Technical Report No. 3 (Revised 2013)

Validation of Dry Heat Processes Used for Depyrogenation and Sterilization

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PDA®
Parenteral Drug Association

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1.0 Introduction 简介

This technical report is an update of PDA's *Technical Report No. 3, Validation of Dry Heat Processes used for Sterilization and Depyrogenation* which was issued in 1981. The technical report focuses on the microbiology and engineering qualification of dry-heat sterilization and depyrogenation processes and the general approach to sterilization and depyrogenation science in batch and continuous sterilizers (ovens and tunnels). This technical report is based on standard depyrogenation and sterilization science.

这份技术报告是1981年发布的PDA第3号技术报告“用于灭菌和除热原的干热灭菌工艺验证”的更新。这份技术报告着重于干热灭菌和除热原工艺的微生物和设计确认，以及批次生产和连续性灭菌器（烘箱和隧道）中灭菌和除热原的通用方法。这份报告的依据是标准除热原和灭菌科学。

The primary objective of the Technical Report Team was to develop a scientific technical report on dry-heat depyrogenation and sterilization processes that provides recommendations for use by industry and regulators. References to appropriate and current scientific publications, international regulatory documents, journal articles, technical papers and books are used where more detail and supportive data can be found.

技术报告团队的主要目的是开发有关干热除热原和灭菌工艺的科学技术报告，能够对用于工业生产和法规提供建议。采用了适宜并是当前的科学出版物、国际法规文件、期刊论文、技术报告以及书籍这些参考资料，其中有更详细和更具支持性的数据。

The Technical Report Team is composed of diverse international team of professionals to ensure the methods, terminology and practices of dry-heat depyrogenation and sterilization processes reflect sound science and can be used globally. This technical report was disseminated in draft for public review and comment prior to publication to ensure its suitability as a recommendation of best practices to industry.

技术报告团队由不同的国际团队专家组成以保证干热除热原和灭菌工艺的方法，术语以及实践能够反映全面的科学性并能够全球通用。这份技术报告在正式发表前以公众评论的形式传播，以保证其作为工业中最佳实践建议的合理性。

1.1 Purpose and Scope 目的和范围

This technical report provides information to the manufacturers of pharmaceutical products for validating dry-heat depyrogenation and sterilization processes. The concepts and methods presented within this technical report are not intended to be a regulatory standard, but rather as points to be considered during the validation of dry-heat processes. Other technically equivalent methods may exist and may be used if they can be supported by sound scientific methods.

这份技术报告提供了关于制药生产企业进行干热除热原和灭菌工艺验证的相关信息。该技术报告中提到的概念和方法不是一项法规标准，但是可作为干热工艺验证中的指导。其他等效的技

术方法也可能存在并被应用，如果这些其他方法有合理的科学方法做支持。

This technical report is intended to give information about current industry practices and approaches to validating dry-heat depyrogenation and sterilization processes. In addition, sections will cover various aspects of dry-heat sterilization using biological indicators.

这份技术报告的目的是为目前工业实践以及干热除热原和灭菌工艺验证方法提供信息支持。此外，报告的一些章节覆盖了干热灭菌使用的生物指示剂的各方面。

This technical report is organized in a chronological fashion, starting with a discussion of the general concepts of depyrogenation and sterilization science which are the foundation upon which to build a robust process. This includes use of biological indicators and endotoxin indicators. Also included are points to consider in equipment design, equipment verification, process development and performance qualification for new systems and the development and validation of processes for existing systems.

该技术报告是以时间顺序排列，以除热原和灭菌科学的通用概念开始，而这是建立稳固工艺的基础。其中包括了生物指示剂和内毒素指示剂的使用。也包括了新系统的设备设计、设备确证、工艺开发以及性能确认，还包括现有系统中工艺设计和验证中所需考虑的问题。

In the discussion of process development, particular attention has been given to the load type, loading patterns, and temperature profiles for depyrogenation and sterilization in both ovens and tunnels. The sections are followed by a brief discussion of items for consideration during routine processing and ongoing maintenance of the validated process.

工艺开发的讨论中，对于在烘箱和隧道中进行除热原和灭菌的负载种类、负载模式以及温度曲线都给予特殊的关注。在已验证工艺的日常操作和持续维护中所需考虑的内容在这一部分也做了简要讨论。

The background sections on depyrogenation/sterilization science and endotoxin/biological indicators are not comprehensive—but provide information specific to dry-heat processes. Information within the technical report is applicable to both forced hot air dry-heat batch processes (chambers) and to continuous processes (tunnels). Information within this technical report does not apply to dry-heat processes used for the sterilization of oil bases and oil based products, fixed processing streams or to those processes using infrared and microwave heating media.

关于除热原/灭菌科学和内毒素/生物指示剂的背景部分并不全面——但是所提供的信息是针对干热工艺的。技术报告中的信息既适用于强制热空气干热批生产工艺（腔体），也适用于连续性工艺（隧道）。本技术报告中的信息不适用于油性基质及油性基质产品，固定工艺流程或者那些使用红外及微波加热介质的工艺中灭菌所用的干热工艺。

Current FDA, ICH, and other regulatory definitions are used except when more clarity is added by the Technical Report Team. Regulatory guidelines offer other definitions that maybe considered. Variations in the use of some terms may differ from company to company and

some may be subject to change in the future. However, the terms used in a validation program must be clearly defined and well understood within the company and clearly defined in internal Standard Operating Procedures (SOPs), standards, and in regulatory filings. For the purposes of this technical report, the following definitions are used.

使用的是当前FDA、ICH以及其他管理当局的名词定义，但技术报告团队添加上更清晰的内容这种情况除外。可以考虑法规指南提供的其他定义。一些术语在各公司之间的使用可能是不同的，而一些术语在未来可能会有变化。但是，验证程序中使用的术语必须清晰定义并且能够在公司内被清楚理解，在内部标准操作规程（SOP）、标准及管理文件中也应清楚定义。本技术报告出于这样的目的，使用如下定义。

2.0 Glossary of Terms 术语表

Bacterial Endotoxin 细菌内毒素

Endotoxins are fever producing substances commonly found in the cell wall of certain Gram negative bacteria.

内毒素是存在于革兰氏阴性菌细胞壁中的致热物质。

Bacterial Endotoxin Test (BET) 细菌内毒素试验（BET）

Assay for measuring active endotoxin by combining a liquid test sample with *Limulus* amebocyte lysate (LAL) reagent and measuring the resulting proportional reaction via visual, turbidimetric, chromogenic, or other validated means of detection.

一种测量活性内毒素的测定方法，将液态供试样品与鲎试剂（LAL）相混合，采用目视检查、浊度法、色谱法或者其他验证过的检测方法测定产生的成比例反应。

Batch Oven 批处理式烘箱

A convection oven with a chamber or chambers where items are dry-heat sterilized or depyrogenated as a single load in a discontinuous process.

一个带有腔体的对流恒温烘箱或者腔体本身能够进行干热灭菌或者除热原，在不连续性工艺中可作为一个独立载体。

The oven typically uses one or more filters to remove air particles.

这种烘箱一般使用一个或多个过滤器来去除空气粒子。

Biological Indicator Challenge System (BI)

生物指示剂挑战系统（BI）

A test system containing viable microorganisms of a pure and specified strain providing a defined resistance to a specified sterilization process (1).

一种检测系统，包括纯的并且是特定菌株的生长微生物，对特定灭菌工艺具有特定的耐受性（1）。

[Synonym: BI challenge system, microbial challenge system, and microbioilogical challenge system.]

【同义词：BI挑战系统，微生物挑战系统，和微生物学挑战系统。】

Biological Qualification 生物确认

A component of performance qualification that demonstrates, by use of biological indicators, that the required lethality is achieved consistently throughout the load.

性能确认的一个组成部分，用以证明，通过生物指示剂的使用，能够在负载的过程中持续达到所要求的致死率。

Commissioning 调试

A well planned, documented and managed engineering approach to the start-up and transfer of facilities, systems and equipment to the end-user that results in a safe and functional environment that meets established design and user requirement specifications.

Commissioning precedes Qualification and includes three phases:

设施、系统以及设备开始并转移到终端使用者的一种有充分计划性、有文件记录并且是基于工程管理的方法，这样可获得安全的并具备相应功能的环境，满足已确定的设计要求和用户需求标准。试运行应先于确认，包括三个阶段：

1. Inspection, testing, and regulation

检查，测试以及调整

2. Adjustment and setting of work

调试和工作设置

3. Functional testing

功能测试

Continuous Convection Tunnel 连续式对流隧道

A convection oven with a conveyor belt that transports articles through several temperature zones that are supplied with heated forced HEPA filtered air. The pre-heat/loading zone warms articles prior to the heat zone, the heat zone heats articles to sterilization or depyrogenation temperature and the cool zone cools articles prior to conveyance out of the unit.

带有传送带的对流烘箱，可传送物品通过几个温度区，这些温度区均供应热强制HEPA滤过空气。在加热区域前，预热/装载区对物品预热，加热段对物品加热达到灭菌或去热原的温度，在运输出去之前的冷却段对物品进行冷却。

[Synonym: Tunnel Sterilizer**]**

【同义词：隧道灭菌器**】**

Convection 对流

The transfer of heat by the circulation or movement of the heated liquid or gas.

通过加热液体或气体的循环或者移动传递热量。

Depyrogenation 除热原

The destruction and/or removal of bacterial endotoxins. A depyrogenation process should demonstrate at least 99.9% or a 3-log endotoxin reduction.

破坏和/或移除细菌内毒素。除热原工艺应该显示内毒素下降至少99.9%或者3个log值。

D-Value D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 dry-heat sterilization, the D-value should always be specified with a reference temperature, D_T. For example, a biological indicator (BI) challenge system with a $D_{160℃}$ = 1.9 minutes, requires 1.9 minutes at 160℃ to reduce the population by one logarithm *(2).*

在指定致死条件下，用作生物指示剂的微生物的数量下降一个对数值或90%的所需时间，以分钟表示。对于干热灭菌，D值应该以参考温度D_T来规定。例如，某一生物指示剂（BI）挑战系统，其$D_{160℃}$=1.9分钟，即要求在160℃时在1.9分钟之内能够减少一个对数值的微生物数量（2）。

Dwell Time 保压时间

The period that items are subjected to a given processing condition.

物品处于给定工艺条件的时间。

[Synonym: Residence Time**]**

【同义词：停留时间】

Endotoxin Indicator (EI) for Depyrogenation 用于除热原的内毒素指示剂（EI）

An article challenged with a vial of endotoxin (or a carrier spiked with endotoxin) designed for use in depyrogenation studies. The endotoxin (a purified lipopolysaccaride) is validated for use in or on an endotoxin indicator. The carrier is made from a material appropriate for the intended depyrogenation processes to which it will be subjected. The endotoxin on a carrier is added at a concentration sufficient to allow recovery of a minimum of 1000 USP endotoxin units/carrier. The endotoxin indicator would allow for accurate indication of at least a 3-log reduction in USP endotoxin units during depyrogenation process challenges *(3,4).*

除热原研究中使用的挑战试验物品同时带有一小瓶内毒素（或者加样有内毒素的载体）。用在内毒素指示剂中的内毒素（一种纯化的脂多糖）是经过验证的。载体是由适用于预期除热原工艺的物料制成。在载体中加入一定浓度的内毒素，该浓度对于保证最低1000 USP内毒素单位/载体的回收率是足够用的。除热原工艺挑战中，内毒素指示剂要求按照美国药典内毒素单位，至少减少3个对数值（3, 4）。

Exposure Phase 暴露阶段

The phase of the process in which the appropriate parameters are maintained within defined ranges for the time (exposure time or dwell period) and temperature determined to be necessary to achieve the desired lethality.

在定义的时间（暴露时间或者保压阶段）和温度范围内，该工艺阶段中要求保持适当的参数，对达到预期的的致死率是必要的。

F-Value (Lethality Factor) F值（致死因子）

A measurement of process effectiveness. F_z^{Tref} is the calculated equivalent lethality (using a specified z-value) for a sterilization process, in terms of minutes at a reference temperature (T_{ref}), delivered by a sterilization process to an item.

工艺效力的测量。F_z^{Tref} 是某一灭菌工艺经计算而得的等效致死率（采用指点定的Z值），在在参考温度下（T_{ref}）的分钟表示，通过灭菌工艺传递至物品。

F_H

A term used when the specific reference conditions of T_{ref}= 160°C and z=20°C are used to calculate the equivalent lethality. For example, when the z-value of the BI is 20 °C a process with an $F_{(T = 160°C, z = 20°C)}$ or F_H equal *to 8* minutes is equivalent (in terms of delivered lethality) to a square wave process of 8 minutes at 160°C. A square wave process that provided an

exposure of 45.2 minutes at 145°C would also yield an F_H of 8 minutes.

当采用指定参考条件T_{ref}= 160°C和z=20°C时，用于计算计算等效致死率采用的一个术语。例如，BI的z值是20℃，$F_{(T=160℃,\ z=20℃)}$或者F_H等于8分钟的工艺（以传递致死率表示），相当于在160℃条件下8分钟的方波工艺。在145℃条件下可提供45.2分钟暴露的方波工艺也能够得到8分钟的F_H。

F-Value for Depyrogenation 除热原的F值

The term F-value may also be used in dryheat depyrogenation processes to calculate the time in minutes equivalent to a lethality or endotoxin destruction effect delivered by dryheat at 250°C. The F-value reference temperature is set at 250°C and the z-value minimum is set at 46.4°C *(5).*

F值的概念也用于干热除热原工艺来计算在250℃条件下干热产生的致死率或是内毒素破坏效果的时间，以分钟表示。F值参考温度被设置为250摄氏度，Z值最小设置为46.4℃（5）。

Heat 热量

Energy that is transferred as a result of a temperature difference between an object and its surroundings.

作为物品和环境之间温度有差异的结果而发生传递的能量。

Heat Penetration 热穿透

Heat penetration testing is a temperature measurement that is used to evaluate the amount of energy that has been transferred to the materials within the load. For measurements of heat penetration, the probes should be placed in the load with the tips of the sensors in contact with the items being evaluated.

热穿透试验是一种温度测试，用于评估已传给装载内物料能量的量。对于热穿透测试，探头应放置在装载物内，让传感器的尖端与待评价的物品相接触。

Heat-up Phase 升温阶段

The phase of a process that occurs prior to the exposure phase. Process parameters are developed for this phase in order to meet applicable user requirements for load conditioning (e.g., pre-heating).

工艺的这个阶段出现在暴露阶段之前。该阶段工艺参数的开发是为了满足装载条件下适宜的用户需求（比如，预热）。

Lipopolysaccharide 脂多糖

A component of the cell wall of Gram negative bacteria.

革兰氏阴性菌细胞壁的一种组成成分。

Load Zone 装载区

Area within in the chamber where materials to be sterilized or depyrogenated may be placed.

腔体内的区域，在该区域内进行物品的灭菌或者除热原。

Maximum Load 最大装载量

The maximum quantity or mass of items permitted in a depyrogenation or sterilization load.
除热原或者灭菌装载方式中物品的数量或质量的最大允许量。

Minimum Load 最小装载量

The minimum quantity or mass of items permitted in a depyrogenation or sterilization load.
除热原或者灭菌装载方式中物品的数量或质量的最小允许量。

Operating Parameters 运行参数

Values (e.g., time, temperature, air-flow) that are controlled and/or measured that collectively define each phase of a process (e.g., heat-up, exposure,
cool-down).
用来定义每一个工艺阶段（如加热、灭菌、冷却）且需要加以收集的控制和测试的参数（如时间、温度、气流）。

Critical Parameters 关键参数

Values that are controlled and/or measured and are linked to safety and efficacy of a product or the process. Failure to meet a critical parameter should result in rejection of the load.
需要控制和/或测量且与产品的安全和功效相关的参数。关键参数不合格时，装载物不得放行。

Key Parameters 重要参数

Values that are controlled and/or measured and are used to assure the ongoing "state of control" and consistency of runs. Failure to meet a key process parameter should result in an investigation with a documented rationale for the disposition of the load.
需控制和/或测试以保证处于“受控状态”并且正常运行。重要工艺参数不合格时，需进行调查，并文件记录装载物处理的原因。

Overkill Design Approach 过度杀灭设计方法

A design approach where minimal information is required about the product bioburden. A worstcase bioburden assumption is used to determine the delivered lethality needed to achieve a Prob-ability of a Non-Sterile Unit (PNSU) of 10^{-6} on or in the items being sterilized. For depyrogenation, the overkill design approach is a 3-log reduction of an endotoxin indicator amount.
是一种需要最小量产品生物负荷信息的设计方法。最差生物负荷情况假设用于确定致死率需要达到在待灭菌的物品上面或里面的10^{-6}菌可能含有1个非无菌单位（PNSU）。对于除热原，过度杀灭设计方法要将热原指示剂量降低3个对数单位。

Parametric Release 参数放行

A sterility release system based upon effective control, monitoring, documentation, and batch records review of a validated sterilization process in lieu of release procedures based on endproduct sterility testing.
一种基于对已验证无菌工艺进行有效控制、监控、文件化管理和批记录审核的无菌放行系统，而非基于成品无菌检验的放行程序。

Penetration Probe 热穿透探针

A thermocouple placed in contact with the load item to measure the temperature of the load item.

放置在装载物品旁与其相接触的热电偶，测量装载物品的温度。

Performance Qualification (PQ) 性能确认（PQ）

Documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications *(6).*

证明一个已连接好的设备及辅助系统能根据批准的工艺及技术要求有效并重现性运行且有文件和记录的相关活动（6）。

Physical Qualification 物理确认

A component of performance qualification that demonstrates that pre-determined physical requirements including temperature distribution and heat penetration are achieved consistently throughout the load.

