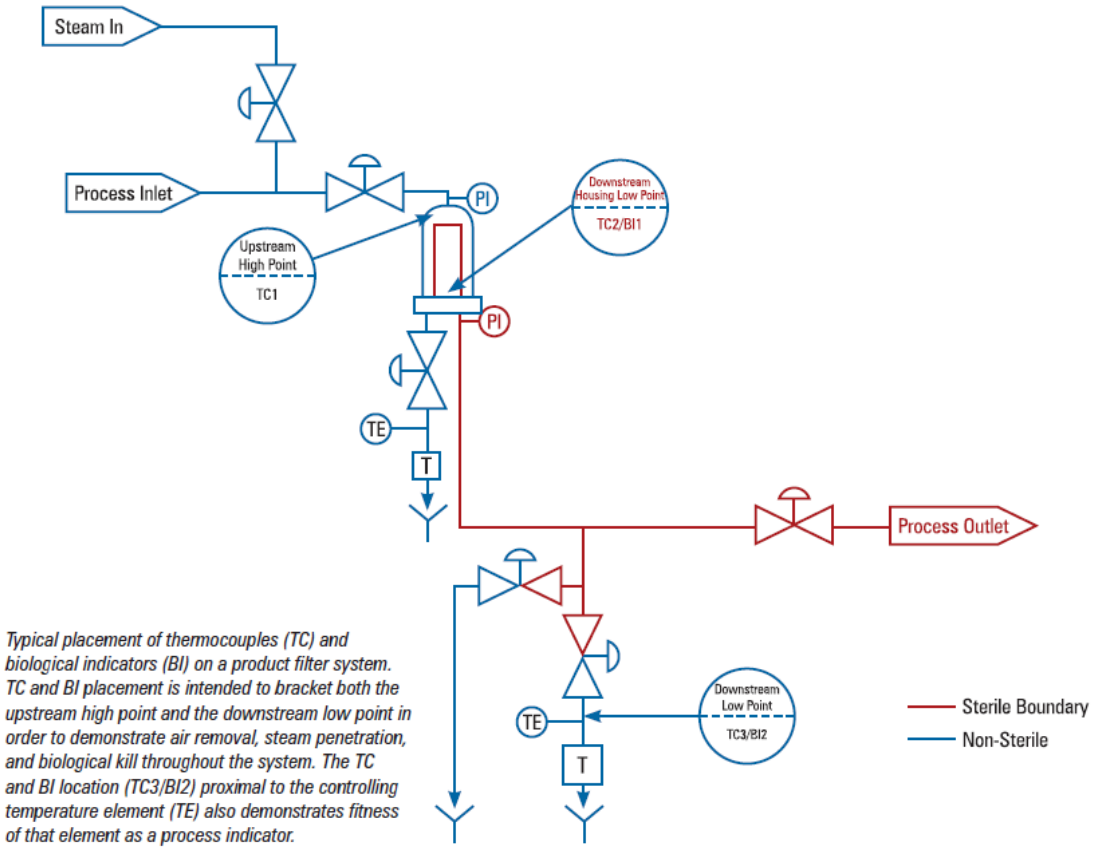
BI Type BI 类型	BI Description BI 描述	Pros 优点	Cons 缺点
Spore Suspension 孢子混悬液	Suspension of spores of known D-value, population, and z-value inoculated onto an item or coupon 已知 D 值，浓度，Z 值的孢子混悬液接种到条上或器具上	• Allows direct inoculation of components (e.g., filters, tubing) being sterilized 可以直接接种到被灭菌部件上（例如滤芯、管道） • Does not obstruct steam, air or condensate flow 不会阻止蒸汽、空气或者冷凝物流动	• Inoculation and recovery method more difficult 接种和回收率方法比较难 • Surviving spores can cause contamination 存活的孢子可能导致污染 • D-value needs to be measured with the coupon or item D 值需要协同条或物件计算 • Introduction of open spore suspensions into a manufacturing facility may present significant regulatory, logistical or product safety issues 开放的孢子混悬液接种到生产厂房设施上可能导致严重的法规、逻辑或产品安全问题
Self-contained BI* 自含式生物指示剂	Growth medium contained inside the primary packaging for the indicator 指示剂内包材里面有培养基	• Convenient packaging 包装方便 • Eliminates aseptic manipulation of the indicator strip, which can lead to indicator contamination (i.e., false positives) 省去了去除指示剂的无菌操作，这种操作可能引起指示剂污染（例如，假阳性） • Simple recovery method 回收率方法简单 • Recovery method and D-value are typically supplied by vendor 供应商提供回收率方法和 D 值 • Potentially eliminates exposure of the area to the spores 潜在的排除了洁净区暴露向孢子的可能指示剂	• Indicator is bulky and not suitable for monitoring small diameter systems 比较大不适合检测小体积的系统 • Glass media container can break when not anchored properly and exposed to a turbulent steam flow 玻璃容器可能碎掉如果没有放好或者暴露在强烈的蒸汽流中

BI Type BI 类型	BI Description BI 描述	Pros 优点	Cons 缺点
BI Carrier BI 载体	Spores added on a carrier (e.g., stainless, paper, plastic, glass, wire) individually packaged to maintain Integrity 孢子添加在单个载体上（例如不锈钢，纸，塑料，玻璃，金属线）并包装好以保持完整	• Allows versatility in size and rigidity based on the selection of the carrier 根据选择载体而有多样硬度和尺寸 • Minimizes exposure of the area to the spores 减少洁净区暴露向孢子的可能 • Widely recognized and used for SIP sterilization validation 广泛认可并用于 SIP 灭菌验证 • Recovery method and D-value are typically supplied by vendor 回收率方法和D值由供应商提供	• Depending on the selection of the carrier, may not be suitable for small-diameter systems 取决于载体特点，可能不适用于小体积系统 • In the case of non-packaged/ bare BI ′ s, the BI ′ s should be aseptically handled. 对于无包装或裸露的 BI，BI 需要进行无菌操作。

✶ Biological indicators should have direct contact with steam. Some BIs are in sealed ampoules that contain spore suspension in liquid media and therefore may not represent actual system conditions. Therefore, these types of indicators should not be used.
备注：生物指示剂需要直接与蒸汽接触。一些生物指示剂是含有孢子混悬液密封安瓶，因此不代表实际的系统条件。因此不能使用这类指示剂。

BI challenge systems are placed adjacent to temperature sensors in the cold spots/and hardest-tosterilize locations within the SIP system. For example, they may be located within cartridge filters, in nozzles, in the highest point in the tanks, in deadlegs where it may be difficult for steam to access or in low point drain/condensate valves. For large filter housings (e.g., > 20 inches or > 1 cartridge), BIs may be placed in the top and bottom of the filter cartridge(s) to evaluate the areas within the housing that could have excessive trapped air and/or excessive condensate pooling. In addition, BIs should be placed in low locations, especially in distal lines where condensate flows to a drain or pools.
生物指示剂挑战系统放在灭菌系统最冷点/和最难灭菌位置的温度探头旁边。例如，他们可能安放在滤芯里、针头、罐子最高点，蒸汽难以达到的死角或者低的排水点/冷凝水阀门。对于大的滤壳（例如，＞20 英寸或者＞1 个滤壳），生物指示剂放在滤壳顶部或者底部来评价可能有多余空气或者/和过多冷凝物的位置。另外，BI 要放于低的位置，尤其是末端有冷凝物流向排水处或蓄水处。

Figure 6.3.2-1 Example of BI Placement
图 6.3.2-1 BI 布点实例



Typical placement of thermocouples (TC) and biological indicators (BI) on a product filter system. TC and BI placement is intended to bracket both the upstream high point and the downstream low point in order to demonstrate air removal, steam penetration, and biological kill throughout the system. The TC and BI location (TC3/BI2) proximal to the controlling temperature element (TE) also demonstrates fitness of that element as a process indicator.
一般放置在产品滤芯系统中的热电偶和生物指示剂的位置。TC和BI放置位置要包括向上蒸汽的高点和向下蒸汽的低点来证明气体移出，蒸汽的穿透和生物灭菌。TC和BI的位置接近控制温度也证明作为指示剂的适用性。

To evaluate the correlation between F_{PHYS} and F_{BIO}, biological indicators should be placed near temperature probes. Biological indicators, TCs, and probes should not block the steam path nor hinder the removal of condensate. Materials used for placement or attachment of the biological indicators inside the system should not hinder the inactivation of the BI or operation of steam traps and sanitary valves. Attachment method must be robust enough to prevent the BI being carried away with the turbulent flow and condensate. For paper strip BIs it is recommended that they be held in place with wire mesh or other suitable method to allow steam penetration while containing the wet BI. Placement and location rationale of biological indicators should be documented.
为了评价F_{PHYS}和F_{BIO}的联系，生物指示剂应放置在温度探头附近。生物指示剂，TCs和探头不能阻止蒸汽流动或冷凝物的排出。用于生物指示剂放置或粘贴的材料不应妨碍生物指示剂的灭活或者疏水阀和洁净阀的操作。粘贴方式要足够结实以防止强烈气流和冷凝水把BI冲走。对于纸条生物指示剂，最好使用金属网或者其它合适方法固定，以便于蒸汽穿透，那时纸条会变湿。放置位置的合理性需要文件化说明。

Figures 6.3.2-2 and **6.3.2-3** depict alternative methods of thermocouple and biological indicator placement in pipe. Materials of construction used for installation (e.g., mesh pouch, wire, clamps, connection gland) should be

compatible with process requirements.
图6.3.2-2和6.3.2-3描述了在管道中防止热电偶和生物指示剂的可选方法。安装用的材质（例如网袋，金属线，夹子，连接压盖）应符合工艺要求

Figure 6.3.2-2 Example of Pipe with BIs and TC Connection Gland

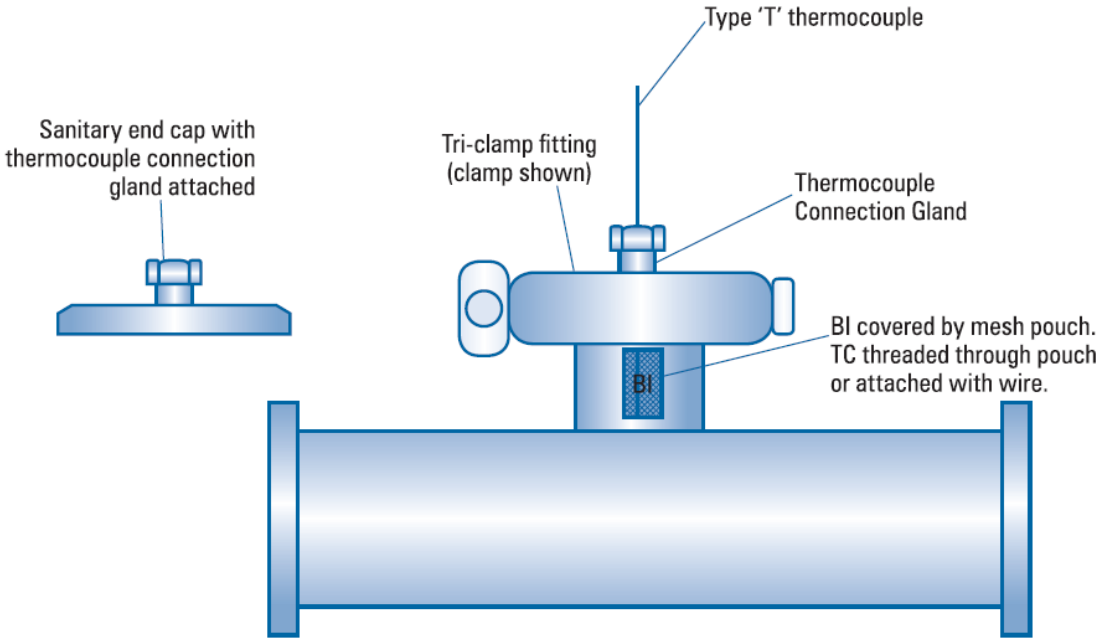
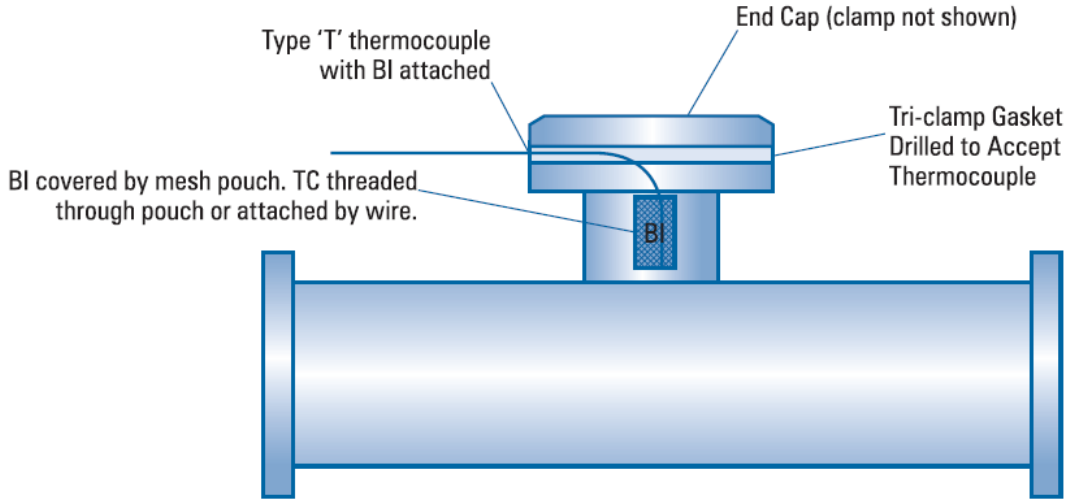


