國際創新生物產品製程開發與審查考量經驗分享

活動時間：2022年10月6日

活動地點：集思北科大會議中心

指導單位：衛生福利部

主辦單位：財團法人醫藥品查驗中心

國際創新生物產品製程開發與審查考量經驗分享

會議邀請函

因應新冠肺炎疫情帶動全球生技醫藥產品市場需求成長，核酸藥物與細胞製劑等創新生物產品製造關鍵技術成為當紅議題，並促使更多生技業者投入。然，在創新生物產品製造過程中，自動化技術、放大製程、儲存、運送與驗證皆與產業化量產效率息息相關，因此財團法人醫藥品查驗中心擬邀請台南梁山工程顧問公司林宗儒專案品質經理分享創新生物產品製程無菌性相關規範，百略醫學科技股份有限公司王秀如協理分享創新生物產品冷鏈儲存及運輸時需注意之法規與經驗，及工業技術研究院生醫與醫材研究所沈欣欣副所長分享細胞治療自動化技術國際趨勢與現況，期望能對於國內核酸藥物研究發展有所助益。**竭誠歡迎各界先進撥冗參加交流！**

■ 活動日期與時間：2022 年 10 月 6 日(星期四) 14:00~17:00

■ 活動地點：集思北科大會議中心感恩廳

■ 指導單位：衛生福利部

■ 主辦單位：財團法人醫藥品查驗中心

■ 活動議程：

時間	講題	講者
13:30-14:00	報到	
14:00-14:10	開場致詞	醫藥品查驗中心
14:10-14:50	創新生物產品製程無菌性相關規範分享	台南梁山工程顧問公司 林宗儒專案品質經理
14:50-15:30	創新生物產品冷鏈儲存及運輸時需注意之法規與經驗分享	百略醫學科技股份有限公司 王秀如協理
15:30-16:00	中場休息	
16:00-16:40	細胞治療自動化技術國際趨勢與現況	工業技術研究院生醫與醫材研究所 沈欣欣副所長
16:40-17:00	綜合討論	

創新生物產品製程無菌性相關規範分享

Ken (Tsung-Ju) Lin

Mobile No.: 0955-111-743, Ken.tj.lin@gmail.com

PROFILE SUMMARY

Over 17 years of diversified experience in laboratory operation and quality system in pharmaceutical industries and familiar with the requirements of pharmacopoeia and regulation, such as USP/EP/JP, PIC/S, ICH, CFR, etc., and with a highly responsibility, as well as able to work under pressure. He also has experience in supporting the pharmaceutical facilities design, startup, commissioning and validation operations.

Mr. Lin has taught local seminars and conferences at TPDA and TPQRI as well as provided training to Taiwan FDA during public and corporate seminars. He is a member of the TPDA LETTER Editorial Committee. His specific areas of expertise include pharmaceutical microbiology, aseptic processing, quality system management, utilities and process qualification, construction and automation system planning.

QUALITY CERTIFICATION

ISO 9001: 2008 internal quality auditor training, Certification no. (2012)0399

PDA Certificate of Accomplishment:

- *Aseptic Processing Training Program, 2013*
- *GMPs for Manufacturers of Sterile and/or Biotechnology Products, 2013*
- *Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: Case Studies in the Manufacturing of Pharmaceutical Drug Products, 2013*

EDUCATION

NATIONAL PINGTUNG UNIVERSITY OF SCIENCE AND TECHNOLOGY (NPUST), TAIWAN

Biological Science and Technology, M.S. 2002 - 2004
Animal Science, B.S. 1998 - 2002

EXPERIENCE

PERSIMMON TAINAN ENGINEERING CONSULTING LTD., TAINAN, TAIWAN

Project Quality Consultant 2016 - present

- BeiGene Taiwan New GTP Site Project
  - Quality System SOP Preparation
  - Facility and Equipment Qualification Document Preparation
  - Media Fill Design
- TaiGen Biotech New Product Filling Project (Taipei, Taiwan)
  - Microbiological Method Validation Document Review
- Shining Biotech New ATMP Manufacturing Site Project (Taipei, Taiwan)
  - Quality System SOP Preparation
  - Facility and Equipment Qualification Document Preparation
- Formosa Laboratories New injectable plant project (Taoyuan, Taiwan)
  - FDA Design Review Package Preparation

  - Quality System SOP Preparation
- Amaran Biotech New injectable plant project (Hsinchu, Taiwan)
  - Design review
- OP Nano Lyophilization filling line project (Yunlin, Taiwan)
  - Production qualification documents preparation
  - Microbiological Lab readiness
- Eirgenix EMS System Validation (Hsinchu, Taiwan)
  - Design documents review
  - RTM preparation
  - Qualification protocol and report review
- Pfizer KUBio Facility- Automation System Validation Project (Hangzhou, China)
  - Deviation and change control management
  - Computer System Validation Plan
  - Computer System Risk Assessment & SOP Development
  - System Risk Assessments and Gap Analysis
  - Computer System Qualification Protocols
- Intech Biopharm MDI & DPI plant ICS (Instrument Control System) Validation (Hsinchu, Taiwan)
  - Risk assessment for the system
  - URS and Design documents review
  - Qualification protocol preparation and report review
- PharmaEssentia Bulk & Fill/Finish Facility- Computer System Validation Project (Taichung, Taiwan)
  - Computer System Validation Plan
  - Computer System Risk Assessment & SOP Development
  - ERP System Risk Assessments and Gap Analysis
  - Computer System Qualification Protocols
- LivaNova Medical Device Manufacturing Facility CMS Design and Qualification (Suzhou, China)
  - Computer System Validation Plan
  - Computer System Risk Assessment
  - Computer System SOP Development
- Alvogen Lotus Site Quality Improvement Project (Nantou, Taiwan)
  - Quality Improvement Project Manager
  - SOP Development
  - Project Cost and Schedule Controls and Management Reporting

SCINOPHARM TAIWAN LTD., TAINAN, TAIWAN

Head of Quality Assurance, Injectable Plant 2012 - 2016

- Attend injectable project meetings and assist the project team with determination of regulatory requirements.
- Development and implementation of quality system.
- Establish and manage training system.
- Responsible for internal and regulatory audits, and also vender qualification.
- Maintain project documentation for preparation of FDA PAI.
- Review and approve qualification document and SOPs
- Provide quality oversight for all validation and qualification efforts
- Provide quality support for vendor qualification
- Works with QA director to review all quality documents compliance with regulatory agencies.
- Demonstrate strong proficiency in the application of the CAPA system, to ensure action, closure and verification of effectiveness of solutions applied to root cause issues originating from internal/external quality audits or other sources.

- Provide review and feedback on validation/qualification plans and reports.
- Provide supervision of QA associates/specialists
- Ensure proper management of deviations.
- Review batch records.
- Ensure that record keeping under FDA requirements are attributable, legible, contemporaneous, original and above all, accurate.
- Ensure that equipment under FDA standards are properly maintained, cleaned and inspected on a routine basis per SOPs.

STANDARD CHEM. & PHARM. CO., LTD., TAINAN, TAIWAN

Supervisor, Quality Control Microbiological Laboratory 2008 - 2012

- Development of quality plans which include inspection, testing procedures and proper documentation.
- Supports internal and regulatory audits, and also vender audits.
- Coordinate and assist program teams to resolve any encountered problems related to inspection and testing activities
- Coordinates and reviews in-process and release testing.
- Ensures department metrics and cycle times are monitored and achieved.
- Oversees daily operation of Microbiology Laboratory.
- Lead OOS/OOT investigations and work closely with quality assurance, process development, manufacturing, and research and development.

Group Leader, Quality Control Microbiological Laboratory 2007 - 2008

- Train junior analysts on assay performance.
- Writes and revises SOPs, methods, protocols, and reports.
- Ensure testing is performed accurately and in compliance with cGMP procedures, established regulatory requirements, SOPs, and other approved test methods.
- Supporting for design and qualification of new facilities and manufacturing sites.
- Implement corrective actions as applicable.
- Troubleshoot aberrant data.
- Maintain qualified instruments.
- Assist with guidance on investigations for quality incidents, CAPAs, and Change Controls.

Microbiologist, Quality Control Microbiological Laboratory 2005 - 2007

- Perform work in compliance with cGMP guidance. (Microbiological testing, Media fills)
- Responsible for ensuring product microbial quality and sterility through environmental and product monitoring, reporting, and trending. Take necessary actions for conditions that are outside of acceptable limits.
- Work with new product development and ongoing improvement project teams to evaluate, test and document the sterilization processes and products.
- Implement procedures related to sterilization processes, clean room standards and environmental monitoring.
- Investigate and disposition any non-conformance related to product microbial quality and sterility.
- Initiate, investigate and implement corrective actions for issues related to microbial quality or sterility.