是性能确认的一个组成部分，证明包括温度分布和热穿透在内的预设的物理要求能够在整个装载过程中始终如一达到要求。

Probability of a Nonsterile Unit (PNSU) 非无菌单位可能性（PNSU）

The number that expresses the probability of occurrence of a non-sterile unit after exposure to a sterilization process. Within the pharmaceutical industry, a design end-point better than or equal to the probability of one non-sterile unit in a million units is expected, i.e., PNSU $\leq 10^{-6}$.

用于表示在暴露于灭菌工艺之后非无菌单位出现的概率的数字。在制药工业中，期望设计的终点要达到好于或者等于一百万单元中出现一个非无菌单位的概率。即PNSU $\leq 10^{-6}$。

Product-specific Design Approach 产品特异性设计方法

A sterilization design approach that is based on the characteristics of the bioburden (on or in the load) and the heat sensitivity of the product that delivers the lethality needed to achieve a PNSU ≤10~6 on or in the items to be sterilized.

是一种基于生物负荷（装载上或内）的特性以及产品的热敏感度的无菌设计方法，传送的致死率需达到灭菌后物品上或物品内的PNSU $\leq 10^{-6}$。

Process Qualification 工艺确认

Documented verification that a system is capable of consistently performing or controlling the activities of the processes it is required to perform or control, according to written and preapproved specifications, while operating in its specified operating environment.

有文件证据证实系统能够持续性执行或者控制工艺活动，根据书面的或者批准的标准执行和控制，其中操作在指定操作环境下进行。

Pyrogen 热原

Any substance capable of eliciting a febrile (or fever) response upon injection or infection (as

in endotoxin released *in vivo* by Gram-negative bacteria *(7).*

注射或者感染时任何能够诱发发热（发烧）反应的物质（比如革兰氏阴性菌内源性释放的内毒素）（7）。

Requalification 再确认

Periodic confirmation to demonstrate that equipment performance has not changed from its qualified state.

周期性确认，证明设备性能没有发生变化偏离其确认状态。

Revalidation 再验证

Repeating partial or full validation of a process after a process change is implemented. Re-validation is change-based, not time based.

工艺发生变化后重复进行的部分或全部工艺的验证。再验证是以变化为基础而不是以时间为基础。

Resistance Temperature Device (RTD) 电阻温度检测器（RTD）

Sensors that exploit the predictable change in electrical resistance of some materials with changing temperature.

利用某些材料的电阻可随温度变化出现可预测变化的传感器。

Routine Operational Process 日常操作程序

Parameters that are specified for ongoing operations.

日常操作指定的参数。

The operational process is typically controlled to produce additional lethality over the qualified minimum parameters (i.e., time and temperature) in order to provide increased sterility assurance.

操作过程通常是受控的，以产生超过已确认的最小参数（即时间和温度）的额外致死率，目的是提供更高程度的无菌保证。

Sterilization Process 灭菌工艺

A process used to render a product free of viable organisms with a specified probability.

用于使产品中不存在规定概率微生物的工艺。

Sterility Assurance Level (SAL) 无菌保证水平（SAL）

Probability of a single viable microorganism occurring on or in an item after sterilization.

灭菌后出现在物品中或物品上的单个可见微生物的概率。

Note: The term SAL takes a quantitative value, generally 10~6. 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 *(8).*

注意：SAL这个术语代表了定量值，通常是10^{-6}。当使用这个定量值来保证无菌时，10^{-6}这个SAL值是一个下限值，但是与10^{-3}这个值相比具有更高的保障程度（8）。

Sterilization Cycle 灭菌循环

A sequence of defined operating parameters (e.g., time and temperature) required to render an item sterile.

所需的一系列定义好的运行参数（比如，时间和温度）使物品达到无菌状态。

Survivor Curve 存活曲线

Graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions *(9).*

在指定条件下随着对暴露于杀菌剂时间的延长微生物数量逐渐减少的图示（9）。

Thermocouple 热电偶

A device for measuring temperature in which a pair of wires of different metals are joined and the free ends of the wires are connected to an instrument (such as a voltmeter) that measures the electrical potential difference created at the junction of the two metals.

一个用于测量温度的装置，该装置上连接有一对不同金属的电线并且电线的自由端连接在仪器上（比如电压计），测量两个金属连接产生的电位差。

Temperature Distribution 温度分布

Temperature measurement of the heating medium (e.g., forced hot air) across the chamber load zone.

腔体装载区域内热介质（比如强迫性热空气）的温度测量。

Thermometric Study 测温研究

The utilization of independent temperature monitoring devices to determine a temperature profile within the load zone and analysis of the collected data.

利用独立的温度监控装置测量负载区域温度曲线并分析收集的数据。

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 *(6).*

一个能够提供高水平科学保证生产工艺能可靠地生产出可接受的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（6）。

Verification 确证

A systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring equipment is fit for use. Approaches include qualification, commissioning and qualification, verification, system validation, or other *(10).*

一种系统方法来确证独立活动或者联合活动的生产系统是符合其预期使用目的的，已经进行适

当的安装并操作正确。这是一个涵盖性术语，包括了保证设备符合其用途要求的多种方法。方法包括确认、调试和确认、确证、系统验证或其他（10）。

Water for Bacterial Endotoxin Test (BET) 细菌内毒素检验用水（BET）

Sterile Water for Injection or other water that shows no reaction with the specific bacterial endotoxin test reagent with which it is to be used, at the limit of sensitivity of such reagent *(11).*

无菌注射用水或者其他水，在这类试剂灵敏度的限值下与指定的细菌内毒素检测试剂不发生反应（11）。

Worst Case Load 最差装载条件

The load configuration that is determined to be most difficult to sterilize or depyrogenate. This is a function of the process control strategy and load item characteristics (e.g., mass, configuration).

经测定认为是最难灭菌或者除热原的装载组成方式。这是工艺控制策略和装载物品特性的一个功能（比如，质量，结构）。

-value -值

The number of degrees of temperature change to change the D-value by a factor of 10. The z value allows integration of the lethal effects of heat as the temperature changes during the heating and cooling phases of the dry-heat process.

D值发生10个因子变化时温度的变化值。z值允许热量的致死效果进行整合，因为在干热工艺的加热阶段和冷却阶段温度会发生变化。

3.0 The Science Of Dry Heat Depyrogenation And Sterilization 干热除热原和灭菌的科学

Dry heat processes can provide sterilization or both depyrogenation and sterilization. The purpose of the process will dictate the validation approach. The following section provides information and science behind depyrogenation and sterilization methods used for dry-heat processes.

干热过程能够实现灭菌或者除菌除热原。该过程的目的将决定验证方法。以下部分提供了用于干热过程的热原去除和灭菌方法背后的信息和科学。

3.1 Depyrogenation 除热原

There are a number of depyrogenation methods used to inactivate or remove bacterial endotoxins *(12,13).* Dry-heat depyrogenation is the primary method used for the inactivation of bacterial endotoxins by thermal destruction. Dry-heat depyrogenation ovens or tunnels have been used for the depyrogenation of heat-resistant materials like glassware, metal equipment, instruments, containers, and heat stable chemicals *(7,12-15).* The development and use of the *Limulus* amebocyte lysate (LAL) assay has also provided a means of assessing the performance of dry-heat endotoxin inactivation on a quantitative basis *(11,16,17).*

用于消除或灭活细菌内毒素热原的方法有很多（12, 13）。干热除热原是用于细菌内毒素灭活的主要方法，方式为通过热破坏。干热除热原烘箱或隧道已用于耐热材料如玻璃器具、金属设备、工具、容器和热稳定的化学物质的除热原（7, 12-15）。鲎试剂测定法（LAL）的发展和使用还提供了在定量的基础上评估干热灭活内毒素的一种手段（11, 16, 17）。

The selected temperature and exposure time should be appropriately validated to demonstrate that the dry-heat depyrogenation process delivers an adequate and reproducible level of endotoxin reduction when operated routinely within the established tolerances. Since dry heat is frequently employed to render glassware or containers free from detectable endotoxins as well as inactivate viable microbes, an endotoxin challenge, where necessary, should be an integral part of the validation program, e.g., by inoculating one or more of the articles to be treated with 1000 or more USP endotoxin units (EU) of standardized lipopolysaccharide *(3).*

选定的灭菌温度和时间应做适当的验证，以证明在已建立的耐受范围内常规操作时，干热除热原工艺可以提供足够的和可重现的内毒素降低水平。由于干热经常被用户提出玻璃器具或容器不可检测内毒素以及灭活微生物，在必要时，内毒素挑战应当作为验证程序的一个组成部分，例如，通过接种一个或一个以上的物品，其中有1000个或更多的标准脂多糖USP内毒素单位（EU）（3）。

The inactivation of endotoxin achieved with dry heat is commonly used for materials that can withstand high temperatures for a period of time. The mechanism of dry-heat bacterial endotoxin inactivation in this case is by incineration.

使用干热实现内毒素灭活通常用于可经受一段时间高温的材料。在这种情况下细菌内毒素干热灭活机理是用灼烧灭菌法。

The heat lethality delivered by these processes will provide a large margin of safety with regard to sterility since dry-heat resistance organisms such as *Bacillus atrophaeus* (formerly *B. subtilis* var *niger)* spores have *D* values of only a few seconds at temperatures used for depyrogenation *(18).* One can, therefore, anticipate microbial reductions well in excess of 10^{100} , and process lethality can actually be defined on the basis of endotoxin inactivation *(18-21).* During the validation of dry-heat depyrogenation processes, dry-heat endotoxin reduction studies are always conducted rather than microbial inactivation studies. This is because the inactivation rate of endotoxin is slower than the inactivation rate of the biological indicator (BI) used (e.g., spores of *B. atropheus).* In practice, the reduction of endotoxin challenge by three or more logs will result in a process that also achieves the probability of non-sterility substantially less than 10~6 *(22,23).*

这些工艺实现的热致死效果可以提供相当大范围的安全性，是因为像萎缩芽孢杆菌（之前称作枯草芽孢杆菌黑色变种）孢子这种耐热性微生物在去除热原的温度下D值只有几秒钟（18）。因此，预计微生物减少远远超过10^{100}，并且工艺杀灭力实际上可以根据内毒素灭活来定义（18-21）。干热除热原的验证，是进行内毒素减少的研究而不是微生物失活的研究。这是因为细菌内毒素灭活率比使用生物指示剂（BI）的灭活率慢（比如，芽孢杆菌孢子）。通常，在内毒素挑战的工艺中减少三个或多个对数级也能实现非无菌小于10^{-6}的概率（22, 23）。

When the inactivation of endotoxin for a dry-heat depyrogenation process has been demonstrated to achieve greater than or equal to a 3 log reduction then it may be assumed that the depyrogenation process will inactivate bacterial endotoxins that could be presented by any given component manufacturing process *(18,19).*

当某一干热除热原工艺的内毒素灭活效果已证明可以下降大于或等于3个对数级时，然后可能会假定，该去热原工艺将可灭活任何给定组分生产工艺的细菌内毒素（18, 19）。

Reduction of endotoxin by thermal incineration is dependent solely on factors such as mass and configuration of the load that affect heat distribution in a chamber or tunnel. The chemical nature of a component impacts only the recovery of endotoxin and not reduction. Therefore, the most accurate assessment of reduction is to use an endotoxin indicator (EI) that is least prone to variables associated with endotoxin recovery techniques. For example, use a EI that is amenable to vigorous vortex mixing*(5).*

用热力焚烧法降低内毒素是仅仅靠诸如大量或负载配置，会影响腔室或隧道内的热分布。组分的化学性质只影响内毒素的回收率或者内毒素没有下降。因此，下降的最准确的评估是使用最不容易与内毒素回收技术变量相关联的内毒素指示剂（EI）。例如，用适合激烈的涡旋混合的EI（5）。

3.2 Endotoxin Indicators 内毒素指示剂

A detailed guideline for preparing and recovering endotoxin challenges has been published *(24).* Process exposure time and temperature are the only determinants for endotoxin reduction. Variables that may affect endotoxin recovery and introduce artifacts are associated with the nature of the endotoxin carrier and may include:

制备以及内毒素回收挑战方面详细的指南已经出版（24）。工艺的灭菌时间和温度对减少内毒素起决定因素。可能会影响内毒素回收率和造成假象的可变因素与内毒素的载体的性质有关，可能包括：

- Formulation of the endotoxin
  内毒素的配方
- Surface type, composition and configuration of carrier
  载体的外观类型、组成和结构
- Inoculum (spike) concentration
  接种物（加样）的浓度
- Method of inoculation and drying of endotoxin
  接种的方法和内毒素的干燥
- Stability and storage of inoculated carriers or items
  接种载体或项目的稳定性和贮存

There are two approaches to selecting a carrier for depyrogenation studies. One method is to inoculate a carrier that has the same chemical properties and configuration as the components that are subject to the study. The second approach is to use a commercial EI, which is heat resistant and can be vortex mixed to achieve recovery of endotoxin with a minimum influence from recovery artifacts.

有两种方法供除热原研究用载体的选择。第一种方法是接种与研究中采用的组分具有相同的化学性质和结构的载体。第二种方法是选择一种商用EI，耐热，可以漩涡混悬实现内毒素的回收率，并且对回收率假象的影响最小。

3.2.1 Preparation and Inoculation 准备和接种

Washing or rinsing using water for bacterial endotoxin testing (BET) or water for injection (WFI) that has been demonstrated to show no detectable endotoxin is recommended to minimize the possibility of intrinsic contamination resulting in false positives.

推荐使用已经证实显示未检测到内毒素的用于细菌内毒素检验（BET）的洗涤或冲洗用水或是注射用水（WFI），可以把因内在的污染而导致假阳性结果的可能性降到最低。

Inoculation or spiking is performed using a small volume of high-potency endotoxin of sufficient quantity to demonstrate at least a 3-log reduction of endotoxin. Els are inoculated with greater than 1,000 international units (IU) of bacterial endotoxin (lipopolysaccharide) **(Note:** One international unit (IU) is equal to one endotoxin unit (EU)) *(23).* Due to absorption or binding of endotoxin to the inoculated surface, it is prudent to inoculate with greater than

1000 IU. A small challenge inoculums volume typically less than or equal to 0.1 mL, should be applied as it lessens the drying time and aids in the fixation process.
接种或加样采用足量的小体积高效价内毒素进行，来证明内毒素至少减少3个对数级。
ELS接种超过1000国际单位（IU）的细菌内毒素（脂多糖）［注：一个国际单位（IU）等于一个内毒素单位（EU）］（23）。由于内毒素与接种的表面存在吸附或结合作用，所以要接种大于1000 IU。应采用通常小于或等于0.1毫升的较少的挑战接种量，这样可减少干燥时间并有助于固定工艺。

Note: The level of endotoxin with which to inoculate a carrier is somewhat controversial. Purified endotoxin, which is used in depyrogenation studies, binds more thoroughly to the carrier surface and is more difficult to recover than natural endotoxin *(25,26).*
注：接种到载体上的内毒素水平是有争议的。用于去除热原研究的纯化后内毒素与载体表面结合得更彻底、更完全，比正常的内毒素回收更加困难（25, 26）。

Fixation method and surface type can affect endotoxin recovery. Air drying the endotoxin challenge solution to the sample surface is recommended and is representative of how endotoxins are naturally affixed to items *(4,24).* Drying Els under an ambient laminar flow hood is commonly conducted. However, studies have demonstrated differences in endotoxin recovery depending on the type of glass and the method of fixation. Other methods of affixing Els include lyophilization or vacuum drying.
固定方法和表面类型可以影响内毒素回收率。推荐使用空气干燥置于样品表面的内毒素挑战溶液，这也能代表内毒素是自然地贴在物品表面上的（4, 24）。一般在层流罩下干燥ELS。然而，研究表明，内毒素回收率取决于玻璃固定的方法上的差异。其他粘附ELS的方法包括冷冻干燥或真空干燥。

3.2.2 Sample Processing 抽样流程

Processing of Endotoxin Indicator samples should conform to a standard procedure and be documented. Dry-heat depyrogenation studies should include appropriate negative and positive controls.
内毒素指示剂的处理应遵照标准程序并记录。干热除热原的研究应该包括适宜的阴性和阳性对照。

Sufficient inoculated items should be set aside to serve as unprocessed EI positive controls. Positive controls should be handled and stored in the same manner as the items to be depyrogenated to quantify the amount of recoverable endotoxin and calculate log reductions. If indicated, uninoculated items may be set aside to serve as a negative controls.
应留出足够量的接种用品作为未处理的EI的阳性对照。阳性对照应按照被去热原化的样品同样的方式进行处理和储存，以量化的可回收的内毒素含量和计算对数的下降值。未接种的用品可能会留出作为阴性对照。

3.2.3 Recovery 回收率

The final testing for recovery of endotoxin spike after treatment with an overkill dry-heat cycle should confirm that spiked endotoxin was reduced by at least 3 logs. Studies demonstrating endotoxin recovery have concluded that vigorous vortex mixing and/or sonicating are essential for endotoxin recovery *(4,24)* For inoculated surfaces that are not amenable to vortex mixing or sonication, a previously screened surface active solution may facilitate the physical removal of endotoxin *(7,27).* The BET method should be sufficiently sensitive to allow endotoxin recovery and quantification of at least a three log reduction of the EI. For example, if the EI spike is approximately 5000 IU/component, then a gel-clot assay should be conducted with an LAL reagent with at least 0.125 IU/mL in sensitivity, and a photometric assay should have a suitable standard curve range of 0.1 to 10 IU/mL or equivalent.
加样的内毒素在经过度杀灭的干热循环处理之后，回收率最终测试应能确认加样的内毒素至少下降3个对数级。研究表明，内毒素回收率可得出结论，涡旋混合和/或超声处理是内毒素回收必不可少的（4, 24），如接种表面不适合涡流搅拌或超声处理，应预先筛选表面活性溶液促进内毒素物质的去除（7, 27）。BET法应该足够灵敏，可保证内毒素回收率并量化为EI至少下降3个对数级。例如，如果EI加样量约为5000 IU/组分，则凝胶测定法需要灵敏度至少为0.125 IU / 毫升的鲎试剂，分光光度测定法应能具有0.1到10 IU /毫升范围的或等效的适宜标准曲线。
All BET analyses of positive controls (unprocessed Els) and recoveries from processed components should be conducted using validated methods.
应当使用经过验证的方法进行控制所有的BET分析（初始的ELS）和被加工零件的回收率。

3.2.4 Results Interpretation/Endotoxin Log Reduction Calculations 结果说明/内毒素对数减少计算

The amount of recoverable endotoxin assayed from the unprocessed positive control should be sufficient to demonstrate a 3-log reduction of endotoxin on the challenged items. When the inactivation of endotoxin resulting from a dry-heat depyrogenation process has been demonstrated to achieve greater than or equal to 3-log of reduction then it may be assumed that the depyrogenation process will sufficiently inactivate endogenous endotoxins that could be present *(22, 23).* **Equation 1** provides a calculation to determine the log reduction of an EI.
在内毒素挑战试验中从初始的阳性对照中可回收的内毒素的量应足以证明下降3个对数级。当某一干热除热原工艺得到的内毒素灭活效果已证明达到了下降大于或等于3个对数级，则可以假定该除热原工艺足以灭活可能存在的内源性内毒素（22, 23）。**公式1**提供了如何测定EI的下降对数值的计算公式。

[Equation 1]

公式1

$$ELR = \log IU_o - \log IU_f$$

where:
其中：

ELR = Endotoxin log reduction

内毒素对数下降值

IU_o = Average recovered positive-control endotoxin concentration (unprocessed)

阳性对照内毒素的平均回收浓度（初始的）

IU_f = Average recovered spike concentration after exposure

灭菌后平均回收加样浓度

Following is an example of **Equation 1** where the average measured endotoxin concentration of the positive control endotoxin indicator was 1,225 IU and the test indicators after heat treatment measured 0.5 IU resulting in an endotoxin log reduction of 3.4. The log reduction for each of the Els should be calculated and documented.

