编号：　　环氧乙烷灭菌验证再确认控制程序
EO sterilization validation, requalification control procedure

1. 目的 Purpose

根据 ISO11135:2014 的要求，对工厂灭菌车间环氧乙烷灭菌过程和产品的验证进行管理和控制。

According to the requirements of ISO11135:2014, to control the EO sterilization process and products validation in plant ETO workshop.

2. 适用范围 Scope

适用于工厂灭菌车间的灭菌柜和产品的灭菌验证。

This procedure is suitable for plant ETO workshop and product validation.

3. 职责 Responsibilities

3.1. ETO 车间负责提供灭菌验证所需的设备和物料，灭菌柜供应商负责灭菌柜的 IQ,OQ 验证及软件验证，并提供相应的验证方案和报告，ETO 车间负责 PQ 验证，包含验证方案和最终报告。

ETO workshop is responsible for the validation materials and facilities, the EO sterilizer supplier is responsible for sterilizer IQ,OQ validation and software validation, providing related validation protocol and completion report. ETO workshop is responsible for products PQ validation including protocol and completion report.

3.2. 实验室负责 IPCD,EPCD 的制备，无菌检测产品样品的准备，残留样品的准备，产品无菌检测，BI 培养，EO/ECH 残留检测。

The lab is responsible for IPCD, EPCD preparation, product sterility test samples, EO/ECH residuals samples preparation, BI incubation and EO/ECH residuals testing.

3.3. 质量经理负责确认验证所必须的资源，审核 IQ,OQ,PQ 方案和报告审核，并批准方案和报告。

The Quality manager is responsible for validation resources, reviews IQ, OQ, PQ protocols and reports, approves the protocols and completion reports.

3.4. 管理者代表审核 IQ,OQ 方案和报告审核，并批准方案和报告。联系客户组织组织协调 PQ 工作，审核 PQ 方案和最终报告。

Quality representative reviews the IQ,OQ protocol and completion report,approves the protocol and completion report. And then contact the customers to cooperate the PQ, review and approve the PQ protocol and completion report.

3.5. 设备服务部 TS department

3.5.1. 依据设备供应商的建议，负责设备的日常维护保养并做好相应的记录，培训操作人员。

According to the facility supplier suggestions, TS is responsible for the facility routine maintenance and records the maintenance items. Also responsible for training the operators.

3.5.2. 依据设备供应商的建议，负责编写设备操作作业指导书及维护保养手册。

According to the facility supplier's suggestions, TS is responsible for the facility operation manual and maintenance manual.

3.6. ETO 车间 ETO workshop

3.6.1. 参与验证方案的制定，确定所验证的产品的验证循环参数，执行灭菌验证。

Participate the validation protocol drawing up, confirm the defined product cycle parameters and conduct the validation.

3.6.2. 负责编制灭菌操作作业指导书，定期对工艺文件和灭菌情况进行检查。

Be responsible for EO sterilization operation manual, periodically review the SOP and sterilization status.

3.7. 质量部门 Quality department

3.7.1. 负责制定验证方案，协助客户准备 PQ 验证方案。

Be responsible for drawing up the validation protocol, assist the customers to prepare the PQ validation protocol.

3.7.2. 负责对验证过程的执行监督，验证的取样，检测安排，并审核检测结果，负责验证结果的审核和评价。

Be responsible for surveillance of validation process, samples retrieval, test arrangement, and review the test results, be responsible for reviewing the validation results and evaluation.

3.7.3. 负责验证记录的审核和验证文件的管理。

Be responsible for reviewing the record and validation document management.

3.8. 供应部门 Supply chain

3.8.1.负责或协助 PCD 样品的准备

Be responsible for or assist the lab for PCD samples preparations.

3.8.2.负责联系客户安排验证和测试需要的样品和物料，按照验证方案准备产品装载。

Be responsible for contacting the customers to arrange the validation samples and materials, according to the validation protocol to prepare the validation load.

4. 过程及设备描述 Process and facility description

在过程开发及准备阶段，根据以下内容，确定过程和设备的要求。

At development and preparation phase, according to listed content to confirm the process and facility request.

4.1. 过程描述 Process description

4.1.1.过程特性描述应至少包括以下内容：Process characteristics description shall include listed content.

a. 识别环氧乙烷灭菌过程的所有阶段；Identify all phases of EO process

b. 识别每一个阶段的过程参数；Identify per phase process parameters

c. 定义过程参数并生成文件。Define the cycle parameters and documented

注意：产品定义时的研发数据可能对灭菌过程的影响。

Note: The data during product design may affect the EO sterilization process.

