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衛生福利部食品藥物管理署委辦計畫

「精進無菌與新興生醫藥品品質管理接軌國際之研究」

無菌產品製造 GMP 作業論壇(一)

日　期　：（北區）民國 110 年 4 月 26 日

（南區）民國 110 年 4 月 19 日

主辦單位：衛生福利部食品藥物管理署

承辦單位：TPDA 社團法人中華無菌製劑協會

講　師　資　料

黃茹蘭　品保經理/伊甸生物醫藥(股)公司(原喜康生技)

時　間　表

時 間	內　　容	講　師
13:00-13:30	報　　到	
13:30-13:40	➢ 長官致詞	TFDA 監管組代表
13:40-14:50	➢ GMP References ➢ General requirements of Technology Transfer ➢ Introduction of Biopharmaceutical Process	伊甸生醫 黃茹蘭 品保經理
14:50-15:10	休　　息	
15:10-16:20	➢ ISPE Guide：Scale-up and Technology Transfer ▪ Scale-up Considerations ▪ Technology Transfer Considerations	伊甸生醫 黃茹蘭 品保經理
16:20-17:00	交 流 討 論 及 課 後 測 驗	TFDA 長官 及講師群

目　　錄

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Scale-up and Technology Transfer

黃茹蘭/Kelly Huang
伊甸生醫 品保經理

課程目標/Learning Objectives

- Introduction of GMP requirements
- To understand technology transfer requirements and package
- To understand scale-up considerations(Upstream/Downstream)

大綱/Outline

1. GMP References
2. General requirements of Technology Transfer
3. Introduction of Biopharmaceutical Process
4. Scale-up Considerations
5. Technology Transfer Considerations