PROFESSIONAL ACTIVITIES

GMP Compliance Inspection, Biologicals Plant of National Health Research Institutes (2016)
Member of TPDA (Taiwan Parenteral Drug Association) Letter Editorial Committee (2015 - present)

Member of Curriculum Advisory Committee, College of Science, National Chung Cheng University (2015)

Member of Self-Evaluation Committee, Department of Life Science, National Chung Cheng University (2014)

Speaker for TTQAA (Taiwan Testing and Quality Assurance Association) workshop (2014) – Suitability testing of microbiological methods

Speaker for TPDA conferences and workshops (2013 - present)

- "Pharmaceutical Quality Risk Management" - training course for Biomedical Translation Research Center (BioTReC) of Academia Sinica (2022)
- "IQ/OQ of Moist Heat Sterilizer"- training course for TFDA Inspectors. (2022)
- "Development and selection of URS for hardware facilities and equipment systems in pharmaceutical factories" - training course for TFDA PPCD (Pharmaceutical Plant of Controlled Drugs) (2022)
- "Cleanroom Management and Highlights of the revision of ISO 14644"- training course for biologicals plant of Institute of Nuclear Energy Research (2022)
- "Plant Expansion Instructions / Utility System Qualification"- training course for biologicals plant of Institute of Nuclear Energy Research (2022)
- "Introduction of Isolator and RABS" - training course for OBI Pharma
- "Data Integrity & Computerized System Validation" - training course for MetaTech Inc. (2022)
- "Implementation of QRM for Pharmaceutical Manufacturing Operations"- training course for MetaTech Inc. (2022)
- "Design, Qualification and Maintenance Of HVAC System"- training course for GwoXi Stem Cell (2021)
- "Pharmaceutical water system maintenance and maintenance plan design points explanation"- training course for TFDA PPCD (Pharmaceutical Plant of Controlled Drugs) (2021)
- "Highlights of the revision of ISO 14644"- training course for ATMP GMP Training (2021)
- "PIC/S GMP Guide Annex 1 Draft, Feb. 2020 Manufacture of Sterile Medicinal products"- training course for Institute of Nuclear Energy Research (2021)
- GMP Counseling for UnicoCell Biomed. (2021)
- "Plant Expansion Instructions / Utility System Qualification"- training course for biologicals plant of National Health Research Institutes (2021)
- "Highlights from the literature on PDA cleaning and disinfection"- TFDA Workshop (2020)
- "Quality Risk Assessment and Management"- training course for Caliway Biopharmaceuticals (2020)
- "SIP"- Sterile Medicinal Products GMP Workshop Part II (2020)
- "USP <85> and <1011>"- training course for Taiwan Biotech Co. (2020)
- "Cleaning and Disinfection Program for Pharmaceutical Facility"- training course for Institute of Nuclear Energy Research (2020)
- "Microbial limit test"- training course for Institute of Nuclear Energy Research (2020)
- "Introduction of USP <1223>"- training course for Institute of Nuclear Energy Research (2020)
- "Aseptic Technology"- training course for Taiwan Biotech Co. (2020)
- "Environmental Monitoring of Sterile Medicinal Products Manufacturing"- training course for NHRI (2019)
- "Practices of Environmental Monitoring and Personal Hygiene in the Processing Location"- ATMP GMP Training Course (2019)
- "Cleaning and Disinfection Program for Pharmaceutical Facility"- training course for Amaran Biotechnology (2019)
- "Microbiological Tests and Microbiological Lab Operation"- training course for Caliway Biopharmaceuticals (2019)
- "Cleaning and Disinfection Program for Pharmaceutical Facility" (2019)
- "Environmental Monitoring Program" & "Cleaning and Disinfecting Cleanrooms"- training course for Caliway Biopharmaceuticals (2019)

- "Planning, Design, Qualification and Maintenance of Water System"- training course for ApexBio Taiwan (2019)
- "Environment monitoring"- training course for Savior Lifetec Corporation's Chunan plant (2018)
- "Environment monitoring"- training course for TFDA PPCD (Pharmaceutical Plant of Controlled Drugs) (2018)
- "Microbiological monitoring in aseptic process"- training course for TFBS Bioscience (2018)
- "Air flow pattern visualization" (2018)
- USP<71> and <1113>- training course for Taiwan Biotech Co. (2018)
- USP<1117> and <1227>- training course for Taiwan Biotech Co. (2018)
- Microbiological examination (USP <61> and <62>)- training course for Taiwan Biotech Co. (2018)
- Introduction of USP general chapter <1223> and Micro Lab consulting for Taiwan Biotech Co (2018)
- Microbiological examination- training course for Yusheng Pharmaceutical Co. (2017)
- "Introduction of U.S. Pharmacopeia" (2016)
- "Reviewing of the factor of impact to microbiological quality in process" (2015)
- Case study in the microbiological quality management using quality risk assessment tools (2015)
- Risk mitigation and controlling of microbiological contamination (2015)
- Aseptic operations and aseptic processing- training course for biologicals plant of National Health Research Institutes (2015)
- Microbial limits testing of non-sterile drug products- training course for Yusheng Pharmaceutical Co. (2015)
- Principle of investigation of microbiological data deviation- training course for Yusheng Pharmaceutical Co. (2015)
- Quality requirements of microbiological testing- training course for Yusheng Pharmaceutical Co. (2015)
- Pharmaceutical microbial testing and quality control practices- training course for Yusheng Pharmaceutical Co. (2015)
- Generation, quality specification and testing directions of water for pharmaceutical purposes (2015)
- Critical factors of aseptic operation- training course for NPUST (2014)
- GMP new trends of drug products (2) Isolation system- training course for NPUST (2014)
- Highlights of sterility testing (2013)

Speaker for Industrial Technology Research Institute of Taiwan (ITRI) workshop (2013) –How to compliance with PIC/S GMP regulations on management of API plant Microbiological lab

Instructor for TFDA's (Taiwan Food and Drug Administration) training courses (2012 - present)

- "Cleaning and Disinfection Operations in the Cell Processing Unit"- Internal Panel of TFDA Project (2020)
- Introduction of PDA Technical Report No. 54-5 Quality Risk Management for the Design, Qualification, and Operation of Manufacturing System (2017)
- Autoclave qualification (2013)
- Operating practice of microbial environmental monitoring (2012)
- Application of disinfectants (2012)

Instructor for TPQRI's (Taiwan Product Quality Research Institute) training courses (2011 - present)

- Quality Control- Microbiological Laboratory (2015)
- Microorganism evaluating and monitoring for environment and water system (2012)
- Disinfectants Efficacy Testing (2012)
- Microbiological testing of non-sterile drug products (2011)

Submitted and accepted articles in TPDA Letter (translation)

- A Revised Aseptic Risk Assessment and Mitigation Methodology. (2018 submitted)
- How to Plan Smoke Studies. (2018 submitted)
- EMA Guideline on Setting Health-Based Exposure Limits. (2017 submitted)

- Complying with Revised Weighing Guidelines. (2016 submitted)
- Cleanability of Pharmaceutical Soils from Different Materials of Construction. (2015 submitted)
- Mitigating Risk for Single Use Assemblies in Sterile Filling. (2015 submitted)
- Best Practices in Adopting Single Use Systems. Jun. 2015 No.72, p. 13-14.
- Gowning Practices Provide Clues to cGMP Compliance. Jun. 2015 No.72, p. 10-11.
- Defining and Presenting Overkill Cycle Validation. Mar. 2015 No.71, p.12-14.

創新生物產品製程無菌性相關規範分享
The Process Sterility Related Regulations On Innovative Bio-product

6-Oct-2022

林宗儒 Ken Lin

Persimmon Taiwan
台南梁山工程顧問公司

OUTLINE

- Regulatory Updates
- Contamination Control Strategy (CCS)
- Manual Aseptic Process Design Principles
- Aseptic Processing Simulations

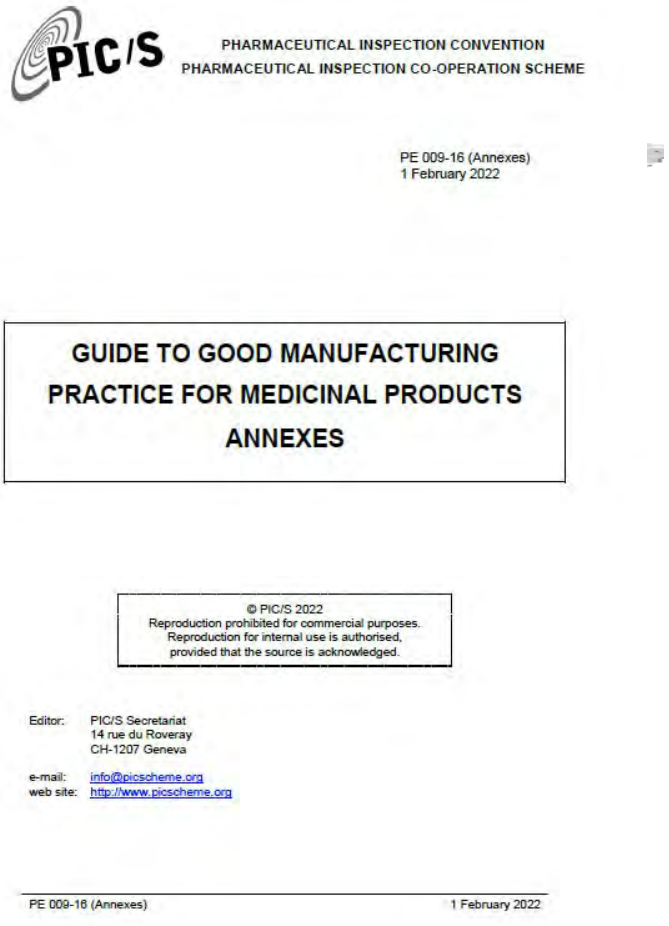
創新生物產品製程無菌性相關規範分享

REGULATORY UPDATES

First February, 2022

PIC/S GMP Annex 2A
Manufacture of advanced therapy medicinal products for human use

PIC/S GMP Annex 2B
Manufacture of biological medicinal substances and products for human use



PIC/S PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 009-16 (Annexes)
1 February 2022

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS
ANNEXES

Editor: PIC/S Secretariat
14 rue du Roveray
CH-1207 Geneva

e-mail: info@picscheme.org
web site: http://www.picscheme.org

PIC/s Guidance on ATMPs and Biological Medicines

- GMP requirements for the production of ATMPs (in Annex 2A) are now in a separate Annex from biological medicines (Annex 2B). (Started from Version 15)

- Annex 2A and Annex 2B replace guidance in various sections of GMP Part 1 for manufacturing ATMPs and biological medicines.