以下是**公式1**的示例，测得的阳性对照内毒素指示剂平均浓度为1225 IU，测试指示剂经热处理后测得的浓度为0.5IU，这给出了内毒素的对数下降值为3.4。应计算和文档记录每个Els的对数下降值。

$$\log 1225 - \log 0.5 = 3.1-(-0.3) = 3.4$$

It is highly unlikely that an overkill dry-heat cycle would yield detectable endotoxin in extracts from undiluted exposed Els. When endotoxin is undetectable, IU_f is the sensitivity of the BET method, such as the labeled sensitivity of a gel-clot reagent or the lowest endotoxin concentration of a photometric standard curve *(11).*

过度杀灭干热循环会使得从未稀释的暴露Els浓缩物中检测到内毒素，这种情况是极不可能的。当内毒素检测不到时，IU_f是BET方法的灵敏度，如标示了灵敏度的凝胶剂或光度标准曲线的最低内毒素浓度（11）。

3.2.5 Glassware Depyrogenation 玻璃器具除热原

Not all aspects of this technical report are applicable to glassware or other containers that are used to package products destined for terminal sterilization. Depyrogenation by washing, rinsing and the sterilization process is as effective as dry-heat depyrogenation, and has the advantage of cost effectiveness. Additionaly, the manufacturing process for glass, which can include temperatures of 815.6°C to 982.2°C, excludes the potential for bioburden and endotoxin contamination. There is no discernible risk for endotoxin contamination of glassware that is promptly packaged after production in a cleanroom environment and subjected to shrink-warp for delivery and storage. Although, a highly unlikely risk, contamination due to exposure to bioburden may take place during the handling, packing and shipping of glass containers by the manufacturer and during processing and post cleaning at point of use.

不是这个技术报告的各个方面都适用于用于包装产品运往终端灭菌的玻璃器具或其他容器。经清洗、冲洗和灭菌工艺的除热原与干热除热原一样有效，并且具有成本效益的优势。此外，玻璃制造工艺其中包括815.6°C至982.2°C的温度，这能排除潜在的微生物和内毒素污染。在洁净

环境里生产后及时包装、并塑封运输和贮存的玻璃器具没有内毒素污染的风险。然而，有一种不太可能发生的高风险，可能在制造商搬运、包装、或运输玻璃器具期间以及在处理期间和在使用点进行清洁时，由于暴露在有菌环境而导致污染。

A quality risk management program should be in place to ensure patient safety throughout the pharmaceutical manufacturing process that includes glassware. A formal risk assessment of the shipping, handling and storage of glass containers using recognized tools (e.g., FMEA, HACCP) should be conducted to determine areas of potential endotoxin contamination with recommended mitigation and post mitigation review. Assessment considerations include:

质量风险管理程序应该确保患者的用药安全，应贯穿整个医药制造过程，包括玻璃器具在内。玻璃容器的运输、搬运和储存应使用正式的风险评估工具（例如，FMEA，HACCP），并用推荐的降低方法和降低后回顾的方法控制潜在的内毒素污染。评估的因素包括：

- Quality audit of glass manufacturer
  玻璃制造商的质量审计
- Storage conditions prior to packaging
  包装之前的储存条件
- Packaging to prevent microbial and endotoxin contamination
  包装以防止微生物和内毒素污染
- Storage conditions prior to and following shipping
  运输之前和之后的贮存环境
- Handling and shipping
  搬运和运输

Steps to mitigate risk could include the inspection of shipping containers upon receipt for water damage or inadvertent in-transit damage that would affect the integrity of shipping container, environmental controls to protect the glassware once packed and/or washed, control of the rinse or wash water step prior to filling through quality of water used (water for injection (WFI) recommended), daily testing of WFI for bacterial endotoxins and microbial counts in order not to exceed limits that would elicit a pyrogenic response, and finally, the bacterial endotoxin testing of each batch of finished sterile product *(28,29).*

降低风险的步骤包括：接收时检查运输容器是否有水渍或是无意造成的可能会影响运输容器完整性的在途损伤；在玻璃容器在包装和/或清洗时给予保护的环境控制；在灌装前的冲洗或清洗水步骤采用有质量保证的水（推荐用注射用水WFI），每日检验WFI的细菌内毒素和微生物计数以监控其不会超出限度，超出限度可能会引起高热反应，最后，每批无菌终产品进行细菌内毒素检验（28, 29）。

3.2.6 F_H-value for Depyrogenation 除热原F_H值

The F-value equation described in Section 3.3.1 may also be used in dry-heat depyrogenation processes to calculate the time in minutes equivalent to a lethality or endotoxin destruction

effect delivered by dry-heat at 250°C. The F-value reference temperature is set at 250°C and the z-value minimum is set at 46.4°C *(5).*

在3.3.1中描述的F值公式可用于干热除热原过程，可计算等效于达到与250°C干热产生的致死效果或内毒素破坏作用的时间，以分钟计。F值的参考温度设定在250°C，Z值最小为46.4°C（5）。

3.3 Sterilization 灭菌

Dry heat is a relatively slow-acting sterilizing agent, generally requiring higher temperatures and longer exposure times than other modes of sterilization. Dry-heat sterilization is carried out in an oven or tunnel supplied with heated filtered air, distributed uniformly throughout the chamber by convection or thermal radiation and employing a blower system and devices for sensing, monitoring, and controlling the operating parameters *(23).* The rate of microbiological destruction associated with devices and items sterilized by dry-heat is influenced by the temperature, uniformity of the heating medium during sterilization, conductivity of the containers and/or equipment to the heating medium, accessibility of the device or item fluid pathway to the heating medium, and physiological state of the bioburden associated with the product *(30).*

干热是一种相对作用缓慢的杀菌剂，一般比其他杀菌方式需要较高的温度和较长的灭菌时间。干热灭菌通过在烘箱或隧道里提供加热的过滤空气来实现，通过对流和热辐射使其在整个腔内均匀分布，并配有风机系统和传感、监控和控制运行参数的设备（23）。微生物破坏的速率与设备有关，并且干热灭菌物料会受温度、灭菌时加热介质的均匀性、容器和/或设备对加热介质传导性、该装置或项目的加热介质流体通路的可达性以及与产品相关的微生物的生理状态的影响（30）。

3.3.1 Mechanisms of Inactivation 灭活机理

Dry heat at temperatures greater than or equal to 160°C is typically used for sterilization, although processes at significantiy lower temperatures have been developed and validated.

通常用于灭菌的干热温度是大于或等于160°C，尽管温度较低的工艺已研发和验证。

Dry heat inactivates microorganisms primarily by oxidizing organic compounds. Sub-lethal dry-heat temperatures induce mutations in *B. atrophaeus* spores, probably as a result of depurination of DNA *(30).* The water content of the microorganism, as well as temperature and time, are considered to be the primary factors affecting inactivation *(23).*

干热使微生物失活主要是通过使有机化合物氧化。亚致死干热温度可引起枯草杆菌黑色变种芽孢孢子突变，这可能是DNA脱嘌呤后的结果（30）。微生物的含水量以及温度和时间，可认为是影响失活的主要因素（23）。

The death of a homogeneous culture of microorganisms exposed to constant lethal stress (also known as the survivor curve) has been shown *empirically* follow fast-order kinetics *(31).* The rate of microbial lethality is a function of the thermal resistance of the microorganism and lethal stress and is independent of the number of microorganisms in the challenge. The

survivor curve can be described using the following semi-logarithmic, first-order model:

从经验出发，某种微生物的均匀培养物暴露于恒定致死强度时的的死亡变化情况（也叫存活曲线）遵循一级动力学（31）。微生物死亡速率是微生物的耐热参数与杀灭时间的函数，与灭菌程序中微生物的数量无关。存活曲线可以用下面的半对数一级动力模式描述：

[Equation 2]

公式2

$$\log N_F = - F_{(TZ)} / D_T + \log N_0$$

where:

其中：

N_F = Number of microorganisms after exposure of *F* equivalent minutes

暴露于F等效时间之后微生物存活数量

F = Equivalent lethality of a process calculated as minutes at a reference temperature *(T)* using a defined temperature coefficient (z)

在参照温度（T）下采用确定的温度系数（z）计算的某工艺的等效致死率

D_T = Thermal resistance value, in minutes, of die microorganism at a specific temperature (T)

耐热值，以分钟表示，在指定温度（T）时的微生物死亡情况

Note: This specific temperature must be the same as the reference temperature used for calculating F-value.

说明：该指定温度必须与F值计算时采用的温度相同。

N_0 = Number of microorganisms prior to exposure

暴露前微生物的数量

3.3.1.1 F_H-Value for Sterilization 灭菌F_H值

F_H is a measure of heat input. The F_H concept is comparable to the F_H concept for moist heat sterilization and references lethality to equivalent times at 160°C. Other reference temperatures can also be considered, but 160°C is primarily used *(30).* F_H values are shown in units of minutes or seconds, and the calculations of F_H use the same equations as the calculations of F_H **(Equation 3).**

F_H是一个热量输出的量度，F_H的概念与湿热灭菌中F_H的概念相一致，参考160度等效灭菌时间的灭菌率。其他参考温度也可以考虑，但主要使用160°C（30）。F_H值以分钟或秒为单位表示，F_H和的计算使用相同的F_H计算公式（**公式3**）。

F_H is a term used to model exposure time to dry heat. By definition, F_H is expressed by a reference temperature so that it truly represents the equivalent exposure time, in terms of lethality, at that reference temperature. Since routine operational processes are not generally square wave processes (i.e., the load does not come up to temperature instantaneously, remains at the precise set point throughout the exposure phase, and then cools down instantaneously), the z-value, or temperature coefficient, is used in the model to calculate the

equivalent lethality at different temperatures during the cycle.

F_H是用于将干热暴露时间模式化的一个术语。根据定义，F_H是以参照温度表示，这样它可以真实代表在该灭菌温度下的等同暴露时间，以致死率表示。由于常规的灭菌程序一般不会是方形波工艺（也就是说在灭菌程序中，被灭菌品不可能瞬间达到设定的灭菌温度，在整个暴露期内均保持在这个精确的设定温度上，然后瞬间完成冷却），Z值，或称为温度系数，用于在半对数模式下在灭菌周期中计算不同温度下的灭菌率。

Theoretical F_H values can be calculated using the following parameters:

F_H的理论值可以采用下列参数计算：

• z-value = *20°C*

Z值等于20°C

• T_{ref} -value =160°C

T_{ref}值等于160°C

The F_H values can be determined using the calculation below **(Equation 3)**.

F_H值可以采用下面的计算公式测定（**公式3**）。

[Equation 3]

公式3

$$F_H \approx \sum_{i=1}^{n} \left\{ t_i \times 10^{\left(\frac{T_i - T_{ref}}{z} \right)} \right\}$$

where:

其中：

F_H = equivalent lethality in minutes

等效致死率，以分钟表示

T_{ref} = reference temperature equal to 160.0°C

等同于160.0°C的参照温度

z = z-value of challenge organism equal to 20.0°C

等同于20.0°C的挑战菌的z值

T_i = measured temperature in °C during the time interval "t_i."

在时间间隔"t_i"期间内的测定温度，以°C表示

t_i = time interval of data recording "i" in minutes

数据记录"i"的时间间隔，以分钟表示

n = the number of data recordings

数据记录数

3.3.1.2 D-value and z-value D值和z值

The decimal reduction time, or D-value, is the amount of time (in minutes) required at a

reference temperature for a one-log, or 90%, reduction of a microbial population under specified lethal conditions. The z-value is the number of degrees of temperature change necessary to change the D-value by a factor of 10. Both D-value and z-value are determined experimentally. The typical z-value used for dry-heat sterilization calculations is 20°C.

10倍下降时间或是D值，是指在指定灭菌条件下，在参照温度时使微生物种群的数量下降一个对数单位，或杀灭90%所需要的时间（以分钟表示）。z值是D值变更一个对数单位时，温度需调节的对数。用于干热灭菌法计算典型的Z值是20°C。

3.3.2 Biological Indicators 生物指示剂

A BI challenge system is a standardized preparation of selected microorganisms used to assess the effectiveness of a sterilization procedure during process development and validation. A BI is characterized by the name of the species of bacterium used, the number of the strain in the original collection, the number of viable spores per carrier, and the D-value. It is important to evaluate the dry-heat resistance of the BI in the actual configuration to be tested for validation, since the resistance of microorganisms may be affected by the substrate upon which they are placed.

生物指示剂挑战系统是一种所选定微生物的标准制剂，用来评估在开发和验证期间评估灭菌程序的有效性。BI是以使用细菌的种类名称，原始采集的菌株数量，每个载体上存活的孢子数量和D值为特征。评估BI在验证中测试的实际条件下的干热耐受性这一点十分重要，因为其所处位置的衬底可能会影响微生物的耐受性。

Microbiological challenges specific to dry-heat sterilization processes should be used. Spore preparations should be clean (in the sense of being essentially free from vegetative microorganisms and microscopic debris), well characterized with respect to their thermal responsiveness, and the "parent" cultures must have been obtained from recognized culture collections [e.g., American Type Culture Collection (ATCC) or the National Collection of Industrial, Marine, and Food Bacteria (NCIMB)].

应使用特定扩于干热灭菌工艺的微生物挑战性试验。这些孢子必须达到一定的纯度（基本没有生长态菌和微小碎片），有确定的耐热特性，其母代菌株应该从公认的菌种库购买［例如，美国培养物保藏中心（ATCC）或国家集工业，海洋和食物中的细菌（NCIMB）］。

3.3.2.1 Biological Indicator Selection and Type of Carrier 生物指示剂的选择和载体的类型

Biological indicators are available in a variety of configurations including spore suspensions in solutions, on paper carriers (i.e., spore strips or discs), as well as other types of carriers. The most common microorganism used, as a BI for the qualification of dry-heat sterilization processes using the overkill design approach, is *B.atrophaeus;* however other dry-heat sterilization-resistant Bis could be acceptable. The following considerations should be made when selecting indicator organisms *(32):*

生物指示剂有多种形式可以选用，包括溶液状态的孢子悬浮液或纸质载体（即孢子条或菌片）

以及其他形式的载体。在应用过度杀灭方法的干热灭菌工艺中，最常采用的生物指示剂是萎缩芽孢杆菌；然而其他耐干热灭菌的生物指示剂也是可以接受的。在选择生物指示剂的时候，应考虑如下因素（32）：

- The resistance of the test strain to the particular sterilization method is greater than the resistance of microorganisms potentially contaminating the item or component
  所选用生物指示剂的试验菌株应比产品或物品的生物负荷高，耐热性更强
- The test strain is nonpathogenic
  试验菌株无致病性
- The test strain is easy to culture
  试验菌株易于培养

The sterilization process can be evaluated in one of two ways. The BI can be exposed to a partial process and the kill rate is calculated, or the BI could be exposed to an overkill process *(33).* A determination of the stability of the population and resistance of the BI should be performed over its shelflife. The actual population and resistance to be used should be based on the desired lethality and the design approach used (e.g., overkill or product-specific approach).

灭菌工艺可以用两种方式之一进行评价。BI可以暴露于程序的一部分，之后计算杀灭率，BI也可以暴露于整个过度杀灭程序（33）。生物指示剂种群的稳定性和耐热性测定应在有效期内进行。应根据期望达到的致死效果和采用的设计方法（例如使用过度杀灭法或产品特异性方法）来决定BI的实际数量和耐热性。

If the reliability of a vendor's certificate of analysis is established through a supplier qualification program and the BI is not modified, then the supplied values for resistance of a BI can be used in lieu of confirmatory testing of each lot. Due to potential shipping and handling concerns, confirmatory spore population testing should be conducted upon receipt of Bis. Shipping and handling procedures should be assessed to ensure no BI adulteration has occurred (e.g., X-ray). It is important to use the same enumeration methodology that the vendor used in order to minimize variables that could lead to differences in spore count. Compendia (e.g., USP, EP, JP) contain monographs defining Bis that may be used in evaluating dryheat sterilization *(2,32,34).* It is recommended that consideration is given to applicable regulatory expectations.