GMP參考資訊/GMP References

ICH Q10

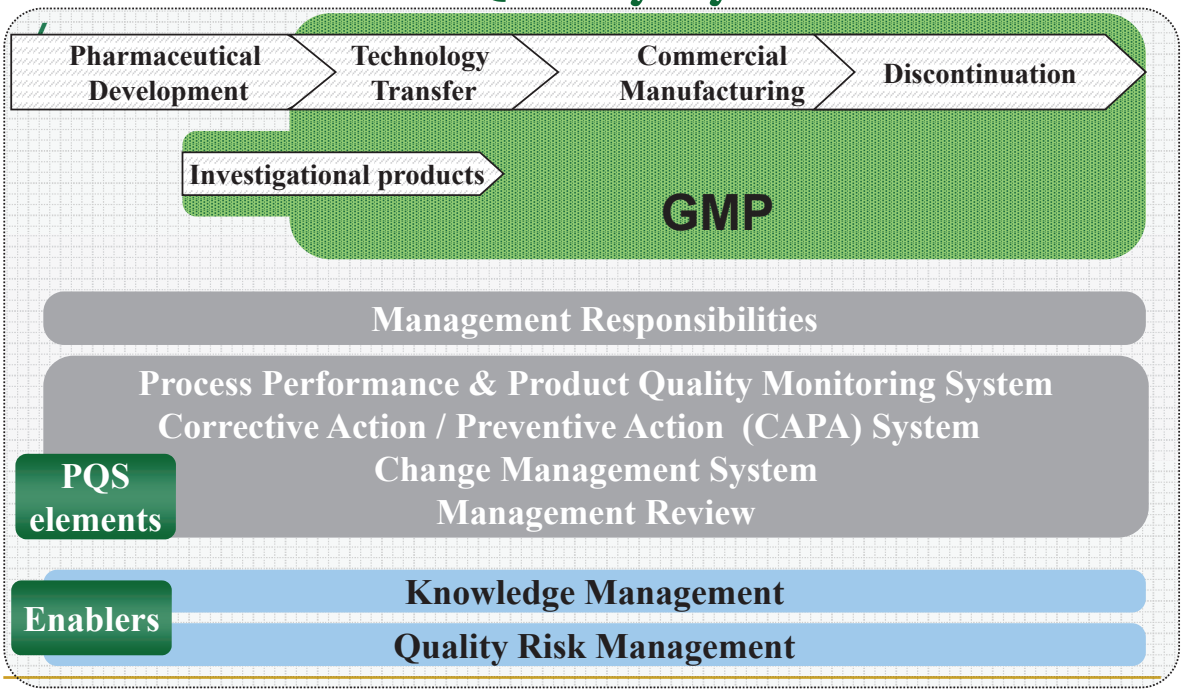
ICH Q10 Pharmaceutical Quality System

Transfer of technology in pharmaceutical manufacturing

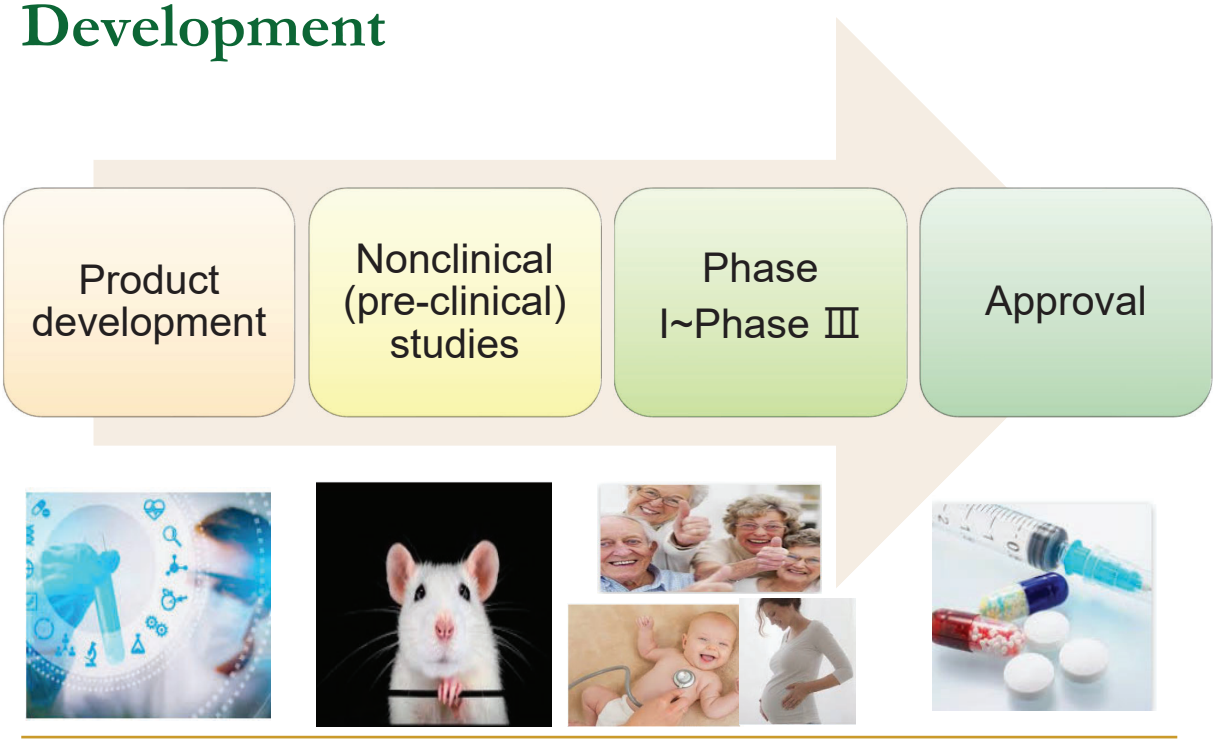
ISPE

Biopharmaceutical Process Development and Manufacturing

製藥品質管理系統/ICH Q10 Pharmaceutical Quality System Model



產品開發歷程/Stage of Product Development



技術轉移/ICH Q10_Technology Transfer (3.1.2)

- The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization.
- This knowledge forms the basis for the manufacturing process, *control strategy*, process validation approach, and ongoing continual improvement.