4.1.2.灭菌过程包含以下阶段 EO sterilization process includes listed phases

a. 预热（如果使用）Preconditioning (if necessary)

b. 灭菌 Sterilization

c. 解析（如果使用）Aeration (if necessary)

4. 1. 3. 各阶段的过程参数应至少包含以下：Per phases process parameters shall include

阶段 phase	过程参数 process parameters
预热（如果使用） Preconditioning(if necessary)	温度，湿度，时间 Temp. RH, time
灭菌 Sterilization	温度，湿度，灭菌暴露时间，EO 浓度，压力 Temp. RH, EO exposure time, EO concentration, pressure
解析（如果使用） Aeration(if necessary)	温度，时间 Temp. time

注意：只有当解析过程对微生物杀灭有贡献时，解析的参数才被认为灭菌过程变量

Note：only the aeration process residuals kill contributes to the micro lethality, the aeration process parameters will be deemed as process parameters.

4.2. 设备描述 Facility description

4. 2. 1. 应确立和记录所有设备的规范，包括预热间（如使用），灭菌柜和解析间（如使用）

Shall define and record all facility specifications, including preconditioning room (if necessary), sterilizer and aeration room (if necessary)

备注：设备设计的一些因素可能受国家或地区法规要求的影响。

Remark:The facility design will be affected by national or regional regulations.

4. 2. 2. 规范包括至少以下方面：Regulate listed aspects:

a. 设备和辅助设施的描述，包括相应的材料；Facility and ancillary equipment description, including related materials

b. 灭菌剂进入灭菌柜的方法；The method that the sterilant injects into the chamber

c. 灭菌过程中使用的其他气体（包含水蒸气）进入灭菌柜的方法；

Other gas (include steam) inject to the chamber

d. 灭菌过程中使用的检测、控制、记录仪表的描述，包括传感器的特性及其位置；

The description of the measures used in the sterilization process, including the sensors' characteristics and positions.

e. 灭菌设备故障的识别 Identify the malfunction of the facility

f. 保护员工和环境的安全设施 Employee protection and environmental safety facility

g. 安装要求，包括控制排放的要求 Installation requirements including evacuation requirements.

4. 2. 3. 用于监视或控制过程的软件应按照质量体系的相关要求进行设计和验证，并有相应的验证方案和报告。

The software used for monitoring and controlling the process shall be designed and validated according to the quality system requirements.

4.2.4. 应规定和规范过程变量的监视和控制方法。Regulate and define the process variables and monitoring &controlling methods.

4.2.5. 应有措施确保控制系统功能的故障不会导致过程参数记录的故障，使无效的过程变成有效。

Shall take effective actions to confirm that the system malfunction will not cause process parameters record invalid, and the invalid process becomes effective.

注：控制系统与监视系统互相独立或者二者互相识别偏差和指示故障。

Note: Control system and monitoring system shall be independent or both have discrepancies and indicate malfunction.

5. 产品定义 Product definition

5.1. 在引入新产品灭菌，或者当前灭菌的产品、包装和装载模式发生改变前，应先进行产品定义。

When introduce new products or current validated products , packaging and load configuration have been modified or changed, shall conduct product definition primarily.

5.2. 应描述与已验证过的产品、包装、装载模式的对于灭菌抗性的等同性并符合产品定义的要求形成文件。

Shall describe the EO resistance of new or modified products, packaging or loading configuration equivalent with current validated products, complies with the product definition and documented.

5.3. 产品设计应允许内部空气的排出，灭菌过程热量、水蒸气和 EO 气体的穿透，灭菌结束后 EO 气体的排出。

The product design shall allow the air evacuation, heat, moisture and EO penetration, EO evacuation after sterilization.

5.4. 产品包装应允许内部空气的排出，灭菌过程热量、水蒸气和 EO 气体的穿透，灭菌结束后 EO 气体的排出。

The product package design shall allow the air evacuation, heat, moisture and EO penetration, EO evacuation after sterilization.

5.5. 灭菌装载应允许内部空气的排出，灭菌过程热量、水蒸气和 EO 气体的穿透，灭菌结束后 EO 气体的排出。

The sterilization load shall allow the air evacuation, heat, moisture and EO penetration, EO evacuation after sterilization.

5.6. 应验证灭菌过程在产品最难灭菌位置的有效性，可以在新产品的过程定义和验证时进行验证，或与已验证过的产品进行等效性分析，或采用 IPCD 验证产品的 SAL.。

Shall validate the effectiveness of the most-difficult-sterilize position, can proceed in product definition and through validation. Or through equivalence study, or compare with the validated IPCD to assure the new product SAL.

6. 定义灭菌过程 Sterilization process definition

6.1. 此过程用于在验证时得到适用于以上第五部分所定义产品的灭菌过程规范，如果客户指定灭菌过程参数要求，ETO 车间应根据此部分内容确定要求的符合性。

Sterilization validation shall be inline with the specification of section 5, once the sterilization cycle parameters are predetermined by the customers, ETO workshop shall confirm the requirements compliance.

6.2. 建立指定产品的灭菌过程，指定产品包括新的或更改的产品、包装及装载模式。

To develop the defined sterilization cycle , including defined products or modified products, package and load configuration.