Principle for Annex 2A

- For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, other guidance documents should be consulted on the validation of specific manufacturing methods (e.g. virus removal or inactivation). The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilisation systems together with the use of closed systems and sterile disposable product-contact equipment can significantly reduce the risk of accidental contamination and cross-contamination.

BSC Used in the Aseptic Processing

- Positive pressure areas should be used to process sterile products, but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons.

- Where negative pressure areas or BSCs are used for aseptic processing of materials with particular risks (e.g. pathogens), they should be surrounded by a positive pressure clean zone of appropriate Grade.

Process Environment Requirements

Operations	Environment Requirement on PIC/S GMP Annex 2A
Where **processes are not closed** and there is exposure of the product to the immediate room environment without a subsequent microbial inactivation process.	Grade A with Grade B background
The use of technologies as e.g. processing inside single use sterile disposable kits, or processing using closed, automated manufacturing platform or incubation in closed flasks, bags or fermenters	Grade A with Grade C background
The **closed system** can be shown to **remain integral throughout the entire usage**	Grade A with Grade D background

22 August, 2022

PIC/S GMP Annex 1 Manufacture of Sterile Medicinal Products

Deadline for coming into operation:

- 25 August 2023 : one year from the date of publication in Eudralex Volume 4
- 25 August 2024 : two years from the date of publication in Eudralex Volume 4 for **point 8.123**

The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Annex 1

Manufacture of Sterile Medicinal Products

Legal context for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation 2019/6 on the Community code relating to veterinary medicinal products. This document provides technical guidance on the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Commission Directive (EU) 2017/1572 for medicinal products for human use, Directive 91/412/EEC for veterinary use, and Commission Delegated Regulation (EU) 2017/1569 for investigational medicinal products for human use and arrangements for inspections supplementing Regulation (EU) No 536/2014 on clinical trials.
This Annex is intended to assist national authorities in the application of the EU legislation. Only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

Status of the document: Revision of the 2007 version of Annex 1.

Document History

Previous version dated 30 May 2003, in operation since	September 2003
Revision to align classification table of clean rooms, to includeguidance on media simultations, bioburden monitoring and capping of vials	November 2005 to December 2007
Date for coming into operation and superseding	01 March 2009/01 March 2010 Note: Provisions on capping of vials were postponed on 01 March 2010

Reasons for changes: The GMP/GDP Inspectors Working Group and the PIC/S Committee jointly recommend that the current version of Annex 1, on the manufacture of sterile medicinal products, is revised to reflect changes in regulatory and manufacturing environments. The new guideline should clarify how manufacturers can take advantage of new possibilities deriving from the application of an enhanced process understanding by using innovative tools as described in the ICH Q9 and Q10 guidelines.
The revision of Annex 1 should also take into account related changes in other GMP chapters and annexes as well as in other regulatory documents. The revised guideline will seek to remove ambiguity and inconsistencies and will take account of advances in technologies.

Deadline for coming into operation:

- 25 August 2023 : one year from the date of publication in Eudralex Volume 4
- 25 August 2024 : two years from the date of publication in Eudralex Volume 4 for point 8.123

9

Document Map

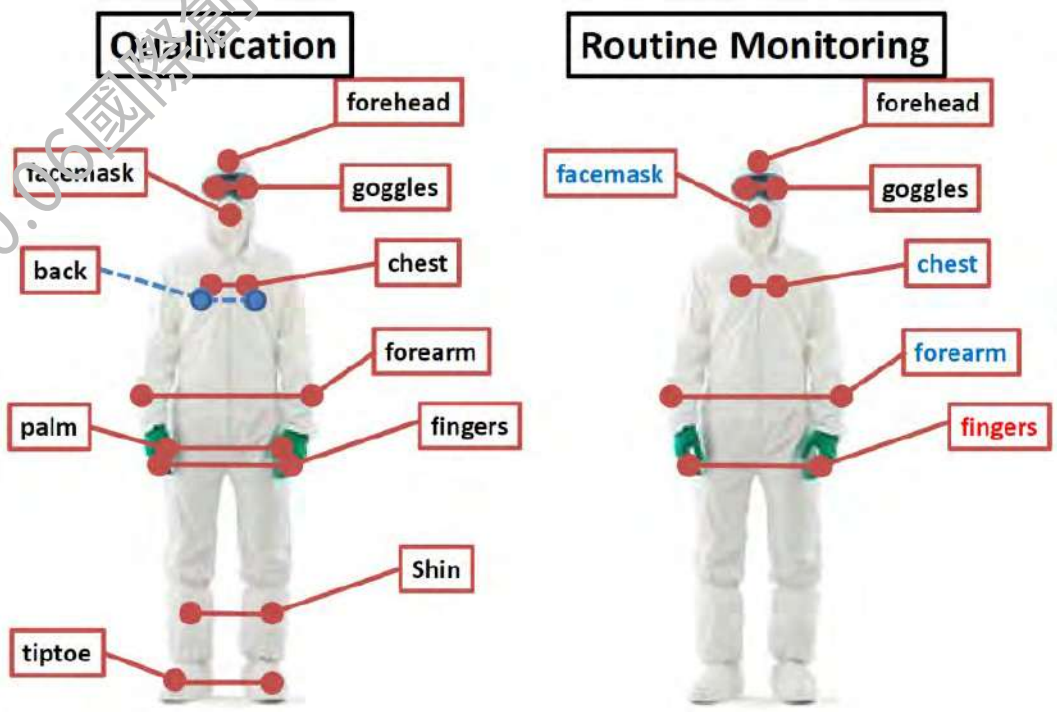
Section Number	General overview
1. Scope	Includes additional areas (other than sterile products) where the general principles of the annex can be applied.
2. Principle	General principles as applied to the manufacture of sterile products.
3. Pharmaceutical Quality System (PQS)	Highlights the specific requirements of the **PQS** when applied to sterile products.
4. Premises	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of Barrier Technology.
5. Equipment	General guidance on the design and operation of equipment.
6. Utilities	Guidance regarding the special requirements of utilities such as water, gas and vacuum.
7. Personnel	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance regarding the **qualification of personnel**.
8. Production and specific technologies	Guidance on the approaches to be taken regarding **aseptic and terminal sterilization processes**. Guidance on the approaches to sterilization of products, equipment and packaging components. Also guidance on **different technologies** such as lyophilization and Form-Fill-Seal where specific requirements apply.
9. Environmental and process monitoring	This section differs from guidance given in section 4 in that the guidance here applies to ongoing routine monitoring regarding the design of systems and setting of action limits alert levels and reviewing trend data. The section also gives guidance on the requirements of **Aseptic Process Simulations (APS)**.
10. Quality control (QC)	Guidance on some of the specific Quality Control requirements relating to sterile products.
11. Glossary	Explanation of specific terminology.

10

Typical Clothing Required For Each Cleanliness Grade

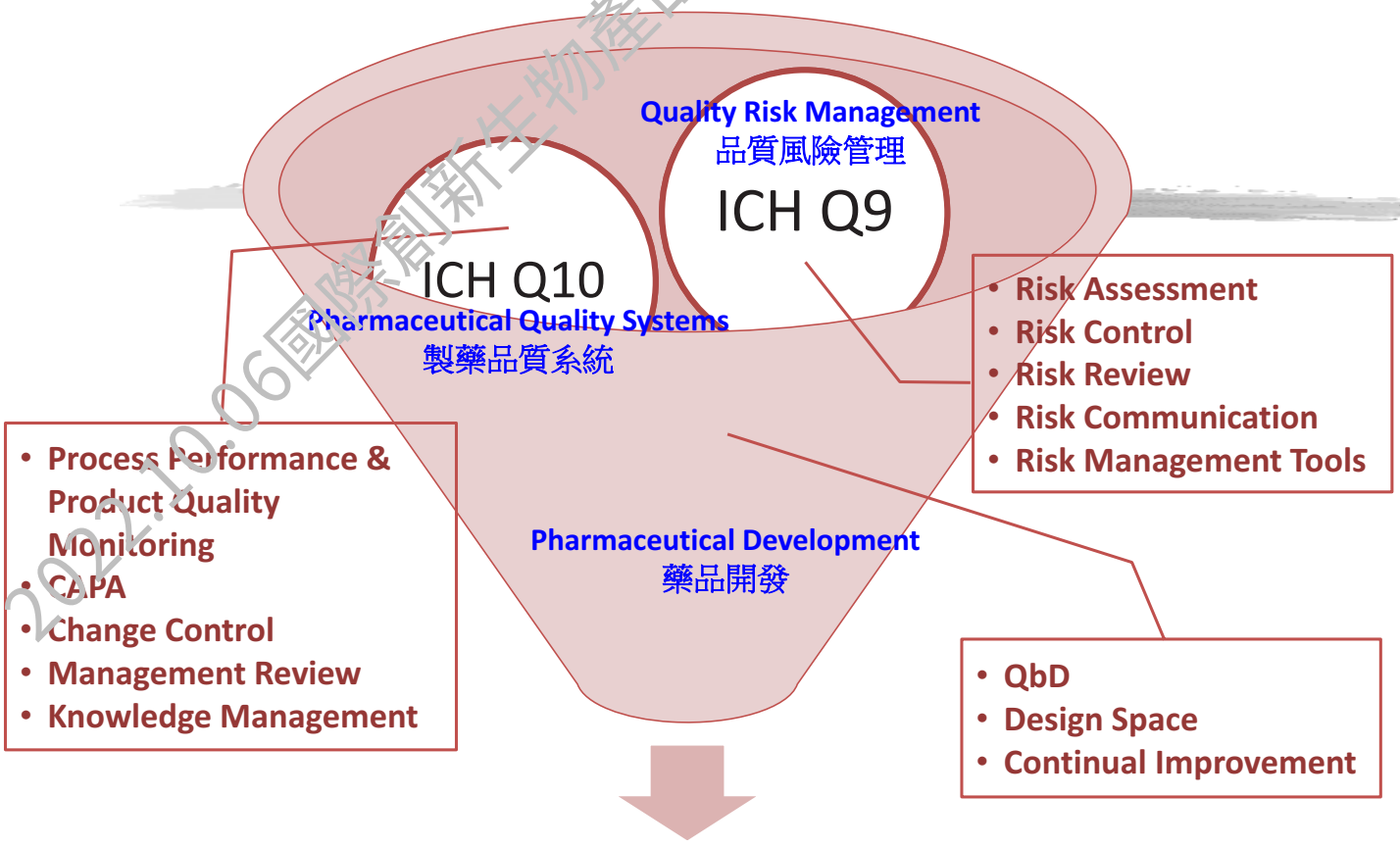
	PIC/S Grade D	PIC/S Grade C	PIC/S Grade B (including access/ interventions into grade A)
Hair Cover	O	O	Sterile headgear should enclose all hair (including facial hair) and where separate from the rest of the gown, it should be tucked into the neck of the sterile suit.
Beard and Moustache Cover	O	O	O
Suit	General protective suit	Single or two-piece trouser suit gathered at the wrists and with high neck. Should minimize the shedding of fibres and particles .	Appropriate garments that are dedicated for use under a sterilized suit should be worn before gowning. The (sterilized) protective clothing should minimize shedding of fibres or particles and retain particles shed by the body.
Gloves*	X	X	Appropriately sterilized, non-powdered, rubber or plastic gloves. Garment sleeves should be tucked into a **second pair of sterile gloves**.
Shoes or Overshoes	Appropriately **disinfected** shoes or overshoes	Appropriately **disinfected** shoes or overshoes	Appropriate sterilized footwear (e.g. over-boots) should be worn. Trouser legs should be tucked inside the footwear.
Face Mask	X	X	Sterile facemask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles.