- 目的是在研發和生產之間，以及在生產場地內或之間轉移產品和製程知識，來完成產品的製造。這些知識構成了生產過程、控制策略、製程驗證方法和持續改進的基礎。

技術轉移的定義/Definition of Technology Transfer

"A logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites".

文件及專業知識的轉讓

委外活動/Outsourced Activities

PIC/S Part I _The Contract Giver

7.4.2 委託者應提供受託者所有必需的資訊及知識，以使其依產品相關的現行法規及上市許可，正確地履行約定的作業。委託者應確保受託者完全認知與本產品或工作有關之任何可能會對其廠房設施、設備、人員、其他原物料或其他產品造成危害的問題；	7.4.2 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his/her premises, equipment, personnel, other materials or other products;

Information transfer

合約/Contract

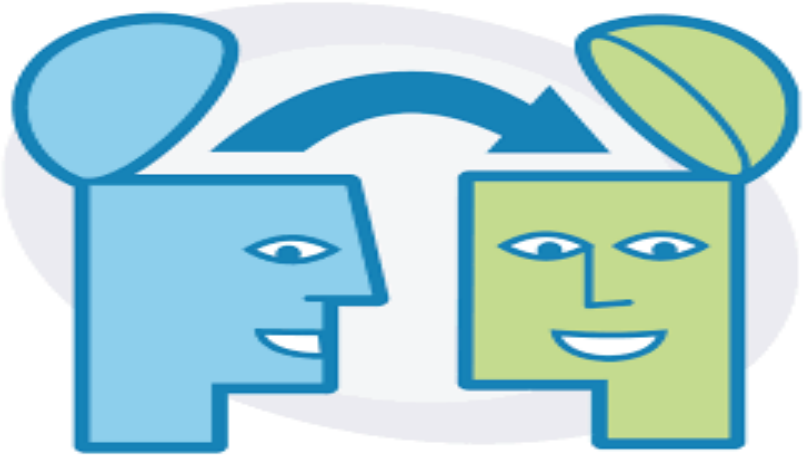
7.11 委託者與受託者間應簽訂契約。該契約明定雙方關於委外活動的個別責任及溝通程序。契約中的技術層面應由具有相關委外活動及優良製造規範之適當知識的勝任人員擬定。委外活動的所有安排均應依產品相關之現行法規及上市許可的規定，並為雙方所同意。	7.11 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties.