Figure 6.3.2-3 Example of pipe with BIs with Ported Gasket



5.4 Qualification Acceptance Criteria
确认接受标准

Acceptance criteria should be clearly defined in the test protocol(s). These criteria should be based on the type of steam in place process, applicable regulatory expectations, and the operating parameters determined in cycle development. Following is a list of typical acceptance criteria that should be considered when qualifying an SIP cycle. This list is not exhaustive and other acceptance criteria may be necessary depending on the specific situation.
测试方案中应明确可接受标准。这些标准应基于工艺使用蒸汽类型，适用的法规要求和灭菌周期中的操作

参数。下表列出的是当确认 SIP 过程是要考虑的接受标准。清单不是全棉的，根据特殊条件可以选择其他必要标准。

SIP system integrity (Pressure/Vacuum test) (optional)
SIP 系统完整性（压力/真空测试）（可选）
A system integrity test may be performed and results should meet the predefined leak rate. A leak rate may be selected based on the complexity, volume, and process risk assessment. Temperature drift during the pressure hold test should be monitored.
系统完整性测试需要进行，结果要满足预定的泄漏率。泄漏率标准要基于复杂性，体积和工艺风险。压力保持试验时要监测温度漂移情况。

Heat up time
加热升温时间
Document the time it takes for all locations to reach the defined process temperature. The time difference (lag time) between the validation probes and the control/monitoring probes to reach minimum exposure temperature should be documented to ensure the cycle has been designed to account for cold spots that are not permanently monitored.
记录所有位置到达设定工艺温度的时间。验证探头和控制/监测探头到达最低暴露温度的时间差要被记录以保证以涵盖了不能持续监测的所有冷点。

Lethality (F_{PHYS})
致死性（Fphys）
Predefined time at temperature and/or *F*0 values should be met and documented ***(29,30)*.**
在一定温度下预定的时间和/或 F0 值要被满足和记录。

Exposure/Dwell time
暴露时间
Predefined exposure time should be met and documented.
预定的暴露时间要被满足和记录。

Lethality (F_{BIO})
致死性（Fbio）
The calculated lethality (F_{BIO}) calculated using the D-value and population of the target organism, and applicable exposure time factors should meet the predetermined acceptance criteria.
计算的 Fbio 要用 D 值和目标微生物数量来计算，而且暴露时间因子要满足预定的可接受标准。

Minimum and maximum temperature during exposure
灭菌时最高和最低温度
Minimum and maximum temperature during exposure should meet predefined criteria and should be documented.
灭菌时最高和最低温度要满足预先设定的标准并且要记录。

Number of functioning probes
功能探头的数量
The number of probes that can fail and still maintain a valid run should be defined. Documentation should include rationale for addressing probe failures.
要定义清楚一定数目的探头失效而能维持有效运行。文件要包括说明探头失败的理由。

Positive and negative controls function as specified
规定阳性对照和阴性对照的功能

Positive control biological indicators show growth after incubation at specified temperatures. If applicable, negative controls show no growth after incubation at specified temperatures.
阳性对照生物指示剂在规定温度下培养后要生长。如果可行，阴性对照在规定温度下培养不生长。

Filter integrity should be verified before use and after SIP by an appropriate method such as bubble point, diffusive flow, pressure hold, or water intrusion. If the filter is directly inoculated with a biological indicator (destructive test), then filter integrity needs to be assured in a separate qualification run.
在 SIP 使用前后腰对滤芯完整性进行测试，测试方法如起泡法、扩散流、压力保持或者水侵入。如果滤芯带着生物指示剂一起培养（破坏性试验），那么滤芯完整性测试要单独确认。

Additional Monitoring:
额外的监控：

Correlation of temperature and pressure for saturated steam
饱和蒸汽的温度和压力的关联

To maximize efficiency of the SIP cycle, adjacent pressure and temperature measurements may be used to evaluate whether saturated steam conditions are within the user-defined range.
为了将 SIP 效果最大化，压力和温度的测量可以用来评价饱和蒸汽的条件是否在使用要求范围内。

Steam pressure
蒸汽压力

Steam supply pressure, as it relates to the control pressure, should be documented.
蒸汽供应压力，因为关系到控制压力，应记录。

Post-SIP hold (optional)
SIP 后保存（可选）

Acceptance criteria (e.g., maintenance of positive pressure) should be defined that ensure system integrity during post-SIP hold.
要确立标准（如，正压的保持）来确保 SIP 后保存的系统完整性。

Steamed equipment may require a hold study if stored. The equipment is steamed-in-place according to the qualified parameters and stored under normal or worst-case operating conditions.
通蒸汽的设备如果储存可能需要储存研究。设备根据确定的参数进行在线灭菌，并且储存在最差和正常的操作条件下。

5.5 Validation Approaches
验证方法

Many operations involve similar or identical process operations (e.g., filtration or sanitization) or equipment (e.g., mixing vessels and bioreactors). In such cases, matrix and/or family validation approaches may be acceptable. It is recommended that these approaches be presented to the appropriate regulatory agencies prior to protocol development and execution. Further information on validation methodology can be found in PDA Technical Report 60: Process Validation: A Lifecycle Approach ***(31)***.
许多操作包括类似或等同的工艺操作（例如过滤或者消毒）或者设备（例如混合容器和生物反应器）。在这种情况下，矩阵或/和分类验证方法可以采用。建议这些方法在开发方案和执行前提交给当局机构。更多

的验证方法可以参考 TR60.

5.5.1 Family Validation

Validation studies may be significantly decreased by grouping equipment or equipment systems into "families." Family validation applies to equipment that is identical or similar, like bioreactors, column housing units, and tanks. A documented approach to the creation of these families is needed to provide the rationale for system equivalence. An example would be a bank of three bioreactors of similar design and size to be used in the manufacture of a single product. One reactor may be validated by three consecutive runs, and the other two may be validated by one confirmatory run each. Justification for using the family approach should be stated in the protocol and report. The degree of similarity should be fully documented in the associated IQ, OQ, and PQ ***(32).***
通过将设备或设备系统分类可以大量减少验证研究。分类验证适用于相似或同类的设备，如生物反应器、？、罐体。创立这类分类的书面方法中要说明系统一致性的原因。一个例子是三个类似设计和大小的生物反应器用于单一产品的生产。一个反应器可以连续三次运行验证，另外两个运行一次确认验证。用分类方法时，要在方案和报告中说明。相似的程度要结合 IQ、OQ、PQ 充分说明。

5.5.2 Matrix Validation
矩阵验证

Matrix validation (also known as bracketing) is conducted at the full range or extremes of a process or equipment parameter (i.e., when a group of different-sized vessels of similar configuration are used in a process, the largest and the smallest vessels are validated). Validation of intermediate-sized vessels can be encompassed by this study with adequate justification.
矩阵验证是在满范围操作或者使用工艺或设备的极限参数（例如当工艺中使用一组相似性状不同尺寸的容器时，最大最小的容器要被验证）。充分说明后这个研究可以包含中间尺寸容器。

6.0 Ongoing Process Control
工艺过程控制

Continuous evaluation, control, and maintenance of SIP cycle performance is critical during the commercial production phase due to the operational importance of SIP processes and the potential for adverse consequences to product quality. Evaluation of SIP cycle performance is typically accomplished through data monitoring and periodic requalification. Control is achieved through investigation and resolution of cycle deviations and equipment/process change control. Finally, to ensure maintenance of steaming performance, effective preventative maintenance and calibration programs are essential.
大规模的产品生产阶段，SIP 程序性能的持续评估、控制及预防维修对于 SIP 工艺和产品质量是非常重要的。通过数据监控及周期性的再确认来实现对 SIP 程序性能的评估是一种典型的做法。通过调查和解决程序偏差及设备/工艺变更控制来实现对 SIP 的控制。最后，蒸汽性能，有效的维修和校验规程的维持是非常必要的。

6.1 Use of Risk Management for Ongoing Process Control
风险管理在工艺过程控制中的应用

On-going process control activities after initial validation ensure that the system and processes supporting SIP continue to operate as intended and achieve the desired levels of sterilization or sanitization as required by the production process requirements. These activities encompass requalification and revalidation, which have traditionally been executed on a periodic basis regardless of historical SIP process performance or potential impact to product quality. Many in industry have begun to concentrate validation efforts through the use of risk management and statistical process control methodologies to identify those systems that pose the greatest risk based on inherent variability or process capability. Depending on the level of automation, ongoing validation activities for very robust processes may be limited to periodic or continual monitoring, with revalidation conducted as an event-driven activity.
在起初的验证后，过程工艺控制行为是为了确保系统和 SIP 支持的工艺能持续地达到预期的目的，并获得工艺生产所要求的理想的灭菌或消毒水平。这些行为包括再确认与再验证。无论历史的 SIP 工艺表现或潜在的对产品质量的影响如何，传统上这些行为都会周期性地执行。行业内很多人已经开始使用风险管理和统计学控制的方法。根据内在的差异性，工艺的能力和精简的验证效果，以识别那些具有最大风险的系统。基于自动化水平，对于那些非常稳定的工艺，过程验证行为可能只是限于周期性或连续性的监控，再验证只限于合规性驱动行为。

6.2 Routine Monitoring
日常监控

Following completion of the cycle development and performance qualification exercises, monitoring of the routine operational cycles should be performed to ensure an ongoing state of control. Critical parameters should be documented and data recorded (critical data) for each cycle. Routine monitoring data should be analyzed to ensure the system has remained in a state of control as demonstrated by the qualification data. The routine operational cycle is typically controlled to produce additional lethality over the qualified MAC to provide increased sterility assurance. Cycles that have not met minimum defined critical cycle parameters should be rejected. Deviations from key parameters should be investigated and their impact assessed to determine whether the cycle is acceptable or not.
在完成程序开发和性能确认后，为了保证日程的受控状态，日常的程序需要予以监控。关键参数需在文件中记录并且对每个周期的数据尤其是关键数据需要进行记录。对日常监控的数据需要进行分析，以保证系