Sampling Points of the Gowning Qualification



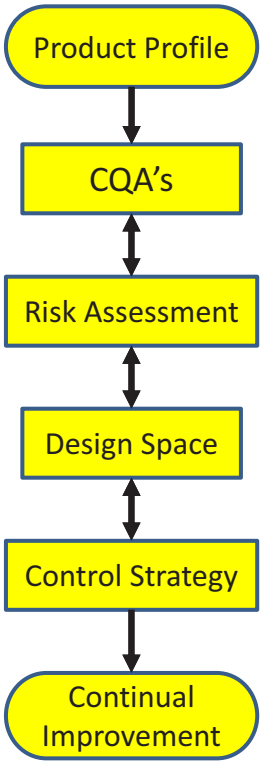
Undress Outdoor Clothing

7.14 Cleanroom gowning should be performed in change rooms of an appropriate cleanliness grade to ensure gown cleanliness is maintained. Outdoor clothing including **socks** (other than personal underwear) should not be brought into changing rooms leading directly to grade B and C areas. Single or two-piece facility trouser suits, covering the full length of the arms and the legs, and facility socks covering the feet, should be worn before entry to change rooms for grades B and C. Facility suits and socks should not present a risk of contamination to the gowning area or processes.



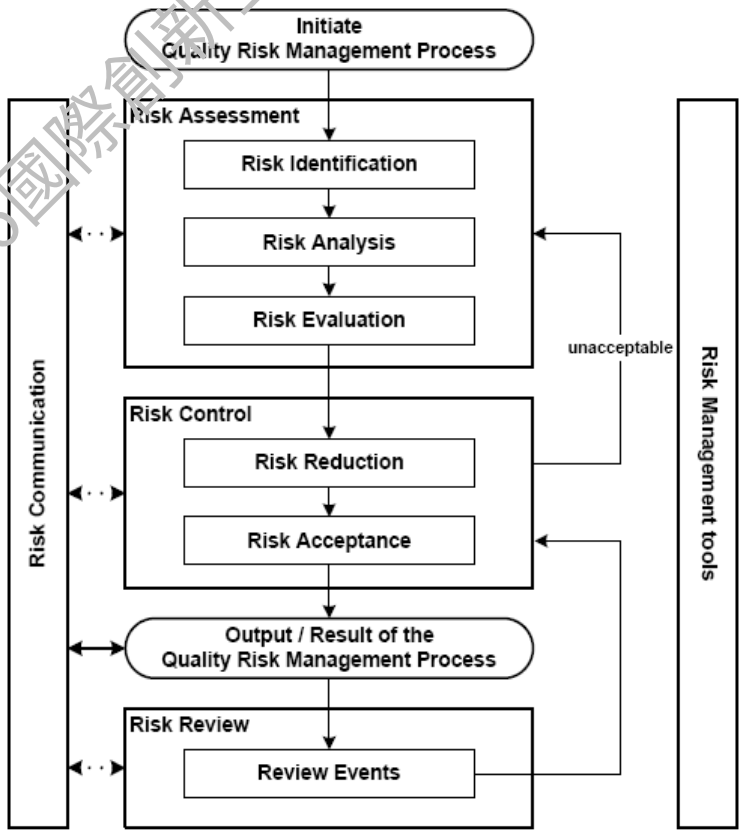
GMP Management System

ICH Q8(R2) - Example QbD Approach



- 品質目標產品概況 Quality Target Product Profile (QTPP)
- 確定可能的關鍵品質屬性
  Determine "potential" critical quality attributes (CQAs)
- 將原物料屬性和製程參數連結到CQA並進行風險評估
  Link raw material attributes and process parameters to CQAs and perform risk assessment
- 發展設計空間 Develop a design space (*optional and not required*)
- 設計與實行管制策略 Design and implement a control strategy
- 管理產品生命週期，包含持續改善 Manage product lifecycle, including continual improvement

ICH Q9 - Quality Risk Management Process



ICH Q10 - Pharmaceutical Quality System

創新生物產品製程無菌性相關規範分享

CONTAMINATION CONTROL STRATEGY (CCS)

PIC/S GMP
Pharmaceutical Quality System

- The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation or Clinical Trial Authorisation, as appropriate, and do not place patients at risk due to inadequate **safety**, **quality** or **efficacy**.

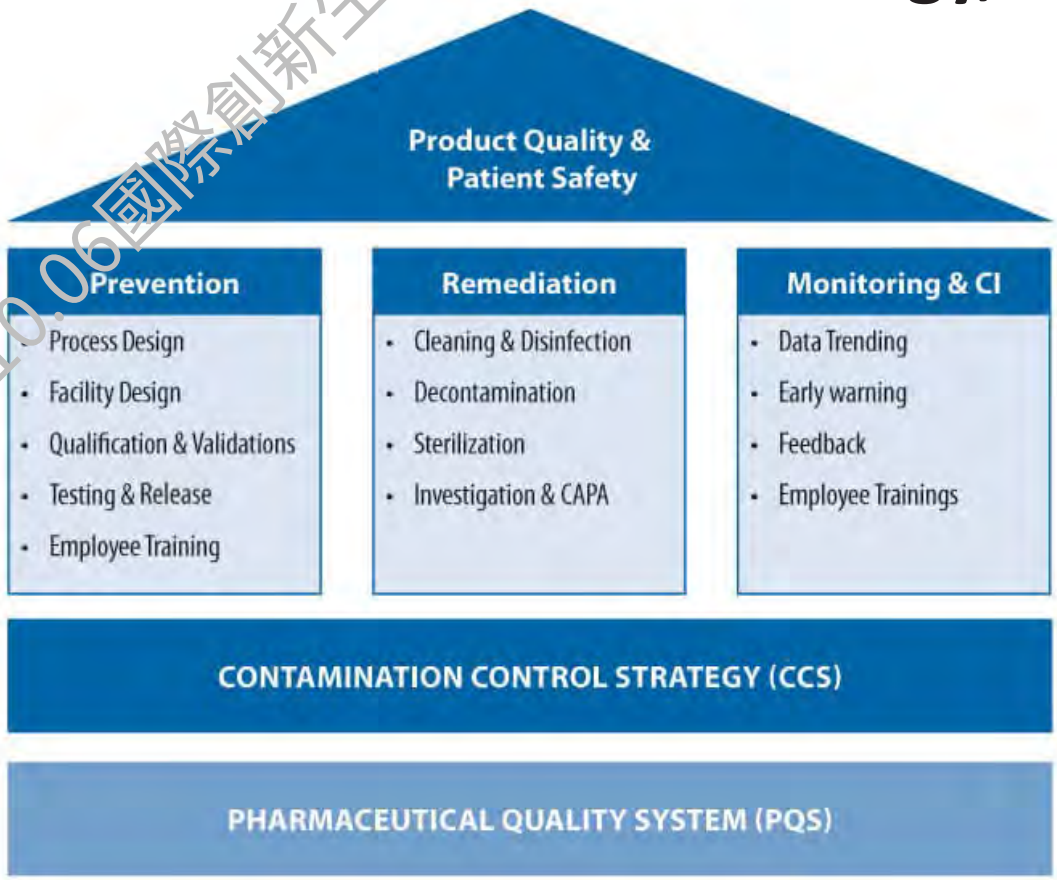
Principle of Annex 1

- The manufacture of **sterile products** is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination.

Contamination Control Strategy (CCS)

- A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality.
- The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, **finished product specifications**, and the associated **methods** and frequency of monitoring and control.

Contamination Control Strategy, CCS



https://www.pda.org/pda-letter-portal/home/full-article/contamination-control-strategies-a-path-for-quality-safety

General Considerations

- As product-release testing cannot and should not be used to provide definitive assurance of microbial safety, companies must employ a comprehensive **microbial control strategy** that is built into the **facility and manufacturing processes**.

