滅菌方法與確效標準解析

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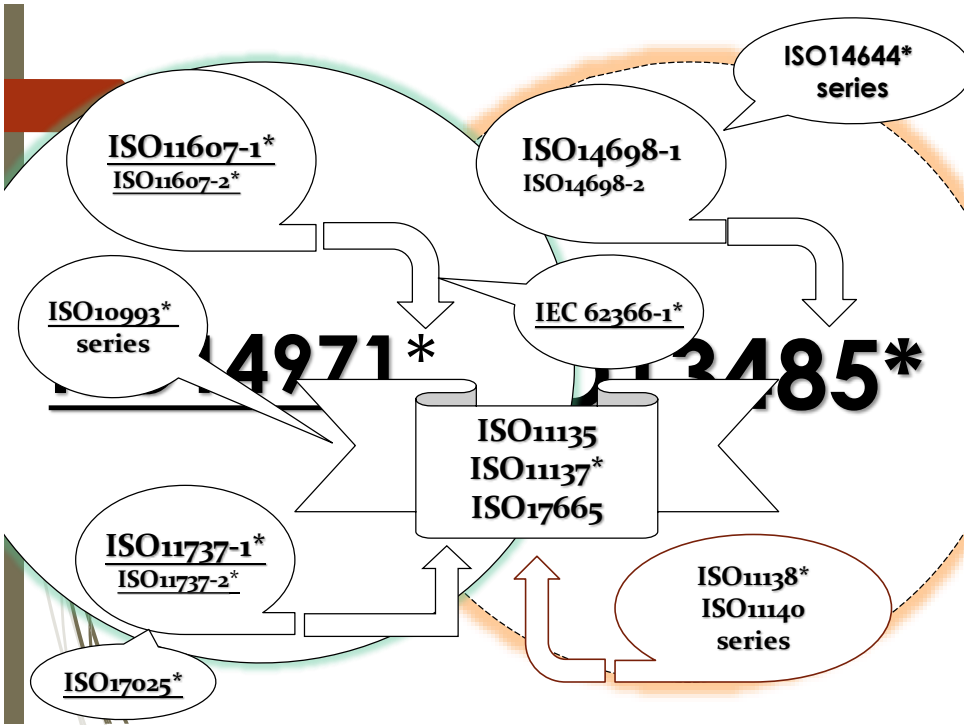
大綱

- 輻射滅菌標準 (ISO11137) 介紹解說
- 輻射滅菌確效規劃執行與例行管控



The standards of Sterilization and package validation

- *ISO 11137 : Sterilization of health care products – Radiation –*
  Part 1: 2018 Requirements for development, validation, and routine control of a sterilization process for medical devices
  Part 2: 2013 Establishing the sterilization dose
  Part 3: 2017 Guidance on dosimetric aspects
  ISO/TS 11137-4:2020 Part 4: Guidance on process control
- *ISO 11135 : 2014 Sterilization of health care products –Ethylene oxide – Requirements for development, validation, and routine control of a sterilization process for medical devices. (Combined ISO 11135-2)*
- *ISO 17665 :2006 Sterilization of health care products – Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices (Now under development ISO/CD 17665)*

ISO/TS 17665-2:2009 - Part 2: Guidance on the application of ISO17665-1
ISO/TS 17665-3:2013 - Part 3: Guidance on the designation of a medical

The standards of Sterilization and package validation

- *ISO 11737-1: 2018 Sterilization of medical devices - Microbiological methods – Part 1 Determination of a population of microorganisms on products*
- *ISO 11737-2: 2019 Sterilization of medical devices— Microbiological methods —Part 2 Tests of sterility performed in the definition, validation and maintenance of a sterilization process*
- *ISO 11607-1: 2019 Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems*
- *ISO 11607-2: 2019 Packaging for terminally sterilized medical devices -- Part 2: Validation requirements for forming, sealing and assembly processes*
- *ISO 14937: 2009 Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

名詞定義

1. Bioburden負荷菌/生菌數：一件產品中的微生物含量。
2. 滅菌(Sterilization)：完全消滅所有微生物，包括細菌(繁殖型及芽胞)真菌和病毒。
3. 無菌(Sterile)：當一件物品當中未含有可生長的生命型式時即可稱為sterile。但在實務卻無法證明完全無菌。因為，滅菌過程中微生物的死亡或減量是以數學指數來表示，所以微生物經過滅菌後的存亡狀態是以機率來表示，機率可以降至很低，但無法降至零。
4. 無菌保證度 (SAL, Sterility Assurance Level)：一種對滅菌效果的估算，針對特定產品與製程，透過對滅菌過程細部的了解及可能存在的微生物資料所建立，對該產品無菌的保證度。通常以$1*10^{-n}$表示。最低要求為10^{-6}，造成非無菌的可能性在一百萬之批量應小於一個。

名詞定義

5.化學指示劑(CI, Chemical Indicator)：作為滅菌產品的滅菌指標。

6.生物指示劑(BI, Biological Indicator)：針對特定滅菌方法呈現最強的抵抗性之菌稱為指標菌。據此指標菌種之生死來判斷滅菌處理是否完全，以作為滅菌製程的指標。

Steam：Bacillus stearothermophilus, ...etc

Dry heat：Bacillus subtilis ATCC 6633

EtO：Bacillus subtilis ATCC 9372

Gamma：Bacillus Pumilus

7.D 值(decimal reduction time value)：為特定溫度下減少90%微生物數量之時間或稱為1log週期(即存活分數為1/10)。

輻射標籤 Gamma Indicator

CODE	DESCRIPTION	NON-IRRADIATED	IRRADIATED
2.01	'plain' indicator, circular, ø 12,5 mm		
2.12.04	14 x 14 mm., with printed circle, text: 'red is exposed'		
2.12.06	14 x 14 mm., with text; 'red is ß exposed'		
2.14	indicator 26 x 12 mm. Can be applied easily and fast with a Meto gun (handapplicator as used in supermarkets)		

生物指示劑
Biological Indicator

- Bacillus Atrophaeus (Subtilis var. Niger)
- Geobacillus Stearothermophilus

Geobacillus stearothermophilus
Bacillus pumilus
Bacillus atrophaeus
strips + suspensions