统的控制状态和确认数据一致。为了得到更高的无菌保证水平，日常生产中程序一般都会采用超过确认的最小可接受水平的致死率参数。程序如果不能满足已定义的最小的关键参数，那么该程序就需要重复进行。为了判断程序是否被接受，关键的参数偏差需要进行调查并评估其影响。

An alarm system for temperature and/or pressure may be used to facilitate the detection of any deviation from the defined process parameters. Alarm conditions should be properly documented.
温度和压力参数报警能帮助我们去发现工艺参数是否发生偏离。

6.2.1 Operational Parameters
操作参数

Critical operational parameters may include the following:
关键的工艺参数应该包括以下几类：

Temperature
温度

Temperature should be monitored at locations as described in section 4.2 to ensure that the minimum process temperature is achieved throughout the system during routine production cycles.
温度监控的位置应按照 4.2 中描述的那样进行选择，以确保日常生产程序中最小的工艺温度值能够被满足。

Temperature and pressure profiles for the SIP cycles should be recorded and assessed on a periodic basis to confirm that no significant change in the qualified state has occurred.
SIP 程序中的温度与压力曲线应该被记录并进行周期性的评估，以确保与验证时的状态没有明显的变化。

Pressure
压力

The system pressure should be monitored at appropriate locations during key phases of the SIP cycle, including air removal, heat up, exposure, steam removal/cool-down and hold.
在 SIP 的关键阶段，包括空气去除、加温段、高温段、蒸汽移除/冷却 和保持阶段，必须对适当的位置进行压力监控。

Steam pressure and temperature measurements conducted in close proximity to the pressure transducer/gauge should correlate to the corresponding saturation pressure in dry saturated steam tables. Correlation criteria should include measurement uncertainty of the pressure instrumentation and/or control system. Steam tables are useful to determine temperature/pressure correlation.
所测得的蒸汽压力应大约是干饱和蒸汽表中的相应的饱和压力，它的推断是：测量温度与测量压力传感器/压力表上显示的压力是近似地。相关标准应涵盖了压力仪表和/或控制系统的不确定性。蒸汽表对决定温度压力的相关性非常有用。

Pressure monitoring post-SIP is important to ensure that system integrity is maintained. Gas used for pressurization of sterile systems should enter the system via an integral, liquid-rated, hydrophobic sterilizing grade filter(s) ***(17).*** Other filters may be considered acceptable for systems not claiming sterility ***(16,17).***
SIP 后的压力监控对于保持系统的完整性是非常重要的。保持无菌系统的压力的气体必须经过一个完整的、液体定级的、疏水性无菌级过滤器。对于非无菌系统，其他类型的气体过滤器也是可以接受的。

It may be necessary to monitor differential pressure across filters to confirm that the maximum pressure differential is not exceeded during the SIP process.

对过滤器两侧的压差进行监控是非常必要的，这样可以确保在 SIP 过程中过滤器可以耐受的压差是不被超过。

Pressure or vacuum hold tests may be conducted to confirm system integrity before SIP. These tests are important from both a quality and safety perspective.
可以执行压力或真空保持试验，以确认系统在 SIP 之前是完整的。这些基于质量和安全角度的检测是非常重要的。

Time
时间

Time duration of cycle phases should be monitored to ensure the SIP cycle remains within the qualified state.
SIP 过程中的时间需要进行监控，以确保 SIP 过程维持在确认的状态。

F_0
***F_0* 值**

Cumulative *F*0 may be used as a process control parameter to end the cycle in lieu of predetermined time and temperature.
可以用累积 *F*0 值的方法控制程序结束的时间，从而代替时间温度法。

Monitoring strategies of SIP parameters and their associated alarms should be designed to provide data appropriate to demonstrate that the SIP process was performed successfully. System monitoring may be automated, manual, or a combination, provided that the data obtained is accurate and easily retrieved. The information recorded for each run should be linked to the validation of the cycle. Resumption of an SIP cycle following resolution of an alarm condition should ensure that the minimum exposure time is achieved.
设计 SIP 参数和相关报警的监控策略时，应使其能提供足够的数据以保证 SIP 程序被成功的执行。系统监控可以采用自动方式、手动方式或者两者混合的方式。无论采用哪种方式只要提供的数据准确、可追溯即可。每次程序运行所记录的信息需同验证程序相符。报警信息处理后再恢复的 SIP 程序应能保证获得最小的暴露（高温度）时间。

6.2.2 Filter Testing
过滤器测试

Integrity testing of the filter cartridge may be performed pre-use and must be performed post-use for sterile applications (i.e., after the system has been used for its intended use; not after SIP). The test frequency may be defined according to the needs of the application ***(17).*** Where possible, the filter should be tested in the housing in which it is to be or was used. Filter testing should be performed with a clear indication of pass/fail. Additional guidance on integrity tests may be found in reference literature.
用于无菌工艺的过滤器，在使用前后都必须进行完整性测试。（例如，系统使用之后，不在 SIP 之后）完整性检测的频率是根据应用的需求来制定地。如果可能，过滤器在使用前后使用后都应在套筒中进行测试。过滤器检测时，应有明确的合格不合格标准。在参考文献中，有过滤器检测的额外指南。

6.3 Change Control/Revalidation
变更控制/再验证

A robust change control system should be in place to maintain the validated state of the SIP process.
应有完整的变更控制系统，从而保证 SIP 工艺处于验证状态。

Any proposed changes to the SIP process (including procedures, hardware, software, cycle configuration, supply

utilities, filter types/sizes) should be evaluated to determine the potential effects of those changes on the SIP cycle and the extent of requalification/revalidation required to demonstrate that the modified process performs as intended and still meets the applicable acceptance criteria.
任何计划去改变 SIP 的工艺（包括程序、硬件、软件、配置、供给的公用系统、过滤器的形式/尺寸）的行为都应去做相应的评估，以评估对 SIP 程序造成的潜在影响及需要进行再确认或再验证的深度。从而证明这些变更能满足最初的改进需求并能持续的维持 SIP 工艺需求。

6.4 Periodic Requalification/Revalidation
周期性再确认/再验证

A periodic review of the system should be performed to ensure the state of control is maintained and to evaluate the impact of cumulative “minor changes” over the review period.
在周期性评估中应确认系统处于受控状态，并评估在此周期内的一些小的变化累计起来的影响。

This should also include review of performance data from various monitoring sources (e.g., process, engineering, maintenance, and calibration data) to verify that there have been no adverse trends or drifting away from the baseline performance established during validation. A review of change control documentation should be conducted as part of the requalification/revalidation.
这些评估应包各种含监控数据的审核（例如工艺，工程和校验数据）从而确认没有不好的趋势和基线漂移。对变更文件的审核是再确认和再验证的一部分。

Review frequency should be based on the system’s intended use and applicable regulatory expectations. Requalification may include supplemental thermal and/or biological indicator testing to verify F_{BIO} and F_{PHY} acceptance criteria for systems claiming sterilization.
审核频次应该基于系统的使用目的和相应法规的期望。再确认可以应包含对热量补充和/或生物指示器测试的确认和系统需要灭菌的 F_{PHY} 接收标准。

6.5 Preventative Maintenance Strategy
预防性维修策略

In order to ensure consistent system performance, a maintenance strategy should be in place that addresses potential changes in material and component performance due to operation, exposure, and time. In particular, the strategy should take into account how thermal and pressure cycles associated with heat-up, exposure, and cool-down may impact the service life of various components, particularly polymeric (elastomeric) components.
为了确保系统性能稳定，应该有一个维护策略，阐述由于操作，暴热和时间造成材料的潜在变化。

A maintenance strategy should include special considerations toward polymer replacement practices due to their criticality in maintaining system integrity and their limited lifetime. Polymer service life may be affected by various operational stresses such as thermal conditions, process frequency, product chemistry, and cleaning frequency.
一个维护策略应该对特别注意一些对系统完整性很关键，又有一定寿命的聚合物部件的更换。 聚合物的服务寿命受多种操作条件影响，如温度调节，工艺的频次，产品的化学兼容性和清洁频次。

Elastomer manufacturer recommendations may be used as a basis for initial determination of replacement frequency. However, manufacturer testing may not sufficiently challenge the elastomer performance under actual usage conditions, so an assessment should be performed to determine adequacy of the replacement frequency..
初次更换频率采用弹性化合物生产商的建议。然而，生产商的测试并不能充分反映弹性化合物在实际使用条件下发生的改变，因此对适当的更换频率要进行一个评估。

SIP performance can be directly impacted by improper functioning of other components such as pressure regulators, steam traps, or isolation valves.
其他部件的功能损坏会直接影响 SIP 的执行，如压力调节阀，蒸汽疏水器或者隔离阀门。

The preventative maintenance program should include periodic inspection and/or replacement of components that are critical to SIP performance. The frequency of the preventative maintenance may be determined based on component maintenance history, manufacturer recommendations, or risk evaluation and mitigation. In addition to specific component maintenance requirements, a review of the overall equipment assembly and operation may be performed to identify issues that could impact SIP cycle performance (e.g., altered piping slopes).
预防性维护程序应该包含对 SIP 运行很关键的部件的周期性检查和更换。预防性维护的频率取决于部件的维护记录，生产商建议或者风险评估和降低。除了对特殊部件的维护要求， 还需要对全部设备组装和操作进行检查，去发现会影响 SIP 回路性能的问题（例如：管道坡度改变）

6.6 Calibration Strategy
计量校验策略

The calibration program should include instruments that are used to control and monitor the cycle. Both the control of the SIP cycle and the confirmation of successful cycle completion are dependent on the proper indication and recording of critical operational parameters. Calibration serves as both the means to maintain instrument performance as well as to document proof of performance.
校验程序应该包含用于控制和监测程序的仪表。SIP 控制回路和确认回路成功完成是依赖于适当的指示和关键操作参数的记录。校验服务同时也是给仪器的性能维护提供证明。

Calibration tolerances and periodicity is determined by instrument capability, history, manufacturer recommendations, and process risk. The impact of instruments found outside calibration tolerances during periodic recalibration evaluations should be investigated. A risk assessment may be used to establish instrument calibration frequency.
校验的精度和周期由仪器的量程，记录，生产商建议和过程风险决定。在周期性再校验中，影响仪器超出校验精度评估要进行分析。针对仪器校验频率可以做一个风险分析。

7.0 Appendices
附录

7.1 Appendix A: Risk Assessment of Steam in Place Processes
附录 A：在线灭菌过程的风险评估

7.1.1 Introduction
简介

Planning and preparation are crucial when designing a steam in place system. A comprehensive risk assessment conducted proactively can save time, effort, and resources during qualification, validation, and routine monitoring. Other benefits include:
在设计一个在线灭菌系统关键时计划和准备工作是很重要的。前瞻性的进行全面的风险评估可以在资质，验证，日常监测期间节省时间，精力和资源。其他的益处包括：

- Improved planning and preparedness for potential failures
  为潜在失败的改进计划和准备
- Increased process understanding
  加强过程理解
- Improved stakeholder relationships through better communication
  通过更好的沟通改善利益相关者的关系
- Increased quality assurance through documentation of the decision-making process
  通过决策过程的文件加强质量保证
- Reduced risk to patients through process modifications to eliminate or reduce high risk steps
  通过变更过程排除和降低风险级别来降低患者风险
- Identification of fault conditions that require monitoring
  环境缺陷的识别需要监控
- Optimization and prioritization of validation resources
  验证资源的优化
- Selection of test methods and acceptance criteria that are aligned with critical quality attributes of products
  试验方法和验收标准的选择符合产品关键的质量属性
- Compliance with regulatory expectations
  符合管法规期望
- Assistance in maintaining a state of process control ***(3)***
  帮助维护过程控制状态