如果通过供应商审计程序确立了供应商检验报告书的可信度，而且生物指示剂没有发生变更，那么可以采用供应商提供的生物指示剂的耐热性数据，而不必对每批生物指示剂的耐热性进行测试。由于可能的运输和处理方面的问题，在接受孢子时，应评估和运输和处理程序，以确保没有生物指示剂劣货（例如，X 光）。很重要的一点是要采用和供应商同样的方法计数，以减少影响孢子准确计数的因素。药典（例如 USP、EP、JP）中有描述可能会用于干热灭菌评价的生物指示剂的专论（2, 32, 34）。建议考虑当地的监管的法规要求。

4.0 Equipment Design 设备设计

The validation of dry-heat depyrogenation and sterilization cycles is dependent upon a number of features including the type of equipment and load to be processed. The dry-heat equipment and its support systems should be designed and constructed to deliver effective processes in a consistent and reproducible manner. Design and construction of the equipment is typically governed by well-designed user requirement specifications. Successful qualification of the equipment includes formal verification of proper design and installation/operational testing to ensure that the design criteria and specification are met.

干热法去除热原和灭菌周期的验证需依据大量的参数，包括设备类型和将要灭菌处理的装载物品。干热设备及其支持系统应当设计和建造成能用始终一致和重现性方式传递有效的灭菌工艺。设备的设计和建造主要是由设计良好的用户需求规范来决定的。设备的成功确认包括适宜设计的正式确证和安装/操作测试，来确保是符合设计标准和质量标准的。

4.1 User Requirements Specification 用户需求标准

Oven and tunnel requirements and the type of load to be processed should be identified as they provide the basis for further specification, design and verification of the equipment. User requirements specifications should be prepared to define installation and process requirements for: temperature ranges, performance requirements (e.g., production capacity), environmental classifications, control strategy, installation location requirements and conditions, safety considerations, and utility requirements.

烘箱和隧道需求以及将要灭菌处理的装载类型应当指明，因为这些内容是进一步明确质量要求、设备的设计和确证的基础。用户需求标准应当制定安装和工艺要求：温度范围、性能要求（如：产能）、环境分类、控制策略、安装位置要求和条件、安全注意事项和实用需求。

The dry-heat process is accomplished by transferring heat to the load through several means, which includes forced convection and conduction. Forced convection is the predominant methodology used in dry-heat processes and is the focus of tunnel and oven design.

干热过程是将热通过以下几种方式传递给载体的，包括强制对流和热传导。在干热过程中强制对流是主要方式，是隧道和烘箱设计的关注点。

Convection heating is the method of transferring heat through a medium by motion of its parts. There are two types of convection heating: natural and forced convection heating. Natural convection heating is a result of the buoyancy forces generated by differences in density caused by temperature gradients in the fluid mass. Forced convection heating is facilitated by the action of a mechanical device (typically a fan), with air passed through HEPA or ULPA filters to provide a low particulate environment.

对流加热是通过部分运动作为媒介来传热的。有两种对流加热方式：自然对流加热和强制对流加热。自然对流加热是温度梯度作用在流体团导致不同密度产生的浮力作用的结果。强制对流加热是靠机械设备（例如风扇）作用，空气通过 HEPA 或 ULPA 提供一个低悬浮粒子的环境。

Heated air is typically forced through high temperature HEPA filters to provide an environment with an appropriate level of particulates suitable for the components being processed. Section 4.1.1 provides design and test parameters for HEPA filters used in dry-heat ovens and tunnels. Heated air is provided to the clean zone that heat the glassware to depyrogenation temperature for the time required for endotoxin reduction.

加热的空气主要是强制通过高温 HEPA 来提供需在适当悬浮粒子水平下灭菌处理组分的环境。4.1.1 章节提供了用于干热烘箱和隧道的 HEPA 的设计和测试参数。加热的空气提供给洁净区用以加热玻璃器达到去除热原的温度，并持续到内毒素下降所需要的时间。

Ovens and tunnels should have nonreactive interior surfaces with smooth seams and corners, high temperature/nonshedding gaskets, sealed fan bearings, and sealed control or access penetrations into the chamber. Sharp corners and expansion joints that could shed or harbor particulates should be minimized.

烘箱和隧道应当有无反应性的内表面，内表面接缝和转角应光滑，高温/不脱落垫圈，密封的风扇轴承和密封控制或穿透进入箱体内的通路。尖锐的拐角和伸缩接缝会脱落或隐藏悬浮粒子，应当减少使用。

Conduction heating is accomplished via two mechanisms. The first is that of molecular interaction whereby molecules at higher energy levels impart energy to adjacent molecules at lower energy levels.

热传导有两种作用机制。第一种是分子间的相互作用，即高能量的分子将能量传递给相邻的低能量的分子。

The second mechanism is via “free” electrons. Pure metallic solids contain the highest concentration of free electrons and non-metals contain the lowest. Thus, the ability of solids to conduct heat varies directly with the free electron concentration; pure metals are the best conductors and non-metals are the poorest conductors of heat.

第二种是经由“自由”电子。纯金属固体包含的自由电子浓度最高，非金属包含的最少。因此，导热能力直接随自由电子浓度变化而变化；纯金属是最好的导热体，非金属是最差的导热体。

4.1.1 High-efficiency Particulate Air or Ultralow Particulate Air Filters 高效空气过滤器或超高效空气过滤器

HEPA or ULPA filters used for dry-heat tunnels and ovens are specially designed to tolerate continuous temperature of up to 350℃ (composite)or 400℃(ceramic). The temperature limit is dependent on sealant type and filter construction. HEPA or ULPA filters are required to maintain the appropriate environmental classification where sterile components are exposed to the environment during cool down.

用于干热隧道和烘箱的 HEPA 或 ULPA 是特别设计的，耐受温度能达到 350℃（复合材料）或 400℃（陶瓷材质）。温度限度取决于密封类型和过滤器构造。要求 HEPA 或 ULPA 能保持适宜的环境等级，无菌组分在冷却过程中是暴露在该环境下的。

A defined frequency of HEPA filter leak testing at process temperature within the heating zone should be performed to provide ongoing assurance of processing condition. Use of organic challenge agents for filters in a heated tunnel or oven is discouraged because the organic agents will collect on filter media, volatilize at high temperatures and condense on cooler downstream surfaces (33, 36).

应按照规定的频率来进行加热区域内和工艺温度下的 HEPA 泄漏测试，以便对工艺条件提供持续性的保证。加热的隧道和烘箱内是不提倡使用有机的挑战性试剂的，因为有机试剂会富集在过滤介质中，在高温时挥发并在冷凝器的下游表面浓缩（33, 36）。

Filters subjected to extreme temperature changes can shed filter materials due to rapid expansion and contraction. Temperature control should be designed to minimize temperature fluctuations of the HEPA or ULPA filters to minimize particle shedding. Consideration should be given to inclusion of a period of time following the heat up phase to allow the environmental conditions within the tunnel or oven to stabilize. Filters should also be constructed of materials that minimize particulate shedding due to temperature changes. Items to consider for high temperature HEPA or ULPA filters include non-ferrous metal frame, high temperature glass fiber media, high temperature sealant, non-shedding filter packing, and high temperature gaskets.

过滤器在经受极限温度挑战时会由于快速膨胀和冷缩而脱落过滤材料。设计的温度控制应当能使 HEPA 和 ULPA 温度涨落程度最小化，以最大程度上减少颗粒的脱落。应当考虑在加热阶段后加一段时间以便让隧道和烘箱内的环境达到稳定。过滤器应当使用随温度变化能减少颗粒脱落的材质。可考虑用于高温 HEPA 或 ULPA 的材质包括有色金属、高温玻璃纤维介质，高温密封剂，不脱落过滤组合件和高温垫圈。

After installation follow filter manufacture's instructions for curing (burn-off) the filters at high temperature. Binders will outgas (burn-off) from the media. Filters installed in vertical frames should be installed with pleats in vertical position to prevent media sag.

安装后，根据过滤器厂家的说明书在高温下烧过滤器（烧化）。介质中的粘合剂排出气体（烧化）。安装在垂直架构中的过滤器在垂直位置应当褶皱安装用以阻止介质下跌。

4.1.2 Batch Convection Oven 批处理式对流烘箱

Batch Convection Ovens are typically controlled and monitored by a programmable temperature control system. The control system should provide appropriate temperature ramp, exposure and cool down. The air flow and pressure differential provided by the oven fan should be monitored. Door interlocks should be controlled to prevent ingress into the oven during the process and until the processed load is unloaded. In addition, the door interlock system on a double door oven should have a mechanism to prevent the opening of either door out of sequence or both doors at the same time.

典型地批处理对流烘箱是由可编程的温度控制程序来控制和监测的。这个控制系统应当提供适

当的温度梯度、暴露和冷却。烘箱风机提供的空气流动和压差的变化应当能被监测。在灭菌过程中以及一直到灭菌装载物卸载时，门联锁装置应是受控的，能够控制阻止进入烘箱。另外，对于双扇门烘箱的门联锁装置应当有阻止任何一扇门的开启或两扇门同时开启的机制。

If using a double door-unit that opens into an environmentally controlled area, maintain a pressure gradient from the unloading area to the chamber to the loading area, with the highest pressure being in the unloading area.

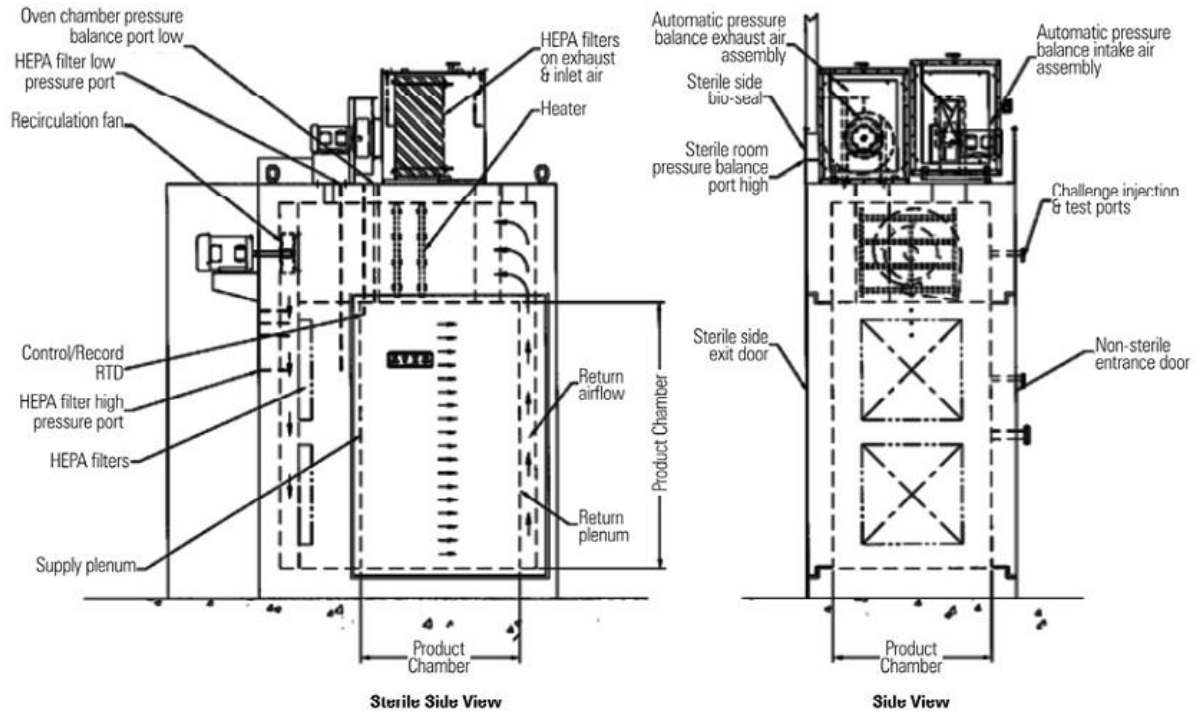
如果使用双门装置，当向环境控制区域开门时，要保持从未装载区域到装载区的压差梯度，未装载区的压力最高。

Air intake and exhaust vents should be filtered to protect load contents from external contamination. A risk assessment of the items being processed may be conducted to determine the type of filter needed. Pressure indicating devices should also indicate differential pressure across the filters to assist with determination of potential filter blockage. Figure 4.1.2-1 is an example of a bath convection oven using forced convection heat transfer showing design elements and air flow direction.

空气进气口和排气口应当有过滤器来保证装载内容物不被外部空气污染。风险评估旨在决定使用哪种类型的过滤器。通过过滤器前后的不同压差来协助确定是否有潜在的过滤器堵塞。图 4.1.2 是一个采用强制对流热交换的批对流烘箱的示例，给出了设计元素和空气对流方向。

Figure 4.1.2-1 Example of Batch Convection Oven Showing Airflow

图 4.1.2 批处理对流烘箱显示气流的示例



按照图由左到右，由上到下顺序翻译

Sterile side view 无菌侧面图

Oven chamber pressure balance port low 烘箱压力平衡低口

HEPA filter low pressure port 高效过滤器低压口

Recirculation fan 循环风机

Control/record RTD 控制/记录 电阻式温度检测器

HEPA filter high pressure port 高效过滤器高压口

HEPA filters 高效过滤器

Supply plenum 送风静压箱

Product chamber 产品室

Side view 侧面图

Automatic pressure balance exhaust air assembly 自动压力平衡排气件

Sterile side bio-seal 无菌侧封盖

Sterile room pressure balance port high 无菌室压力平衡高口

Sterile side exit door 无菌侧安全出口

Product chamber 产品室

Automatic pressure balance intake air assembly 自动压力平衡进气件

Challenge injection test ports 挑战试验进样口

Non-sterile entrance door 非无菌进口

Image courtesy of Despatch industries 示意图由迪斯派奇工业公司提供

4.1.3 Continuous Convection Tunnel 连续对流隧道

A continuous convection tunnel moves a predetermined quantity of items on a conveyor at a predetermined rate through a heated tunnel to a sterilize and/or depyrogenate. A typical continuous convection tunnel may include three zones: a load/preheat zone to prewar glassware, a hot zone where glassware is exposed to process temperature for sufficient time to effect sterilization/depyrogenation, and a cool zone to bring the glassware to room temperature prior to exiting the sterilizer. Figure 4.1.3-1 is an example of a continuous convection tunnel using forced convection heat transfer showing design elements and air flow direction. However, equipment design may vary according to the environment in which it is placed and the vendor used.

连续对流隧道是将定量物料通过匀速传送带经过加热隧道进行灭菌和/或去除热原。典型的连续对流隧道包括三个区域：装载/预热区，用来预热玻璃器具；加热区，玻璃器具在工艺温度下暴漏足够长时间达到无菌/去除热原状态；冷却区，是在玻璃器具离开灭菌器之前，将其冷却到室温。图 4.1.3-1 是一个采用强制对流热交换的连续对流隧道的示例，给出了设计元素和空气对流方向。但是，设备的设计应当根据安装的环境和供应商而有所变化。

Conveyor speed is a critical parameter that correlates to exposure time and should be documented. Conveyor speed may be variable to more readily accommodate different size containers in the same tunnel. Temperature control of the hot zone is required. Temperature

distribution can vary if the tunnel is full, empty or partially full. High-limit temperature controls are also required for continuous processes.

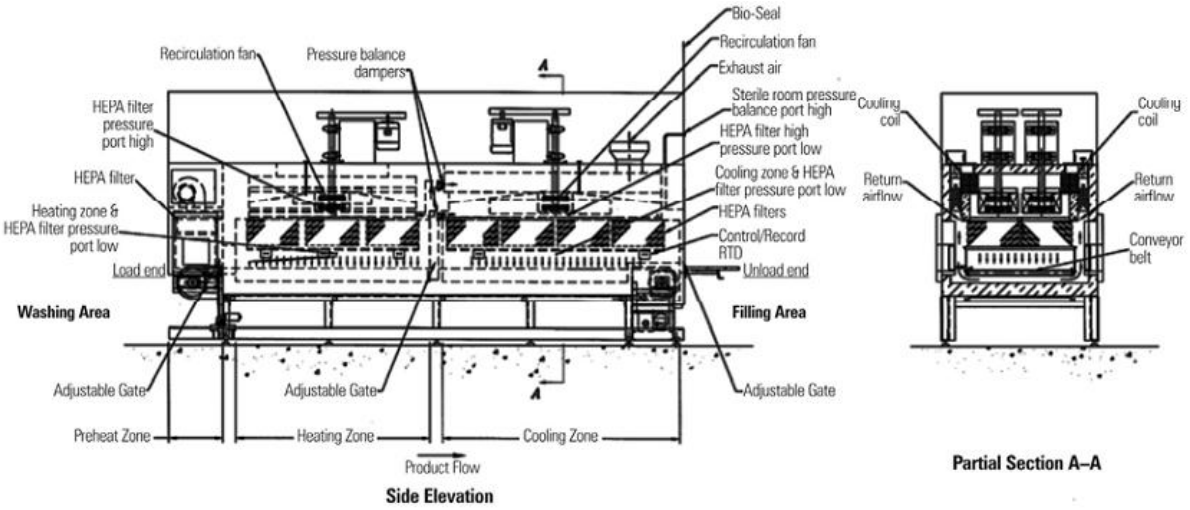
传送带速度是与暴露时间有相互联系的一个关键参数，应当作记录。在同一隧道中，为更好的适应不同尺寸的容器，传送带速度应当随之改变。加热区的温度应进行控制。温度分布能够随隧道是满载、空载或部分装载情况而有所变化。对于连续灭菌工艺还要求得有高限温度控制。

Various procedures for maintaining hot zone integrity with pressure differentials between the sterile core and the preparation area are available. As depicted in Figure 4.1.3-1, continuous sterilizer airflow should be in balance with the exhaust and should move from the cool zone to the entry zone maintaining positive pressure in order to provide a sterile barrier. Differential pressure ranges across these zones will minimize cool zone air entry into the discharge area. Positions of gates between zones should be set and documented. Cool zone temperature should be monitored to assure that items exiting the tunnel are cooled to the appropriate temperature.