Agreement

General requirements of Technology Transfer

轉出方與接收方/Sending Unit And Receiving Unit

Sending unit **Receiving unit**



接收方的困惑/Confused

挑戰/Challenges

關鍵技術
認知不足

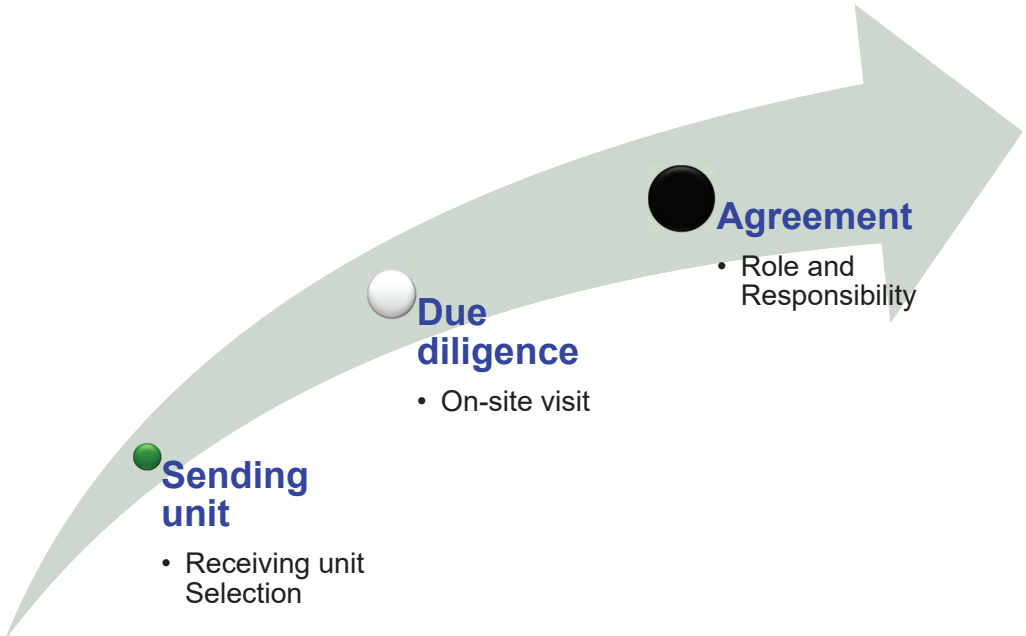
SU and RU have insufficient awareness of the key technical issues in the technology transfer process.

- **Technology transfer package**
- **Critical process parameters (CPPs)**
- **Critical quality attributes (CQAs)**
- **Reproducibility of the production process**
- **Pre-identify the risks**
- **Quality comparability**

通則要求/General Requirements

- Sending site should prepared the technology transfer documents.
- The process should be validated at that facility when producing materials for marketing.
- The risk assessment for the initial technology transfer process should be reviewed in regard to the technology transfer.
- The technology transfer plan should be approved by both the sending site and the receiving site prior to starting the technology transfer process.
- Where changes to the scope of the technology transfer plan are considered necessary, they should be approved by both the sending site and the receiving site.

盡責調查/Due diligence



挑選接收方/Selection of Receiving unit

Assess the legality, suitability and ability of receiving unit

轉出方的責任/Responsibility of SU

Validation documentation

Criteria, critical steps associated with the product

Assess the suitability and preparedness of RU

Health, safety and environmental issues.

Monitor and review the performance of receiving unit

接收方的責任Responsibility of RU

Problems of process identification	Differences in facilities, systems identification	Develop relevant operating procedures
Site/production Capability	Gap analysis/ change in the process	Perform a side-by-side comparison of equipment, facility

接收方/Receiving Unit

1.Ensure all products, materials and knowledge are suitable for intended purpose 2. Inspection by authority (Marketing Authorization)	1.Should not subcontract to a third party 2.Should not make unauthorized changes

共同責任/Shared Responsibility

SU

Verification

RU

Qualification(IQ/OQ)
Develop transfer protocol
Training
Execute the protocol
Document any changes
Document the execution

歐盟規範/Chapter 7 of The EU GMP

- Chapter 7 of the EU GMPs requires ***Quality Agreements*** to define the responsibilities of the contract giver and the contract acceptor.

品質協議/Quality Agreement

- A comprehensive written agreement between parties involved in the contract manufacturing of drugs that defines and establishes each party's manufacturing activities in terms of how each will comply with CGMP.

FDA :Contract Manufacturing Arrangements for Drugs

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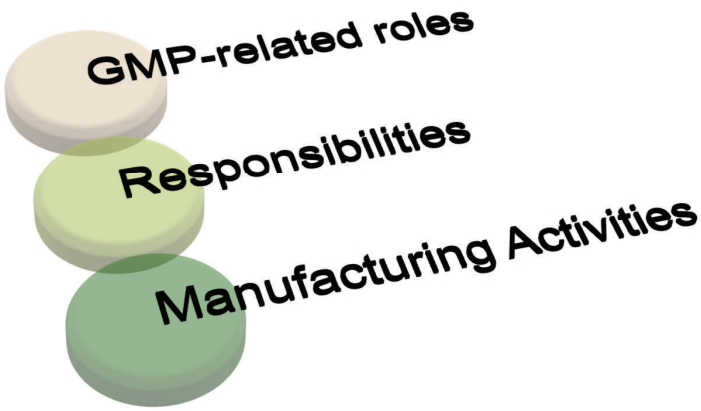
品質協議的範疇/Scope of Quality Agreement