Additional guidance on risk assessment tools and performing risk assessments may be found in published literature ***(3,6,30-34)***.
在公开发布的文献里的附加指南里(3,6,30-34)可以找到对风险评估工具和执行的风险评估。

This appendix provides a risk assessment example for illustrative purposes only. The example provided focuses on a bioburden-controlled biologic manufacturing process. The overall process is first evaluated to identify process steps with the potential to adversely impact product quality. Those steps are then further analyzed to identify actions that may be taken to reduce the likelihood of failure.
本附录提供风险评估示例仅用于说明目的。提供的示例重点在生物制造工艺的生物负荷。整个过程是首先评估对产品质量有潜在不利影响的步骤。然后进一步分析以确定采取减低失败的可能性的行动。

7.2 Risk Assessment Tools
风险评估工具

7.2.1 Hazard Analysis and Critical Control Point (HACCP)
危害分析与关键控制点（HACCP）

HACCP ***(6)*** analysis is a rigorous system that may be used to analyze processes to identify hazards and establish measures that may be instituted to mitigate risk and ensure product quality. It is a complete system that focuses on preventative measures rather than end product testing. In the context of HACCP analysis, a hazard is defined as any biological, chemical, or physical condition that may adversely impact the safety, efficacy, and quality of the product being analyzed.
危害分析与关键控制点（HACCP）分析是一个严密的系统，它可以用于分析危害识别过程和建立可降低风险保证产品质量的措施。它是一个完整的系统，重点是预防性措施，而不是最终产品的测试。在危害分析与关键控制点分析方面，危害被定义为可能对产品的质量、安全、有效性产生不利影响的任何生物，化学的，或物理条件。

A complete HACCP analysis results in the identification of points or process steps that must be controlled to ensure product safety, efficacy, and quality. These steps are referred to as critical control points (CCP). The HACCP system is based on the following preparation steps and seven principles:
一个完整的危害分析与关键控制点分析识别的点或过程步骤必须加以控制，以确保产品的安全、有效、质量可控。这些步骤称为关键控制点（CCP）。HACCP 系统基于以下的基本步骤和 7 项原则：

Preparation Steps for HACCP
HACCP 基本步骤

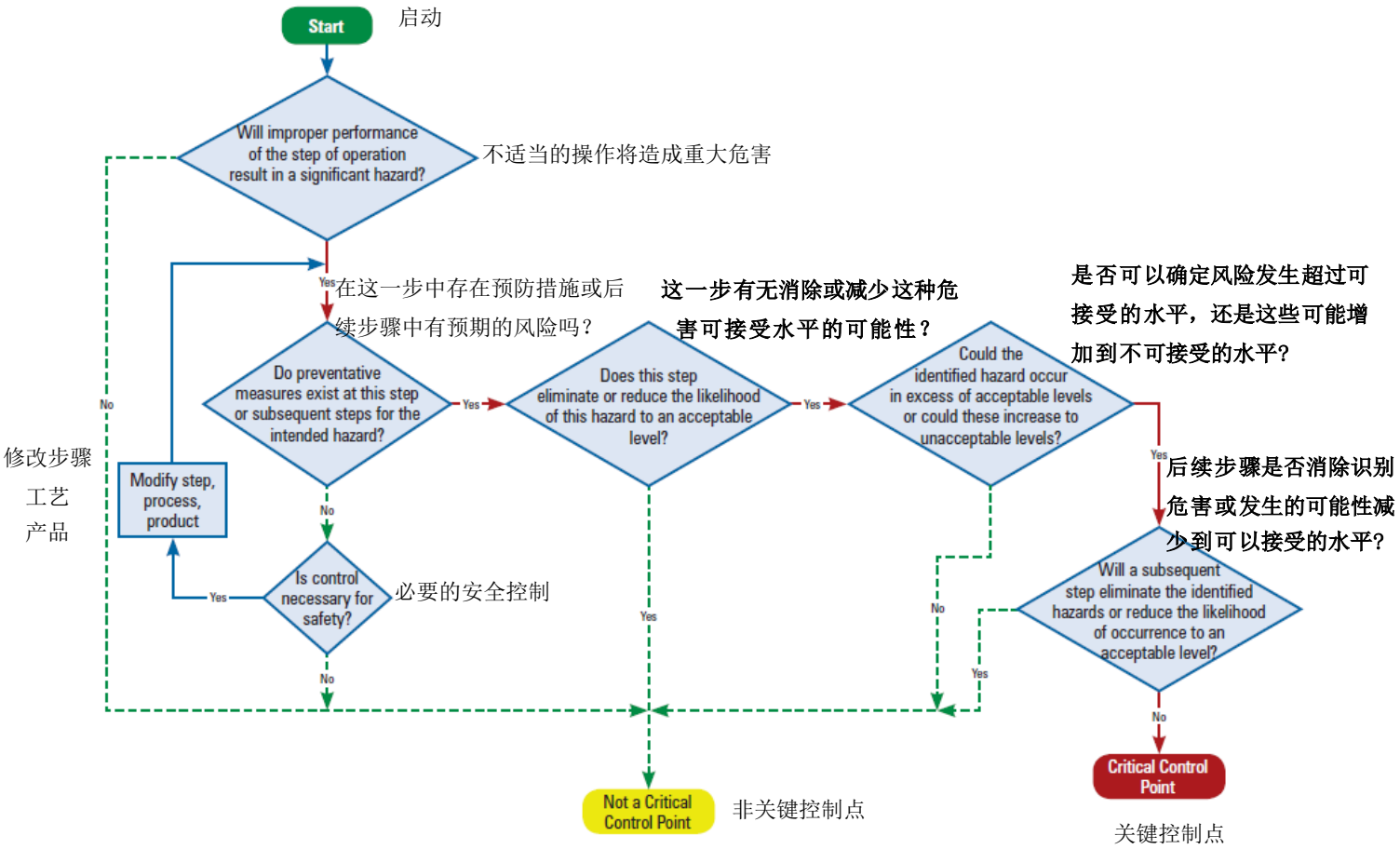
1. Assemble the team
   组建团队
2. Describe the product and process
   描述产品和过程
3. Identify the intended use
   确定预期用途
4. Develop and verify a process flow diagram (include nonstandard or abnormal conditions)
   制定和验证过程流程图（包括不标准和不正常条件）

Seven Principles of HACCP
HACCP 的 7 项原则

1. Conduct a hazard analysis
   进行危害分析
2. Determine the critical control points (CCPs). (see CCP decision tree, Figure 8.2-1)
   建立关键控制点（见 CCP 决策树，图解 8.2-1）
3. Establish target levels and critical limits
   建立目标水平和关键限度值
4. Establish a system to monitor the CCPs
   建立监督关键控制点的系统
5. Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control
   确立关键控制点监控系统显示这些控制点失控时应采取的纠正措施

6. Establish procedures to verify that the HACCP system is working effectively
   建立确保 HACCA 系统有效运作的程序
7. Establish documentation concerning all procedures and keep records appropriate to these principles and their application
   建立涉及所有程序的档案并保存

Figure 8.2-1 Critical Control Point Decision Tree
图解 8.2-1 关键控制点决策树



7.2.2 Failure Mode and Effects Analysis (FMEA)
故障模式及影响分析

FMEA is a detailed tool that may be used to identify potential failure modes and engineer them out of the process, improve reliability, or put controls in place to identify the failure modes before product quality is impacted. An FMEA may be conducted using either a quantitative approach assigning a risk priority number (RPN) or a qualitative approach assigning a level of risk (high, medium, low). Either method results in a risk prioritization rank (RPR) that is calculated based upon the following:
FMEA 是一个详细的工具，可用于确定潜在的失效模式和工程师筛选工艺过程，提供可靠性，或者在影响产品质量之前采取合适的措施识别故障模式。FMEA 可进行定量的方法提出一个风险优先级（RPN）或定性方法提出一个水平（高，中，低）。两种方法的结果在风险优先等级（RPR）是以以下为基础计算出的：

- Severity of the result of the failure
  故障结果的严重程度
- Occurrence (frequency of occurrence of the failure)

发生（发生故障的频率）

- Detection (how likely the failure is to be detected)
  检测（故障被检测到的可能性有多大）

The scales used to quantify severity, occurrence, and detectability must be defined as part of the FMEA setup and training. The scales may be based on available data or they may be subjective and based on professional experience. The process may be assessed and a risk ranking determined using these scales. Risk ranking establishes relative risk and identifies process steps that may benefit from the implementation of mitigating actions In this example, a qualitative approach has been selected. **Table 8.2.2-1** provides a more detailed example of scales that are typically used in a qualitative FMEA assessment.
用于确定严重程度、发生率和可检测性的标准必须规定为 FMEA 方案和培训的一部分。上述标准可以根据现有的数据或可能是主观的和基于专业经验判断。可以评估这个过程和使用这些标准确定风险等级。风险等级建立相对风险和识别过程中的步骤，可以从这个例子减缓措施的实施效益 ，选择了定性的方法。表 8.2.2-1 提供的更详细的例子，通常用于定性的 FMEA 评估的标准。

Table 8.2.2-1 Risk ranking assignment chart
表 8.2.2-1 风险等级分配图

Risk category 风险等级	High 高	Medium 中	Low 低
Severity 严重性	**The process failure will result in direct to patient health and is life threatening** **过程失效将直接导致病人的健康和生命威胁**	Process failure is indirect, moderate, or will have a slight impact to patient health; harmful but not life threatening. 过程失效是间接的，适中的，还是会有病人的轻微的影响健康危害；但没有生命威胁。	**Very little or slight impact to patient health 非常小或轻微的影响到患者的健康**
Occurrence 发生概率	**There is a high probability that process failure will occur and will result in the unwanted event** **有很高的概率过程发生故障，会导致不必要的事件**	Process failure occurs occasionally, but not often; may result in the unwanted event. 偶尔，但不是经常；发生过程失败可能会导致不需要的事件。	**Process failure rarely occurs not likely to result in an unwanted event** **过程失效很少发生不可能导致不必要的事件**
Detection 可检测性	**If the process failure occurs it will probably not be detected by existing controls** **如果过程失效，它可能不会被现有控制检测到**	If the process failure occurs, it may be detected with existing controls. 如果过程失效，它可以用现有控制检测到	**There is a high likelihood that existing controls will detect the process failure 有一个很高的用现有控制将检测过程失败可能性**

7.3 Example of HACCP for a New SIP Process
新的 SIP 过程的 HACCP 的例子

The example uses two risk management tools. Hazard Analysis and Critical Control Point (HACCP) analysis is used to assess the impact of individual manufacturing steps. Failure Mode and Effect Analysis (FMEA) is used to perform a more detailed risk assessment of individual SIP process steps to identify risks as well as actions that may be taken to preclude or minimize failures.