滅菌種類的介紹

影響滅菌效果的主要因素：

- ♦時間
- ♦殺菌劑的強度(溫度、濃度、劑量)
- ♦微生物的耐受性

滅菌方法的選擇要素

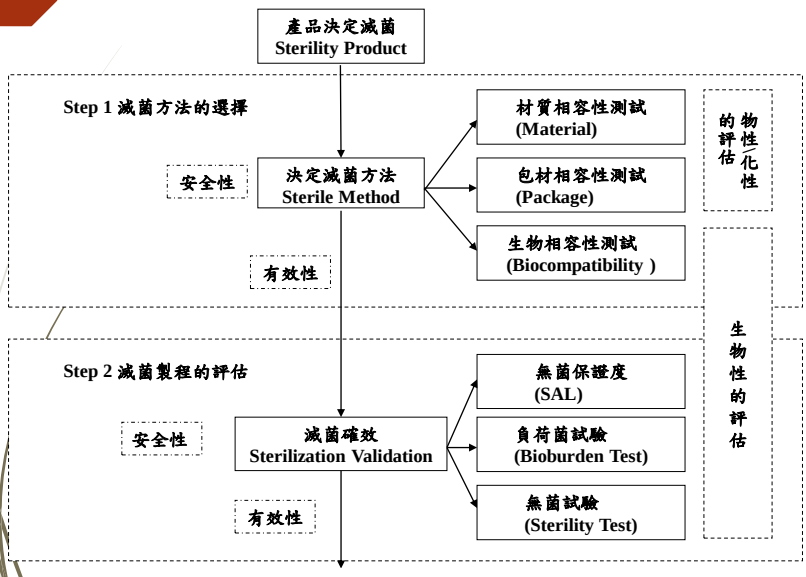
- ♦能達到10^{-6}的無菌保證度(SAL)
- ♦不會影響產品的功能及其品質規格
- ♦沒有滅菌劑殘留的問題
- ♦較低的成本(最短的時間、最少的投資)
- ♦優先考慮傳統的滅菌方法

滅菌種類的介紹

FDA將無菌醫療器材在滅菌製程中所使用的滅菌方法區分為三大類別：

定義	傳統滅菌方法 (Traditional)	非傳統式滅菌方法 (Non-traditional)	新穎性非傳統式滅菌方法 (Novel Non-traditional)
安全及有效的使用歷史	有	無	無
滅菌確效之文獻資料	有	有	少或無
經510(k)或上市前許可(premarket approval, PMA)等上市前審查認可	有	有	無
經FDA品質系統查廠認可 (satisfactory FDA QS inspections)	有	有	無
經FDA採認之滅菌確效標準	有	無	無
滅菌方法舉例(Examples of Sterilization Methods)	•乾熱Dry Heat •環氧乙烷（在固定容量之容器中）Ethylene Oxide (EtO) with devices in a fixed chamber •濕熱或蒸氣Moist Heat or Steam •輻射Radiation, (e.g., gamma, electron beam)	•過氧化氫Hydrogen Peroxide (H2O2) Gas Plasma •臭氧 Ozone (O3)	•二氧化氯(ClO2) •環氧乙烷（散擔法或注射法）Ethylene Oxide-in-a-Bag •高強度光或脈衝光High Intensity Light or Pulse Light •微波Microwave Radiation •聲波Sound Waves •紫外線 Ultraviolet Light •蒸發化學殺菌劑系統Vaporized Chemical Sterilant Systems (e.g., hydrogen peroxide or peracetic acid)

滅菌方法的選擇



滅菌管理技術分析圖

E-beam irradiators -

Classification by electron energy

-Low energy, 80 keV – 1 MeV表層改質

*maximum range of penetration: 60 mg/cm2 *applications: surface curing of thin films, lamination, production of antistatic, antifogging films, wood surface coating, surface sterilization of a pharmaceutical component

–Medium energy, 1 – 5 MeV交鏈鍵結/消毒殺菌

*typical penetration depths in unit density material: 5 – 20 mm *applications: cross-linking, polymer rheology modification, color enhancement of gemstones, sterilization of medical products and food irradiation

–High energy, 5 – 10 MeV醫療產品滅菌與交鍊鍵結

*maximum range of penetration: 50 cm at 10 MeV for 0.15 g/cm3 product density *applications: medical product sterilization, cross-linking, food irradiation for disinfestation and shelf-life extension, wastewater treatment, polymer rheology modification, color enhancement of gemstones

X-ray irradiators

- **Classification by: electron beam properties (initial electron energy, energy spectrum, acceleration principle), EB/X-ray converter, conveyor systems**

- **Characteristics:**
  - **high penetration**
  - **low efficiency of EB/X-ray conversion**
  - **broad energy spectrum**

Radiation – Different Facility

	Gamma Rays	E beam 10 MeV	X Rays 7 MeV
Source	Cobalt -60	E beam	E beam with target
Penetration	Big (entire pallet)	Limited: one side about 400mm at density 0.1	Big (entire pallet)
Homogeneity	Good: about 1.5 for pallets of about 400kg	Limited(Dmax/min) about 1.5(one side) to 2.8 (double side)	Very Good: Better then 1.3 for pallet of about 400kg
Treatment time	Some hours (Big Lot)	Second(Very small lot)	Less Hours(Small Lot)
Parametric release	Yes	Yes	Yes
ISO11137 accepted	Yes	Yes	Yes
Tolerance for inhomogeneous loading pattern	Good	Small	Very good
Unit	Pallet	Box	Pallet

輻射劑量計 DOSIMETER

FWT-60 SERIES RADIACHROMIC DOSIMETERS

Specifications

Type of Dosimeter: radiochromic thin film

Dose Range: 0.5-200 kGy (0.05-20 Mrad)

Dose Rate Dependence: Independent to over 10E12 Gy/sec

Intrinsic Sensitivity: The response (change in absorbance divided by thickness) is independent over unit thickness. Calibration of one thickness is applicable to all thicknesses.