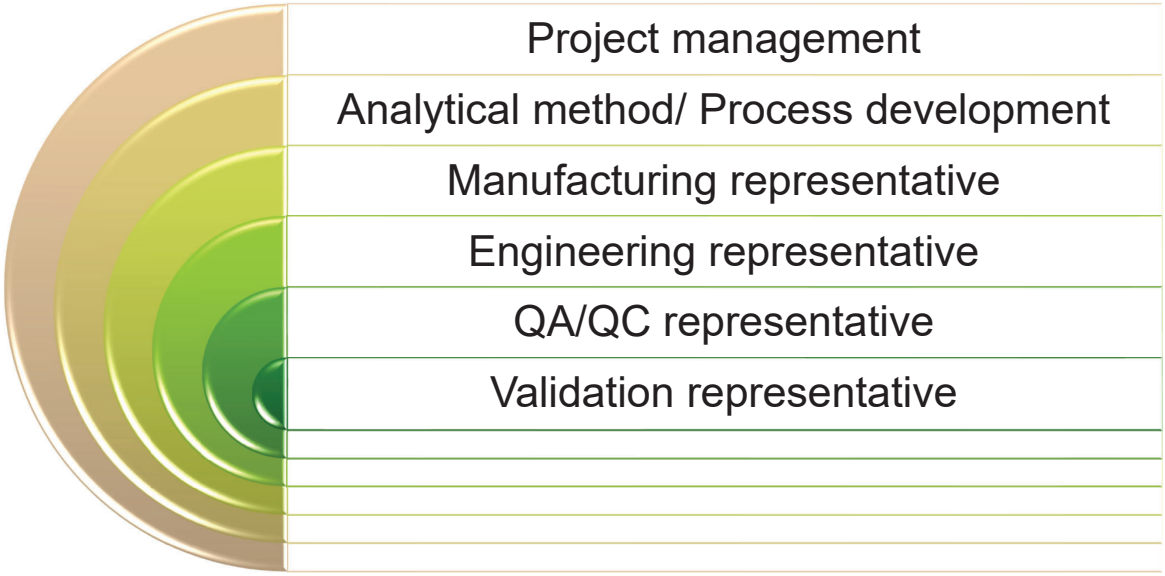
品質協議的要素/Elements of a Quality Agreement

Purpose/Scope	• Materials or service to be provided
Definitions	• Precise meaning of terms
Resolution of disagreements	• How the parties will resolve disagreements about product quality issues or other problems
Manufacturing activities	• To document quality unit and other activities associated with manufacturing processes
Life cycle/ revisions	• To document the Life cycle and change history of agreement

技轉流程/General Process of Technology Transfer

- Form TT team
- Consolidate knowledge for transfer and agree high level TT proposal
- Identify risks, conduct risk assessment, and develop TT plan
- TT execution/process qualification
- Finalize TT and perform review