该例子使用两个风险管理工具，危害分析与关键控制点（HACCP）分析是用来评估对个别的制造步骤的影响。失效模式与影响分析（FMEA）是用来执行个别 SIP 工艺步骤来识别风险以及可能采取的防止或减少失败的行动更详细的风险评估。

The example presented here describes a bioburden-controlled, biologic manufacturing process. A flow chart of the manufacturing process from pre-culture to bulk (API) filling is shown in **Figure 8.3-1** and includes typical manufacturing steps such as cell culture, media and buffer preparation, harvest，recovery, purification, and bulk filling.
这里介绍的例子描述了生物负载控制，生物制造工艺。从预培养到大容量 (API) 充填的制造过程工艺流程图见图 8.3-1 所示，包括典型的生产步骤，如细胞培养 ，培养基和缓冲液的制备，挑取，回收，提纯，灌装。

The process steps highlighted in **Figure 8.3-1,** the Production Bioreactor System and the Purification System, are further detailed below:
图 8.3-1 强调的工艺步骤，生产的生物反应器系统和提纯系统，进一步地详述如下：

Table 8.3-1 documents two process steps identified during the HACCP analysis. The HACCP decision tree, shown in **Figure 8.2-1,** was used to determine if an individual process step was a CCP.
表 8.3-1 文档在 HACCP 分析过程中确定了两个过程步骤。图 8.2-1 所示的 HACCP 决策树用于确定是否是一个单个流程步骤是关键控制点。

The Production Bioreactor Vessel was identified as a CCP because achievement and maintenance of sterility was critical to ensure continued protein production during the cell culture process. As a result of the CCP being identified, the system was further assessed by establishing critical limits, monitoring procedures, and corrective actions using a standard HACCP analysis table. Then an FMEA assessment was performed on the SIP process to further identify individual failure modes. The entire production bioreactor system was deemed to require steam in place sterilization. Performance Qualification of the SIP sterilization process requires following an overkill sterilization approach using temperature monitoring and biological indicator challenges.
生物反应器容器被确定为关键控制点是因为实现和保持无菌的关键是确保在细胞培养过程中持续蛋白质的生产。通过建立临界界限，监测程序，并使用标准的 HACCP 分析表的纠正措施进一步评估关键控制点（CCP）的识别系统。然后在 SIP 过程中执行 FMFA 评估来进一步确认个别的失效模式。整个生物反应器被视为需要蒸汽在线灭菌。对 SIP 灭菌过程的性能鉴定需要使用温度监测和生物指示剂挑战性试验的过度灭菌方法。

The second chromatography step in the Purification System was also analyzed and no CCPs were identified. This determination means that though the process step is important, there are monitoring procedures in place (bioburden monitoring being a key one) to ensure that the process does not exceed limits. The amount of qualification and the requirements for any subsequent requalification can be determined and justified based upon this assessment. This portion of the manufacturing process need only undergo a steam in place sanitization procedure since a low bioburden level is acceptable and a filtration procedure is in place after the purification steps and prior to proceeding to the bulk API fill steps.
同样对第二步色谱法分离纯化系统进行分析并确定没有关键控制点。这意味着尽管过程步骤很重要，有在线过程监控（生物负载监控是关键的一个）以确保过程不会超过限度。可以确定合格的总数和之后任何再确认的要求并且根据评估调整。制造过程中的这部分只需要经过在线蒸汽灭菌程序以后低生物负载水平是可以接受的，并且纯化步骤后和散装 API 填充步骤之前的过滤程序是准备就绪的。

Figure 8.3-1 Manufacturing Process Flow Diagram Depicting Stages of HACCP Analysis

Figure 8.3-1 Manufacturing Process Flow Diagram Depicting Stages of HACCP Analysis
图8.3-1 描述HACCP分析的生产工艺流程图

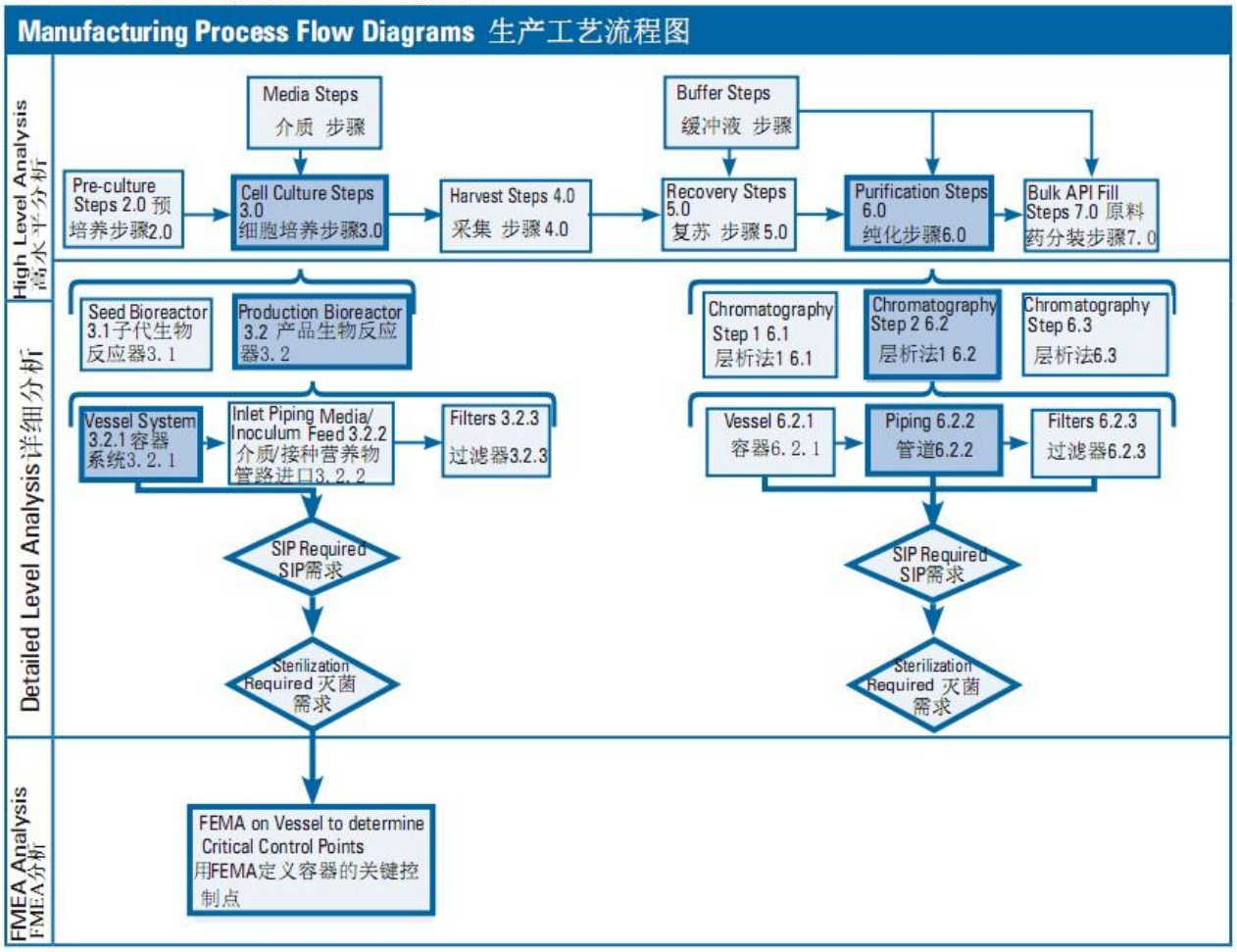


Table 8.3-1 HACCP Analysis Table 表 8.3-1 HACCP 分析表

Step Ref.	Process step 过程步骤	Hazard No. 危害编号	Hazards 危害	CCP Yes/No	CCP Rationale 关键控制点说明	Critical limits 控制限	Monitoring procedure 控制程序	Corrective Actions 纠正措施
3.2.1	Production Bioreactor Vessel 生物反应器	3.2.1-1	Inadequate SIP exposure time and/or temperature 不合适的 SIP 灭菌的时间和（或）温度	YES 是	Maintenance of sterility critical in this step to ensure protein production. 在这步保持无菌是关键的确保蛋白质的生产	Exposure Temperature:121 ℃ plus measurement Uncertainty 灭菌温度：121 度加不确定度 Exposure Time: 12 minutes minimum plus safety margin for robustness 灭菌时间：12 分钟，加上安全最低限度 Sterilization Required 灭菌要求	Monitor time and temperature during every SIP process 监控每一个 SIP 过程时间和温度 Manual check of all steam traps to ensure adequate air removal prior to initiating cycle 手动检查所有蒸汽疏水阀，确保在启动周期之前，有足够的空气排除。 Periodic calibration of all temperature probes 定期校准温度探头 Bioreactor sample bioburden Monitoring 抽样检查生物反应器生物负载	Verify calibration of all measuring equipment Shorten calibration cycles as necessary 核实所有测量设备的校准周期必要时缩短校准 Verify steam trap function Replace as necessary 核查蒸汽疏水阀的功能必要时更换 Investigate SIP run and previous runs to ascertain root cause 调查 SIP 运行和以前运行区别确定根本原因
		3.2.1-2	Microbial contamination 微生物污染	YES	If sterilization is inadequate, then contamination could occur, resulting in termination of production and culture disposal. 如果灭菌是不充分的，并可能受到污染，造成生产和培养终止。	Axenic culture (no contamination) 无菌培养（无污染） Sterilization Required 灭菌要求	Verify bioreactor samples do not contain contamination 抽样检查生物反应不含污染物	Perform root cause investigation and implement countermeasures to prevent reoccurrence 进行根本原因调查及实施对策防止再发生

Step Ref.	Process step 过程步骤	Hazard No. 危害编号	Hazards 危害	CCP Yes/No	CCP Rationale 关键控制点说明	Critical limits 控制限	Monitoring procedure 控制程序	Corrective Actions 纠正措施
		3.2.1-3	No SIP after line breakages for calibration or maintenance 在没有 SIP，线路损坏后进行校准和维护	YES 是	When the system is no longer in a closed condition, system integrity and sterility must be restored through SIP following line breakage. 当该系统不再是在一个封闭的条件下，通过下面 SIP 恢复系统的完整性和无菌	Exposure Temperature:121 ℃ plus measurement uncertainty 灭菌温度：121 度加不确定度 Exposure Time: 12 minutes minimum plus safety margin for robustness 灭菌时间：12 分钟，加上安全最低限度 Sterilization Required 灭菌要求	Monitor time and temperature during every SIP process 监控每一个 SIP 过程时间和温度 Manual check of all steam traps to ensure adequate air removal prior to initiating cycle 手动检查所有蒸汽疏水阀，确保在启动周期之前，有足够的空气排除。 Periodic calibration of all temperature probes 定期校准温度探头 Bioreactor sample bioburden Monitoring 抽样检查生物反应器生物负载	Develop line-breaking procedure that includes SIP of the line after maintenance completion 制定包括维修完后 SIP 程序

Step Ref.	Process step 过程步骤	Hazard No. 危害编号	Hazards 危害	CCP Yes/No	CCP Rationale 关键控制点说明	Critical limits 控制限	Monitoring procedure 控制程序	Corrective Actions 纠正措施
6.2.2	Purification System 提纯系统 Chromatography Step 2 – Piping 色谱法 步骤 2-管道	6.2.2-1	Inadequate SIP exposure time and/or temperature e 不合适的 SIP 灭菌的时间和（或）温度	No	Final filtration step prior to bulk API filling in place to reduce or remove bioburden 最后的过滤工序到批量 API 填充到位，去减少或消除生物负载	Bioburden and endotoxin levels meet predetermined criteria 微生物和内毒素水平达到预定标准 Sanitization Only Required 只有卫生要求	Monitor time and temperature during every SIP process Manual check of all steam traps to ensure adequate air removal prior to initiating cycle Periodic calibration of all temperature probes Product bioburden monitoring	Verify calibration of all measuring equipment Shorten calibration cycles as necessary y 核实所有测量设备的校准周期必要时缩短校准 Verify steam trap function Replace as necessary 核查蒸汽疏水阀的功能必要时更换 Investigate SIP run and previous runs to ascertain root cause 调查 SIP 运行和以前运行区别确定根本原因
		6.2.2-1	Microbial Contamination 微生物污染	No	Final filtration step prior to bulk API filling in place to reduce or remove bioburden 最后的过滤工序到批量 API 填充到位，去减少或消除生物负载	Bioburden and endotoxin levels meet predetermined criteria 微生物和内毒素水平达到预定标准 Sanitization Only Required 只有卫生要求	Purification sample bioburden monitoring procedure in place	Perform root cause investigation and implement counter measures to prevent reoccurrence 调查 SIP 运行和以前运行区别确定根本原因 Extend SIP cycle