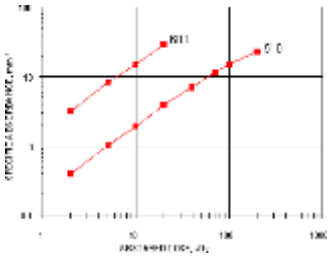
Peak color wavelength: 605 nm

Wavelength of interest: 510 nm and 600 or 605 nm

Color Build Up Time: Typically within 1 hour

Color Change: Unirradiated: clear; irradiated: deep blue

UV Sensitivity: Will color when exposed to wavelengths less than 350 nm.



滅菌原理與特性介紹

加馬射線可由^{60}Co或^{137}Cs產生，高穿透性的輻射線，可均勻、全面的穿透已包裝完畢之醫療用品，直接對其中之菌體造成死滅性的破壞，達到滅菌目的。

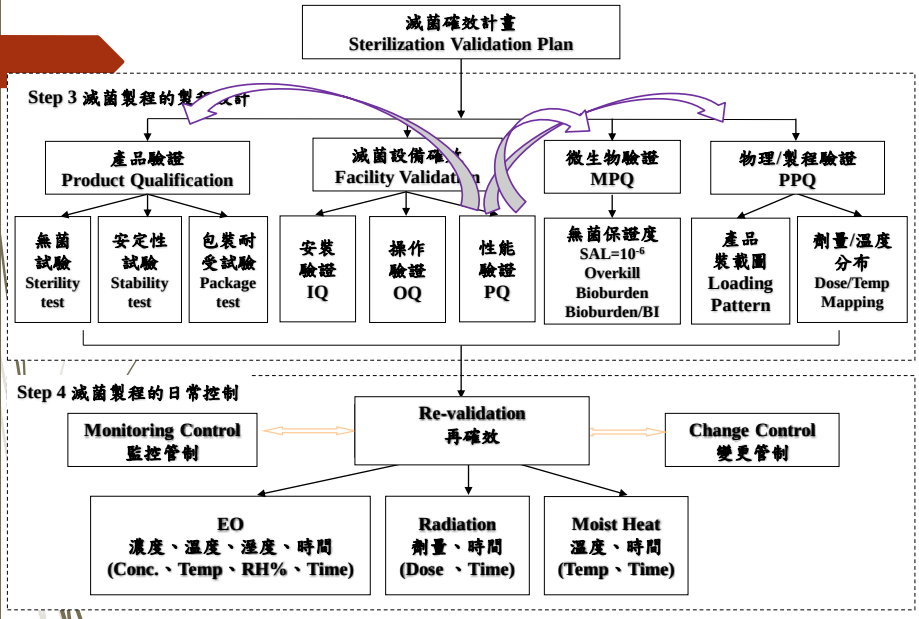
^{60}Co加馬射線的光子能量為1.17 Mev與1.33 Mev，均不足以引發原子核變化(須大於10Mev才會激發原子核），且^{60}Co射源密封於雙層不銹鋼管中，根本不與被照射物接觸，因此不會有輻射線殘留。

滅菌原理與特性介紹

γ-原理

一、間接作用：細胞內外水分子受γ-ray照射產生自由基和H_2O_2，這些水分解生成物對細胞重要分子誘發反應，致使變質失去新陳代謝作用，使微生物死亡。

二、直接作用：細胞的組成要素受γ-ray照射後，引起激發及電離作用，致使高分子受到破壞，失去新陳代謝作用而死亡



滅菌管理技術分析圖

輻射滅菌標準的介紹

- ISO 11137-1:2006/Amd 1:2013/Amd 2:2018Sterilization of health care products - Radiation -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.醫療保健產品滅菌-輻射–第一部分：醫療器材滅菌製程開發、確效與日常管制的要求
- ISO 11137-2:2006/2012/2013 Sterilization of health care products - Radiation -- Part 2: Establishing the sterilization dose.醫療保健產品滅菌-輻射–第二部分：滅菌劑量的評估
- ISO 11137-3:2006/2017 Sterilization of health care products - Radiation -- Part 3: Guidance on dosimetric aspects.醫療保健產品的滅菌-輻射–第三部分：劑量測定的指引
- ISO/TS 11137-4:2020 Part 4: Guidance on process control 製程管制指引

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ISO 11137-1: 2006/2013 /2018

1 Scope
2 Normative references
3 Terms and definitions
4 Quality management system elements：
5 Sterilizing agent characterization
6 Process and equipment characterization
7 Product definition
8 Process definition
9 Validation (IQ、OQ、PQ)
10 Routine monitoring and control
11 Product release from sterilization
12 Maintaining process effectiveness

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ISO 11137-2: 2006/2012/2013

1. Scope
2. Normative references
3. Abbreviations, terms and definitions
4. Definition and maintenance of product families for dose setting, dose substantiation and sterilization dose auditing
5. Selection and testing of product for establishing and verifying the sterilization dose
6. Methods of dose establishment
7. Method 1: dose setting using bioburden information
8. Method 2: Dose setting using fraction positive information from incremental dosing to determine an extrapolation factor
9. Method VDmax - Substantiation of 25kGy or 15kGy as the sterilization dose
10. Auditing sterilization dose
11. Worked examples

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ISO 11137-3：2006/2017

1. Scope
2. Normative references
3. Terms and definitions
4. Measurement of dose
5. Establishing the maximum acceptable dose
6. Establishing the sterilization dose
7. Installation qualification
8. Operational qualification
9. Performance qualification
10. Routine monitoring and control

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ISO/TS 11137-4：2020

1 Scope

2 Normative references

3 Terms, definitions and symbols

4 Principles applied in validating and controlling an irradiation process

5 Establishing process target doses

6 Routine monitoring and control

7 Release of product from the irradiation process

8 Maintaining process effectiveness

Annex A Examples of setting process target dose ranges and interpretation of process output

This document provides additional guidance to that given in ISO 11137-3 on meeting the requirements specified in ISO 11137-1, ISO 11137-2 and ISO/TS 13004 for the establishment and control of a radiation sterilization process using gamma, e- beam, and X-ray.

ISO 11137-1 Introduction

為完整有效的達到滅菌的製程確效, 應考量以下幾點:

a) 原料或零組件的微生物狀態；

b) 應用於產品的清潔和除污流程的確效和日常控制；

c) 產品製造組裝和包裝的環境控制；

d) 設備與製程的管制；

e) 人員及其衛生的管制；

f) 產品包裝的材料和方法；

g) 產品的儲存狀態；

1 Scope

1.1 This part of ISO 11137 specifies requirements for the development, validation and routine control of a radiation sterilization process for medical devices.