6.3. 已经通过 IQ,OQ 验证的灭菌柜，可以用于新产品或指定产品的灭菌参数研究。

The sterilizer through IQ, OQ and PQ will be used new products or defined product sterilization study

6.4. 应有文件和记录以支持灭菌循环参数的有效性。

Document and record shall support the sterilization cycle effectiveness.

6.5. 选择 ISO11135:2014 附录 A 或 B 中选择一种方法以确定达到无菌保证水平（SAL）的灭菌暴露时间。

Choose one of the method in annex A or B in ISO11135:2014 to confirm the EO exposure time that assure the product SAL.

6.6. 灭菌验证和常规监控的生物指示剂（BI),需符合以下条件：

The BI used validation and routine monitoring shall comply with listed requirements:

a. 符合 ISO11138-2:2006 条款 5 和条款 9.5 的要求；

Comply with clause 5 and clause 9.5 of ISO11138-2:2006.

b. PCD 比待灭菌产品的初始生物负荷具有等同或更高的 EO 抗性；

The EO resistance between PCD and product bioburden has the same EO resistance.

c. BI 放置在合适的 PCD（过程挑战装置）中；

The BI shall be placed in the appropriate PCD.

应确定用于过程定义、验证及常规监控的 PCD 的有效性。PCD 应比最难灭菌位置的产品生物负荷等同或更高的 EO 抗性。

Shall confirm the effectiveness of PCD OF process definition, validation and routine monitoring.The EO resistance of PCD shall higher or equivalent than the most-difficult-sterilize product bioburden.

注：生物指示剂的选择、使用及 D 值计算见 ISO14161:2009

Note: BI choice, use and D value calculation see ISO14161:2009.

6.7. 在定义灭菌过程中，如使用工业化生产的生物指示剂，应符合 ISO11138-1 的相关条款要求；

During EO sterilization process, once industrial BIs are used, they shall comply with the requirements of ISO11138-1.

6.8. 在定义灭菌过程中，如使用化学指示剂，应符合 ISO11140-1 的相关条款要求；

During EO sterilization process, once CIs are used , they shall comply with the requirements of ISO11140-1.

注：化学指示剂不能单独用于灭菌验证，且不能证明产品是否达到所需的 SAL.

Note: CI cannot be used in sterilization validation, and cannot assure the required SAL.

6.9. 在灭菌验证过程中，如进行产品无菌检测，需符合 ISO11737-2 的要求。

During validation process, once conducting product sterility test, it shall comply with the requirements of ISO11737-2.

7. 验证 Validation

验证是为了证明以上第六部分定义的灭菌循环参数能有效地，可重复地用于装载产品的常规灭菌。验证包含安装确认（IQ）,运行确认（OQ）和性能确认（PQ）,在验证方案被批准后开始进行验证。

The validation is to demonstrate the cycle parameters effectiveness of section 6, can reproducible delivery the product load sterilization parameters. Validation including IQ, OQ, and PQ.

安装确认（IQ）：确认设备及其附属设施设备按规范进行了供应和安装；

IQ, confirm the equipment and ancillary facility supplied and installed according to the predefined specification.

运行确认（OQ）：确认设备能力符合设计规范的性能要求；

OQ, confirm the equipment complying this the designing specifications

性能确认（PQ）：是在验证过程中，用产品装载确认设备能持续地符合预先确定的灭菌循环参数下运行，并达到要求的 SAL.。

PQ, during validation process,to confirm that the equipment that can deliver the required sterilization cycle parameters reproducibily with product load, and assure the required SAL.

对于指定的灭菌设备，IQ 和 OQ 可能只需要进行一次，对于新产品或新的灭菌循环参数，PQ 都要进行。

For defined the sterilization equipment, IQ, OQ maybe experience one time, PQ shall be conducted for new products or new sterilization cycle.

7.1. 安装确认（IQ）

7.1.1.设备 Equipment

7.1.1.1. 灭菌工程中使用的设备包括所有辅助设备都要符合设计规范；

The sterilization equipment and all ancillary facility shall comply with the design specification.

7.1.1.2. 灭菌设备必须符合适用的安全标准；

The equipment design shall comply with the safety standards.

7.1.1.3. 应规定设备的操作程序，操作程序包括但不限于：

Shall regulate the equipment operation procedure, including but not limited:

a. 每一步的操作步骤；

Per step operation procedure

b. 故障情况，故障的指示和处理措施；

Malfunction status, malfunction indication and actions.

c. 维护和校验；Maintenance and calibration

d. 技术支持的联系人清单；Technical support contact name list

7.1.2.安装确认（IQ）

7.1.2.1. 设备的安装和相关的服务应符合建筑和工程图纸。安装应符合相关国家和地区的法律法规。

Equipment installation and related service shall comply with the architecture and engineering drawing's specifications. Installation shall comply with related country and region's regulation.