7.4 Example of FMEA for a Steam in Place Process
失败模式和影响分析（FMEA）用于在线蒸汽过程的例子

A more detailed risk assessment of the SIP was warranted since the HACCP analysis identified the Production Bioreactor System SIP process as a CCP. In this case, the FMEA works well at the component level to challenge the design and operation of the system and identify potential areas of failure.
在线灭菌（SIP）更为详细的风险评估是必要的，因为危害分析和关键控制点（HACCP）分析确定了生产生物反应器系统在线灭菌过程作为一个关键控制点（Critical Control Point）。在这种情况下，FMEA 在组件层次挑战设计和系统操作以及辨识出潜在的失败区域上运行良好。

7.4.1 Risk analysis
风险分析

Severity, occurrence, and detection were considered in the estimation of risk for each cause and process failure. Qualitative risk assignments including Low, Medium, and High rankings were used as shown in **Table 8.2.2–1.**
在对每个原因和过程失败的风险评估中，都要考虑严重程度、发生几率和检测。质量风险分析包括低、中和高等级如图 8.2.2-1 所示。

7.4.2 Risk Evaluation
风险评价

Risk evaluation was also performed using a qualitative risk prioritization ranking (RPR) approach. Since the occurrence of non-sterile liquid product is considered unacceptable due to patient risk, severity is always rated as high and not included in the risk prioritization ranking chart. Therefore, the RPR was performed based on likelihood of detection and occurrence frequency. **Table 8.4.2-1**uses color-coding to depict the RPR including Low (green), Medium (yellow) and High (red).
风险评估也使用质量风险优先级排名（RPR）方法来进行。因为非无菌液体产品的存在由于患者风险的原因被看做是不可接受的，总是被认为是高严重程度，并且不包括风险优先级排名表。因此，执行 RPR 是基于检测的可能性和发生的频率。表格 8.4.2-1 用不同颜色做标记的方法来描述质量风险优先级排名（RPR）的低（绿色），中（黄色）和高（红色）。

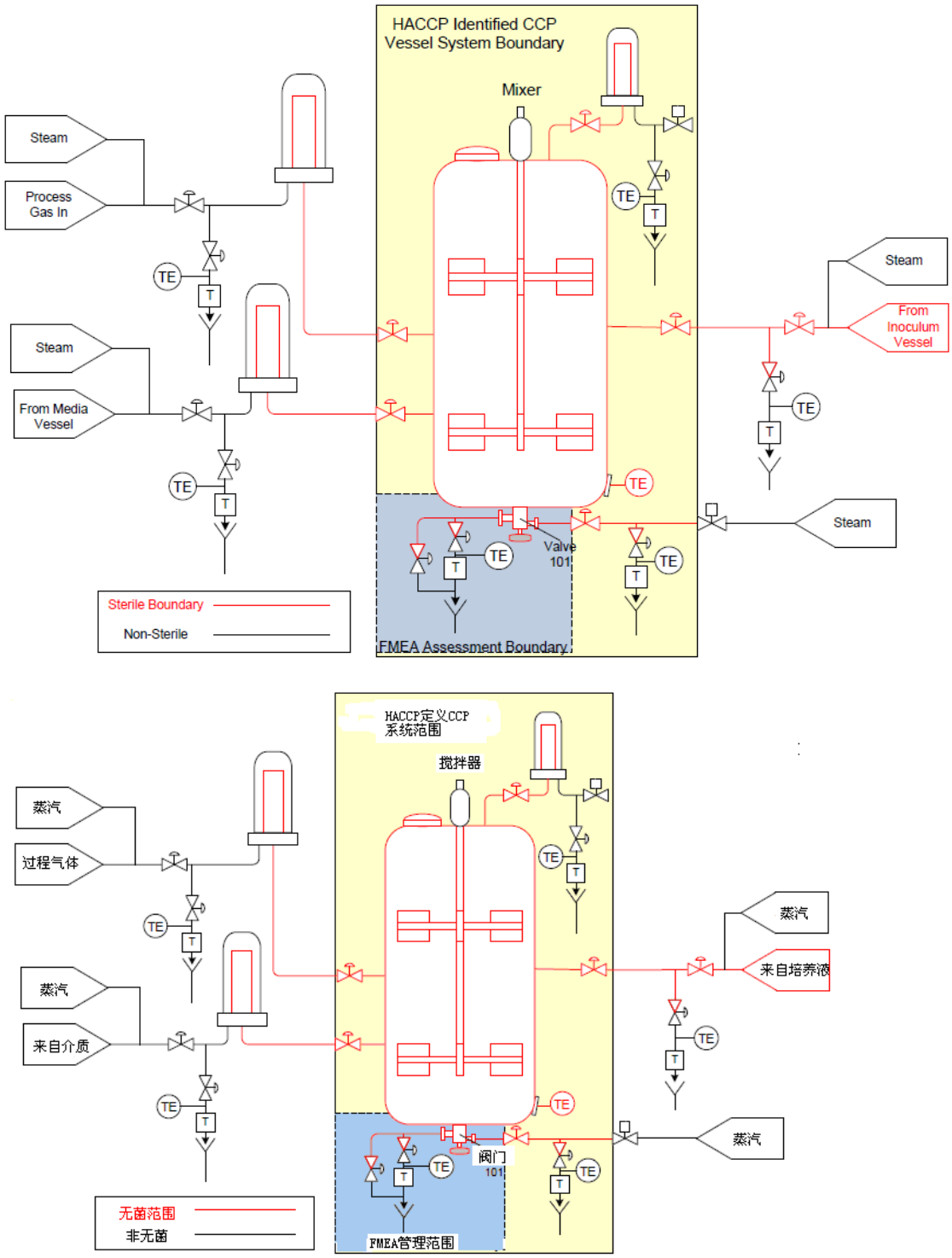
Table 8.4.2-1 Risk Prioritization Ranking Chart
表 8.4.2-1 风险优先级排列表

		Detection 检测		
		Low 低 (High likelihood failure will be detected) （高失败可能性高且将被检测到）	Medium	High (It is not likely failure will be detected)
Occurrence 发生几率	High 高	This cause is likely to occur, but when it does it will be detected 危害很可能发生，但发生时将被检测到。 Risk is Medium 风险是中	This cause is likely to occur and may be detected 危害很可能发生，并且可能被检测到。 Risk is High 风险为高	This cause is likely to occur and is not likely to be detected 危害很可能发生，并且不太可能被检测到。 Risk is High 风险为高
	Medium 中	This cause could occur and will be detected 危害可能发生，并且将被检测到。 Risk is Low to Medium 风险为中偏下	This cause could occur and may be detected 危害可能发生，并且可能被检测到。 Risk is High 风险为高	The cause may occur and it will not be detected 危害可能发生，并且检测不到 Risk is High 风险为高
	Low 低	This cause is not likely to occur and if it does, it will be detected 危害不太可能发生，如果发生，将被检测到 Risk is Low 风险为低	The cause is not likely to occur and if it did it, may be detected 危害不太可能发生，如果发生，可能被检测到 Risk is Low or Medium 风险中偏低	The cause is not likely to occur and not likely to be detected 危害不太可能发生，并且不太可能检测到 Risk is Medium 风险为中

7.4.3 Risk Assessment
风险评估

A risk assessment was conducted on the bioreactor vessel system using the FMEA tool. **Figure 8.4.3-1**depicts the CCP boundary identified during the HACCP analysis. A smaller boundary has been added to show the scope of FMEA used in this example. This figure has been simplified for the purpose of this exercise and is not an accurate representation of a complete bioreactor system.
在生物反应器系统中利用 FMEA 工具实施风险评估。图 8.4.3-1 在危害分析和关键环节控制点（HACCP）分析期间描述了关键控制点界限的确认。添加一个更小的界限来显示在本例中 FMEA 使用的范围。这个图表已经简化了这个练习的目的，并且不是一个完整的生物反应器系统的准确表达。

Figure 8.4.3-1 Example of Bioreactor Vessel System
图 8.4.3-1 生物反应器系统的例子



The assessment of the manufacturing and SIP process is shown in **Table 8.4.4-1.** Qualitative values (Low, Medium, and High) were assigned to each failure for frequency of occurrence and likelihood of detection. The combination of the occurrence and detection values was used in the risk prioritization chart to determine the current RPR. The acceptability of each failure cause was determined using the RPR. High RPRs were generally considered unacceptable and mitigation actions were investigated to reduce the risk. A Medium RPR required

investigation for further mitigation and then a final determination was made as to its acceptability. Mitigation may be accomplished either through re-engineering or increased monitoring to reduce the RPR.
生产过程和 SIP 过程的评价见表 8.4.4-1。定性值（低，中，高）被分配到每次故障发生的频率和检测可能性上。发生频率和检测值的集合体被用在风险优先级表格中来确定当前的优先级排名（RPR，risk priority ranking）。每次故障原因的接受性通过应用 RPR 来确定。高 RPRs 通常被认为是不可接受的并研究缓解措施降低风险。中 RPR 需要调查进一步的缓解并最终测定它的可接受性。缓解可能完成或通过再加工或增加监控来降低 RPR.

7.4.4 Risk Reduction/Post-mitigation RPR
风险降低/快速缓解 RPR

A means of reducing the risk was developed with preference given to engineering controls over procedural controls wherever possible. The occurrence frequency and likelihood of detection were evaluated after each of the mitigation actions was implemented. For all cases in this example, the mitigation actions were able to reduce all RPRs to “Low,” which is considered an acceptable level of risk.
降低风险的一种手段是优先开发尽可能在过程控制之上应用工程控制。每个降低措施的实施后都要对发生频率和检测的可能性进行评估。对于这个例子中的所有情况，缓解措施能够降低所有的 RPRs 到“低”，这是个被认为可以接受的风险水平。

Table 8.4.4-1 Assessment of Manufacturing SIP Process
表格 8.4.4-1 生产在线灭菌（SIP）过程评估

Part/Component 零件/组件	Functional Description 功能描述	Unwanted Event 意外事件	Ref # 序号	Causes/ Process Failure 故障/过程失败	Potential Effects of Failure Mode 潜在影响	SEVERITY 严重程度	Root Cause of Failure 失败的根本原因	OCCURRENCE 发生频率	Current Controls 目前的控制方法	DETECTION 发现的频率	Initial Risk Prioritization Number 初始风险优先级别	Risk Accepted (Yes/No) 风险是否接受（是/否）	Recommended Action 建议措施	SEVERITY Post- mitigation 缓解后严重性	OCCURRENCE Post-mitigation 缓解后发生率	DETECTION Post-mitigation 缓解后发现率	Risk Prioritization Rank Post- mitigation 缓解后风险优先级别	Risk Accepted Post-mitigation 缓解后风险接受
Steam trap on vessel drain pipe work 设备强室内排水管上疏水阀运行	Steam trap allows condensate and air removal from system during SIP. 疏水阀在SIP时允许冷凝水和空气从系统中移除	SIP Failure SIP失败	1.1.1	Fails open 未打开	Temperature and pressure not achieved in the system as steam 系统内达不到成为蒸汽所需要的温度和压力	H	Defective parts or standard failure mode for a steam trap 有缺陷的零件或疏水阀的标准失效模式	M	Will be detected by the control system as temperature and pressure set points will not be met; The SIP will not progress to the exposure phase 控制系统监测到的温度和压力值到不到设定值，SIP不会运行到暴露阶段	M	M	N	Add preventive maintenance schedule for steam traps annually 增加对疏水阀的预防性维护计划	H	L	M	M	Y
													Add quarterly steam trap evaluation 增加疏水阀的季度评估	H	M	L	M	Y
													Add preventive maintenance schedule for steam traps annually and quarterly steam trap evaluation 增加疏水阀年度预防性维护计划和疏水阀的季度评估	H	L	L	L	Y
			1.1.2	Fails closed 未关闭	Condensate and air not removed from the vessel and pipe work Temperature control affected at those locations 室内冷凝水和空气不去除和管路运行温度控制对这些位置有影响	H	Blockage or defective parts 堵塞或有缺陷的部分	L	Drain temperature probe above this trap will be in condensate and therefore will be reading a low temperature; The control system will not progress SIP into the exposure phase if this temperature is low 阀门上的排水温度探头处于冷凝水中，因此测得是个低温。如果温度低，控制系统不会使SIP运行到暴露阶段	L	L	Y						
			1.1.3	Operates at too high or low a temperature 温度过高或过低时的操作	Temperature and pressure may not be achieved. Depends upon the steam supply capacity and extent of the failure 受限于蒸汽供应能力和失败程度，温度和压力达不到要求	H	Wrong steam trap installed 错误的疏水阀安装	M	Will be detected by the control system as temperature and pressure set points will not be met; The SIP will not progress to the exposure phase 控制系统监测到的温度和压力达不到设定值，SIP不会运行到暴露阶段 Equipment specification standards in place 设备在线规范标准	L	M	N	Further develop engineering standard for steam trap 对疏水阀进一步提高工程标准 Check ordering details, model numbers, inventory Check maintenance procedure 检查采购细节、型号、库存、检查维修过程	H	L	L	L	Y