This part of ISO 11137 covers radiation processes employing irradiators using,

a) the radionuclide 60Co or 137Cs,

b) a beam from an electron generator

c) a beam from an X-ray generator

1.2 排除spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeld-Jakob disease.(如狂牛症), 不含無菌標示,不含品質系統,不需BI做滅菌監控,不規範照射系統操作的職業安全 ,不含再滅菌的要求

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3 Terms and definitions

3.1 absorbed dose/dose劑量: quantity of ionizing radiation energy imparted per unit mass of a specified material

NOTE 1 The unit of absorbed dose is the gray (Gy) where 1 Gy is equivalent to the absorption of 1 J/kg.

NOTE 2 For the purposes of this part of ISO 11137, the term dose is used to mean "absorbed dose

3.2 bioburden 負荷菌: population of viable microorganisms on or in product and/or sterile barrier system

3.3 biological indicator 生物指示劑: test system containing viable microorganisms providing a defined resistance to a specified sterilization

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3 Terms and definitions

3.4 calibration校正: set of operations that establish, under specified conditions, the relationship between values of a quantity indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards

3.5 change control: assessment and determination of the appropriateness of a proposed alteration to product or procedure

3.6 correction: action to eliminate a detected nonconformity

NOTE A correction can be made in conjunction with corrective action (3.7).

3.7 corrective action: action to eliminate the cause of a detected nonconformity or other undesirable situation

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3 Terms and definitions

NOTE 1 There can be more than one cause for a nonconformity.

NOTE 2 Corrective action is taken to prevent recurrence whereas "preventive action" (3.24) is taken to prevent occurrence.

NOTE 3 There is a distinction between correction and corrective action.

3.8 D value/ D10 value D 值: time or radiation dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

NOTE For the purpose of the ISO 11137 series, the D value refers to the radiation dose necessary to achieve the 90 % reduction.

3.9 development 開發: act of elaborating a specification

3.10 dose mapping 劑量分布圖: measurement of dose distribution and variability in material irradiated under defined conditions

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3 Terms and definitions

3.11 dosimeter輻射劑量計: device having a reproducible, measurable response to radiation, which can be used to measure the absorbed dose in a given system

3.12 dosimetry輻射劑量學: measurement of absorbed dose by the use of dosimeters

3.13 establish建立: determine by theoretical evaluation and confirm by experimentation

3.14 fault失效: one or more of the process parameters lying outside of its/their specified tolerance(s)

3.15 health care product(s)醫療保健產品: medical device(s), including in vitro diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

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3 Terms and definitions

3.16 installation qualification/IQ 安裝驗證: process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

3.17 irradiation container 照射容器: holder in which product is transported through the irradiator

NOTE The holder can be a carrier, cart, tray, product carton, pallet or other container.

3.18 irradiator operator 照射系統操作者: company or body responsible for irradiation of product

3.19 maximum acceptable dose 最大可接受劑量: dose given in the process specification as the highest dose that can be applied to a defined product without compromising safety, quality or performance

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3 Terms and definitions

3.20 medical device 醫療器材: instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of: ...以下省略

3.21 microorganism 微生物: entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

NOTE A specific standard might not require demonstration of the effectiveness of the sterilization process in inactivating all types of microorganisms, identified in the definition above, for validation and/or routine control of the sterilization process

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3 Terms and definitions

3.22 operational qualification/ OQ操作驗證: process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

3.23 performance qualification / PQ 性能驗證: process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification

3.24 preventive action預防措施: action to eliminate the cause of a potential nonconformity or other undesirable potential situation NOTE 1 There can be more than one cause for a potential nonconformity. NOTE 2 Preventive action is taken to prevent occurrence whereas "corrective action" (3.7) is taken to prevent recurrence.

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3 Terms and definitions

3.25 primary manufacturer: body responsible for the design and manufacture of a medical device, together with the safety and performance of that medical device when placed on the market

3.26 process interruption製程中斷: intentional or unintentional stoppage of the irradiation process

3.27 process parameter 製程參數: specified value for a process variable

NOTE The specification for a sterilization process includes the process parameters and their tolerances.

3.28 process variable製程變數: condition within a sterilization process, changes in which alter microbicidal effectiveness

EXAMPLES Time, temperature, pressure, concentration, humidity, wavelength.

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3 Terms and definitions

3.33 services 服務: supplies from an external source, needed for the function of equipment

EXAMPLES Electricity, water, compressed air, drainage.

3.34 specification規格: approved document stipulating requirements

3.35 specify 標準化: stipulate in detail within an approved document

3.36 sterile 無菌的: free from viable microorganisms

3.37 sterility無菌: state of being free from viable microorganisms

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven(see 3.39 sterilization)

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3 Terms and definitions

3.38 sterility assurance level/ SAL 無菌保證度: probability of a single viable microorganism occurring on an item after sterilization

NOTE The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value but provides greater assurance of sterility than an SAL of 10^{-3}.

3.39 sterilization 滅菌: validated process used to render product free from viable microorganisms

NOTE In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number it can never be reduced to zero [see "sterility assurance level" (3.38)].

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3 Terms and definitions

3.40 sterilization dose 滅菌劑量: minimum dose to achieve the specified requirements for sterility

3.41 sterilization process滅菌製程: series of actions or operations needed to achieve the specified requirements for sterility

NOTE This series of actions includes pretreatment of product (if necessary), exposure under defined conditions to the sterilizing agent and any necessary post treatment. The sterilization process does not include any cleaning, disinfection or packaging operations that precede sterilization.