技轉團隊/Transfer Of Technology Team

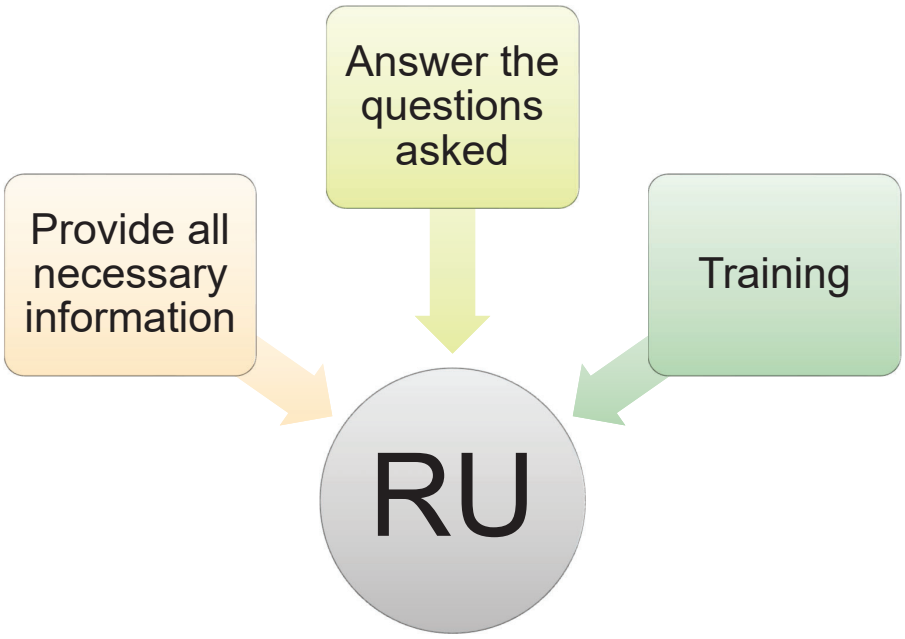


專案管理的權責/Responsibility of Project Management

Identifying appropriate contact personnel within the owner's (SU)and contract facility's organization(RU).

- Communication
- Deliverable
- Timeline
- Cost
- Resource

提供方的職責/ Responsibility of SU

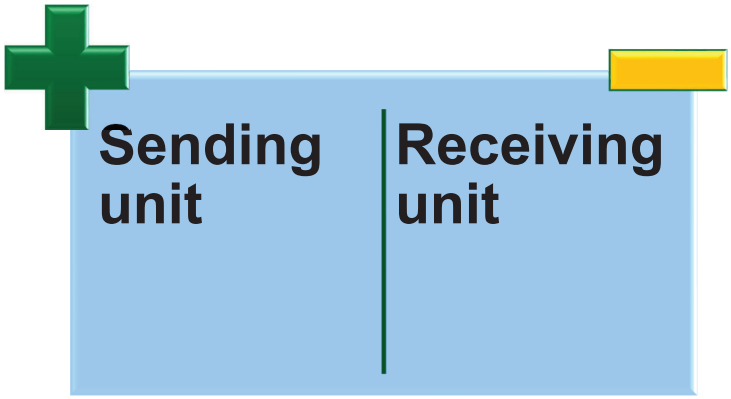


品保的職責/QA Representative

工程與確效/ Engineering And Validation

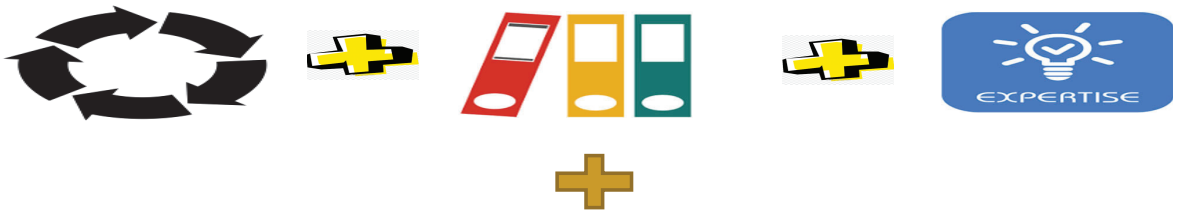
差異分析/Gap Analysis

***Gap analysis**:* Identification of critical elements of a process which are available at the SU but are missing from the RU.



技轉關鍵要素/Key Element Of TT

- Transfer of technology requires a documented, planned approach using trained and knowledgeable personnel working within a quality system, with documentation of data covering all aspects of development, production and quality control.