Microbial Control Strategy

- **Control through Facility Design**
  - Design meet applicable ISO standards (e.g., 14644) and/or other relevant expectations
  - An environmental monitoring program should be established and reviewed on a scheduled basis for effectiveness
  - Pharmaceutical water used for manufacture should be tested for microbial safety. (USP<1231>, FDA Guidance for High Purity Water System)
  - **Risk-based Approach**

Microbial Control Strategy

- **Control through Equipment and Instrumentation Design and Maintenance**
  - The use of **presterilized, disposable manufacturing equipment** should be used throughout the manufacturing process whenever possible.
  - For **non-single-use equipment**, the efficacy of the disinfectant process should be validated, a cleaning program should be established, and the **product contact surfaces should be sterilized using a validated process**.

Microbial Control Strategy

- **Control through Analyst and Operator Gowning and Qualification**
  - Operators that participate in GMP manufacturing must have documented training that demonstrates their ability to comply with GMP expectations and aseptic processing.
  - Analysts that enter cleanrooms or similar clean areas should be trained and certified on the necessary gowning and aseptic procedures.

Microbial Control Strategy

- **Control Confirmed by Microbiological Process Monitoring**
  - Microbial control should be established and monitored throughout the entire manufacturing process
    - Bioburden
    - Endotoxin
    - Sterility
    - Mycoplasma, and
    - Adventitious viruses

Microbial Control Strategy

- **Control Confirmed by Microbiological Process Monitoring (Cont.)**
  - Analysis of **raw material, production media, and process indicators** (e.g., dissolved oxygen, glucose) may all be used to assess microbial control throughout the entire process.
  - **Critical filtration** steps, such as bioburden reduction and sterile filtration, should include **post-filtration integrity checks** to confirm the function of the filter.

創新生物產品製程無菌性相關規範分享

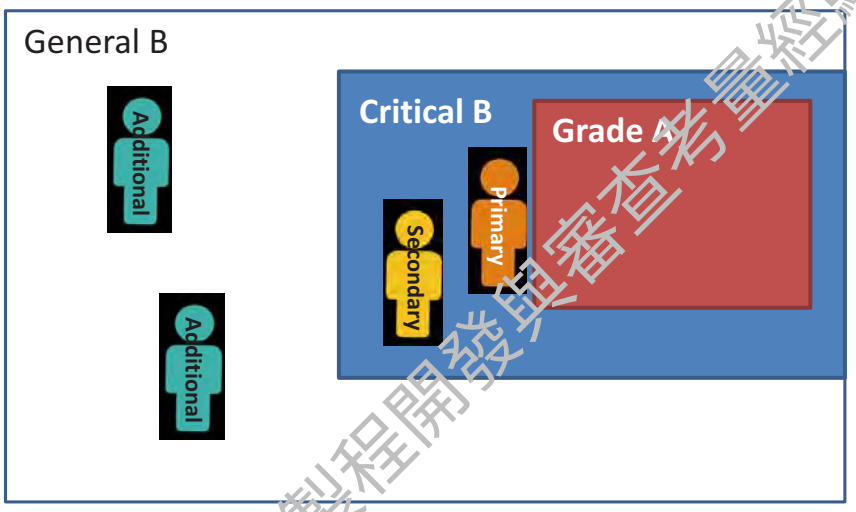
MANUAL ASEPTIC PROCESS DESIGN PRINCIPLES

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Adequate space to perform the work. 足夠作業空間
- All exposed product and product-contacting components should continuously remain in First Air, i.e., the work location first in the path of HEPA-filtered air.
  產品暴露與產品接觸組件嚴格遵守最乾淨氣流(First Air)原則
- Aseptic manipulations should be made in First Air, not having passed over any other components or blocked by the operator's hands.
  無菌操作在最乾淨氣流下進行
- The operators should decontaminate or change their gloves on a frequent basis. 操作員的手套應時常消毒或更換

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- The operators should work as a team. The primary operator(s) should perform all tasks inside the ISO 5 environment. The secondary operator(s) assists in the introduction/removal of items from the ISO 5 environment, and may assist the primary operator(s) with less critical tasks inside that environment. Additional support operator(s) may be necessary to support activities exclusively in the surrounding environment.
團隊作業。



Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- The primary operator should wear sterile gloves and sleeves and never contact a non-sanitized or non-sterilized item. 主要操作員穿戴無菌手套與袖套，嚴禁接觸未經消毒或滅菌的物品
- The primary operator(s) performs the critical aseptic manipulations within the ISO 5 environment. The secondary operator(s) acts as a support person to minimize the potential of the primary operator touching non-sterile or non-disinfected surfaces. The hands of the primary operator should remain in the ISO 5 environment at all times. (There may be exceptions to this related to positron emission tomography products or radioactive products.) The secondary operator(s) should put on sterile gloves/sleeves prior to any activity inside the ISO 5 environment, or in transfers of items to/from the primary operator. Anytime the primary operator is required to leave the ISO 5 environment, gloves and sleeves (if appropriate) should either be changed or gloves should be re-sanitized prior to reentry to ISO 5. 主要操作員執行關鍵無菌操作，次要操作員協助主要操作員儘量減少其接觸未經消毒或滅菌的物品的機會。主要操作員的手應始終保持在A級區中，離開A級區應更換手套/袖套，重新進入A級區時應消毒手套。次要操作員在A級區進行任何作業前，或是將物品移入移出設備時，應穿上無菌手套/袖套。

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Sterilized items should be introduced to the ISO 5 area by aseptic removal of the final wrap around the item as it is being introduced. 已滅菌物品須脫去最後一層包裝後才能移入A級區
- Extra subassemblies and utensils should be sterilized and available for immediate use in the event a replacement is needed. 備用組件與器具應滅菌，並在需要更換時立即使用。
- Sterile tools and utensils should be employed wherever possible *to handle sterile materials during their processing,* rather than the direct contact with the operator gloves. There should be sterile supports or hangers for tools inside the ISO 5 environment in order to minimize contact between the tool and surfaces of the workspace. 應使用無菌工具或器具操作無菌材料，不能與操作員手套直接接觸。A級區的工具應有無菌支架或吊架，盡量減少工具與工作區表面接觸。
- The process should be designed so that samples can be taken with minimal risk of contamination. When withdrawing samples from a sterile container, it is preferable to take all desired samples from a container in a single step and then subdivide that sample as required. Alternatively, the residual left in the original container post-production can be used as the test sample. The use of technologies such as sterile septum or connectors should be considered to minimize the risk during sampling. 採用污染風險最小的方式(無菌隔膜/無菌連接)進行取樣。無菌取樣需一次取樣，再依需求分樣；或用生產後的殘餘產品進行分析。

PDA TR No. 62

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Wherever possible, materials being introduced into the process should be pre-measured into a tightly sealed container prior to sterilization and addition. 原料使用於製程時，在滅菌與添加之前，盡可能先秤好分裝於密封容器中
- Electrical equipment and controls pose a contamination risk and should be located outside the processing environment, if possible. If that is not possible a second operator (not the primary operator) should adjust equipment settings as necessary. Pay special attention to equipment which exhausts air (e.g., mixers, blenders, etc.) that could contaminate the environment. 電器設備與裝置存在污染風險，應安裝於製程區外。若不可行，則由次要操作員執行該設備之調整。應特別注意會排氣的設備(混合/攪拌器)
- Liquid transfers should be made using peristaltic pumps located outside the aseptic environment, rather than through the use of automatic pipettes, due to concerns regarding exhausted air. In order to minimize equipment movement and the risk of contamination, containers can be premarked to indicate the amount of material to transfer. 由於擔心排氣污染，應使用位於無菌環境外的蠕動泵進行液體轉移，而不是使用自動移液器。為了最大限度地減少設備移動和污染風險，容器可以預先標記以指示要轉移的材料量。

PDA TR No. 62

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Perform as much of the process inside the ISO 5 environment as possible in order to minimize the removal and reentry of in-process materials in suitable containers. This may require the placement of small equipment within the environment. 盡可能在A級區執行製程，並且儘量減少製程中原料在容器中的移進移出。這需要在A級區中放置小型設備。
- When containers of in-process materials must be removed from, and later returned to, the ISO 5 environment the containers should be aseptically wrapped in a pre-sterilized covering which should be properly removed and discarded prior to reentry. Alternatively, the exterior of the container(s) can be re-sanitized prior to reentry. 需要在A級區進出的裝有製程中原料之容器，應先包覆預先滅菌的覆蓋物，在重新進入A級區前正確取出並丟棄，或是容器外部可以在進入前重新消毒。
- Sanitize the operating environment when it is empty, and sanitize each nonsterilizable item/ equipment as it is first introduced and transferred into the next cleaner level of the aseptic processing environments. Do not introduce a large item into the environment in mid-process. **Note:** If sanitization of the operating environment/equipment is performed by the primary operator, sterile gloves/sleeves should be changed before aseptic manipulation of product is performed. 在操作環境淨空時執行消毒，以及針對不可滅菌的物品/設備首次移入與轉移到到更潔淨區域時進行消毒。不要在製程中移入大項物品。注意：若消毒是由主要操作員執行，則在無菌操作前必須更換手套/袖套。

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Product contact surfaces shall be sterilized. Sterility should be maintained with protective layers which can be removed as materials are transitioned to cleaner environments. 產品接觸面應進行滅菌。應使用保護層保持無菌狀態，當材料轉移到更清潔的環境時，保護層可以去除。
- Significant aseptic assembly in the processing environment should be avoided through the use of sterilized pre-assembled items. This will reduce the extent of manual assembly required. 通過使用經滅菌的預組裝物品，以避免在製程環境中進行大量無菌組裝。 這將減少所需的手動組裝的程度。
- Process steps not required to be aseptic should be performed outside the ISO 5 environment by other operator(s). 不需要無菌的製程步驟應由其他操作員在 A 級區之外執行。
- Once the process design has been established, it should be rehearsed several times and documented in air flow studies using all of the required items and placebo materials to refine the steps, location of items, etc. This ensures the process design is practical and reduces risk of contamination to a minimum. The use of engineering runs to develop the process is strongly encouraged. 當製程設計確立後，應多次演練並記錄下氣流研究，使用所有必需的物品與安慰劑物質以完善步驟、物品位置等。這確保了製程設計的實用性並將污染風險降至最低。強烈建議利用工程試製(engineering run)來開發製程。