应有用无菌核心区域与准确区域之间的压差来保持加热区完整度的各种不同的程序。如图 4.1.3-1 所示，连续灭菌器的气流应当通过排气保持平衡，而且为了提供无菌屏障，从冷却区到进入区的气流应当保持正压。通过这些区域的差异性压差范围将会使从冷却区进入排气区的空气量降到最低。各区之间门的位置应当设置并记录。应当监测冷却区温度，确保出隧道的物料已经冷却至适宜的温度。

Figure 4.1.3-1 Continuous Convection Tunnel

图 4.1.3-1 连续对流隧道



Side elevation 侧视图

Pressure balance dampers 压力平衡阻尼器

Recirculation fan 循环风机

HEPA filter pressure port high 高效空气过滤器高压力口

HEPA filter 高效空气过滤器

Heating zone & HEPA filter pressure port low 加热区&高效空气过滤器低压力口

Load end 载区末端

Washing area 清洗区域

Adjustable gate 调节阀

Product flow 产品工艺流程

Preheat zone 预热区 ⟶Heating zone 加热区 ⟶Cooling zone 冷却区

Bio-seal 生物密封

Exhaust air 排气

Sterile room pressure balance port high 无菌室压力平衡高口

HEPA filter high pressure port low 高效空气过滤器高压低口

Control/record RTD 控制/记录 电阻式温度检测器

Unloaded end 卸载末端

Filling area 灌装区

Partial section A-A 局部剖视

Cooling coil 冷却旋管

Return airflow 回风回流

Conveyor belt 传送带

Image Courtesy of Despatch Industries 示意图由迪斯派奇工业公司提供

Cool zones should be sanitized by a qualified sanitization process at a frequency determined by risk, e.g., after preventive maintenance or accessing the cool zone(s). Several methods are available to ensure that the cool zone is sufficiently decontaminated. These methods include cool zone self-decontamination by thermal means or exposure to disinfectants/sterilants (e.g., vaporized hydrogen peroxide) and by manual cleaning and sanitization methods. Controls to accommodate these methodologies may be incorporated in the hot air tunnel. Disinfectants/sterilants could also be drawn from the room into the cool zone.

冷却区应当用经过确认的清洁方法进行清洁，清洁频率以风险而定，例如，定期维修之后或进入冷却区。有几种方法能够确保冷却区足够清洁。这些方法包括冷却区采用加热方法的自净化或暴露于消毒剂/杀菌剂（例如，干雾过氧化氢），进行手工清洁和消毒的方法。为适应这些方法而做的控制应整合进热风隧道中。消毒剂/杀菌剂也可以在房间中之后进入冷却区使用。

Continuous tunnels typically include data recorders to monitor the process and print process reports. Physical parameters monitored include:

典型的连续式隧道包含数据记录器用以监测工艺和打印工艺报告。监测的物理性数据包括：

- Conveyor speed
  传送速度
- Temperature of the preheat zone

预热区温度

• Heat and cool down zones

加热和冷却区

• Forced air fan alarms and zone pressure

加压气流风机和区域压力

• System alarm should indicate when physical parameters deviate from process specifications.

报警系统应当包括当物理性参数偏离工艺标准时的报警

5.0 Equipment Qualification 设备确认

This section addresses various systems that comprise the process equipment. Each system is individually checked, where possible, for proper operation during factory acceptance testing, commissioning and installation qualification. Materials of construction should be verified against user requirement specifications (URS) and manufacturer's specification.

这一部分讲述了组成工艺设备的不同系统。每一个系统要单独测试，如果有可能的话，以便在工厂验收测试、试运行和安全确认过程中能正确操作。构成材质应当根据用户需求标准（URS）和生产商的标准而进行核实。

Qualification of equipment controls typically includes verification of alarms, set points, temperature control, interlocks and sequence of operations. Operational Qualification of the dry-heat equipment should include functionality testing of all process steps to ensure correct sequence of operation. Additional functionality testing should focus on the critical process parameter alarms to ensure that the equipment can reliably indicate nonconforming and unsafe operating conditions. Critical alarm testing can be done as a separate test during OQ or included in the testing of overall operation of the unit.

典型地，设备确认包括警报、设置点、温度控制、联动装置和操作程序的确证。干热设备的运行确认应当包括所有工艺步骤的功能性测试来确保正确的操作程序。另外，功能性测试应当关注工艺参数警报来确保该设备能真实地反映出异常或不安全的操作状态。关键报警测试应当作为 OQ 的一个单独测试或包括在整个单元操作测试中。

A series of tests is performed on the unit to determine if the electro/mechanical operations described in the equipment specification perform as stated. The final check involves execution of a series of processes to verify that each system component interacts correctly and repeatedly in the programmed sequence of events. Table 5.0-1 is a suggested list of items that can be checked during this phase of the verification:

对设备进行一系列测试是为了确定电子/机械操作是否如设备标准所描述的一样。最终的测试包括执行一系列工艺来确认每一个系统组件在每个编程程序事件都能够正确地进行相互作用并具有可重现性。表 5.0-1 列出了确证阶段中需要检查项目的清单：

Table 5.0-1 Example of Equipment Qualification Checklist

表 5.0-1 设备确认检查清单举例

Checklist Item 检查项	Batch (Oven) 批处理（烘箱）	Continuous (tunnel) 连续式（隧道）
Electrical Program Logic—ensure that each step is in the correct sequence and that is repeatable 电气程序逻辑——确保每一步骤的顺序正确并有可重现性。	×	×

Verification of alarms—ensure alarms operate as specified (e.g., system overloads, interlocks) 报警确证——确保按指定条件操作会发生报警（例如，系统过载，联锁装置）	×	×
Door Interlocks—must work correctly, not allowing access during the process. 门联锁装置——必须正确运行，在运行中不允许进入。		×
Gasket Integrity— Ovens: check for positive/negative pressure seal of all door gaskets Tunnels: check that the leakage rate does not exceed a predetermined value at all panel gaskets from zone to zone and to the external environment. 垫圈的完整性—— 烘箱：检查所有门垫圈的正压/负压密封 隧道：检查区与区之间、区与外界环境之间所有板垫片漏气的速度不能超过预设值。	×	
Air balance—check that the ⊿P meets defined requirements respective to the preparation section through the tunnel. 风量平衡——检查通过隧道的各自准备区域的⊿P 满足既定的要求。	×	×
Vibration Analysis—check blowers for correct dynamic balancing to minimize vibration 振动分析——检查鼓风机，是否能调整动态平衡来使振动降至最低。	×	×
Louver Balance Ability—check that louver/linkage mechanisms can be actuated and adjusted for balance. 散热孔的平衡能力——检查散热孔/联动机制可以为达到平衡状态而被驱动和进行调整。	×	×
Louver position—document position of manually adjusted louvers (as applicable) 散热孔的位置——在文件上记录手动调节散热孔的位置（如果可能）	×	
Gate balance ability—check that gate control mechanisms	×	×

can be actuated and adjusted for balance. 门的平衡能力——检查门的控制机制可以为达到平衡状态而被驱动和进行调整。		
Blower rotation—check that blowers rotate in the specified direction 风机旋转性——检查风机的转向是否符合规定		×
Blower revolutions per minute (RPM)—verify that the correct blower RPM is achieved. 风机每分钟转速（RPM）——确证可达到正确的风机 RPM。	×	×
Heater elements—check that all heater elements operate 加热器部件——检查所有加热器部件均可运行	×	×
Room balance—check that the ⊿P balance is positive from the sterile core to the preparation area when the tunnel or double door batch oven is in operation. 室内平衡——检查在隧道或双门烘箱在运行时从无菌区到配置区的⊿P 是正值。	×	×
Verify HEPA filter integrity. 确证 HEPA 滤器的完整性。	×	×
Temperature sensor---ensure temperature sensor are installed appropriately (location, orientation) 温度传感器——确保温度传感器合理安装（位置、方向）	×	×
Belt speed—verification of correct belt, speed controlled and recorder 传送带速度——确证正确传送，速度控制和记录。		×

Proper calibration tolerance and calibration frequency should be established for instruments used to monitor critical operational parameters or critical quality attributes using the appropriate standard (e.g., NIST, ISO).

应当用适宜的标准（如：NIST、ISO）建立合适的校准公差和校准频率，用以监测关键操作参数或关键质量属性。

Environmental conditions depend on control of particulates with HEPA or ULPA filters and pressurization of clean zones and chambers. Testing includes verification that particulates levels, clean zone pressurization and air flow and balance meet design specifications. Empty chamber temperature distribution is qualified to verify that air flow has been properly balances to minimize “cool” spots and meet pre-determined specifications.

环境条件依靠 HEPA 或 ULPA 滤器的控制以及洁净区域和腔内的增压作用。检测项包括悬浮粒

子水平、洁净区增压情况、气流和平衡满足设计要求的确证。空载腔的温度分布能够确证气流已得到适宜的平衡从而使“冷”点降至最少，并且满足预设的质量标准。

5.1 Environmental Qualification 环境确认

The particulate quality in ovens or tunnels should be appropriate for the exiting environment classification (15). Airflow parameters established should be appropriate to maintain temperature uniformity and air quality under dynamic conditions. Airflow velocity readings are used to determine airflow uniformity across HEPA filters during equipment qualification.

烘箱或隧道中的悬浮粒子限度应当符合现有的环境等级（15）。气流参数的建立应当适合于保持动态条件下温度的均一性和空气质量。气流速度读数用于确定在设备确认过程中通过 HEPA 滤器的气流的均一性。

Operational testing should include verification that the HEPA filtered aseptic environment is maintained (37). Particulate testing is commonly conducted with the oven operational, but not in a heating mode. Testing can also be performed at operating temperature as well as during heat-up and cool down phases if needed. Samples should be drawn from identified worst case locations. Sample ports are beneficial in accomplishing this; however, care should be taken to limit excessive length or bends in tubing from sample ports to the particle counter. When performing particle testing at operating temperature, the probe should be connected to a heat exchanger to cool the air prior to entry into the instrument. Particulate concentration at a given location should meet applicable standards (37).

运行测试应当包括经 HEPA 过滤的无菌环境保持的确证（37）。悬浮粒子测试通常是在烘箱操作中进行，但不是在加热模式下。如果需要，测试也应当在升温和冷却状态下进行。应当从经鉴别出的最差点位置取样。按这种原则选取的取样点是最有益的，但也应当关注取样点到粒子计数器的导管的长度和弯曲度的限度值。当在操作温度下进行粒子测试时，探头应当连接在一个热交换器上，用来冷却进入粒子计数器的空气。给定位置的悬浮粒子浓度应当满足相应的标准（37）。

Room differential pressure requirements for the oven or tunnel should be established in the URS. Unit air flow and temperature distribution is impacted by the room differential pressure, which reinforces the importance of having specific room air balance design criteria with double door ovens separating classified areas. Required air pressure differentials should be verified via operational testing of the sterilizer. The minimum pressure differential established is dependent on the system design. Air balance between the sterilizer and the outside environment should be verified.

烘箱和隧道内区域压差要求应在用户需求标准中说明。单个区域气流和温度分布受室内压差影响，这就加强了双门烘箱分隔不同级别区域要有专门区域气流平衡设计标准的重要性。符合要求的气流压差应当通过无菌柜的运行试验来确证。最小压差的确定依照系统设计。无菌柜与外部环境的气压平衡应当经过确证。

5.2 Uniformity of Heating Media 加热介质的均一性

The first step in performing temperature distribution studies is to establish appropriate air flow to ensure thermocouple accuracy.

温度分布研究首先是要建立适宜的气流来确保热电偶的准确性。

In batch ovens, the source discharge louvers should be adjusted and their position documented so that a controlled flow is obtained across the face of the discharge section. Airflow has a direct effect on temperature profile within the chamber. Louver adjustments may be necessary to achieve temperature uniformity throughout the empty chamber. After the air flow pattern and uniform temperature profile is established, monitor the particulate quality of the discharge air at process temperature and ensure that it falls within pre-established acceptable limits.

在批处理式烘箱中，应当调整并记录排气区散热孔的位置，这样能得到穿过排气区截面的受控气流。气流对箱体内的温度曲线有直接影响。有必要通过调节散热孔来达到空载箱体内温度的均一性。在气流模式和均一温度曲线建立后，检测在工艺温度时排放气体的悬浮粒子数并确保这些数据在预先设定的可接受限度之内。

In continuous tunnels, the supply air should be adjusted to obtain a controlled flow throughout the tunnel. Typically, supply air flow is adjusted by changing fan speed or damper position. Note: Not all continuous tunnels have adjustable dampers. Consideration should be given to monitoring the particulate quality of the supply air at process temperature and ensure that it falls within pre-established acceptable limits.

在连续式隧道中，供应的空气应当进行调整使得整个隧道中的气流都能受控。典型地，通过改变风机速度或阻尼器位置来调节气流。注意：不是所有的连续式隧道都有可调节的阻尼器。应当考虑监测在工艺温度时供应的空气中悬浮粒子数，用以确保粒子数是在预先设定的可接受限度之内。

Data obtained from the empty oven or tunnel testing will be used as a basis for all future flow pattern modifications. The number and type of tests necessary to demonstrate repeatability may be determined from an evaluation of the results obtained.

来自空载烘箱或隧道测试的数据将用作所有将来气流模式变动的依据。所需的用以证明重现性的试验次数和类型，可以通过评估获得的数据来确定。

5.3 Empty Chamber Temperature Distribution (Ovens and Tunnels) 空载箱体的温度分布（烘箱和隧道）

Determination of the temperature distribution is an important factor in the qualification of dry-heat process equipment. Temperature distribution studies in an empty chamber confirm that the air balance and heated air supply will provide even heating. Typically, multiple empty chamber distribution tests are performed to confirm reproducibility of heat-up time and cool locations as well as heating medium uniformity. These studies also confirm that the dry-heat

equipment is performing as intended. The temperature setpoint established during process development should be based on the ability of the unit to heat all areas, including any cool locations, to the minimum required temperature specification for sterilization/depyrogenation.
在干热工艺设备的确认中温度分布的测定是一个重要因素。空载条件下的温度分布研究是确认气流平衡和加热的气流能均匀加热。典型的，多次空载分布测试能证实加热时间的重现性和冷却位置以及加热介质的均一性。这些研究也确认了干热设备的性能如预期的一样。在工艺开发中温度设置点的确定应当根据加热所有区域的设备加热能力，包括任一冷却点位置，使达到无菌/除去热原状态的温度限度最小化。
Batch oven temperature distribution should be performed by placing an adequate number of thermocouples throughout the chamber load zone so that horizontal, vertical and lateral planes are represented. Thermocouples should not contact internal surfaces of the oven. A minimum of one temperature distribution thermocouple should also be placed in close proximity to the temperature control thermocouple. The average chamber or heat zone temperature should correlate with the control thermocouple temperature.
批处理式烘箱的温度分布采用在整个箱体内安装足够数量的温度探头的方式进行，包括水平方向、垂直方向和侧面，位点要具有代表性。温度探头不应与烘箱的内表面接触。最低要有一个温度分布探头安装在靠近温度控制探头的位置。箱体或加热区域的平均温度应当与控制的探头温度一一对应。
Continuous tunnel temperature distribution should be performed by placing an adequate number of thermocouples equally distributed across the belt width. The thermocouples may be either temporarily affixed to the belt or to a mounting bar that travels down the length of the tunnel so that the entrance, exit and load zone across the belt of the unit are measured. Thermocouples should not contact internal surfaces of the tunnel. Thermocouple placement height should be representative of the anticipated load in the load zone. A thermocouple should be placed in close proximity to the control thermocouple where possible or its location should be correlated to the control thermocouple.
连续隧道的温度分布应当靠在传送带上等距离安装足够的温度探头的方式来实现。温度探头既可以临时安装在传送带上也可以固定在安装条上，这样的话，沿着隧道，有传送带通过的进出口和装载区的温度可被测定。温度探头不应当与隧道内表面接触。装载区温度探头的安装高度应当具有预期装载的代表性。可能的话，温度探头应当安装在靠近控制温度探头的位置或者安装位置与控制温度探头一一对应起来。
During performance of the temperature distribution qualification runs, critical and key operating parameters should be confirmed and documented. Tunnels should operate at nominal set points for belt speed and hot zone set point temperature. Expected temperature variability throughout the tunnel may be derived from manufacturer’s specification.
在温度分布性能确认运行期间，应当确定并记录关键性的和重要的运行参数。隧道应当在正常

的传送带速度设定值和加热区温度设定值下进行操作。整个隧道内温度的预期变动情况应源自生产厂家的质量标准。

6.0 Process Development 工艺开发

The goal of process development is to identify critical and key operating parameters that will result in a load meeting the minimum acceptance criteria for depyrogenation / sterilization. The items that constitute the load should be determined before process development. The thermal dynamics of the chamber and the thermal profile of the items and loading patterns are determined during process development. The processes should be representative of actual manufacturing conditions (e.g., spraying vials with water to simulate vial washing), and the development process should be well documented.

工艺开发的目的是为了确认关键和主要的运行参数，这些参数能够保证某种装载满足去热原/灭菌的最低可接受标准。组成装载的物品必须在工艺开发前确定下来。腔体的热力学性质及物品和装载模式的热力学属性将在工艺开发过程中进行测定。灭菌工艺应能代表实际的生产条件（例如使用经过水喷淋的方式模拟清洗过的西林瓶），并且开发工艺的过程需要进行良好的记录。

6.1 Process Design Approaches 工艺设计方法

The principal process design approaches used in the development of depyrogenation and sterilization processes are the overkill design approach and the product specific approach. Both of these approaches are able to provide a process that delivers the appropriate level of sterility assurance or endotoxin reduction to the items being depyrogenated or sterilized.

用于去热原和灭菌工艺开发的首要工艺设计方法为过度杀灭方法和产品专属方法。两者都能够实现对物品去热原或灭菌以达到无菌保证或降低内毒素的合适水平。

6.1.1 Overkill Design Approach 过度杀灭设计方法

The overkill design approach may be used for both depyrogenation and sterilization processes to achieve the desired level of lethality. For depyrogenation processes, the overkill approach should demonstrate a minimum of a 3 log reduction of endotoxin at the coolest location in the worst case load.