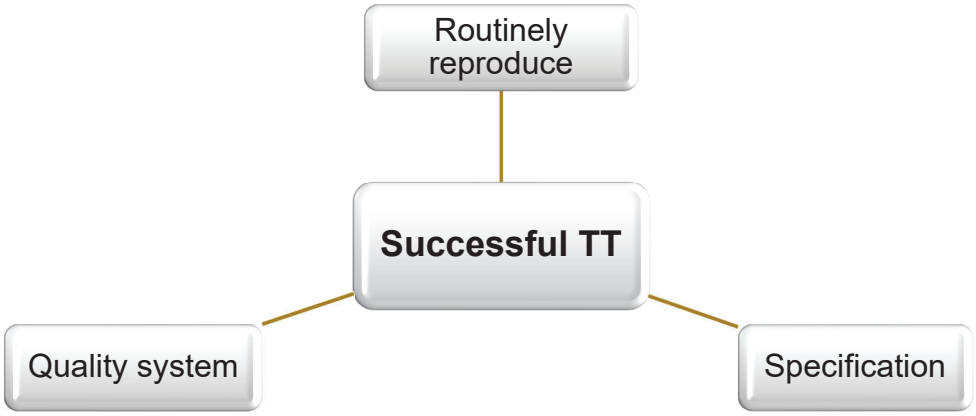
Quality system

達成技轉的基本要求/General Requirement For Successful TT

- Comprehensive project plan based on QRM principles
- Capabilities of the SU and the RU should be similar
- Performed a comprehensive **gap analysis** including technical risk and potential regulatory gap
- Adequately trained staff at the SU and the RU

技轉成功的定義/Definition Of Successful TT

- If there is documented evidence that the RU can **routinely reproduce** the transferred product, process or method against a **predefined set of specifications as agreed with the SU.**



生產場地/Premises

SU ➡ RU

- Layout
- Construction of buildings
- Heating, ventilation and air conditioning (HVAC)
- Temperature, relative humidity
- Water, power, and compressed air

設備/Equipment

A list of equipment

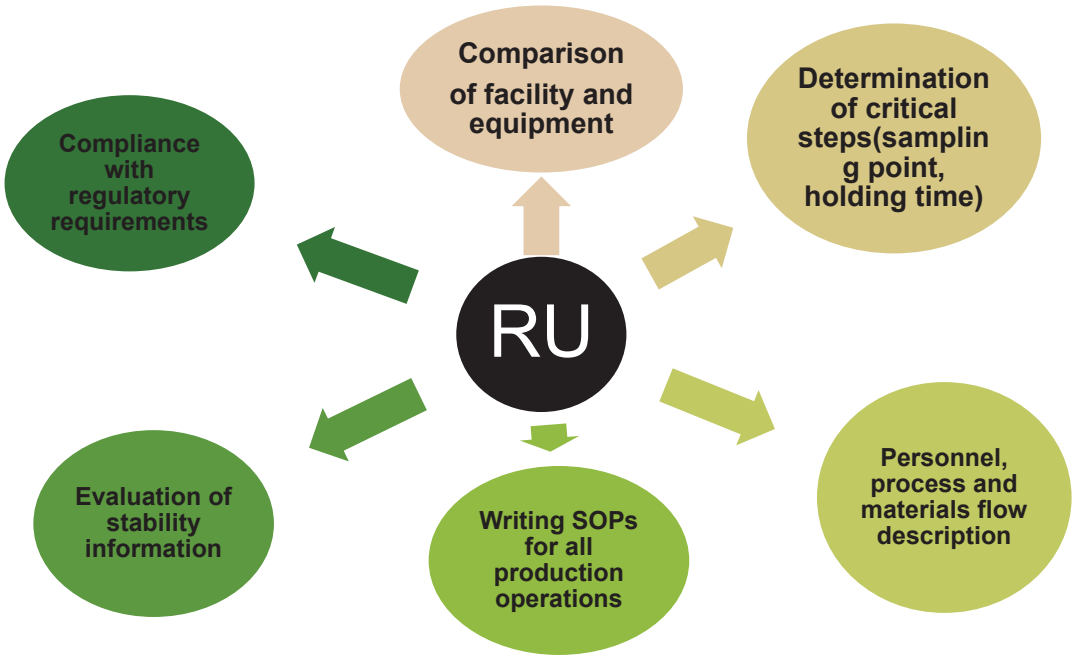
- Qualification and validation
- Drawings;
- Manuals;
- Maintenance logs;
- Calibration logs; and
- Procedures (e.g. Regarding equipment set-up, operation, cleaning, maintenance, calibration and storage).