3.42 sterilizing agent 滅菌劑: physical or chemical entity, or combination of entities having sufficient microbicidal activity to achieve sterility under defined conditions

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3 Terms and definitions

3.43 test for sterility 無菌試驗: technical operation defined in an official pharmacopoeia performed on product following exposure to a sterilization process

3.44 test of sterility無菌的試驗: technical operation performed as part of development, validation or requalification to determine the presence or absence of viable microorganisms on product or portions thereof

3.45 transit dose傳遞劑量: dose absorbed during travel of product or source to or from the non-irradiation to the irradiation position

3.46 uncertainty of measurement量測不確定性: parameter, associated with the result of a measurement, that characterizes the dispersion of values that could reasonably be attributed to the measurand

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3 Terms - ISO11137-2

3.47 an validation 確效: documented procedure for obtaining, recording d interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

3.1.9 sample item portion/SIP取樣比例: defined portion of a health care product that is tested

3.1.10 standard distribution of resistances/SDR: reference set of resistances of microorganisms and corresponding probabilities of occurrence 微生物抗性和相對應發生概率參考值

3.1.13 sterilization dose audit: exercise undertaken to confirm the appropriateness of an established sterilization dose

3.2.13 VDmax25: maximal verification dose for a given bioburden, consistent with the attainment of an SAL of 10^{-6} at a specified sterilization dose of 25 kGy 。在特定負荷菌數下的最大驗證劑量，可在指定的25 kGy滅菌劑量下一致達到SAL 10^{-6}。

4 Quality management system elements

4.1 Documentation 文件化

4.2 Management responsibility 管理責任符合ISO13485

4.3 Product realization 產品實現-採購、鑑別、追朔、校正、輻射劑量計使用

4.4 Measurement, analysis and improvement — Control of nonconforming product 量測分析和改善-異常產品管制

5 Sterilizing agent characterization

5.1 Sterilizing agent 滅菌劑

5.1.1 The type of radiation to be used in sterilization processing shall be specified.

5.1.2 For electrons or X-rays, the energy level of the electron beam shall be specified. If the energy level for electrons exceeds 10 MeV or the energy level for electrons used to generate X-rays exceeds 5 MeV, the potential for induced radioactivity in product shall be assessed. The outcome of the assessment and the rationale for decisions reached shall be documented

5.2 Microbicidal effectiveness 殺菌效力

Reference to these general studies on microbial inactivation is not required by this part of ISO 11137.

5 Sterilizing agent characterization

5.3 Material effects 材料的影響

- The effects of radiation on a wide variety of materials used to manufacture medical devices have been comprehensively documented and the resultant documentation is of value to those designing and developing medical devices that are to be sterilized by radiation. This part of ISO 11137 does not require the performance of studies on material effects, but does require performance of studies of the effects of radiation on product (see 8.1).

5.4 Environmental considerations 環境的考量

6. Process and equipment characterization

6.1 Process：製程差異應鑑別與確認並載明監控的方法

6.2 Equipment ：照射系統與其操作的方法的規範及軟體的控制及其設備的描述如下(for gamma irradiator)-設備驗證-IQ

a) 照射系統及其特性； b) 放射性物質活度與射源立體位置圖；

c) 照射系統配置圖； d) 已照射產品與未照射產品的區隔；

e) 輸送系統結構與操作； f) 輸送系統路徑與輸送帶速度的範圍；

g) 照射容器的規格材料與結構；

h) 照射系統及輸送系統的操作與保養方式； i) 射源所在位置；

j) 計時器或輸送系統失效時射源自動回歸儲存位置與輸送帶停止

k) 如射源未回歸預定位置時，射源如何回歸儲存位置與輸送帶如何自動停止或對產品的影響；

7 Product Definition

7.1 應詳細載明被滅菌產品與包裝材料

7.2 應詳細載明被滅菌產品與包裝材料及其裝載形式的變更

7.3 被滅菌產品的狀態(含負荷菌量)應予以規範以達滅菌效果

7.4 被滅菌產品應加以分類以符合ISO 11137-2

7.5 製程的類別應加以區分以免影響產品照射劑量

7.6 應定期審查製程分類

8 Process Definition

8.1 應建立最大可接受劑量(最高劑量)
Establishing the maximum acceptable dose

8.2 應評估滅菌所需劑量(最低滅菌劑量)
Establishing the sterilization dose

8.3 界定最高劑量與滅菌劑量範圍
Specifying the maximum acceptable dose and the sterilization dose

8.4 在不同射源的最高、確效與滅菌劑量的轉換
Transference of maximum acceptable, verification or sterilization dose between radiation sources

8. Process definition

8.1 Establishing the maximum acceptable dose

8.1.1 The maximum acceptable dose for product shall be established. When treated with the maximum acceptable dose, product shall meet its specified functional requirements throughout its defined lifetime.

8.1.2 Basic technical requirements to establish the maximum acceptable dose shall include:

a) a facility capable of assessing product with regard to its intended function;

b) product representative of that to be produced routinely;

c) an appropriate source of radiation capable of precisely and accurately delivering the required doses (see 8.4.1).

8. Process definition

8.2 Establishing the sterilization dose

8.2.1 The sterilization dose shall be established for product.

8.2.2 One of two approaches, as described in a) and b) below, shall be taken in establishing the sterilization dose:

a) a knowledge of number and/or resistance to radiation of the bioburden is obtained and used to set the sterilization dose or

b) a sterilization dose of 25 kGy or 15 kGy is selected and substantiated; in substantiating a sterilization dose of 25 kGy or 15 kGy, the primary manufacturer shall have evidence that the selected sterilization dose is capable of achieving the specified requirements for sterility (see 1.2.2)

8. Process definition

8.2.3 Basic technical requirements to establish the sterilization dose shall include:

a) a competent microbiological laboratory to perform determinations of bioburden in accordance with ISO 11737-1 and tests of sterility in accordance with ISO 11737-2;

b) product representative of that to be produced routinely;

c) an appropriate source of radiation capable of precisely and accurately delivering the required doses (see 8.4.2).

NOTE Guidance on dosimetric aspects of radiation sterilization can be found in ISO 11137-3.

8. Process definition

8.3 Specifying the maximum acceptable dose and the sterilization dose

The sterilization dose and the maximum acceptable dose shall be specified for product.

8.4 Transference of maximum acceptable, verification or sterilization dose between radiation sources

8.4.1 Transference of maximum acceptable dose

評估證實劑量在二種射源的殺菌效力無差異並文件化紀錄

8.4.2 Transference of verification dose or sterilization dose

驗證劑量和滅菌劑量需證實二種射源的殺菌效力無差異且只能γ<->γ , E-beam <->E-beam, X-ray <->X-ray. 若產品含有水則需再確認操作條件

9. Validation

9.1 Installation qualification (IQ)
安裝驗證

9.2 Operational qualification (OQ)
操作驗證

9.3 Performance qualification (PQ)
性能驗證

9.4 Review and approval of validation
確效審查與核准

10. Routine Monitoring and Control

10.1 照射前中後產品的搬運程序應加以規範

10.2 產品接收、裝載、卸載、操作和放行應計數與檢查與解決異常

10.3 應區分未照射與已照射產品.