7.1.2.2. 设备的安装由供应商负责，并提供相应的方案和报告，工厂需要按照《生产设备控制程序》进行审核并验收；

The supplier shall be responsible for the equipment installation, providing related protocol and completion report. plant shall review and accept the equipment according to the requirement of 《production equipment control procedure》

7.1.2.3. 应规定 EO 钢瓶的安全存储环境，确保不发生聚合反应，保证使用质量符合要求；

The EO cylinders storage condition shall be controlled, to assure that the EO not to be polymerized, and the gas quality complies with the requirements.

7.1.2.4. 在安装确认前，应确认所有将用于安装验证的测试仪器均已校验；

Before equipment installation, all measures shall be calibrated.

7.1.2.5. 安装设备的图纸，管路分布，及其他的辅助设施应在安装确认中定案；

The drawings, plumber distribution and other ancillary facility shall be confirmed .

7.1.2.6. 安装过程中对系统的更改应评估其对设计和灭菌过程的影响，并记录在 OQ 验证报告中；

During installation, the system design change shall be evaluated (EO sterilization affection) and document in the OQ validation report.

7.2. 运行确认（OQ）

7.2.1.在运行确认前，所有用于检测、控制、指示或记录的仪器（包括测试仪器）均已校验；

Before OQ, all measuring,control,indication and record measures (including testing measures) shall be calibrated.

7.2.2.操作确认应证明已安装设备能在规定的范围内运行指定的灭菌循环；

Shall confirm that the equipment that installed can deliver the defined sterilization cycle reproducibily.

7.2.3.按《ETO 车间设备操作验证和再确认程序》对设备进行 OQ 验证和再确认。

According to the 《 plant equipment operation validation and re-qualification procedure》to conduct OQ and requalification.

7.3. 性能确认（PQ）

7.3.1.总则 General requirements

7.3.1.1. 性能确认包括物理性能确认和微生物谁能确认，并在指定的灭菌设备上进行；

PQ validation includes PPQ and MPQ and is conducted in defined sterilizer.

7.3.1.2. 在引入新产品，或更改产品、包装、装载形式、灭菌循环参数时，都需要进行性能验证。除非通过等效性评估，新产品，更改产品、包装形式和装载方式与已验证的产品具有等同的 EO 抗性，可以追加入已有的产品族和 EO 加工组。如果 EO 抗性大于已验证的产品或 PCD，完整的 PQ 必须实施。

PQ shall be conducted once introduce new product, modified product, package, load configuration or cycle parameters change excluding through equivalence evaluation, the EO resistance of validated products with new or modified products, package, load configuration are same, that can adopted into current product family or EO processing group. Once the EO resistance is higher than current validated product PCD, full PQ shall be conducted.

7.3.1.3. 性能验证可以使用可销售产品或与可销售产品相似的物料，证明设备能可持续地交付灭菌循环过程，并且达到所需的无菌保证水平 10^{-6}。

PQ validation shall use saleable products or non-saleable materials, demonstrating the equipment can deliver the sterilization cycle reproducibily and attain the required SAL 10^{-6}

7.3.1.4. 应规定产品的灭菌方式，包括装载模式，PCD 的选择；

Shall regulate the sterilization validation method, including the choice of load configuration and PCD.

7.3.1.5. 如验证中使用的是可销售产品，应在验证方案定义产品处置；

During PQ study, shall define the products disposal once using saleable products.

7.3.1.6. PQ 验证中所使用的灭菌装载，应为最具挑战性的灭菌装载；

The PQ validation load shall use most challenge routine load.

7.3.1.7. 如果验证装载有不同的装载模式，应评估其对灭菌过程的影响；

Once PQ has different load configuration, shall evaluate the sterilization effect.

7.3.1.8. 如果使用模拟装载，其挑战性应于最具挑战的产品装载等同或大于最具挑战的灭菌装载；

Once the dunnage load to be used in the PQ, it shall be the same or higher challenge than the most routine challenge.

7.3.1.9. 如果产品装载在验证过程中重复使用，应在 2 次灭菌循环间隔中充分解析，一则防止产品残留影响下一个灭菌循环的微生物杀灭性，二则也是对作业人员的安全防护；

Once adopt re-used validation load, it shall be fully aerated once the second cycle starts, the first is to prevent the residual kill affecting the MPQ, the other is to protect the operators.

7.3.1.10. 如果验过程中使用化学指示剂，应符合 ISO11140-1 的要求，并结合生物指示剂和物理监控；

Once validation process adopting CIs, they shall be comply with the requirements of ISO11140-1, and in combination with BIs and physical profile.

7.3.1.11.验证过程中使用的生物指示应符合 ISO11138-1:2006 及 ISO11138-2:2009 第 5、9.5 部分的要求。

CIs used in PQ shall comply with the requirements of partial clause of ISO11138-1:2006 and ISO11138-2:2009 section 5 and 9.5

7.3.2.微生物性能确认 MPQ

7.3.2.1. 微生物性能确认应验证产品在指定的灭菌循环达到所规定的无菌保证水平（SAL）,验证在指定的灭菌柜内进行；

MPQ shall confirm the predefined sterilization cycle in defined sterilization cycle can attain the required SAL.