过度杀灭设计方法可同时被用于去热原和灭菌，并达到期望的致死率水平。对于去热原工艺，过度杀灭法应证明在最困难的装载模式下的最冷点，内毒素水平能够下降至少 3 个 log。

Sterilization processes use BIs with a known population and resistance to demonstrate the lethality achieved. *Bacillus atrophaeus* is the organism typically chosen for this purpose because of its specific resistance properties to dry heat. The validated sterilization process must deliver a probability of a non-sterile unit (PNSU) that is less than or equal to 10^{-6} (See below for calculation of PSNU and an example). It is important to consider the potential for thermal degradation of the items being sterilized when this method of process development is used.

灭菌工艺使用已知菌落数和耐受性的生物指示剂（BI）证明能够达到致死率。枯草芽孢杆菌（*Bacillus atrophaeus*）是一种常规选择，因为该微生物对干热有特殊耐受性。经过验证的灭菌工艺必须能够实现非无菌单位（PNSU）小于或等于10^{-6}的可能性（见下述PSNU的计算和范例）。

当使用该工艺开发方法时，必须要考虑灭菌物品存在热降解的可能性。

Calculation of PNSU

PNSU计算

The probability of a nonsterile unit at the minimum *FR* delivered in the load can be calculated using the following equation:

最小 *FR* 条件下，装载内非无菌单位的可能性可以通过以下公式计算：

[Equation 4]

公式4

$$\log PSNU = - F_H/D + \log N_0$$

Where:

其中：

F_H = lowest F_H calculated within load

装载内计算而得的最低F_H

$D = D_{160C}$ -value of the BI

BI的D_{160C}值

N_0 = initial population of BI

BI的起始菌落数

Therefore:

因此：

If *FH* = 30 minutes

D_{160C} -value = 2 minutes

$N_0 = 10^6$

如果F_H = 30分钟

D_{160C}值 = 2分钟

$N_0 = 10^6$

Then:

则

log PSNU = -30/2 + 6

log PSNU = -15 + 6

log PSNU = -7

PSNU = 10^{-7}

Therefore, in this example, the predicted probability of a nonsterile unit at the coolest area within the load (lowest FH value) is 10^{-7} (not more than 1 nonsterile unit in 10^7 units), which is well below of the accepted standard of 10^{-6}.

因此，在上述例子中，在该装载的最冷点的预期非无菌单位的可能性为 10^{-7}（10^7 单位中不超过 1 个非无菌单位），低于可接受标准 10^{-6}。

6.1.2 Product Specific Design Approach 产品专属设计方法

The product specific design approach may be used to develop sterilization cycles for heat labile items. The process is dependent on studies to determine the number and heat resistance of microorganisms in the product. Once the heat resistance and population of the bioburden organisms is characterized, a process can be designed that will result in a PNSU of 10^{-6}. Bioburden should be periodically monitored; the frequency of monitoring should be determined through a risk assessment *(38).*

产品专属设计方法可用于不耐热物品的灭菌工艺开发。这种工艺取决于测定产品携带微生物的数量和耐受性的研究。一旦负荷微生物的耐热性和数量被界定，能达到 PNSU 不超过 10^{-6} 的灭菌工艺将能够设计出来。微生物负荷应进行定期监控；经风险评估确定监控频率（38）。

Inactivation of the microbial challenge to a predetermined level demonstrates that the desired probability of survival of the product bioburden is achieved. For additional detail on the product specific design approach to sterilization, see PDA Technical Report No. 1 *(39).*

微生物挑战菌灭活至预定水平可以证明能够达到预期的产品微生物负荷残存率。有关产品灭菌的专属设计方法的其他具体信息，请参见第一号 PDA 技术报告（39）。

6.2 Defining Operating Parameters 定义运行参数

Critical operating parameters for dry-heat depyrogenation and sterilization processes are temperature, exposure time (conveyor speed). Additional key parameters to be considered in ovens and tunnels may include time and temperature during and heat up and cool down phases and pressure differentials.

干热去热原/灭菌工艺的关键运行参数为温度、暴露时间（传送带速度）。对于烘箱和隧道，还需要额外关注的主要参数包括压差以及恒温/升温/冷却阶段的时间和温度。

Process operational parameters should be developed to ensure the achievement of a minimum PNSU of a least 10^{-6} for sterilization processes using a challenge organism and/ or a minimum 3 log reduction in endotoxin for depyrogenation processes. These parameters should be achieved within the loads or components being processed and should be used as a starting point for process or process development. Temperature studies should be performed to determine worst case conditions in the load.

工艺操作参数的开发应确保灭菌工艺使用的挑战菌满足最低的 PNSU 达到至少 10^{-6} 的水平，和/或去热原工艺实现内毒素下降至少 3 个 log 单位。在装载物及部件进行灭菌时，必须达到这些相关参数，并且上述参数应作为工艺或工艺开发的起始点。装载应进行温度研究，以确认装载的最差条件。

Once this has been established, testing of additional loads/component configurations may be reduced or eliminated where thermometric study results confirm sterilization and/or depyrogenation conditions to be greater (i.e., yields a higher *FR* value) than the "worst case" load.

一旦建立了最差条件，可能会减少或去除对额外的装载模式/部件组合的测试，如果温度研究结果确认其他灭菌和/或去热原条件比“最差条件”装载模式更好（例如产生更高的 *FR* 值）。
Development study results should be verified during initial validation and qualification runs.
工艺开发研究结果必须在起始验证或确认运行中进行确证。

6.3 Batch Oven Process Development 批处理式烘箱工艺开发

Batch oven process development consist of identification of loading patterns and worst case load, temperature distribution studies to verify heating uniformity of the load zone, and heat penetration studies to demonstrate temperature being delivered to the items in the load for the appropriate time. Development of the batch oven process is typically determined using temperature measurements and may be confirmed with BI or EI challenge testing.
批处理式烘箱工艺开发包括，确认装载模式及最差装载条件，证明装载区域热均一性的温度分布研究，证明温度可在合适时间内到达装载内各物品的热穿透研究。批烘箱工艺开发通常使用温度测量方法进行确认，也可采用 BI 或 EI 挑战试验确认。

6.3.1 Developing Loading Patterns 开发装载模式

The 'worst case' load should be determined on the basis of load mass, configuration or other parameters and verified. Process parameters should then be developed to achieve the required conditions of time and temperature for the load. For ovens, industry experience demonstrates validation of maximum load for a given load configuration is considered sufficient to validate loads of less mass (i.e., minimum loads).
“最差”装载条件应基于装载物品，构成或其他参数并进行验证。之后开发出的工艺参数应能达到装载要求的时间和温度条件。对于烘箱，工业经验证实了对于某一给定装载组合的最大装载的验证足够证明相对较小量的装载情况（例如最小装载量）。
For each load configuration, there should be adequate space within and around the load to permit sufficient circulation of air to ensure both the penetration of the load by heat and the effective removal of moisture. Consideration should be given to the type of wrapping (e.g., nylon) or containers employed to protect items against contamination (both microbial and particulate) before, during and after sterilization/depyrogenation to ensure adequate air movement and moisture removal.
对于每种装载组成，装载内部和周围必须有足够的空间实现空气流通，以保证对装载物的热穿透性和去除水分的有效性。应考虑用于保护其在灭菌/去热原前/中/后免受污染（微生物和颗粒）的物品的包裹（例如尼龙）或容器类型，同时要保证有适当的空气流通及水分去除。
Items too large to fit on a cart should be raised off the floor to allow air circulation. The positioning of trolleys within the oven must be reproducible and included in load pattern documentation (i.e., load placement orientation). Load orientation should be taken into consideration since can have an effect on item heat up. Load support structure (e.g., trays, racks, carts) materials of construction should not generate particulates and should be able to

withstand the heating process without degradation. For instance, non-anodized aluminum is a source of particulate matter and is not recommended.

物品太大而无法装上推车的应高于地面放置，确保空气流通。置于烘箱内的推车位置应能重复实现，并在装载模式中有记录规定（例如，装载位置定向）。需要考虑装载方向，因为会影响物品升温。装载支持结构（例如托盘，支架，小车）材料应不产生颗粒，并能耐受加热工艺不产生降解。例如，非电化铝是产生颗粒物质的来源，不推荐使用。

Identification of worst case location or hardest to sterilize/depyrogenate locations in the load should be performed by analysis of heat penetration studies. Heat penetration studies using F_H values may be useful to identify hardest to sterilize/depyrogenate areas.

最差条件位置或者灭菌/去热原的最困难位置的确认需要通过热穿透研究分析获得。采用 F_H 的热穿透研究可用于确认灭菌/去热原的最困难位置。

6.3.2 Loaded Batch Oven Temperature Distribution Studies 已装载批处理式烘箱的温度分布研究

The primary purpose of loaded temperature distribution (studies) is to verify temperature distribution of the heating medium across the load to be processed. These studies may be conducted concurrently with heat penetration studies. Temperature thermocouples should be placed in the load but should not be in contact with the items or oven hardware (e.g., carts, shelves, trays). Diagrams detailing specific temperature sensor locations for each load should be provided.

装载物的温度分布（研究）的主要目的是为了确认工艺过程中热介质穿过装载物的温度分布情况。这些研究可能与热穿透试验同时进行。温度热电偶应被放入装载物内，但是不能接触物品或烘箱硬件（例如推车，支架，托盘）。应有图片详细描述温度探头在每个装载中的位置。

During performance of the temperature distribution qualification runs, operating parameters should be confirmed and documented. Acceptance criteria throughout the exposure phase of the process may include a maximum:

在进行温度分布性能确认时，运行参数应被确认和记录。工艺的整个暴露阶段的可接受标准可包括最大值：

• Maximum variation in the temperature measured by each probe

每个探头测得温度的最大差值

• Maximum variation in the temperature measured from probe to probe

探头与探头之间测得温度的最大差值

• Maximum difference in temperature between the probes and the control temperature set point.

探头测得温度与设定温度之间的最大差值。

6.3.3 Loaded Batch Oven Heat Penetration Studies 已装载批处理式烘箱的热穿透研究

Before loaded-chamber heat penetration studies are performed, load characterization through

item-mapping studies could be necessary to identify appropriate monitoring location(s) within individual load items. This can be referred to as item-temperature mapping because it is done to determine the location within the item or package that is the most difficult to heat.

在进行已装载的腔体热穿透研究前，通过物品分布研究得到的装载特性可以用于确认在各个装载物品中合适的监测位置。上述研究可认为是物品-温度分布研究，因为其用于确定物品或包装内部最难加热的位置。

Heat penetration (studies) qualification demonstrates that the desired amount of energy has been transferred to the materials or surfaces of the items within the load. Heat penetration data may be used to calculate F-values for each probe location. Temperature probes should be positioned in the load to determine the slowest-to-heat location(s) within the load that would be representative of the most difficult to depyrogenate/sterilize locations. These studies are generally conducted under worst case operating conditions (minimum time and temperature set point).

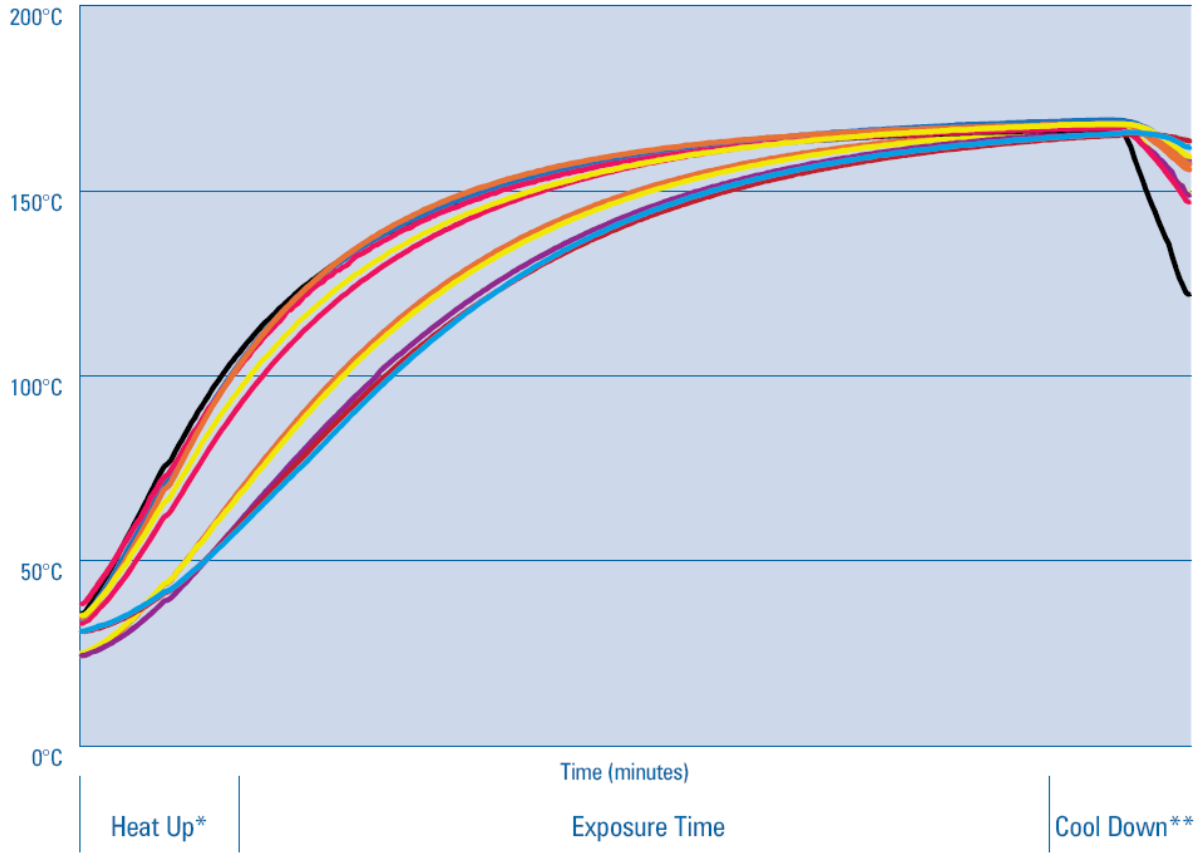
热穿透（研究）确认证明了预期量的能量已传输到装载中的物料或物品表面。热穿透数据可能被用于计算每个探头位置的 F 值。温度探头应被放置在装载物中，用于确认加热最慢的位置，这样的位置可代表最难去热原/灭菌的位置。这些研究通常在最差操作条件（最短时间和最低温度设定）下进行。

Additionally, probes are typically placed in contact with items throughout the load in a geometric pattern, as well as in any cold spots within the load zone that may have been identified through item temperature mapping studies. For loads consisting of items that may have different heat penetration characteristics, probes should be placed in representatives of each item type. Temperature sensor locations for each qualification load and the rationale for selecting locations should be documented. See Figure 6.3.3-1 for an example of a load profile in a batch oven.

另外，放置的探头通常按几何图形模式与装载内的物品接触，并且要放置在装载区域的冷点处，冷点位置已经通过物品温度分布研究得到了确认。对于由不同热穿透特性的物品组成的装载，探头放置应能代表每一种物品类型。每一种进行确认的装载方式，其温度探头位置以及选择该位置的理由应当作记录。批处理式烘箱的装载特性范例见图6.3.3-1。

Figure 6.3.3-1 Load Profile - Batch Oven

图6.3.3-1 装载特性——批处理式烘箱



升温*　　暴露时间　　冷却时间**

* Heat up equals the time the oven temperature controller reaches its set-point.

升温段相当于炉温达到设定温度的时间。

** Total cool down is not represented in this figure.

总冷却时间未在该图中显示。

The effectiveness of the process evaluated in a heat penetration study should be determined by analyzing the calculated FR values for all temperature probes throughout the load. This data should be used to determine if any cold spots exist that would provide "worst case scenario" (i.e., most difficult to depyrogenate/ sterilize) location for the execution of the subsequent performance qualification studies. If BI or EI challenge studies are conducted concurrently with the heat penetration studies, the calculated lethality and/ or endotoxin reduction should meet predefined acceptance criteria.