10.4 輻射變色指示計(CI)只供作經過照射的辨識

10.5 產品裝載應依製程規範

10.6 輻射劑量計應貼於預定的監控位置

10.7 應規範輻射劑量計偵測頻率以達製程監控目的

10.8 應參考γ射源衰減調整時間設定或輸送帶速度，射源與被照射器相對位置應加以監控

10.9 E-beam和X-ray製程規格與輸送帶速度應加以監測與紀錄

10.10 應紀錄製程中斷或製程異常所採取行動

10.11照射紀錄應可追朔至照射日的批次紀錄

11. Product Release from Sterilization

11.1 產品滅菌放行應完成相關測試、校正、保養或再確效工作與其記錄 。

11.2 產品放行前應審查的紀錄應加以規範， 其他可參考品質系統ISO13485。

12 .Maintaining Process Effectiveness

12.1 Demonstration of continued effectiveness

12.1.1 General:為維持建立的滅菌劑量持續有效性應進行證明

a)監測產品Bioburden確認其值符合規定的bioburden limit

b)定期 dose audit以監測產品微生物對輻射的抗性

12.2 Recalibration再校正

12.3 Maintenance of equipment設備的保養(Preventative maintenance)

12.4 Requalification of equipment設備的再驗證

12.5 Assessment of change異動的評估(irradiator or product)

輻射滅菌確效計畫規劃

A.產品定義與分類(Product Definition and Family)

1.產品介紹：代號、名稱、批號、類別

2.產品包裝及裝載模式：透氣包裝袋、紙箱規格

3.產品的微生物含量(Bioburden)：是否具有代表性產品 Master Product或 PCD。

B.滅菌設備確效(Facility Validation Report):由滅菌設備廠完成(IQ & OQ/Compliance with ISO11137)

1.照射滅菌系統文件(Facility Documentation)

2.照射滅菌系統測試(Facility Testing)

3.劑量偵測設備校正(Equipment Calibration)

4.照射系統劑量分佈(Facility Dose Mapping)

輻射滅菌確效計畫規劃

C.產品驗證(Product Qualification)

1.產品及包裝材料的評估(Product and Packaging Materials Evaluation)-最大劑量(Max. Dose)

2.滅菌劑量決定(Sterilization Dose Determination)-MPQ 最小劑量(Min. Dose)

D.製程驗證(Process Qualification) PPQ

1.決定產品的裝載型式(Determination of Product Loading Pattern)

2.產品的劑量分佈圖(Product Dose Mapping)

E.審核與確認確效報告(Review and Certification of Validation Report)

F.滅菌劑量稽核(Sterilization Dose Auditing)

Bioburden test/Verification dose and Sterility

輻射化學效應直接作用

- 輻射生物學家提出輻射線與物質直接碰撞的靶理論，認為照射作用主要是由於這種直接碰撞引起的。
- 游離輻射使產品產生各種粒子、離子及質子過程：
  - 初級輻射(Primary radiation)-是使物質形成離子、激發態分子或分子碎片。
  - 次級輻射(Secondary radiation)-是使初級輻射的產物相互作用，生成與原始物質不同的化合物。
- 初級輻射一般無特殊條件，而次級輻射與溫度等其他條件有關。

輻射滅菌對材質的影響

- 醫療器材選擇滅菌方法時，應評估產品材料與包裝的相容性，製造廠商須完成滅菌相關測試排除不相容的方法
- 輻射照射(Gamma/E-beam滅菌)是屬於快速滅菌的方法，但須注意輻射照射對高分子材料的產品與包裝的不良影響。
- 加馬射線對材質的影響：

A.斷鏈作用(分子鏈的斷裂)

B.交聯作用(分子鏈交聯鍵結的形成)

- AAMI TIR17:2008 Compatibility of materials subject to sterilization

塑膠材料的輻射耐受性

Polymer	Radiation Stability	Radiation Dose to Produce Significant Damage(Mrads)
Polycarbonate(PC)	優(輕微變黃)	100+
Polyesters(Aromatic)	優	100
Polyethylene(PE)	優(輕微變黃)	100
Polypropylene(PP)	良-差	10
Polystyrene(PS)	優(可能輕微變黃)	1000
Polyvinyl Chloride(PVC)	良(變色/加穩定劑)	50-100
ABS(Acrylonitrile–butadiene-styrene)	優	100
Polyacetals	差	1-2
PMMA(Polymethyl methacrylate)	差	5
Polyamides(Nylons)(Aliphatic)	良(輕微變色)	50-100
Cellulosics	可	20
PTFE(Polytetrafluoroethylene)	差	1

優:1000kGy以上 良:200-1000kGy 可:50-200kGy 差:低於20kGy

建立最大可接受劑量
Establishing the Maximum Acceptable Dose

- When treated with the maximum acceptable dose, product shall meet its specified functional requirements throughout its defined lifetime.
- Functionality and safety
- Biological safety (ISO 10993-1)
- Overdose Ratio (ODR) Definition: A dose within the processing capabilities of the irradiator.
- ODR= Maximum Dose / Minimum Dose

Radiator Source	Typical ODR
Gamma/X-ray	1.4-2.0
Electron Beam	1.6-3.0

Test Program

Sequence of activities：

- Choice of the materials for the product and/or package and Design of device
- Design test program (validation protocol)
- Choice the maximum dose
- Test samples