7.5 Appendix B: Lyophilizer SIP Design and Cycle Considerations
附录 B：冻干机 SIP 设计和循环周期注意事项

Lyophilizers are unique, complex systems, with limited guidance available relative to SIP. The concepts discussed here apply to lyophilizers used for aseptic processing, but can be applied to other equipment and systems.
冻干机是独特而复杂的系统，相对于 SIP，可用的指导是有限的。这里讨论的概念适用于冻干机无菌生产过程，但也能应用到其他的设备和系统。

The typical components of the lyophilizer include the chamber, shelves, ram, condenser, heating and cooling system, chamber vacuum pumps, vent and compressed gas filters, CIP spray devices (for some lyophilizers), and chamber isolation valve. An example lyophilizer schematic is shown in **Figure 8.5-1.**
冻干机的典型组件包括腔室、隔板架、活塞、冷凝器、加热和冷却系统、真空泵、呼吸器和压缩空气过滤器、CIP 喷淋设备（对某些冻干机）和腔室隔膜阀。例如冻干机示意图如图 8.5-1 所示。

7.5.1 Lyophilizer Chamber, Shelves, and Ram
冻干机腔室、架子和活塞

The lyophilizer chamber is a large vessel that contains hollow shelves on which the product vials are placed. The shelves are typically raised and lowered by a large hydraulic piston (ram). The distance between each shelf in the shelf stack is maintained by positioning rods or a similar mechanism. The lyophilizer ram is typically protected by a flexible bellows that separates the ram piston from the lyophilizer chamber. When designing an SIP cycle for a lyophilizer, it is important to ensure that the moving components in the lyophilizer chamber, such as the shelves, positioning rods, etc. are fully exposed to steam. This is commonly accomplished by raising and lowering the shelves during the SIP cycle.
冻干机前室是个很大的容器，里面包含放置瓶装产品的中空隔板架子。隔板架子通常通过一个大型液压活塞来升降。置料隔板架子之间的距离是由定位棒或者类似机理来保持的。冻干机活塞通常是由波纹管来保护，用其将活塞和冻干机腔室分隔开。当冻干机设计 SIP 循环周期时，确保冻干机腔室内的组件（如隔板架子、定位棒等）可以移动是很重要的，这样可以使组件能充分的暴露在蒸汽环境下。通常通过再 SIP 循环周期内升降板架来完成灭菌工序。

7.5.2 Lyophilizer Condenser
冻干机冷凝器

The lyophilizer condenser contains cooling coils that condense the sublimated water vapor into ice. Two types of condensers may be used in a lyophilizer: internal condenser, in which the cooling coils are located inside the lyophilizer chamber, and external condenser, in which the cooling coils are located in a separate sanitary vessel that is connected to the lyophilizer chamber.
冻干机冷凝器包含的冷却盘管将冷凝水升华结成冰。两种类型的冷凝器可被用于冻干机：内部冷凝器，就是将冷凝盘管安装在冻干机腔室内部；外部冷凝器，就是冷却盘管安装在一个连接在冻干机腔室上的一个独立的清洁容器中。

For production lyophilizers that use external condensers, it is important to have separate temperature monitoring probes for the lyophilizer chamber and condenser. Separate temperature monitoring probes are not required for internal condensers.
对于使用外部冷凝器的生产型冻干机，冻干机腔室和冷凝器有单独的温度监控探头是重要的。内部冷凝器则不需要独立的温度监控探头。

External condensers are typically large sanitary vessels that can be difficult to access. Temperature mapping of external condensers can be difficult because limited access impedes placing temperature sensors. Since external condensers are often cold points, consideration should be given to installation of appropriate access for temporary probes or installation of permanent probes at these locations.
外部冷凝器通常是大型清洁容器，很难进入。外部冷凝器的温度测绘是很困难的，因为有限的进入阻碍了放置温度感应。因为外部冷凝器经常到冷点，所以应该考虑在这些位置合适的入口安装临时性或者永久性探头。

7.5.3 Heating and Cooling System
加热和冷却系统

Heating and cooling fluid is supplied to each shelf via flexible hoses connected to fluid inlet and fluid outlet manifolds either inside or outside of the lyophilizer chamber. Any penetrations into the system for the heating and cooling system should be of sanitary design. All flexible hoses must be designed to withstand the temperature and pressure/vacuum of a typical steam SIP cycle.
通过软管连接到流体入口和流体出口，给每个板层提供加热和冷却液。任何渗透到系统的加热和冷却系统应该进行洁净设计。设计时要考虑所有软管必须能够承受 SIP 期间的温度和压力/真空。

The heating/cooling system should be vented and remain off during SIP to prevent damage to the equipment. The heating/cooling system can be turned on during the cooling phase of the SIP cycle, if shelf temperatures are below temperatures that could damage the equipment.
在 SIP 期间，加热/冷却系统应被排空且处于关闭状态,防止损伤设备。如果板层温度低于可能损坏设备的温度，在 SIP 周期冷却阶段加热/冷却系统可以打开。

7.5.4 Chamber Vacuum Pumps
冻干箱真空泵

Lyophilizers often use multiple types of vacuum pumps: a liquid ring vacuum pump is typically used for the SIP process, and high-vacuum pumps are used for freeze-drying. These pumps are not compatible with moisture and therefore should be isolated during the SIP cycle.
冻干机经常使用多种类型的真空泵:液环真空泵通常用于 SIP 过程,应用高负压泵用于冷冻干燥。这些泵都不能与水分兼容,因此 SIP 期间应该受到隔离保护。

7.5.5 Vent and Compressed Gas Filters
排气及压缩空气滤芯

Lyophilizers contain one or more sterilizing grade vent filters and/or compressed gas filters. Depending on lyophilizer design, these filters may be steamed in place or may be sterilized separately and connected using an aseptic design.
冻干机包含一个或多个灭菌级别的排气过滤器和/或压缩气体过滤器。根据冻干机设计,这些过滤器可能通过在线 SIP 或离线灭菌后通过无菌组装方式连接。

7.5.6 Clean-in-Place (CIP) Spray Devices
在线清洁喷淋设备

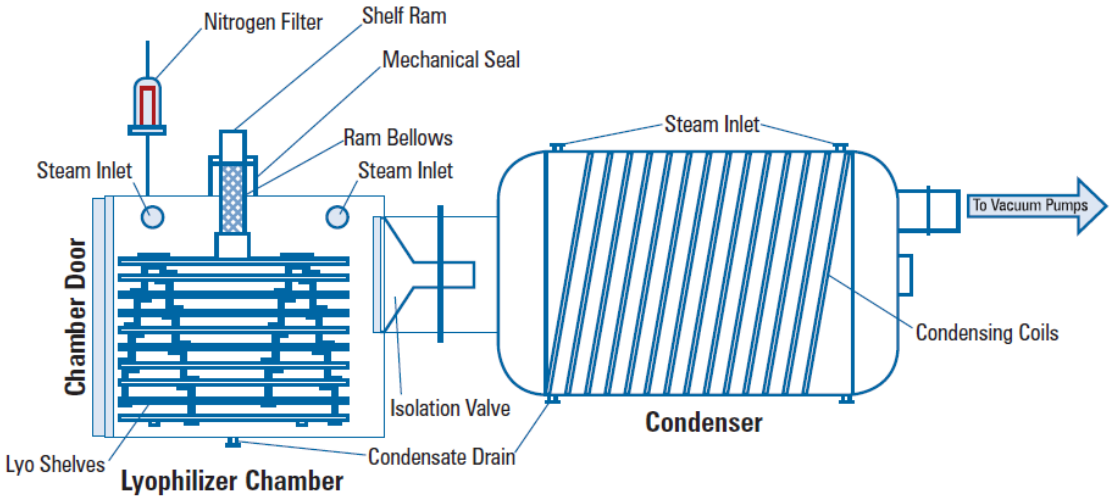
If a lyophilizer has spray devices for CIP of the chamber and condenser, it is important that these penetrations are sterilized as part of an SIP cycle. This is typically done by introducing steam into the lyophilizer chamber and condenser through the spray devices during the SIP cycle.
如果一个冻干机有喷淋装置用于对冻干箱和冷凝器进行在线清洁，重要的是,这些组件应通过 SIP 灭菌。通常是通过 SIP 期间将蒸汽引入到冻干机室和冷凝器来实现。

7.5.7 Chamber Isolation Valve
冻干室隔离阀

Lyophilizers with external condensers use isolation valves to allow separation of the lyophilizer chamber from the condenser. These valves are generally of two types: butterfly valves or piston valves. The isolation valves should remain open during SIP to ensure sterilization of the valves and the connection between the lyophilizer chamber and the condenser. Special attention should be given to the isolation valve and to the connection between the lyophilizer chamber and the condenser because this can be a cold spot in the lyophilizer system. The flange between the condenser and lyophilizer chamber needs to be designed so that the flange gasket is flush to prevent pooling of condensate.

带外部冷凝器的冻干机使用隔离阀使到冻干机室与冷凝器分开。这些阀门通常有两种型式:：蝶阀或活塞阀门。在 SIP 期间隔离阀应保持开放，确保阀门及冻干腔室和冷凝器的接口能被灭菌。要注意阀门和接口主要是因为这些可能是系统的冷点。设计上冷凝器和冻干机室之间的法兰法兰垫片是平的冲洗以防止凝结水的蓄积。

Figure 8.5-1 Simplified Schematic of a Lyophilizer and Condenser



7.5.8 Post-sterilization Leak Test
灭菌后泄漏试验

Because lyophilizers operate under vacuum, it is important to leak test the lyophilizer after sterilization. Most lyophilizers have vacuum leak test cycles built in that pull a vacuum on the lyophilizer and then seal off all inputs to the lyophilizer. The vacuum leak test passes if the increase in pressure in the chamber is less than a predetermined amount over a pre-determined time. The acceptance criteria for a vacuum leak test will vary based on lyophilizer volume and design, and should be determined with the aid of the lyophilizer manufacturer. It is important to ensure that the chamber is thoroughly dry to prevent “virtual leaks” caused by sublimation of residual moisture. Most post-SIP leak tests are performed after a chamber drying cycle.