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- The manufacturing process should be documented in sufficient detail to allow operators to understand and conform to the desired practices. The secondary or support operator(s) should complete the batch record. 製造過程必須充分詳細地文件化以便操作員理解與遵守所需的規範。
- Environmental monitoring practices should be non-intrusive in order to avoid potential for contamination in the ISO 5 environment. Air sampling during processing may be performed with specially designed equipment that does not compromise the environment and may include settling plates. Surface monitoring should be performed using contact plates or swabs after processing has been completed. 環境監測不得干擾製程，以避免在A級環境中潛在的污染。製程中的空氣取樣可以使用不影響環境的專門設計設備進行，並可包括使用落菌培養皿。製程完成後，應使用培養皿接觸或擦拭法進行表面監測。

PDA TR No. 62

ASEPTIC PROCESSING SIMULATIONS

Aseptic Processing Simulations (Media Fills)

- Bracketing approach vs. Matrix approach.
- The method selection would be part of the risk assessment.
- During execution of the APS each operator working at a biosafety cabinet (BSC) must be performing simulated aseptic manipulations. However, the media fill/APS may be performed in one or more representative BSC as determined by a **risk assessment**.
- Used processing solutions (e.g., media or wash solution) should be included in the aseptic process simulation.

Aseptic Processing Simulations (Media Fills)

- The numbers of containers, size of containers and type of containers to be used in the APS needs to be considered during the APS design process and **adequate incubation space** needs to be planned to meet these needs.
- Simulation with anaerobic conditions is not systematically required.
- For the initial aseptic process evaluation **three consecutive runs** should be executed which include **the most complex aseptic processing steps**.
- In some ATMP processes where there is no sterilization filtration in the manufacturing process, APS runs of the entire manufacturing process are expected. Challenges can arise if these products are manufactured in ISO 7/Grade B environments.

Main References

- PIC/S GMP part 1: Good Manufacturing Practice for Medicinal products and Annex 1 for Sterile Medicinal Products
- PIC/S GMP Annex 2A, Manufacture of advanced therapy medicinal products for human use
- PDA Points to Consider for Microbial Control in ATMP Manufacturing, 2022
- PDA TR62 Recommended Practices for Manual Aseptic Processes. 2013.

Persimmon Tainan
台南梁山工程顧問公司

Contact Me

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細胞治療自動化技術國際趨勢與現況

Speaker: 沈欣欣

Topic: 細胞治療自動化技術國際趨勢與現況
跨領域整合建構細胞產品之自動化智能化生產系統

主要研究領域

1. 高階植入式生醫材料醫療器材設計與製程研發。
2. 細胞治療產品品管與量產技術研發。
3. 高階植入醫材或細胞治療產品 GMP/GTP 生產確效與臨床試驗 IND/IDE 申請。
4. 促成複合醫材與細胞治療產品所需之上、中、下游技術整合，並與臨床實務結合，推動跨領域產業技術應用。

個人簡介

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工研院醫材中心組織再生複合醫材技術組 副組長

研究專長：生物材料與細胞治療、高階植入式醫療器材產品設計、3D 積層製造植入式醫療器材、皮膚組織列印工程系統與組織工程等再生醫學技術與產品研發領域

重要成果：

- 愛迪生獎（Edison Awards）(111)
- 全球百大科技研發獎（R&D 100 Awards）(110)
- 第十屆、十四屆、十六屆、十七屆、與十八屆國家新創獎(102、106、108、109、110)
- 第十八屆國家新創獎/精進績獎(110)
- 經濟部科技女傑獎(101)
- 2020 年新竹區傑出經理獎(109)
- 工研院產業化貢獻獎(107、110、111)
- 工研院傑出研究獎(102、106、107、111)
- 國內外專利申請 163 件，獲證 94 件
- 期刊、研討會與學術論文 121 篇
- 研究技術報告 217 件

細胞治療自動化技術國際趨勢與現況

跨領域整合建構細胞產品之自動化智能化生產系統

BDL/ITRI

cytiva

細胞製劑製造產業的解決方案

FlexFactory configurable single-use platform

FlexFactory single-use technology reduces capital expenses and contamination risk, and enables multi-product facilities. Integrated automation streamlines productivity and data analysis.

KUBio modular biomanufacturing environments

Comprehensive biomanufacturing solutions for cGMP production that dramatically reduce risk and time to market.

Cytiva 沒有貼附型細胞之產品，但 Danaher 集團的 PALL 有相關產品

Product image is a representative example for illustration purposes; actual image may vary

經濟部
工業技術研究院 Industrial Technology Research Institute

ThermoFisher SCIENTIFIC

生物製造流程與解決方案 – 上、中游

(slide 6)

HyPerforma Rockeer/Glass Bioreactor

Cell line development/culture media and feeds

Bioprocess Automation Software

HyPerforma G3 Bioprocess Controllers

Single-Use and Sterilizable Sensors

Contaminatnt and impurity QC testing

HyPerforma 5:1/10:1 20:1 single-use Bioreactor

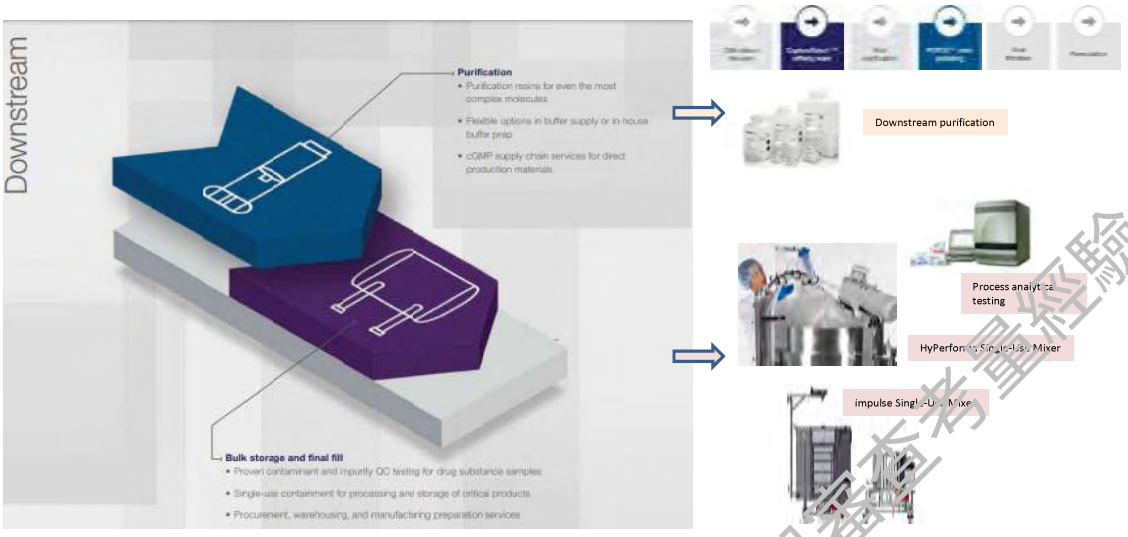
Harvestainer BioProcess Container

Harvestainer Microcarrier Separation System

Ref.: Thermo-bioprocessing-by-design-brochure

ThermoFisher SCIENTIFIC

生物製造流程與解決方案 – 下游



經濟部 工業技術研究院 Industrial Technology Research Institute

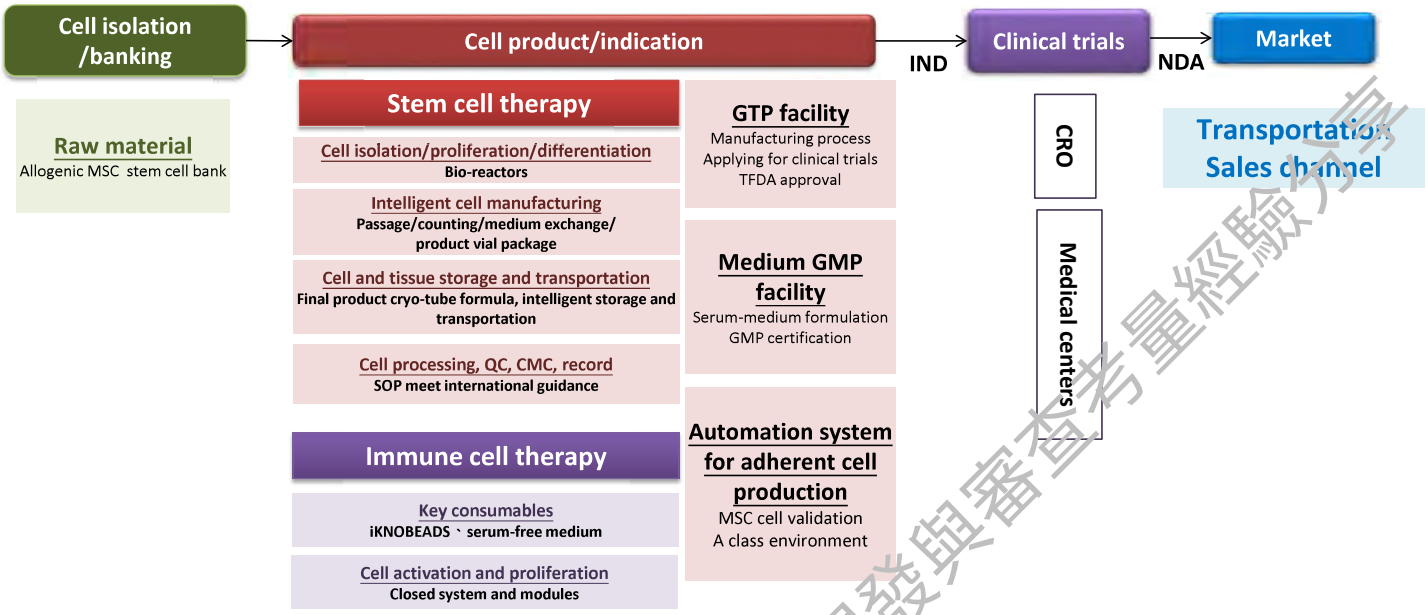
CDMO Opportunity - Develop Intelligent and Automation Technology