7.3.2.2. 微生物性能验证（MPQ）应证明产品（PCD）/装载在指定的灭菌柜内达到指定的 SAL;

MPQ shall demonstrate PCD and load in defined sterilizer can attain the required SAL.

7.3.2.3. 选择 ISO11135:2014 附录 A 或 B 的方法，或部分阴性法确定灭菌暴露时间，从而证明产品无菌保证水平；

Choose one of the method in annex A or B of ISO11135:2014,or fraction-negative method to define the EO exposure time, so as to assure the product SAL.

7.3.2.4. 如果灭菌过程参数是在一个开发用的灭菌柜中实现的，微生物性能确认应在生产用的灭菌柜内至少进行三个短周期或半周期循环以确认灭菌循环参数的有效性；

Once the sterilization cycle parameters is realized in a development chamber, the PPQ shall be conducted in the production chamber at least three fractional cycles or half cycles to confirm the cycle parameters effectiveness.

7.3.2.5. 如果使用半周期法进行进行微生物新能确认，在半周期循环结束后，所有的内置挑战装置（IPCD）均需显示阴性，外置挑战装置（EPCD）可部分显示阳性，证明 EPCD 的抗性大于 IPCD, 并可用于常规灭菌监控；

Once use half cycle approach to perform PPQ, after completion of the half cycle, all IPCDs shall show no growth, partial EPCD may show positive, that demonstrate EPCD's EO resistance are higher than IPCD, and can be used routine sterilization.

7.3.2.6. 如采用 D 值计算灭菌暴露时间，需确认在半周期循环过程中，所有 IPCD 均显示阴性，D 值计算详见 ISO14161:2009。

Using D value calculation method to define the EO exposure time, it is necessary to confirm that all IPCDs shall no growth after completion half cycles.

7.3.3.物理性能验证 PPQ

7.3.3.1. 物理性能验证应确认：PPQ validation

a. 常规灭菌装载的灭菌循环符合规定的接受标准 acceptable validation load

b. 过程的再现性 Process reproducibility

PPQ 应包含 3 次连续的验证测试，以确定产品装载的温湿度分布，从而确定最低进入预热间（或灭菌柜）的温度。PPQ 可以和 MPQ 同时进行，但在 3 个半周期循环后，至少再进行一个全周期循环进行确认；

PPQ shall include three consecutive test, to confirm the load physical profile and determine the minimum temperature entering the preconditioning room (or sterilizer). PPQ can be conducted in parallel with MPQ, after three half cycles, at least one full cycle shall be conducted to confirm the load physical profile.

如果验证失败的原因可归因于验证有效性无关的因素：如停电、一些设备停止运行、外部监控设施失

灵等，无需进行额外的三个半周期循环。

Once the validation failure is due to the unnecessary factors like power off, facility malfunction, external monitoring facility malfunction, no need additional three half cycles to be conducted.

7.3.3.2. 物理性能确认需确认以下方面：PPQ shall confirm listed aspects:

a. 应确定进入预热柜（如使用）或灭菌柜的最低环境温度；

Determine the minimum temperature entering to the preconditioning room (if used) or sterilizer.

b. 应确定预热结束后，产品装载的温湿度范围；

Define the load temperature and RH range after completion of the preconditioning.

c. 应确定预热结束后至灭菌开始的最大产品转运时间；

Define the transfer time after completion of preconditioning and start of the sterilization

d. 如果使用参数放行，灭菌柜应记录：

Once parametric release is adopted, the sterilization cycle shall document:

i. 确保完全气化的 EO 气体注入到灭菌柜中；

Confirm fully vaporized EO gas injected to the sterilizer

ii. 确认 EO 注入过程中压力的上升，所使用的的重量，或 EO 浓度；

Confirm the pressure rise during EO injection, EO weight, or EO concentration.

iii. 确认灭菌柜内产品的温湿度和其他参数（如适用）；

Confirm the product physical profile in the sterilizer(if necessary)

iv. 确认灭菌柜内产品装载的温湿度分布；

Confirm the load physical profile in the sterilizer

v. 确认解析间的产品装载温度分布。

Confirm the load physical profile in the aeration room

7.4. 验证的审核和批准 Review and approve the validation activities

此项活动是对验证结果和数据进行审核，是否达到验证的要求，并批准最终验证报告。

This action is to review the validation results and data that attain the validation request.

7.4.1.在 PQ 验证活动开始前，依据章节 5,6,7 部分的要求完成验证方案，并确认指定的灭菌循环参数，经客户，品管和相关负责人审核批准后生效；

Before PQ validation activity, according to section 5,6,7 to complete the validation protocol, to determine the sterilization cycle. Through customer , quality department and relevant person review

and then valid.

7.4.2.对进行验证的相关人员进行培训；

To train relevant person related to the validation activities.

7.4.3.按照验证方案进行产品验证，在验证过程中若发生偏差，需评估偏差对灭菌验证的影响，可接受的理由需记录在偏差报告中，并被方案和最终报告批准者批准。

According to the validation protocol to conduct the validation, once deviation occurred, need to evaluate the sterilization validation affect, and acceptable rationale will be documented in the deviation record, and approved by the reviewers and approvers.