由于冻干机在真空条件下运行，所以灭菌后冻干机的泄漏试验是非常重要的。大多数冻干机进行真空泄漏试验时都是把将冻干机抽真空，封闭所有入口。如果再既定时间内，冻干机内的压力的增长低于既定值，就算通过真空泄漏试验。真空泄漏试验的验收标准会根据制造商确定的冻干机的体积和设计的不同而变化。重要的是要确保室内彻底干燥,以防止残留水分升华引起的“假漏”发生。多数在线蒸汽灭菌后（post-SIP）的泄漏试验都是在干燥周期之后进行的。

7.5.9 Cycle Considerations for Lyophilizers
冻干机循环注意事项

SIP for lyophilizers differ in a few important considerations from other systems being considered. Following are some of the main considerations for lyophilizers:
冻干机的在线蒸汽灭菌某些重要的注意事项和其他系统不同。冻干机一些主要注意事项如下：

- Lyophilizers are rated for deep vacuum (typically £100 micrometers Hg) and are fitted with multiple vacuum pumps, including liquid ring pumps that make it possible to evacuate the system before and after SIP. This design allows the use of vacuum/steam pulses to remove air from the system during the SIP cycle.
  冻干机为高真空(通常是£100 微米汞柱),配有多个真空泵,包括 SIP 前后用来疏通系统的液环泵。这种设计可在 SIP 循环中，用真空/蒸汽脉除去系统中的空气。

- Lyophilizers operate under deep vacuum after SIP, requiring the system to have a lower leakage rate after SIP than systems that are maintained under positive pressure after SIP.
  SIP 后，冻干机在深真空条件下操作，要求系统在 SIP 后的泄漏率比持续正压下的低。

- Lyophilizers contain moving parts that must be exposed to steam during SIP (e.g., the lyophilizer shelves, a lyophilizer ram covered with a bellows or other device, and chamber isolation valve). If these moving parts remain stationary during the SIP cycle, they should be in a position to allow surfaces that are in contact with the lyophilizer chamber to be exposed to steam during SIP.
  冻干机包含的移动部件在 SIP 过程中，必须暴露在蒸汽中(如冻干机的架子，装满了风箱和其他设备的内胆,室、隔离阀)。如果这些可移动部件在 SIP 循环中保持固定，其表面就应该与冷冻干燥室接触，并暴露在蒸汽中。

- Lyophilizers are typically divided into a lyophilizer chamber and external condenser that must each be steamed in place. The external condenser is normally defrosted before SIP can begin.
  冻干机通常分为冷冻干燥室和外冷凝器，都这两个部分都必须在线蒸汽灭菌。一般外冷凝器是在 SIP 开始之前进行解冻。

- Lyophilizers require sterilizing grade vent filters to release vacuum at the end of the lyophilization cycle (and at the end of the SIP cycle). While this does not differ from many other systems, sterilization of the vent filters must be considered.
  冻干机需要消毒级的通气过滤器在冻干循环结束时(和 SIP 循环结束时)释放真空。虽然这和其他系统没什么不同，但必须考虑通气过滤器的消毒问题。

- Other considerations, such as thermal stress on lyophilizer components (lyophilizers may operate from <-70 ℃ to >121 ℃) and the handling of heat transfer fluids in the lyophilizer shelves and condenser are part of the lyophilizer design and need to be considered during SIP cycle development.
  SIP 循环过程中其他需要注意的有，比如冻干机部件的热应力(冻干机可能在< -70 ℃ 和> 121 ℃ 条件下操作)， 冻干机架子的导热流体的处理。

7.5.10 8.5.10 Pre-SIP Phases for Lyophilizers
7.5.11 冻干机 SIP 前阶段

Lyophilizers typically require several pre-SIP preparation phases before performing the actual SIP cycle. These pre-SIP phases may include:
通常，冻干机在进行真正的 SIP 前需要 3 个准备阶段。这 3 个 SIP 前阶段包括:

Defrost Phase: The defrost phase removes residual ice from the condensers in preparation for cleaning and SIP. The condenser coils are defrosted by heating them for a predetermined time and temperature. Steam may be injected into the condenser to speed up the defrost process. The condenser should be thoroughly defrosted before SIP.
解冻阶段:冰解冻阶段去除了冷凝器内残留的冰，为清洁和 SIP 做准备。冷凝管在既定的温度和时间内加热解冻。将蒸汽通入冷凝器可加快解冻过程。SIP 前，冷凝器必须完全解冻。

Cleaning Phase: Cleaning the equipment prior to SIP ensures that soils are reduced to acceptable levels. Most modern lyophilizers are cleaned by a CIP cycle, although some may be cleaned manually. Cleaning and cleaning validation for lyophilizers is outside the scope of this document.
清洁阶段:在 SIP 前清洁设备，以确保污染物能降低到可接受限度内。大多数现代冻干机都是采用 CIP 循环来清洁，但还是有部分采用手动清洗。
本文不涉及冻干机的清洁和清洗验证。

Pre-SIP Leak Test Phase: Sometimes a pre-sterilization leak test (vacuum or pressure hold test) is performed. This test is performed to detect leaks that could compromise personnel or equipment safety before beginning the SIP cycle. If a vacuum hold test is used, the lyophilizer must be thoroughly dried before beginning the test, to prevent "virtual leaks" caused by sublimation or evaporation of residual moisture.
SIP 前泄漏试验阶段:有时会进行灭菌前泄漏试验验(真空或压力测试)。该试验是用来在 SIP 循环前，协调人员或设备的安全性。为了防止残留水分升华或蒸发引起的"假漏"发生，如果进行真空试验,在测试前必须保证冻干机完全干燥。

7.5.12 8.5.11 Typical SIP Phases for Lyophilizers
冻干机 SIP 的主要阶段
The typical phases for SIP of a lyophilizer include:
冻干机 SIP 的主要阶段包括：

Heat-up/Air displacement phase: Remove air from the lyophilizer using one or more vacuum pulses to evacuate air to a predetermined level. The system is pressurized with steam to heat up the system following each vacuum pulse. See Table 5.2-1 for a more detailed description of the air removal phase.
加热/排气量阶段: 采用一个或多个真空脉冲将冻干机内的空气排到空气中，直到内部空气达到预定的水平。系统用每个真空脉冲加压，蒸汽加热。。排气阶段更详细的信息见表 5.2-1。
Heat-up phase: Pressurize chamber with steam to bring chamber/condenser temperature to specified temperature.
加热阶段: 用蒸汽把冻干室加压，从而使冻干室/冷凝器温度达到指定温度。

Exposure phase: Hold the chamber at the specified temperature for a predetermined amount of time.
暴露阶段:冻干室在预定时间内保持指定温度。

Steam removal: Evacuate steam from the chamber/condenser.
除蒸汽:将冻干室/冷凝器内的蒸汽疏散。

Vacuum dry/cool-down phase: Remove excess moisture from the lyophilizer chamber and condenser. Chamber drying is necessary to prevent residual moisture in the system during the Post-SIP test. The order of the vacuum dry and cool-down differ by company (some choose to cool down after drying, since the heat facilitates drying). Allow the chamber to cool down to ambient temperature. Shelves and condenser coils may be used to speed cool-down after the chamber temperature falls below a safe temperature.

真空干燥/冷却阶段:除去冻干室和冷凝器的多余水分。冻干室必须干燥以防止 SIP 后的试验中系统必有残留水分。不同公司真空干燥和冷却的顺序不同(有时会选择干燥后冷却,因为设施是加热干燥的)。冻干室应冷却到室温。当冻干室温度降到安全温度以下时，架子和冷凝管应加速冷却。

Post-SIP leak test phase: Perform a vacuum hold test to ensure the lyophilizer is integral before loading product into the lyophilizer chamber.
SIP 后泄漏试验阶段:在产品装入冻干室之前要进行真空试验以确保冻干机的密封性。

7.5.13 8.5.12 Validation Considerations for Steam in Place
在线蒸汽灭菌验证的注意事项
Many of the principles that apply to SIP of other systems and equipment apply to SIP of lyophilizers. Lyophilizers used for aseptic processing require evaluation of a few special considerations during validation:
许多适用于其他系统和设备的 SIP 的原则也适用于冻干机。但用于无菌过程的冻干机在验证过程中需要评估一些特定的注意事项:

• Definition of sterile boundaries – the design review for a lyophilizer needs to include a clear definition of the sterile boundaries based on an assessment of risk to the product.
无菌分界线的定义——冻干机的设计综述需要包含一个基于产品的风险评估无菌分界线的清晰定义。

This is especially important when considering the SIP cycle for an external condenser. Because the condenser is connected to the lyophilizer by a tube separated by a large piston or butterfly valve, some pharmaceutical manufacturers consider the condenser to be outside the sterile boundary They then assign the separating line at the isolation valve, much in the same way that the sterile boundary for a formulation vessel may be at the bottom valve or steam trap. Other manufacturers include the condensing chamber within the sterile boundary.
在 SIP 循环中，外部冷凝器是特别重要。因为冷凝器是通过一根被一个大活塞或蝴蝶状阀门隔离的管子与冻干机相连，一些制药厂商考虑认为冷凝器可以非无菌，用独立阀门设计了分界线，同样在底阀和蒸汽管道内也设计了无菌的分界线。其他厂家则将要求冻干室应无菌。

It is important that the location of the sterile boundary be clearly defined in the user requirements and/or design specification for the system. This definition should be accompanied by a risk assessment that evaluates factors such as mass flow from the lyophilizer chamber to the condenser, and the effect of failures of vacuum pumps or cooling systems on the sterility of the lyophilizer chamber.
无菌分界线的位置非常重要，根据用户需求和/或系统的设计规范明确定义。这个定义应附有风险评估,评估冻干室到冷凝器的流量，无效真空泵的影响或冻干机无菌室冷却系统等因素。

Placement of temperature sensors: Some SIP cycles for lyophilizers may include raising and collapsing the lyophilizer shelves, to ensure moving parts are adequately sterilized. In these cases, temperature sensors should be carefully placed so that they are not damaged by or cause damage to the lyophilizer.
温度传感器定位:一些冻干机的 SIP 循环可能包括架子的升降，以确保可动部件完全灭菌。在这些情况下,温度传感器应小心放置以免受损或毁坏冻干机。

Placement of biological indicators: If a condenser is considered within the sterile boundary for an SIP cycle, careful consideration should be given as to where and how biological indicators should be placed in the condenser. This is especially important as the condenser, unlike the lyophilizer chamber, is not typically designed for easy access. Addition of access ports to the condenser during construction of the condenser chamber may be worthwhile if the condenser is considered within the sterile boundary. This is especially true for large condensers

that may be several meters in length and diameter. The majority of the BIs should be placed on the shelves, in the chamber, and in the chamber drain.
生物指标剂的定位:如果认为 SIP 循环的冷凝器是无菌的,应仔细考虑生物指示剂应放在在哪里以及怎么放。这一点对于冷凝器尤其重要,因为与冻干室不同，冷凝器的设计是不方便进入其内部的。如果需要无菌冷凝器，那么在制造过程中就要考虑到，增加冷凝器的通道。确实存在长度和直径数米的冷凝器。多数生物指示剂都放在冻干室或排水管的架子上。
Condensation on lyophilizer shelves and floor: Lyophilizer shelves are large flat surfaces with great thermal mass. This means that condensate may accumulate on lyophilizer shelves, causing problems in sterilization validation. Condensation of steam is, of course, part of the sterilization process, but excessive condensate pooling on shelves and floor should be assessed during SIP cycle design and validation.
冻干机架子和地板的凝结:冻干机架子是个大平面，接触大量热流。这意味着冷凝水可能会聚集在货架处,从而在灭菌验证中发生问题。当然,蒸汽冷凝是灭菌过程的一部分，但如果再 SIP 循环设计和验证过程中，有过量的冷凝水流到池货架和地板上，就要评估了。

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