Danaher / Cytiva, Danaher / Pall, Thermal Fisher as reference

	ITRI	Danaher / Cytiva	Danaher / Pall	Thermal Fisher
Immune cell, CAR-T Manufacturing equipment	✓ Personalized closed culture module ✓ Cell isolation and purification system	• Personalized closed culture module	• Bio-reactor	• Bio-reactor
Immune cell, CAR-T Consumables	✓ iNO beads ✓ Serum-free medium	• Hyclone culture medium • Culturing bag	• ---	• Gibco medium • Culturing bag
Adherent cells (MSC, fibroblast) Manufacturing equipment	✓ Cell isolation and purification system ✓ Bio-reactor for scale up	• Personalized cell isolation system	• Porous matrix in bio-reactor for scale-up	• Bio-reactor
Adherent cells (MSC, fibroblast) Consumables	✓ Serum-free medium ✓ Fiber matrix for cell adherent ✓ Corning HyperFlask	• ---	• Porous matrix plate for cell adherent	• Nunc Cell Factory dish

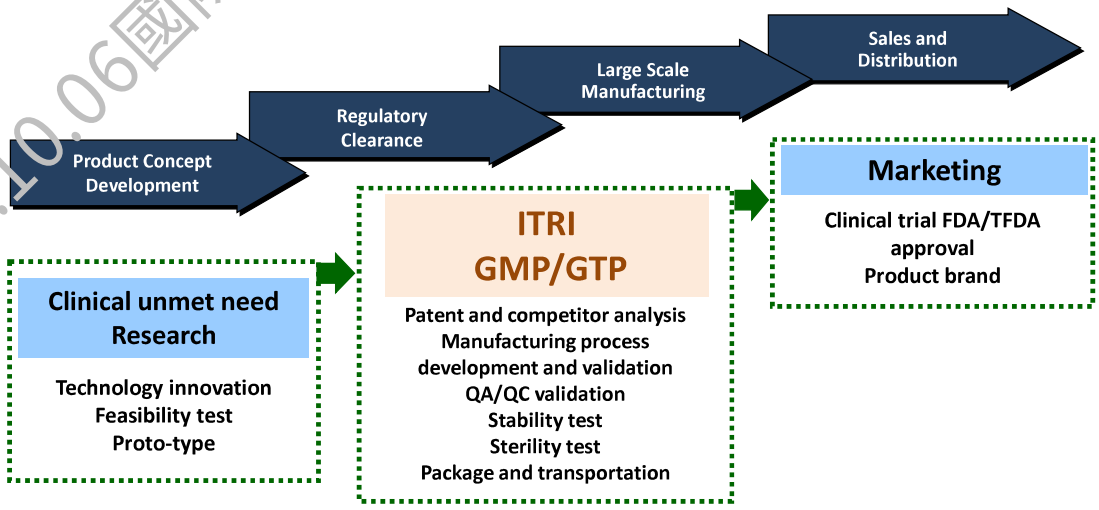
ITRI's core technologies for industry

- Focus on key technologies for cell therapy, including key consumables, automated production hardware and software and quality control processes, etc. To fulfill the industry chain in advance, helping to get through the last mile.



ITRI's GTP/GMP Facility
Bridging the research to market

For cell therapy and implantable medical device



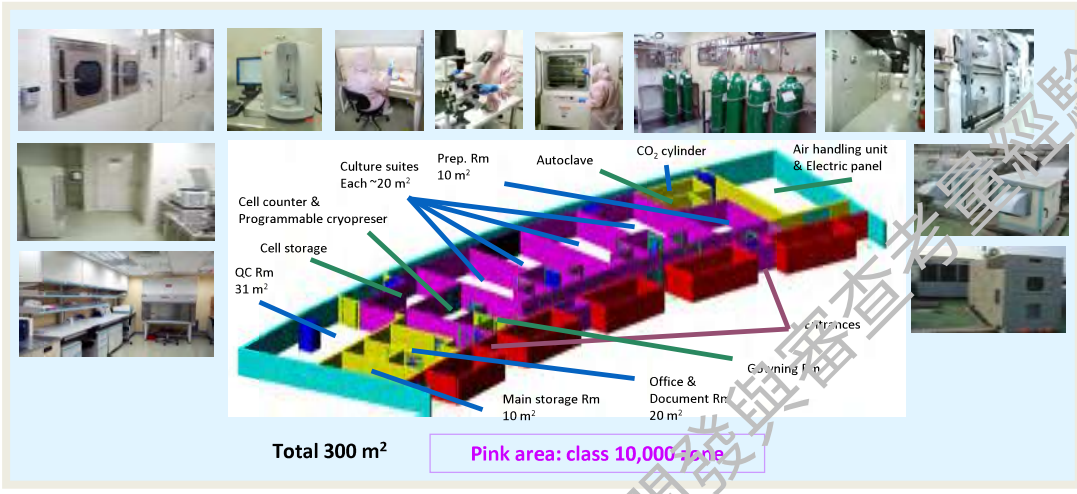
ITRI GTP - the first facility in Taiwan facilitate clinical trial practices of industry

Certification for factory and QC protocol

Drug manufacturing license

TAF-Accredited Certificate

Proficiency Test Certificate



Medical device GMPII for cell culture medium

Hardware finished in 2016, GMP certificated in 2020

Current supply the serum-free, chemical defined cell culture medium for clinical trials

- Annual production capacity 50,000 liters

- MSC stem cell serum-free medium manufacturing
- MSC proliferation, differentiation, preservation formulation
- Immune cell medium development
- Customized medium development

Medical device GMP for implantable biomaterial

Brining high level, class II/III medical device technologies to clinical trial and market

With experience to approach
US FDA 510K,US FDA PMA, CE, TFDA

International certifications
ISO13485,CE and TFDA GMP

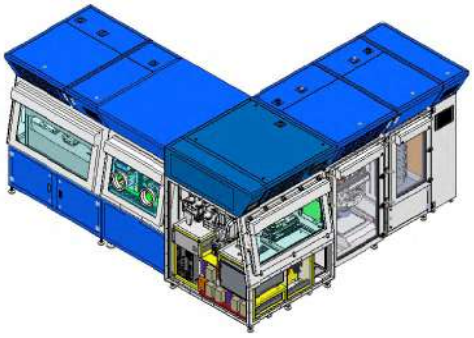
Cell therapy
– the manufacturing limitation and bottle-neck

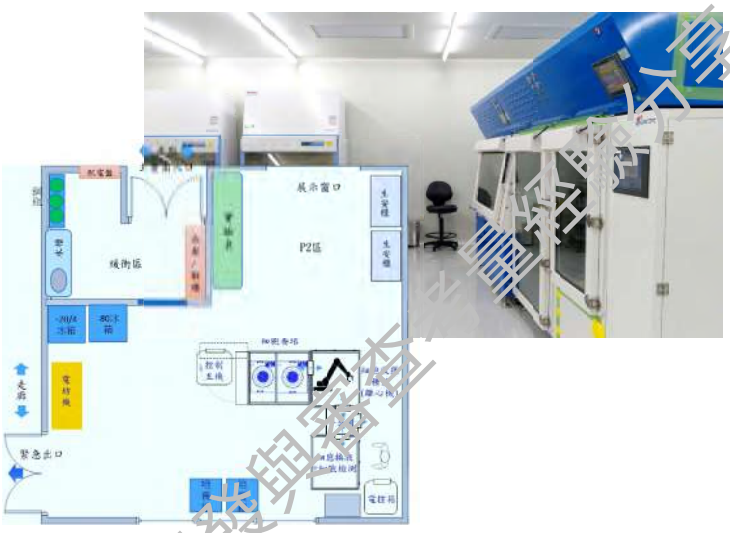
Automation: reducing labor and improving yield
Closed manufacturing system: reducing the risk of contamination

1. The manufacturing of cell and gene therapy products still depend on manual operation
2. The culture space and time are even more limited
3. Products quality rely on the operator's experience and judgment - human error, the batch variation, contamination risks

CompacT SelecT™（Sartorius）

Multi-disciplinary integration within ITRI and between industry
Automated production system for adherent cells



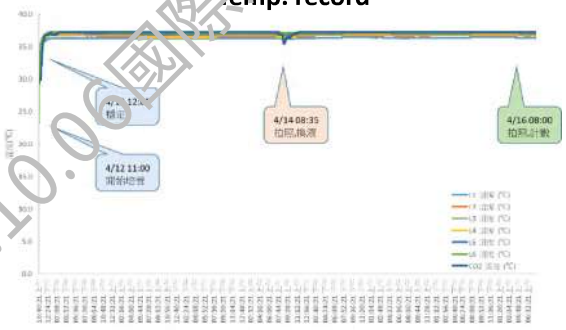


Maximum capacity：
36X Corning HyperFlask → 900X T75

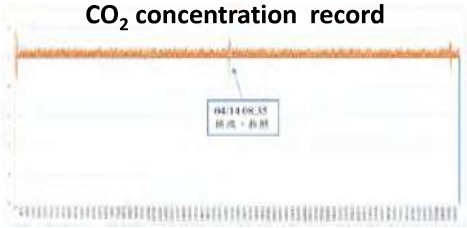
System validation 1

Temperature, humidity, and CO_2 concentration consistency
Cell growth rate is consistant with manual operation