在热穿透研究中进行评估的工艺有效性，应当对装载中所有温度探头计算出的F_R进行分析后确定。该数据应用于确定是否有最冷点存在，以提供“最差条件”（即最难去热原/灭菌）位置，用于后续的性能确认研究。如果BI/EI挑战试验与热穿透研究同时进行，灭菌率和/或内毒素降低水平应符合预定的可接受标准。

6.4 Continuous Convection Tunnel Process Development 持续传送隧道工艺开发

Continuous convection tunnels are typically used to sterilize and depyrogenate containers

before filling with final product. In most instances the container washer, depyrogenation tunnel and filling machines constitute an integrated continuous flow operation.
持续传送隧道通常用于最终产品灌装之前容器的灭菌和去热原。在大多数情况下，容器清洗机、去热原隧道和灌装机组成了一个完整的持续流操作。
Tunnels may operate at a fixed belt speed and the number of containers varied according to the demand from the filling machine. A variable speed belt offers greater operating flexibility and is more common in newer installations.
隧道可以采用固定的传送速度运行，容器数量根据灌装机的需求而变化。可变化的传送速度提供了更大的操作灵活性，这已经在最近的设备安装中变得更普遍。
The period during which the containers remain within the hot zone, also referred to as the "sterilization/depyrogenation dwell time," is set by conveyor belt speed. Required dwell time in the tunnel hot zone can be empirically derived by thermal analysis during empty and loaded chamber studies.
容器处于高温区的时间，也即称为“灭菌/去热原驻留时间”，是由传送带速度设定的。所需的隧道高温区驻留时间可以根据空载和满载的热分析进行经验推导而得。
6.4.1 Developing Loading Patterns - Continuous Tunnels 开发装载模式——持续隧道
The worst case load should be determined on the basis of load mass, configuration or other parameters. Process parameters should then be developed to achieve the required conditions of time and temperature for the load. Load items should be placed into the tunnel so they remain upright, thus requiring placement on the belt in a "tight" load, so that items that may be disturbed will be held upright by the neighboring items. To maintain this load, either the belt speed must be consistent with the washer speed, or if the belt speed is to remain constant, the width of the load must be varied.
最差条件装载方式应基于装载物、组合或其他参数确定。随后开发工艺参数，使之达到装载要求的时间和温度条件。装载物品应竖直放置在隧道上，这样传送带上的放置方式将是一种“紧密”装载，分布的物品需要相邻物品支持以保持竖直状态，为了维持该装载方式，传送带必须与清洗机速度一致，或者传送速度恒定，但是装载宽度将会发生变化。
In tunnels, exposure time is controlled by belt speed and set-point temperature. The temperature of the glass is affected by exposure temperature, airflow, and the mass of glassware *(40).* Exposure temperature is maintained by a feedback control loop which controls temperature at a relatively constant steady state, but may vary as the load conditions change. For example, at start-up when glass first enters the tunnel, the introduction of cold containers may cause the tunnel temperature to drop. The severity of the drop is dependent on the response characteristics of the control system. Airflow should be regulated and relatively constant so not to impact temperature.
在隧道中，暴露时间由传送带速度和设定点温度控制。玻璃的温度受暴露温度、空气流速和玻

璃器具质量的影响（40）。暴露温度通过反馈控制环维持，该控制环可控制温度在一个相对稳定的状态，但是可能会随着装载条件的变化而变化。例如，起始阶段，玻璃器具先进入隧道，进入的冷容器将导致隧道温度下降。下降的严重程度取决于控制系统的响应特性。空气流速应受控制并且相对恒定，这样就不影响温度。

The relationship between the washing speed, drying/heating/cooling zone belt speed, and the filling speed should be established. The conveyor belt should be loaded in a uniform manner to provide reproducible thermal conditions within the heating zones. Irregular gaps in the components will produce non-standard but typically more effective thermal conditions. These situations may occur in production operation and are of no consequence; however they should be avoided during qualification studies. The process must provide components from the cooling zone into the aseptic area at a suitable temperature for filling.

应当建立清洗速度、干燥/加热/冷却区传送带速度和灌装速度之间的关系。传送带应以统一的方式进行装载，以便使加热区域的热力学条件具有可重现性。各组件间的非常规间隙将产生非标准但是典型的更有效的热力学条件。这些情况可能在生产操作过程中发生，并且不会产生不良后果；然而，这些情况应在确认研究中避免出现。该工艺必须能够实现组件从冷却区进入无菌区，并以合适的温度进行灌装。

Loads should be introduced into the heating zone in a manner representative of actual manufacturing conditions. Thermometric conditions should be determined when the load enters and exits the hot zone.

装载物进入加热区的方式应能代表实际生产条件。温度条件应在装载进入和离开加热区时进行确认。

The largest load mass/unit area may be validated as representative of the range of items to be qualified. Selection of the worst-case challenge(s) is conducted using scientific rationale and/ or determined through heat penetration or challenge studies *(39).*

最大装载质量/单位面积可作为代表被确认物品的范围进行验证。选择最差挑战条件需要根据科学的理由和/或由热穿透或挑战研究确定（39）。

For dry-heat tunnels, the worst case load for each temperature setting must be determined by calculating the throughput of items (expressed in mass/time), considering belt speed/item passage time and the number and weight of items being processed in a unit of time (tunnel capacity). The belt speed should be set to ensure that the dwell time within the hot zone provides the required biological inactivation or endotoxin reduction.

对于干热隧道，每种设定温度下的最差装载方式必须通过计算物品产量（以质量/时间表达）确定，还要考虑传送带速度/物品通过时间以及单位时间内隧道处理的物品数量和重量（隧道产能）。传送带速度设定必须确保在加热区的驻留时间能够实现微生物灭活或内毒素降低的要求。

In summary, selection of a "worst case" load simplifies the validation approach to tunnel depyrogenation by running studies under conditions which produce a "worst case" challenge

seen in production for the following three categories: belt speed, mass per unit area and rate of mass loading. The steps can be summarized as follows:

总之，选择装载的最差条件简化了隧道去热原的验证方法，该简化方式通过对以下三类生产中可能发生的最差条件挑战进行研究来实现：传送带速度、单位面积的质量和质量装载速度。步骤概述如下：

• Select the container that produces the maximum mass per unit area

选择产生最大单位面积质量的容器

• Set the belt speed to the maximum for any container

选择任何容器的最大传送带速度

• Load the tunnel at the maximum rate

以最大速率装载隧道

6.4.2 Loaded Tunnel Temperature Distribution 已装载隧道的温度分布

Loaded tunnel temperature distribution studies assess the impact of the load on the ability of the hot zone to maintain temperature uniformity and may be conducted concurrently with the heat penetration development studies.

已装载隧道的温度分布研究评估了装载方式对加热区维持温度均一性的影响，可与热穿透研究试验同时进行。

For measurements of loaded temperature distribution, the temperature sensors may be attached to the load near the probed containers, so that the sensing portion is sufficiently above the container to allow free flow of air around the sensor. The sensing element should not touch the containers. These temperature sensors can be used to measure the temperature uniformity across the width and length of the load during traverse of the pack through the hot zone. Any cool areas found across the belt width during the empty chamber studies should be taken into account during placement of the temperature sensors on the load.

对于装载物的温度分布检测，温度探头可粘附在靠近被探测容器的装载物上，以便于探测部分处于容器上方，使探头能够充分与自由流动的空气接触。探头电阻不能与容器接触。在包裹穿过加热区时，这些温度探头可在装载物宽度和长度的范围内用于测量温度均一性。任何空载时发现的传送带宽度上的冷点，在装载模式下放置温度探头时都应考虑到。

Temperature sensor locations should be documented. During performance of the temperature distribution qualification runs, operating parameters should be confirmed and documented. The tunnel should be operated at nominal set points for belt speed and hot zone set point temperature. Steady state or equilibration time should be defined. Operating parameters to be confirmed may include:

温度探头的位置应作文件记录。在进行温度分布确认时，运行参数应进行确认和记录。隧道应在标示的传送带速度和加热区设定温度下操作。稳定状态或平衡时间应作定义。需确认的操作

参数可能包含：

• Minimum and maximum temperature measured at each probe position

每个探头位置测得的最低和最高温度

• Variation in the temperature between probes

不同探头间的温度差值

• Difference between the probes and set point temperature

探头测得温度与设定温度间的差值

6.4.3 Loaded Tunnel Heat Penetration Studies 已装载隧道的热穿透研究

Heat penetration studies verify that the worst case load under worst case operating conditions (increased belt speed and lower set point temperature) reaches and maintains depyrogenation temperatures. Endotoxin challenge studies can be conducted concurrently with the loaded heat penetration studies. During these studies, the EI glassware and the glassware used for temperature sensors should be separate items, i.e., do not use treated with endotoxin glassware for the temperature sensors, Studies should be performed in triplicate.

热穿透研究可证实在最差操作条件（更高的传送带速度和更低的设定温度）下的最差装载方式能够达到并维持去热原的温度。内毒素挑战试验可以与装载热穿透试验同时进行。在进行这些试验时，带EI的玻璃容器与装有温度探头的玻璃容器必须不同，即不能在涂有内毒素的玻璃容器中放置温度探头，试验应重复进行三次。

When preparing glass loads, residual water left by the normal washing process should be replicated, if present, by the addition of representative amounts of water in the items containing sensors. Line set up should ensure that the load is received into the hot zone as dry as possible.

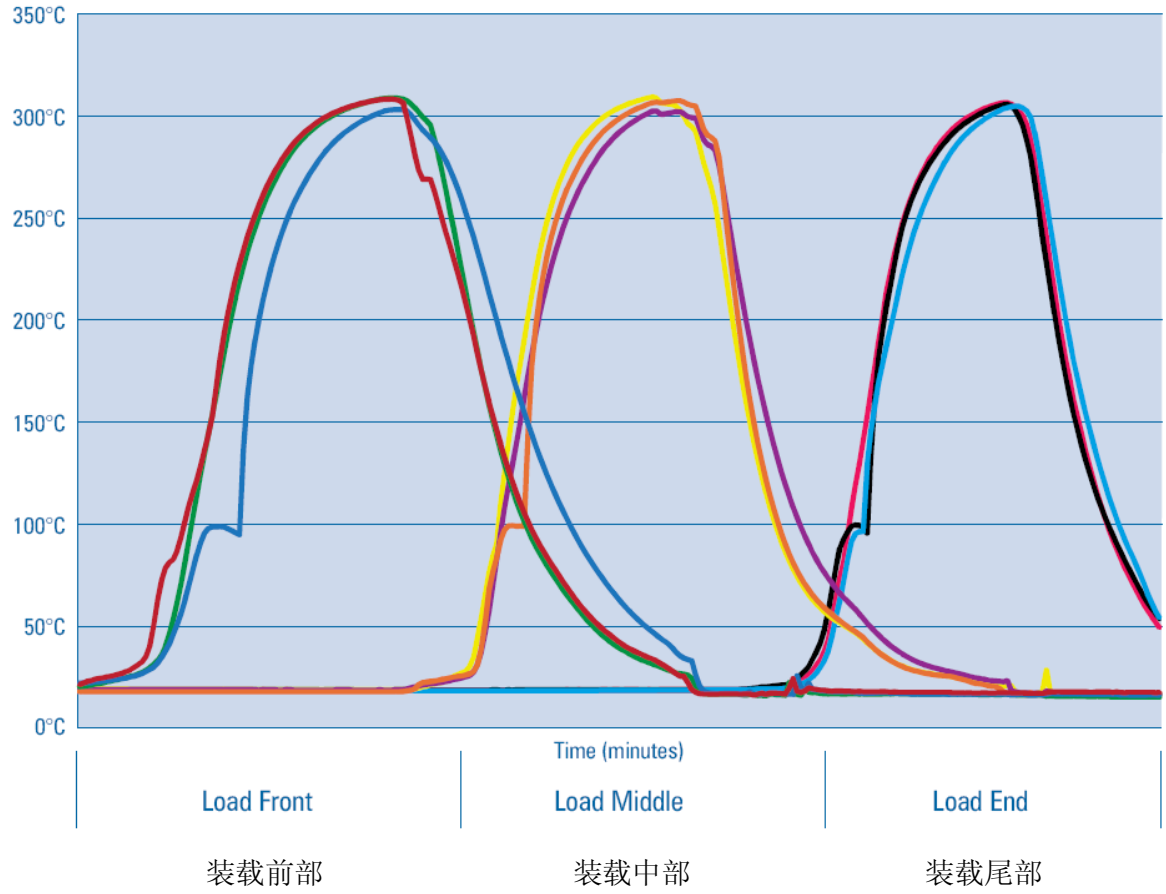
在准备玻璃器具装载时，如果正常清洗过程中会有残留水，则试验时需要在带探头的物品中加入相应量的水。建立的生产线应能保证装载进入高温区时尽可能的干燥。

A sufficient number of probes should be used to provide an adequate profile of the temperature penetration in the load. Probes should be placed in contact with the interior of individual items. Load probe placement should take into account any cool areas found in the temperature distribution studies. Diagrams detailing specific temperature sensor locations should be provided. See Figure 6.4.3-1 for an example of a load profile in a continuous tunnel. During performance of the loaded heat penetration studies, operating parameters should be documented.

应有足够数量的探头用于热穿透试验以描述该装载方式的温度特性。探头应接触容器内表面放置。装载中探头放置的位置应考虑温度分布试验中发现的所有冷点。应使用示意图具体描述各个温度探头放置位置。连续隧道装载特性的范例见图6.4.3-1。在进行装载热穿透试验时，应记录运行参数。

Figure 6.4.3-1 Glass Vial Load Heat Penetration Profile - Continuous Convection Oven

图 6.4.3-1 玻璃西林瓶热穿透特性——连续传送烘箱



* The vial glass was probed with thermocouples inside glass vials so that the tip was positioned at the junction of the side wall and bottom. Probed vials were positioned equal distance across the load at the front, middle, and end of the load. Viewing the figure from left to right, the three temperature profiles represent the heating curves of the front, middle and end of the load as it enters and leaves the heating space.

* 对于玻璃西林瓶，热电偶放置于瓶内部，使探头顶部处于瓶壁与瓶底的连接点上。装有探针的西林瓶等距放置在装载的前、中、后部。从左至右观察上图，三部分温度特性代表装载随着进入和离开加热区形成的装载前、中、后部的加热曲线。

The following are examples of typical qualification acceptance criteria:

以下是典型的确认可接受标准的范例：

• F_H-values: Calculation of an F-value at each probe location may be a useful tool to help in assessing process comparability, evaluating process repeatability, or location of cool areas. Note: There is no minimum F_H-value acceptance criterion for depyrogenation. Endotoxin inactivation efficacies cannot be accurately correlated with standard dry-heat lethality conventions (F_H) which rely upon a linear destruction model *(30,41,42).*

F_H值：计算每个探头位置的F值将有助于评估工艺的可比性，评价工艺重现性，或是冷点位置。

注意：对于去热原工艺而言无最小F_H值可接受标准。内毒素灭活的有效性不能与标准干热灭菌率（F_H）建立精确的关联关系，F_H是基于线性杀灭模型的（30, 41, 42）。

• Minimum and maximum temperatures achieved.

能够达到的最低和最高温度。

• Variation in the temperature between probes.

不同探头之间的温度差异。

• Minimum dwell time achieved above a defined temperature.

高于指定温度的最小驻留时间。

7.0 Performance Qualification 性能确认

Performance qualification is the process of obtaining and documenting evidence that the equipment, as installed, consistently operates in accordance with predetermined criteria. Physical qualification and endotoxin qualification studies are performed to ensure the depyrogenation/sterilization process as developed is reproducible.

性能确认是对已安装的并持续按预设的标准运行的设备进行的获取和书面保存证据的过程。进行物理和内毒素确认研究以确认开发的除热原/灭菌过程是可重现的。

7.1 Physical Qualification 物理确认

Physical qualification verifies temperature profiles within the oven or tunnel and to ensure that treated items within reach the required sterilization/depyrogenation temperature for the specified time period.

物理确认是证实干热灭菌柜或隧道烘箱内的温度分布性质，以确保内部待处理的物品在规定的时间内能达到要求的灭菌/除热原的温度。

The reproducibility of temperature profiles developed in process development is confirmed by performing temperature distribution and heat penetration qualification with worst case loads. Calibrated temperature probes should be placed in the coolest locations established during process development temperature distribution and heat penetration studies. Confirm during heat penetration qualification that items exiting the tunnel to the filling suite are cooled to a product-safe temperature.

工艺开发中开出的温度曲线的重现性应通过最差装载条件下的热分布和热穿透进行确认。校准过的探头应置于在工艺开发温度分布和热穿透研究中确定的最冷点处。在热穿透确认中，需要确定被灭菌物品自隧道口离开后达到灌装工位时，能够冷却到对产品安全的温度。

7.2 Biological Qualification 生物确认

Biological qualification is a component of performance qualification that demonstrates by use of endotoxin or Bis, that the required endotoxin inactivation or lethality is achieved consistently through-out the load. Indicators should be placed in numerous locations in the load, including the most difficult to depyrogenate or sterilize locations.

生物确认是性能确认的一部分，通过使用内毒素或生物指示剂来确认对装载物品的灭活或杀灭力能持续达到要求。指示剂应放在装载物内的数个地方，包括除热原/灭菌效果最差的位点。

For dry-heat depyrogenation, validation data should demonstrate that the process consistently reduces endotoxin by 3 logs. The validation is performed by inoculating articles to be treated with a minimum of 1,000 International Units (IU) of endotoxin per article. The inoculated articles are then tested for endotoxin using the *Limulus* Amebocyte Lysate (LAL) test or equivalent BET to demonstrate that the endotoxin has been reduced by at least 3 logs from the original concentration after treatment in the dry-heat depyrogenation process *(11,16,17).* Where depyrogenation has been satisfactorily demonstrated, sterilization is

assured due to the lower resistance of microorganisms to dry-heat as compared to bacterial endotoxin.

对于干热除热原，验证数据应能证明该工艺能持续保证内毒素下降3个log值。验证是采用接种后物品进行，每件物品用至少1000国际单位的内毒素进行处理。接种后的物品之后以鲎试剂或等效的BET进行检测，以证明经干热除热原工艺处理后，内毒素相对最初浓度下降了3个对数值（11, 16, 17）。如除热原效果可证明是有效的，因菌体对于干热的抵抗力不如细菌内毒素，灭菌效果则完全可认为是有保证的。

For dry-heat sterilization, the validation data should demonstrate that the process consistently delivers a microbial survivor probability for the challenge organism of not less than 10^{-6}. The number of Bis and number of processes required for performance qualification (PQ) should be specified and sufficient to cover the expected range of conditions in the load during routine processing, including any cold spots identified *(30).* The placement of Bis in a PQ load is determined based on data generated during process development. Each heat penetration probe should be placed in the load adjacent to a BI location.

对于干热灭菌，验证数据应证明该工艺始终保证对挑战菌株有不低于10^{-6}的微生物残存概率。性能确认（PQ）中生物指示剂的数量和程序的执行次数应明确，数量应足够可覆盖日常灭菌的各种装载预期状况，并且要包括任何经鉴定的冷点（30）。PQ装载中生物指示剂的放置位置应基于工艺开发的所得数据来确定。每个热穿透探头应放置在紧邻BI的位置。

7.2.1 Biological Indicator Testing 生物指示剂测试

The manufacturer should provide directions for use, including the medium and conditions to be used for the recovery of microorganisms after exposure to the sterilization process *(2).* Good aseptic technique should be used when testing Bis to prevent inadvertent contamination due to handling. If a positive BI occurs, an investigation should be performed to determine if the result was due to failed BI or post exposure contamination.