7.4.4.在产品过程定义、IQ、OQ、PQ，以及生物指示剂培养结果等过程中产生和收集到的信息都应记录在案，并审核其符合接受标准。

Production definition, IQ,OQ and PQ, BIs incubation results and other information collected shall be documented, and review the results complying with the acceptance criteria.

7.4.5.验证结束后，完成最终报告，并由质量，相关负责人和客户审核和批准。

After completion of validation, complete the final report, reviewed and approved by quality department, related person and customers review and approve.

7.4.6.验证报告应描述或引用详细的验证产品、装载模式、灭菌循环参数，包含以下方面：

Validation report shall detail the validation product, load configuration, cycle parameters, including listed aspects:

注：速率可以通过达到规定压力变化的时间来确定（△P/T）

Note:Rate can be confirmed through time and pressure change (△P/T)

a. 进入预热柜的最低环境温度；

Minimum ambient temperature entering to the preconditioning room

b. 产品在预热间的时间，预热间的温度、湿度

Preconditioning time, precondition room temperature, RH.

c. 产品装载的温度、湿度分布

Product load physical profile

d. 预热结束后的产品装载的温湿度范围

The product load temperature and RH range after completion of preconditioning.

e. 确定预热结束后至灭菌开始的产品转运时间

Define the product transfer time after completion of preconditioning and start of sterilization

f. 灭菌真空度和抽真空速率

Initial vacuum level and vacuum rate

1. 真空保压时间和泄露率

Vacuum retaining time and leakage rate.

注：抽真空速率通常有范围规定

Note: The range of vacuum rate

g. 处理/或湿气停留时间

Conditioning/moisture dwelling time

1. 压力变化/或达到初始真空度的速率，相对湿度

Pressure change/ the rate to attain the initial vacuum, RH

2. 蒸气脉冲注入/抽真空次数（如使用)

Steam pulsed injection /vacuum time (if necessary)

3. 灭菌柜温度(The sterilizer temperature)

4. 处理末期产品装载的温湿度分布(The product load profile after conditioning)

5. EO 气体注入和灭菌暴露时间(Vaporized EO gas injection and EO exposure time

h. 灭菌后清洗 Rinse

1. 真空度和速率（△P/T）Vacuum and rate

2. 惰性气体/过滤空气注入压力变化和速率（△P/T）Inert gas /filtered air injection pressure change and rate.

3. 重复的次数 Repetition times

i. 解析 Aeration

1. 解析间温度 Aeration Time

2. 解析间的压力变化（若有）Pressure change of aeration room (if used)

3. 解析间的换风次数 Air change rate of aeration room

4. 产品装载的温度分布 Product load temperature profile

7.4.7.若采用参数放行，验证报告应包含：

If parametric release is adopted, validation report shall include:

1. 直接检测灭菌柜内的相对湿度

Directly measure RH of the sterilizer

2. 直接检测灭菌柜内 EO 浓度范围，用于建立参数放行的标准

Direct measure the range of EO concentration of the sterilizer, to establish the parametric release criteria

3. 至少有两个温度探头监测灭菌柜内的温度

At least two temperature sensors to monitor the temperature of the sterilizer

8. 常规灭菌过程监测和控制 Routine sterilization process monitor and control

8.1. 常规监控是用已验证的灭菌循环对产品进行灭菌

Routine monitor is to use validated sterilization cycle to sterilize product

a. 记录并保存每一批次的灭菌循环批记录，以使产品达到放行标准

Record and document per sterilization cycle, to attain the release criteria

b. 产品进入预热间的最低环境温度

The minimum temperature entering to the preconditioning

c. 产品进入灭菌柜的最低温度

The minimum temperature entering to the sterilizer

d. 产品装载在预热间预热的时间

Preconditioning time

e. 预热结束至灭菌开始的时间间隔

The transfer time from completion of preconditioning and start of sterilization

f. 产品在灭菌柜内的预处理

Conditioning in sterilizer

g. EO 注入和灭菌暴露时间

EO injection and exposure time

h. 灭菌暴露阶段的温度和压力

The temperature and pressure of EO exposure time

i. 如果压力作为灭菌过程的主要控制参数，至少用一种以下的次要检测量确认 EO 气体进入灭菌柜

Once pressure is as the main control parameter during sterilization process, at least use one of list inferior measures to confirm that EO gas entering to the sterilizer

1. EO 浓度 EO concentration
2. EO 重量的减少 EO weight reduction
3. 使用 EO 的体积 EO volume used

j. EO 注入时间 EO injection time

k. 惰性气体注入（如使用）Inert gas injection (if used)

l. 灭菌暴露时间 EO exposure time

m. 灭菌柜抽真空时间 Vacuum time

n. 灭菌结束后清洗次数和压力变化（△P/T）Rinse time and pressure change

o. 解析 时间、温度、压力变化（若负压解析）Aeration, time, temperature , pressure change (if negative aeration adopted)

8.2. 如果常规监控使用生物指示剂，应符合章节 6.6，6.7 的要求，如果常规监控的 PCD 与验证使用的 PCD 不同，则其 EO 抗性至少≥MPQ 时的 PCD.