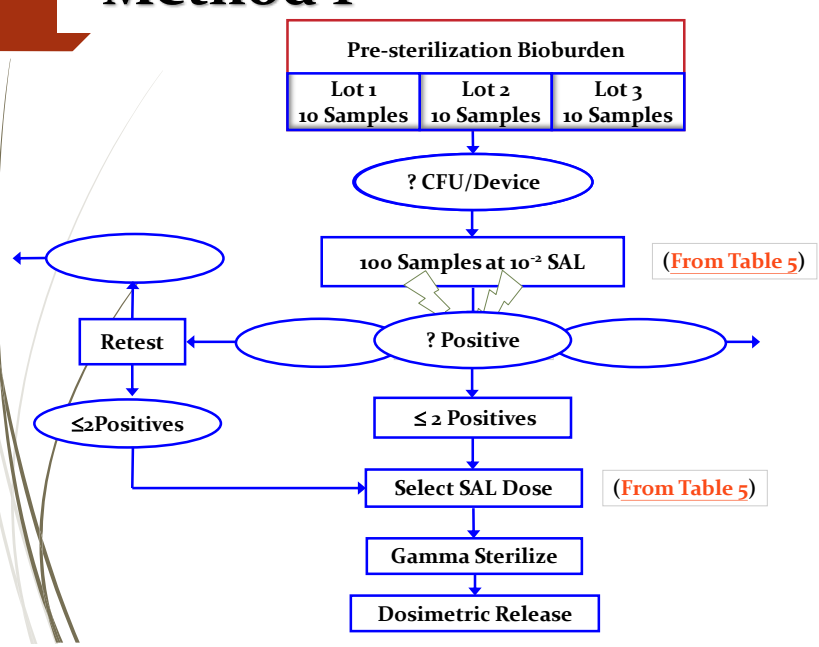
Select single dose or multiple doses for testing samples：

- A) single dose ≧ Anticipated Maximum Routine processing Dose
- B) Multiple dose which span the range of doses might be observed (ex: 35, 40, 45, 50 kGy)

滅菌劑量決定- MPQ
Dose Setting - Irradiation

	Method 1	Method 2A	Method 2B	VDmax25	$VD_{max}15$
Rationale	Bioburden	B. resistance	B.resistance	Bioburden	Bioburden
Max Bioburden	10^6	<1000	<1000	<1000	<1.5
Verification(SAL)	10^{-2}	10^{-2}	10^{-2}	10^{-1}	10^{-1}
Verification Dose	1.3-21.2kGy	2 kGy (9 doses)	1 kGy (8 doses)	0-8.1kGy	0-2.3kGy
Sterilization(SAL)	10^{-3}~10^{-6}	10^{-6}	10^{-6}	10^{-6}	10^{-6}
Sterilization Dose	11.0~36.3 kGy	6.0~25 kGy	6.0~25 kGy	25 kGy	15 kGy
No. of Samples (B.)	3 lots/10 each	None	None	3 lots/10 each	3 lots/10 each
No. of Samples (S.)	100	840	780	10	10
SIP Allowed	Yes	Yes	No	Yes	No
S. Passing Criteria	≤ 2 positive	≤ 2 positive	≤ 2 positive	≤ 1 positive	≤ 1 positive

Method 1



Method 1 : Table 5

Table 5 - Radiation dose (kGy) required to achieve a given SAL for an average bioburden equal to or greater than 1.0 having standard distribution of resistances

Average Bioburden	Sterility Assurance Level					Average Bioburden	Sterility Assurance Level				
	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}		10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
1.0	3.0	5.2	8.0	11.0	14.2	110	8.1	11.1	14.3	17.8	21.3
1.5	3.3	5.7	8.5	11.5	14.8	120	8.2	11.2	14.5	17.9	21.5
2.0	3.6	6.0	8.8	11.9	15.2	130	8.3	11.3	14.6	18.0	21.6
2.5	3.8	6.3	9.1	12.2	15.6	140	8.4	11.4	14.7	18.1	21.7
3.0	4.0	6.5	9.4	12.5	15.8	150	8.5	11.5	14.8	18.2	21.8
3.5	4.1	6.7	9.6	12.7	16.1	160	8.5	11.6	14.9	18.3	21.9
4.0	4.3	6.8	9.7	12.9	16.2	170	8.6	11.7	15.0	18.4	22.0
4.5	4.4	7.0	9.9	13.1	16.4	180	8.7	11.8	15.1	18.5	22.1
5.0	4.5	7.1	10.0	13.2	16.6	190	8.8	11.9	15.1	18.6	22.2
5.5	4.6	7.2	10.2	13.4	16.7	200	8.8	11.9	15.2	18.7	22.3
6.0	4.7	7.3	10.3	13.5	16.9	220	9.0	12.1	15.4	18.8	22.4
6.5	4.8	7.4	10.4	13.6	17.0	240	9.1	12.2	15.5	19.0	22.6
7.0	4.8	7.5	10.5	13.7	17.1	260	9.2	12.3	15.6	19.1	22.7

Method 2A &2B

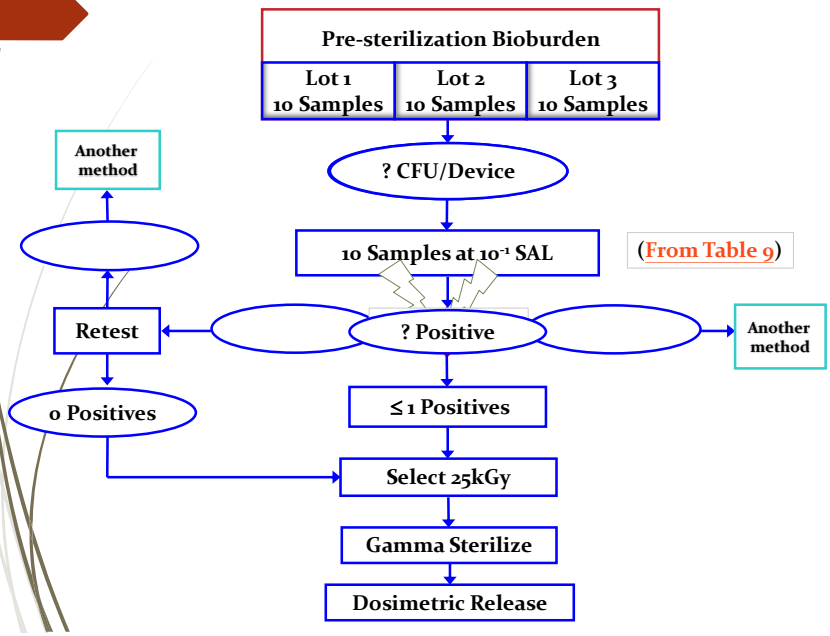
Table 21 — Number of product items for irradiation at various incremental doses- Method 2A