生厂商应提供使用说明，包括用于微生物暴露于灭菌工艺后回收率测定的培养基和条件（2）。在测试Bis时，需采取良好的无菌保障技术，以防止由于操作造成的意外污染。若BI出现阳性结果，要通过调查来确认是BI的问题还是暴露后发生了污染。

If a suspension is used for direct or carrier inoculation, the following are some points to consider:

若混悬液用于直接或间接接种测试，应注意以下几点：

• Determine the spore population, confirm purity, and identity of the BI.

测定孢子数量、纯度及BI鉴定。

• Stock suspension should be predominantly spores in a non-nutritive liquid.

储备混悬液应是置于无营养液中的强力孢子。

• Determine the D-value. This is done on the item being sterilized if the BI is inoculated onto the item.

测定D值。如果BI是接种在物品上，则在物品灭菌后进行测定。

• Preparation of the BI needs to be carefully controlled for purity protecting the D-value, protecting the count, etc.

BI制备时需小心的控制纯度以保护D值、保护数量等。

• Determine worst case inoculation site on the item to be inoculated based on slowest to heat location

测定物品上的最差接种点，一般为升温最慢的地方。

7.2.2 Endotoxin Indicator Testing 内毒素指示剂测试

The inoculation of endotoxin onto clean bottles/vials and other materials to be depyrogenated and the subsequent recovery of endotoxin spike from treated components is the widely accepted method of demonstrating overkill (3-log reduction of endotoxin by a given depyrogenation process). The stages of such testing via dry-heat depyrogenation process are:

内毒素接种在干净瓶中或其它除热原的容器中，之后测定加样于灭菌处理组分中的内毒素的回收率是已广泛得到接受的证明过度杀灭（给定的除热原工艺使内毒素下降3个log值）的一种方法。采用干热除热原工艺的一些测试阶段如下：

• Preparation and inoculation/endotoxin spike application and controls

准备和接种内毒素加样制品和对照

• Dry-heat treatment process

干热处理工艺

• Recovery

回收率

• Endotoxin log reduction calculation

内毒素下降log值的计算

Actual items, or a representative coupon of the surface type to be depyrogenated, are often used in these studies, since heat resistance and effectiveness of the depyrogenation process may be influenced by the type of carrier used. Adsorption of the endotoxin spike to the carrier surface is the biggest obstacle affecting recovery. Studies using flint glass, borosilicate glass, polystyrene and polypropylene have demonstrated variability in the adsorption of endotoxin based on the container surface *(43).* Commercially available Els or endotoxin challenge vials may be used in place of actual production items or representative coupons, provided that it is demonstrated that they present an equivalent or worst-case challenge to the depyrogenation process.

将要除热原的实物或是具代表性的表面类型的样片常用于此类研究，这是因为耐热性和除热原工艺的有效性会受所用载体类型的影响。加样于载体表面的内毒素的吸收是最大一个影响回收率的因素。使用含铅玻璃、硼硅玻璃、聚苯乙烯-聚丙烯进行的研究结果表明，内毒素的吸收值

会因其容器表面的不同而发生变化（43）。商业化的EI或内毒素挑战瓶可以取代实际产品或是具代表性的样片，可提供证据证明这是除热原工艺中的等同或是最差情况的挑战。

Preliminary studies with the selected endotoxin indicator, the inoculation, drying and recovery methodology should be conducted prior to performing depyrogenation validation studies.

采用所选内毒素指示剂的初步研究，接种、干燥和回收率方法学应在执行干热除热原研究之前进行。

7.3 Process Equivalency 工艺等效性

It may be possible to establish the equivalence of two or more dry-heat batch processes (chambers) or continuous processes (tunnels) that are of similar design (including utilities being supplied). A robust risk analysis process is recommended to make this determination. Analysis includes, but is not limited to, a design and engineering evaluation. Some factors to consider include:

也许有可能建立2种或以上具有相似设计（包括供应系统）的干热批处理式工艺（烘箱）或连续式工艺（隧道）的等效性。在决定之前必须进行充分的风险分析。分析包括但不仅限于，设计和工程评估。以下因素供参考：

- Chamber or tunnel size and configuration
  烘箱或隧道的尺寸和结构
- Airflow dynamics
  空气动力学
- Temperature come-up and uniformity
  升温和均一性
- Conveyor speed
  传送带速度
- Temperature equilibration time
  温度平衡时间
- Materials of construction
  材料构成

Regulatory approval may be required to support a reduction in qualification testing. Initially, all processes must be qualified and meet operating parameter acceptance criteria in order to demonstrate equivalency.

减少确认测试项可能需要经法规许可。首先，所有工艺都需确认，并符合运行参数的可接受标准，以证明其等效性。

Operational equivalence can be established by an analysis of all the process data associated with a validated process in the new equipment. Chamber and load profiles should be compared using the same critical process parameters. The specifications, acceptance criteria, and load configuration should be the same as those used in the established sterilization

validation process of the existing equipment. Comparable criteria to be demonstrated should include parameters such as:

可以通过对新设备上的已验证工艺获得的所有工艺数据进行分析建立运行等效性。腔室和装载物性质应采用相同的关键工艺参数进行对比。质量标准、可接受标准和装载方式应和之前用于建立当前设备经验证的无菌工艺使用的相一致。需证明的对比标准包括如下参数：

• Load configurations

装载方式

• Temperature distribution

温度分布

• Heat penetration, *F* value range

热穿透，F值范围

• BI or EI inactivation

BI或EI灭活

• Heat-up and cool-down times of the product/item

产品/物品的升温和冷却时间

A more detailed discussion on process equivalency can be found in ANSI/AAMI/ISO20857, *Sterilization of health care products—Dry heat—Requirements for the development, validation and routing control of a sterilization process for medical devices (30).*

更多有关工艺等效性的详细论述，参见*ANSI/AAMI/ISO20857有关健康产品灭菌——干热——医疗器械产品灭菌过程开发、验证、日常监控的要求（30）*。

8.0 Ongoing Process Control 持续工艺控制

Ongoing control and monitoring of the process is conducted on a continuous basis after completion of performance qualification and release of the equipment for use. Important elements of the ongoing control program include review of critical operating parameters for routine release, evaluation of changes, periodic revalidation of equipment, an effective preventative maintenance program to include filter integrity testing, instrument calibration, inspection of component wear (i.e., belts), and periodic revalidation of the process as necessary to confirm effectiveness.

在完成了性能确认和设备放行可使用之后，工艺的日常控制和监测应持续进行。日常控制的重要要素包括：用于日常放行的关键运行参数的回顾、变更评估、设备周期性再验证、包括滤芯完整性测试、仪器校准、部件磨损程度检查（即皮带）在内的有效预防性维护程序以及工艺的定期再验证，这些对于有效性确认都是必要的。

8.1 Routine Release 日常放行

Procedures for ongoing monitoring of routine operational processes should be developed, performed and documented to ensure product sterility and ongoing state of control. Critical and key parameters should be documented, reviewed, and maintained for each process. All critical parameters must be met for load release. Key parameters not met should be investigated and load disposition determined following investigation results. The following operating parameters should be monitored.

日常操作程序的持续监控程序应当开发、执行并有文件记录，以确保产品无菌度和持续状态的控制。每种工艺的关键和重要参数应有文件记录、进行审核和保存。所有关键参数都必须符合装载放行的要求。重要参数不是必须要进行调查，装载物的处理方式决定了随后的调查结果。以下关键运行参数应监测：

Oven

烘箱

• Time at temperature (such as minimum heat-up time, minimum exposure or dwell time, and minimum cool-down time)

处于该温度的时间（如：最少加热时间、最少暴露或保留时间、最少冷却时间）

• Temperature set-point

温度设置点

• Differential pressure as applicable (e.g., between double door batch oven and a room)

不同压差，如适用的话（如：双开门灭菌柜和房间之间）

Tunnel

隧道

• Temperature

温度

• Conveyor belt speed

传送带速度

• Differential exposure pressure (between tunnel and clean room/cold zone/tunnel room)

暴露压差（隧道与洁净室/冷点/隧道室之间）

Additionally, compendial sterility or BI testing may be required to support product release

另外，可能需要药典方法的无菌检验或BI测试来支持产品放行。

8.2 Preventive Maintenance 预防性维护

A good preventive maintenance program should be established and documented to assure that ovens and tunnels remain mechanically sound and capable of continuously meeting process requirements. Vendor recommendations should be taken into consideration when writing a preventive maintenance program. The example checklist below has been developed to provide points to consider when establishing a preventive maintenance program.

应建立良好的预防性维护程序应建立并有文件记录，以确保烘箱和隧道能正常运转并有能力持续符合工艺要求。起草预防性维护性程序时应考虑供应商的建议。以下是建立预防性维护程序时应考虑的示例检查项清单：

Check the oven/ tunnel blowers for excessive vibration

检查烘箱/隧道的送风机是否震动过大

Visually inspect and test all critical filters

目视检查并测试所有关键滤芯

Lubricate motors

润滑发动机

Visually inspect the conveyer and belts for unusual wear (tunnel)

目视检查传送带和皮带有无异常磨损（隧道）

Inspect the motors of the conveyor, recirculation fan, fresh air fan, and exhaust air for unusual wear

检查传送发动机、再循环风扇、新风风扇和排气有无异常

Inspect the cooling water system control valves

检查冷却水系统控制阀门

Inspect pneumatic lines for leaks, cracking or moisture

检查启动管线有无泄漏、裂纹或受潮

Define replacement frequency of HEPA or ULPA filters

确定HEPA或ULPA的更换周期

Inspect door seals

检查门的密封性

Inspect tubing of the differential pressure transducers

检查压差传感器管道

Check and inspect the tunnel and oven screens for debris and broken glass that may impact equipment operation

检查隧道和烘箱屏幕内是否有影响设备运行的碎片和碎玻璃。

8.3 Change Control / Revalidation 变更控制/再验证

In order to maintain the state of control of a depyrogenation/sterilization process, a change control program should be in place. This program should document any changes to the depyrogenation/sterilization equipment or process as well as any changes made to a product/item to be depyrogenated/sterilized. The change control program should include documentation of any testing required to ensure the validated state of control.

为了保持除热原/灭菌程序的控制状态，必须有明确的变更控制程序。该程序应能以文档记录灭菌/除热原程序设备或工艺的任何变更，以及待除热原/灭菌产品/物品的任何变更。该变更控制程序应包括任何可以确保处于受控验证状态的测试文件。

Equipment or process changes should be evaluated to determine potential effects of those changes and should demonstrate that the modified equipment or process performs as intended and continues to meet the established acceptance criteria. Similarly, any changes made to a product /item to be depyrogenated/sterilized should be reviewed to identify the potential impact that the change has on the existing validation. Consideration should be given to the worst case product/item that was selected for use in validation testing, as well as any impact to the thermal conductivity of the product/item. The assessment of equipment, process, and product/item changes should determine if revalidation is required.

设备或工艺的变更应进行评估以确定这些变更的潜在影响，且要证明改进后的设备或工艺能按预期运行，并能持续符合已建立的可接受标准。类似地，待除热原/灭菌的产品/物品的任何变更，应进行回顾来确定对已有验证状态的影响。应考虑在验证测试中所选使用的产品/物品最差情况，以及对产品/物品热传递性的任何影响。通过对设备、工艺、产品/物品变更的评估，来确定是否需要再验证。

Change control requests should identify documents that may be affected by the change and should include:

变更控制要求应能识别出受变更影响的文件，应包括：

• A description of the proposed change

提出的变更的描述

• A documented reason/rationale for the proposed change

提出的变更的书面原因/理由

• A description of the tests needed to revalidate the process after the change is made; or a technical rationale supporting that the change has no impact on the sterilization process efficacy (minor change)

变更发生后，工艺再验证需要进行的测试项的描述，或有技术性理由来支持变更对无菌工艺效

力没有影响（次要变更）

• Supporting documentation for tests performed, interpretation of results and conclusions
进行测试时的支持文件、结果解释和结论。

• Confirmation that documents affected have been updated
确认受影响的文件已升版

• Approval of the change control package by the Quality Unit
质量部门批准变更控制

8.4 Periodic Requalification of Equipment 设备周期性再确认

Equipment should be requalified on a routine schedule to ensure there has not been an undetected change. Requalification should be performed and documented using qualified operational parameters and acceptance criteria. Results of the requalification should demonstrate that the equipment's performance has not changed from its qualified state.
设备应定期进行再确认以确保没有出现未发现的变更。应采用已确认的操作参数和可接受标准进行再确认，并有文档记录。再确认结果应能证明设备性能未发生变化偏差其确认状态。

The worst case load configuration in depyrogenation/sterilization processes should be included in requalification runs. Requalification could also include an empty chamber run to assess temperature distribution.
除热原/灭菌工艺中最差装载情况应包括在再确认运行中。再确认应包括空载运行以评估温度分布情况。

Requalification should also include review of change control documentation, deviations, preventative maintenance records and routine process data. Refer to Section 8.3 for information regarding change control. Software, set points and control system operation should also be reviewed during the requalification to assure that no unexpected changes have occurred.
再确认也应包括对变更控制文件、偏差、预防性维护记录和日常工艺数据的回顾。参考8.3章节有关变更控制的信息。在再确认中，软件、设定点和控制系统操作也应做回顾，以确保没有意外的变更发生。

8.5 Parametric Release 参数放行

Parametric release is a sterility release program for product based on effective control, monitoring and documentation of a validated sterile-product manufacturing process where sterility release is based on demonstrated achievement of critical operational parameters and performance attributes in lieu of end -product sterility testing *(38).*
参数放行是一种产品无菌放行程序，是以已验证的无菌产品制备工艺的有效控制、监控和文件记录为基础的，其中无菌放行是基于已证明达到了关键操作参数和性能属性的，代替了终产品无菌测试（38）。

The elements of a parametric release program build on a foundation of the entire quality

system including: change control, training, written procedures, planned preventative maintenance, failure mode/risk analysis, prevention of human error, validation, calibration, and product release requirements.

参数放行程序的各要素要建立在全面质量体系之上，包括：变更控制、培训、书写程序、计划性预防性维护、失败模式/风险分析、预防人为差错、验证、校准、及产品放行需求。

Parametric release can only be applied to products terminally sterilized in their final containers or packaging *(44,45).* Regional regulatory approval is needed prior to the use of parametric release *(46).* Once a product is approved for parametric release, it cannot be released based on a sterility test.

参数放行只适用于在最终容器或包装中灭菌的产品（44, 45）。需要当地法规部门的许可才可以使用参数放行（46）。一旦产品经批准采用参数放行，则不能凭借无菌检验结果放行。

The following are considerations for a parametric release program to reduce the risk of producing and releasing non-sterile product. For additional detail on parametric release principles that may also be applied to dry-heat sterilization, see PDA Technical Report No. 30:

以下是为了降低生产和放行非无菌产品的风险而进行的参数放行程序需考虑的一些方面。有关参数放行原则方面的更多细节也可以用热灭菌，参见PDA第30号技术报告。

• Quality risk management that includes well-justified risk assessments to identify risks and take corrective and preventative measures to reduce and control those risks to an acceptable level *(39).*

质量风险管理包括基于良好判断的风险评估以鉴别风险，并采取纠正和预防措施去降低和控制风险至可接受的水平（39）。

• Personnel with competency in engineering and microbiology specifically trained in sterilization practices and sterility assurance should provide oversight in the validation and ongoing quality control of the sterile manufacturing process *(38,45).*

人员应具有工程和微生物学胜任力，且在灭菌操作和无菌保证方面经过特殊培训，能在无菌制备工艺的验证和日常质量控制中提供监督（38, 45）。

• Package integrity data should include validated container closure testing after exposure to worst-case sterilization processing to ensure that the sterilized product maintains its sterility over the shelf life of the product *(38,46).*

包装完整性数据应包括暴露于最差条件灭菌后的容器密封性测试，以确保在产品储存期内可以保持无菌状态（38, 46）。

• Bioburden control of the pre-sterilization bioburden through a properly designed manufacturing facility and processes and an established bioburden monitoring program *(38).*

灭菌前生物负荷的控制通过正确设计的生产设施或工艺及建立生物负荷监测程序来实现（38）。

• The system of handling products must ensure that non-sterile products are segregated from sterilized product *(38,45).*

处理产品的系统必须确保能使非无菌和灭菌产品分离（38, 45）。

• The sterilization system including the sterilizer, monitoring and control instruments and supporting utilities are designed and calibrated to monitor and control the critical operational parameters and performance attributes *(38).*

灭菌系统包括灭菌器、监测和控制仪器和支持部件是经设计和校准的，能监测和控制关键操作参数和性能属性（38）。

• Biological indicators are well characterized and appropriately selected to provide a worst case challenge to process *(38).*

生物指示剂应充分鉴定并正确选择，使之对工艺能有最差条件的挑战（38）。

• The physical parameters of the sterilization process must be defined, reproducible and measurable and should be recorded *(44,45).*

灭菌工艺的物理参数必须是已定义的、可重现和可测量的，并需进行记录（44, 45）。

• For heat labile products, the product specific approach may be used. When using this approach, bioburden should be well characterized.

对热不稳定的产品可采取产品特异性方法，当使用这种方法时，生物负荷情况应做鉴定。

• Process development which includes load definition, load pattern and determination of operational parameters should ensure that the required physical and biological lethality are delivered to the product resulting in the achievement of less than or equal to 10^{-6} PNSU *(38).*

包括装载物定义、装载方式及操作参数确定在内的工艺开发应确保所需的物理/生物致死率能传递至产品，并获得PNSU不低于或等于10^{-6}的效果（38）。

• Equipment qualification and process validation should be performed *(38).*

应进行设备确认和工艺验证（38）。

• Ongoing process monitoring and control should ensure the validated state of the sterilization process including load release procedures and criteria, requalification and revalidation requirements, preventative maintenance and change control programs *(38).*

日常过程监测和控制应确保灭菌过程处于验证状态，包括：装载物的放行程序和标准、再确认和再验证需求、预防性维护和变更控制程序（38）。