BIs used in routine monitoring shall comply with the requirements of section 6.6,6.7, If the PCD that is used for routine release is different from that used in the MPQ, it should be at least as is the PCD used in MPQ.

8.3. 如果日常监控采用化学指示剂，应符合章节 6.8 的要求。

CIs used in routine monitoring shall comply with the requirements of section 6.8.

8.4. 如使用参数放行，需满足以下条件

If parametric release is used, listed requirements need to be satisfied

a. 直接检测灭菌柜的相对湿度 Directly measure the RH of the sterilizer

b. 灭菌柜内至少有两个温度探头 At least two temperature probes in the sterilizers

c. 直接检测灭菌柜的 EO 浓度 Directly measure the EO concentration of the sterilizer

9. 灭菌产品的放行 Product release

9.1. 应以文件形式写明某一具体产品的灭菌标准和已验证的灭菌循环参数

Document per product sterilization standard and validated sterilization cycle parameters

a. 确认常规灭菌过程中的批记录数据在可接受范围内

Define the acceptance tolerance of the recorded data

b. 确认生物指示剂显示阴性

All BIs show no growth

注：灭菌产品在正式放行前可能需要其他的测试结果（如 EO/ECH）残留，内毒素及物理性测试。

Note: Other test results like EO/ECH residuals , endotoxin and physical testing shall be needed before sterilized products release.

9.2. 如果过程不符合放行标准，应发起偏差报告，调查原因。如果对设备进行维修或更改，应确认是否为重大变更，如果是轻微的变更，通过评估后，无需进行必要的验证，如果是重大变更，则需要进行必要的验证。

Once the process doesn't comply with the release criteria, the deviation report shall be initiated, and start the investigation. Once the equipment is maintained or changed , it is necessary to evaluate the impact of the sterilization process. Once determining the minor change, no full validation is needed, once deemed as significant change, full validation needs to be conducted.

9.3. 如果灭菌产品没有符合 9.1 的要求，灭菌产品应被判定为“不合格”产品，按《不合格控制程序》的要求进行处理。

Once the requirements of section 9.1 is not satisfied, the sterilized products are non-conformity products, shall be handled according to 《non-conformity products control procedure》

9.4. 如果销售的产品用于验证，其产品处置应符合产品发行标准才能进行放行。

If saleable products are used for validation, the disposal shall comply with the products release criteria.

注：关于单独批次产品的灭菌和放行要求，见 ISO11135:2014 附录 E 部分的内容。

灭菌产品的最终检验和放行执行《最终检验和放行程序》

Note: For single batch product sterilization and release requirements, see ISO 11135:2014 annex E.

10. 灭菌循环参数有效性的维护 Cycle parameters effectiveness maintenance

10.1. 总则 General

10.1.1. 应保持产品初始生物负荷的稳定性 The product bioburden shall maintain stable

10.1.2. 用于控制、监测灭菌过程的仪器仪表应按《测量和监控装置控制程序》中的规定进行定期校验。

The measures used for control, monitoring shall periodically calibrated according to 《measuring and monitoring control procedure》

10.2. 设备维护 Maintenance

10.2.1. 按照程序文件的要求计划并实施预防性维护保养，维护保养程序应遵循设备制造商的建议和相关的国家、地区的要求。

Perform the equipment preventive maintenance according to the defined schedule, the maintenance procedure

10.2.2. 维护保养完成并做好记录后，方可实施常规灭菌。

Complete the maintenance and documented, the routine sterilization sterilization can be started.

10.2.3. 保存设备维护保养记录，维护保养计划，程序和记录应由指定负责人定期审核，并记录审核结果。

Archive the facility maintenance record, maintenance schedule , procedure and documented, and then the designated person periodically review the results and document the review results.

10.3. 再确认 Requalification

10.3.1. 每年对 IQ,OQ,及 PQ 进行回顾，包含评估表，从而确认再确认的活动范围，包括设备稳定性及微生物学研究以确认灭菌循环参数的持续有效性。通常再确认的周期为 12 个月±1 个月。如客户有特殊要求，与客户协商进行再确认。评估表的决定应以文档形式记录。

Per year review the IQ,OQ and PQ reports, including assessment sheet so as to confirm the extent of requalification activities, including equipment stability and through microbiological study to confirm the effectiveness of the sterilization cycle. Normally requalification shall be performed within 12 months ±1 months.Once the customers have additional requirements, cooperating with the customer to conduct the requalification. The assessment shall be documented.