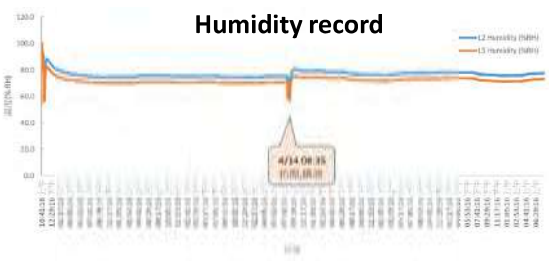
Temp. record



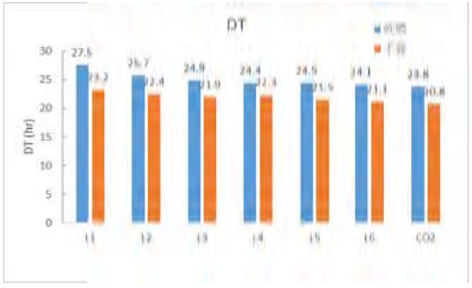
CO_2 concentration record



Humidity record



Cell doubling time comparison with manual operation

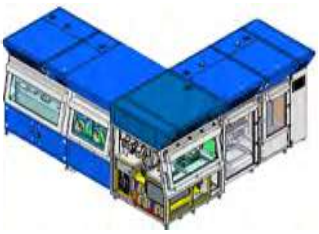


System validation 2

Aseptic and dust-free cleaning SOP and validation

By each operation module

- Cleaning operation SOP
- Sterilization SOP
- Real time monitoring SOP of cleanliness (more than 3 times validation)
  - Airborne particle count test
  - Airborne microbe test
  - Dropping microbe test



Fulfill PIC/S GMP sterilization requirement – A class area, class 100

A class area Class 100

潔淨區域等級 (0.5μm 微粒子數/立方呎)	ISO 等級標準[b]	≥0.5μm 微粒子數/立方公尺	浮游微生物行動水準[c] (cfu/立方公尺)	落菌培養皿微生物行動水準[c,d] (直徑 90mm; cfu/4小時)
100	5	3,520	1[e]	1
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

System validation 3

H_2O_2 Sterilization SOP and validation

H_2O_2 test paper positioning inside the cavity

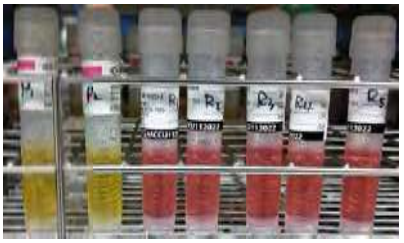
H_2O_2 fumigation for more than 5 mins, till test paper color change

Robotic control shift to sterilization mode

Stand static for a period of time

Degas

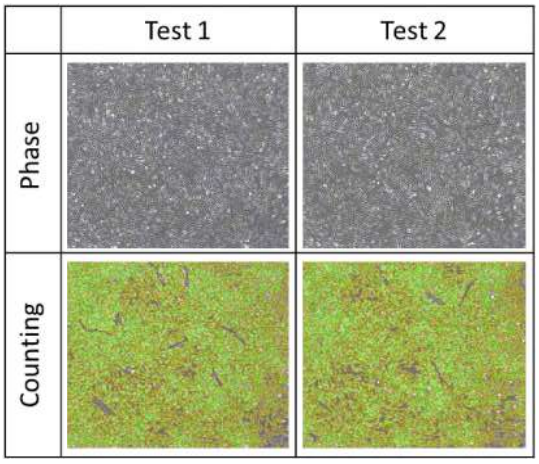
Sterilization culturing test



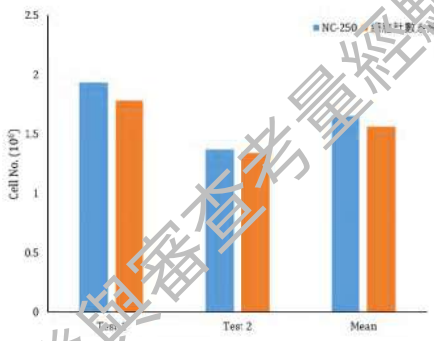
Yellow:
positive control
Red:
Test sample negative

System validation 4

Real-time cell counter and monitoring



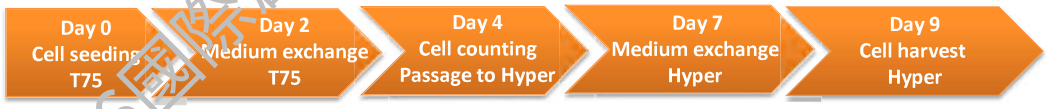
分析項目		自動化細胞生產系統		
		Test 1	Test 2	Mean ± SD
細胞數	NC-250	1.93x 10^6	1.37x 10^6	1.65±0.40 x 10^6
	細胞計數系統	1.78x 10^6	1.34x 10^6	1.56±0.31 x 10^6

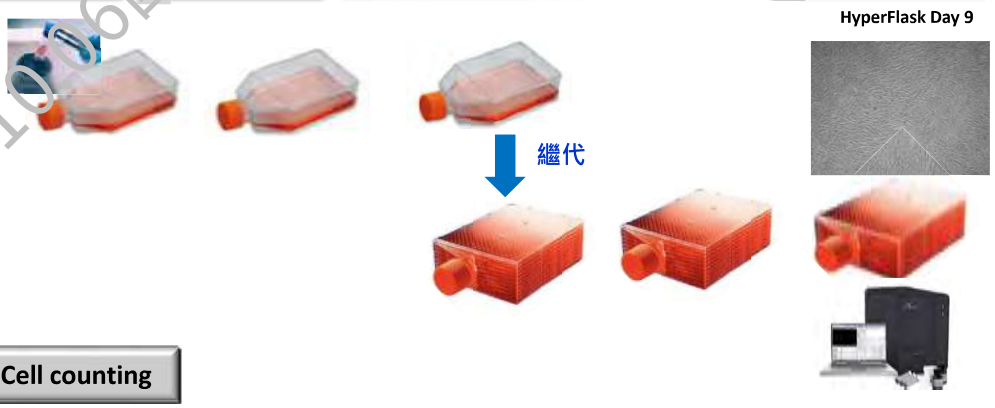


The same trend can be observed for comparing to the commercially available product (NC-250 counting system) from the two test results.

System validation 5

- MSC stem cell automation production procedure
- The cells are well characterized to be in spec. of regulation





Cell counting

1.5x10^5/ T75 → 2.71x10^6/Hyper → 5.91x10^7/Hyper

Cell activity, surface marker and function maintained after automation production

➢ **T75 harvest**

清消滅菌 → T75入料 → CCD檢測 → T75換液 → CCD檢測 → T75收穫

分析項目			允收標準	結果
細胞特性分析	收穫細胞存活率		≥ 90%	99.%
	倍增時間		≤ 30h	21.7h
	細胞表面抗原	CD34	0.2%	1.64%
		CD73	≥ 95%	99.93%
		CD90	≥ 95%	99.93%
		CD45	≤ 0.2%	0.00%
		CD105	≥ 95%	98.44%
		CD19	≤ 0.2%	0.00%
		CD14	≤ 0.2%	0.00%
		HLA-DR	≤ 0.2%	0.00%
	三分化	硬骨分化	Pass	Pass
		軟骨分化	Pass	Pass
		脂肪分化	Pass	Pass
無菌檢測	操作時落菌盤檢測		Negative	Negative
	培養過培養液無菌檢測		Negative	Negative

➢ **T75 passage to HyperFlask**

清消滅菌 → T75收穫&繼代 → HF換液 → HF收穫

分析項目			允收標準	結果
細胞特性分析	收穫細胞存活率		≥ 90%	97.1%
	倍增時間		≤ 30h	25h
	細胞表面抗原	CD34	0.2%	0%
		CD73	≥ 95%	99.72%
		CD90	≥ 95%	99.75%
		CD45	≤ 0.2%	0%
		CD105	≥ 95%	98.[illegible]%
		CD19	≤ 0.2%	[illegible]0
		CD14	≤ 0.2%	[illegible].3%
		HLA-DR	≤ 0.2%	0.02%
	三分化	硬骨分化	Pass	Pass
		軟骨分化	Pass	Pass
		脂肪分化	Pass	Pass
無菌檢測	操作時落菌盤檢測		Negative	Negative
	培養過培養液無菌檢測		Negative	Negative

Multi-discipline integration keep facilitating the regenerative medicine technologies

New Taiwan CDMO start-up is planning to integrate IC, mechanical, chemical engineering and bio-medical industry capacity to supply high efficiency manufacturing and development service globally.

- Process design
- SOP validation
- Customization

Cell manufacturing

Bio-data bank

- Proteomics
- Genomics
- Transcriptom analysis

- Mechanical design
- Precision mechinary
- Customized module

Automation system

Gene editing

- Virus : LV, RV
- Non-virus：liposome、nano-particle

- Pathogen analysis
- Functional test
- SOP validation

QC and identity

Clinical trial

- Operation SOP
- Trial protocol
- Biostatistics

- Cell bank
- Cold chain
- Transportation SOP

Storage and transportation

Safety test

- GLP toxicity and pharmacology
- Cell fate
- CRO/animal center

Frontior technology | Industry capability | Medical center

Thank you !

2022.10.06國際創新生物產品製程開發與審查考量經驗分享