Batch No.	Nominal incremental dose (kGy)									Product held for Stage 3 experiment	Total product Required
	2	4	6	8	10	12	14	16	18		
1	20	20	20	20	20	20	20	20	20	100	280
2	20	20	20	20	20	20	20	20	20	100	280
3	20	20	20	20	20	20	20	20	20	100	280

Table 26 — Number of product items for irradiation at various incremental doses- Method 2B

Batch No.	Nominal incremental dose (kGy)								Product held for Stage 3 experiment	Total product Required
	1	2	3	4	5	6	7	8		
1	20	20	20	20	20	20	20	20	100	260
2	20	20	20	20	20	20	20	20	100	260
3	20	20	20	20	20	20	20	20	100	260

VDmax 25



Method VDmax25 : Table 9

Table 9 - Values of VD_{max}^{25} and SIP dose reduction factors for levels of average bioburden ≦ 1000 CFU

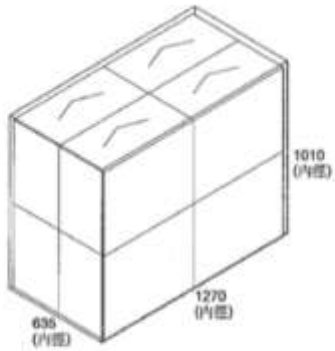
Average bioburden	SIP=1.0 VD_{max}^{25} (kGy)	SIP dose reduction factor (kGy)		Average bioburden	SIP=1.0 VD_{max}^{25} (kGy)	SIP dose reduction factor (kGy)
≦0.1	0.0	n/a[a]		50	8.8	3.25
0.15	0.9	n/a[a]		55	8.9	3.23
0.20	1.4	n/a[a]		60	8.9	3.21
0.25	1.8	n/a[a]		65	9.0	3.20
0.30	2.2	n/a[a]		70	9.1	3.19
0.35	2.5	n/a[a]		75	9.1	3.17
0.40	2.7	n/a[a]		80	9.2	3.15
0.45	2.9	n/a[a]		85	9.1	3.11
0.50	3.1	n/a[a]		90	9.1	3.08
0.60	3.4	n/a[a]		95	9.1	3.05
0.70	3.6	n/a[a]		100	9.0	3.01
0.80	3.8	n/a[a]		110	9.0	2.96
0.90	4.0	n/a[a]		120	9.0	2.91
1.0	4.2	4.17		130	8.9	2.86

Method VDmax : Table 10

Table 10 — Values of VD_{max}^{15} for levels of average bioburden ≤ 1,5

Average bioburden	SIP = 1,0 VD_{max}^{15} (kGy)	Average bioburden	SIP = 1,0 VD_{max}^{15} (kGy)
≤ 0,1	0,0	0,50	1,8
0,15	0,5	0,60	2,0
0,20	0,9	0,70	2,2
0,25	1,1	0,80	2,3
0,30	1,3	0,90	2,2
0,35	1,5	1,0	2,1
0,40	1,6	1,5	1,7
0,45	1,7		
NOTE If VD_{max}^{15} = 0,0 kGy, product items are not irradiated			

產品裝載圖
Product Loading Pattern



Shrink Wrap 1270x635x1010

	紙箱 (內徑)	紙箱 (外徑)	紙箱 凸出	棧運箱 (內徑)	棧運箱 (外徑)	棧運箱 凸出
長度:	615.00 毫米	615.00 毫米	0.00 毫米	1270 毫米	1270 毫米	0 毫米
寬度:	310.00 毫米	310.00 毫米	0.00 毫米	635 毫米	635 毫米	0 毫米
高度:	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Dose Mapping – Performance Qualification

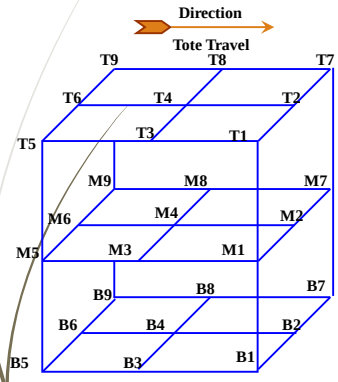
What is PQ?

–PQ performed with product in a specific loading pattern

–Determine location and magnitude of min and max dose

–Determine relationship between min and max and routine monitoring position

Dose Mapping



T1:	29.8	M1:	34.1	B1:	29.6
T2:	28.8	M2:	31.6	B2:	30.7
T3:	31.5	M3:	39.5	B3:	31.4
T4:	30.0	M4:	34.0	B4:	32.8
T5:	30.7	M5:	37.6	B5:	32.0
T6:	29.8	M6:	32.2	B6:	30.4
T7:	33.7	M7:	41.8	B7:	32.0
T8:	33.1	M8:	40.8	B8:	33.4
T9:	33.0	M9:	39.8	B9:	34.5

最高劑量區： M7
HIGH DOSE
最低劑量區： T2
LOW DOSE

Dose Audit - Frequency of determinations of bioburden

Average bioburden	≧ 1.5	< 1.5	< 1.5	All
Setting using	All	Method 2 or VDmax 25	Method 1 or VDmax 15	All
Frequency	three months	three months	one month	each batch (生產間隔< Frequency)

Dose Audit – Method 1 or 2(VDmax 15 or 25)

1. Obtain samples of product: select 110 (20)from a signal batch of product
2. Determine average bioburden
   - Perform bioburden test on 10 (10) samples
   - Calculate the average bioburden
3. Perform verification dose experiment
   - Irradiate 100 (10) samples at verification dose previously determined
   - Conduct test of sterility on each irradiated product
4. Interpretation of results

Dose audit：Interpretation of results

Positive (Method 1 &2)	≦2	3 or 4	5 -15	> 15
Positive (VD_{MAX}15 &25)	≦1	2	3 -6	> 7
Dose Audit	accepted	Repeat the sterilization dose audit	corrective action and repeat the sterilization dose audit.	Stop sterilization
Sterilization Dose	-	augment the sterilization dose	augment the sterilization dose	until the sterilization dose is re-established using another method

感謝聆聽 敬請指正

Kenny Kuo