10.3.2. 如果再确认过程中发现灭菌循环参数无法达到产品的 SAL，应调查原因并采取相应的措施。

作为调查的一部分，应考虑之前灭菌产品的 SAL，并评估其使用的风险，如果调查证明不能达到要求的 SAL，则应建立新的灭菌循环参数，实施完整的 PQ,以达到要求的 SAL。调查和后续的措施需以文件形式记录，必要时执行《不合格品控制程序》。

Once the sterilization cycle parameters cannot attain the require SAL during requalification, the investigation shall be initiated, as part of the investigation, the previous sterilized products.

10.3.3. 应保存再确认数据，方案，报告和相应的纠正措施（如必要）的文件记录。

Document the requalification data,protocol,report and relevant correct actions record (if necessary)

10.3.4. 对规定设备上的灭菌循环参数按定义的周期，按照再确认方案进行，如客户有特殊要求，与客户协商再确认。

According to the sterilization cycle definition period, according to the requalification protocol to perform. Once the customers have special requirements, coordinate the customers to conduct the requalification.

10.3.5. 如果再确认过程中发现灭菌循环参数无法满足产品无菌保证水平，应调查原因并采取相应的纠正预防措施，作为调查的一部分，应对之前灭菌的产品 SAL 进行评估，评估其使用的风险。如果调查结果证明现有的灭菌循环参数不能达到要求的SAL,则应进行新的PQ以确立新的灭菌循环参数，调查和后续的措施需以文件形式记录，必要时执行《不合格品控制程序》

Once requalification cannot satisfy the product SAL with defined sterilization cycle, initiate the investigation and related correct action, as part of the investigation, the previous sterilized products shall be evaluated.Once the investigation indicates that the sterilization cycle cannot satisfy the required SAL, the full PQ shall be performed to define the new sterilization cycle parameters.Investigation and subsequent actions shall be documented.

10.3.6. 应保持再确认数据、方案、报告和相应的偏差及纠正预防措施的文件记录。

Document the requalification data, protocol, report and relevant deviation and corrective actions.

10.4. 变更评估 Change control

10.4.1. 对于灭菌过程、产品、灭菌设备、灭菌循环参数变更应评估其对灭菌过程的影响。

Evaluate the sterilization effect for the sterilization process, products , equipment, cycle parameters change.

10.4.2. 确认 IPCD 或 EPCD 的有效性，视情况做再次确认。

Confirm the appropriate of the IPCD and EPCD, if necessary reconfirmation is needed.

10.4.3. 产品装载模式发生变更时，应评估其适用性，评估的结果以文件形式记录并得到批准

Evaluate the suitability of the product load change, document the result and approved.

10.4.4. 每次灭菌过程、设备、或产品及装载发生变更时，都要进行评估，从而确认是否有必要重新进行验证。

Once sterilization process , equipment or product and load configuration have changed, shall evaluate the sterilization effect to determine the full validation is necessary or not.

10.4.5. 在确定过程定义时，OQ 或 PQ 的实施范围时，应考虑变更的重要程度。

During product definition, performing OQ and PQ, shall consider the extend of the change.

10.4.6. 评估的结果，包括所做的决定形成文件，执行《变更控制程序》

10.4.7. The evaluation results , including decision making, shall follow 《change control procedure》

10.5. 等效性验证 Equivalent validation

10.5.1. 过程等效性 Process equivalence

使用相同过程参数的灭菌设备，通过 IQ,OQ 验证，可通过以下任一种方法确认其等效性；

The equipment with same sterilization cycle parameters, through IQ, OQ validation, using listed one of the methods to qualify the equivalence.

a. 与原有的灭菌柜有相同的再现灭菌循环参数的能力

The sterilizer can deliver the same sterilization cycle parameters reproducibility with the previous sterilizer.

b. 用简化的 MPQ 确认产品能够达到所需的 SAL，及 PPQ 确认产品装载分布的一致性，采用简化的 MPQ/PPQ 的理由应以文件形式记录并形成文件。

Using reduced MPQ to confirm the products SAL, and through PPQ to define the product load physical profile. The rationale shall be documented.

c. 应确定不同地理位置对产品和装载模式的影响

Shall confine the affect of the load configuration in different geographical position.

10.5.2. 产品追加 Product adoption

如果新产品与已验证过的产品或内置挑战装置（IPCD）有相同或更小的 EO 抗性，新产品可以追加

入现有的产品族或 EO 加工组。对新产品及已验证的产品或内置挑战装置（IPCD）进行评估，评估的结果，包括做出的决定应以文件形式记录。

Once the EO resistance of new products are same or lower than current validated products or IPCD, the new products can be adopted to current product family and EO processing group.Evaluate the new products and validated products and IPCD, document the evaluation results and decisions.

10.6. IQ,OQ,PQ 文件中引用的标准、文件、表单需注明版本号。
The cited standard , document, spreadsheet of IOQ,OQ,,PQ shall noted document version.

11. 相关文件 Relevant Documents

历史记录 **History Record**

Version No. 版本号	**Eff. Date** 生效日期	**CCN No** 变更号	**Description of Change** 变更内容
01			