雙方比較/Comparison Between SU And RU

GMP requirements should be satisfied and intended production volumes and batch sizes (e.g. same, scaled-up or campaign) should be considered. Factors to be compared include:

—minimum and maximum capacity;
— material of construction;
— critical operating parameters;
— critical equipment components (e.g. filters, screens, and temperature/ pressure sensors);
— critical quality attribute; and
— range of intended use.

接收方的活動/Process Development At The RU



Technology Transfer Package

技術轉移組合/Technology Transfer Package

- Process description
- Production protocols
- Process development report
- Technology transfer protocol
- Technology transfer report

流程描述/Process Description

- Flow chart of the process stages
- Quantities of all materials
- Scale of historic manufacture versus proposed scale of operation
- Specific processing conditions (e.g., Times, temperatures, and pressures)
- Sequence of the activities (e.g., Order of addition of reagents)
- Expected theoretical yield and output weight of product
- Quality critical parameters
- Permitted tolerance ranges for key parameters (e.g., Yield impacting parameters)
- Detail of other materials and by-products generated
- Detail of material recycle and solvent recovery procedures, and any materials requiring special disposal
- Mass and energy balance information
- A representative and predictive laboratory scale process

製程計畫書/Production Protocol(report)

- Flow chart of synthetic pathway
- Operating parameters and ranges
- A point check in the process(IPC) or may be a continuous measurement(IPM)
- Sampling
- Specifications
- Methods of analysis
- Conclusions(report)

Understanding its manufacturing process

技轉計畫書/Technology Transfer Protocol

Objective;	Scope;	Key personnel responsibilities;	Comparison of materials, methods and equipment;
The evidence that each critical stage has been satisfactorily accomplished before the next commences;	Identification of critical control points;	Experimental design and acceptance criteria for analytical methods;	Information on trial production batches, qualification batches and process validation;

Change control for any process deviations	Assessment of end-product;	Arrangements for keeping retention

技轉報告/ Technology Transfer Report

- A documented summary of a specific technology transfer project.
  - The scope of the transfer
  - Procedures
  - Acceptance criteria
  - Results achieved
  - Any deviations or action taken
  - Conclusions

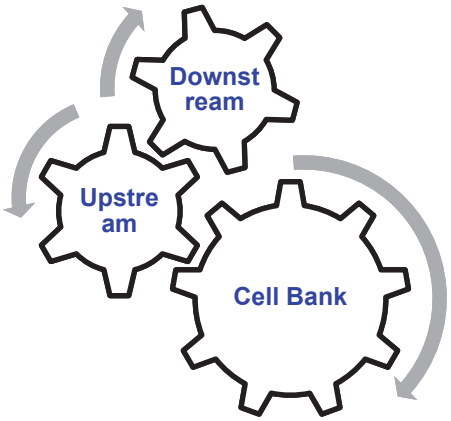
技轉文件需求/Documentation Required For Transfer Of Technology (TOT)

Key task	Documentation provided by SU	Transfer documentation
Project definition	Project plan and quality plan (where separate documents), protocol, risk assessments, gap analysis	Project implementation plan **TOT protocol**
Quality agreement		
Facility assessment	Plans and layout of facility, buildings (construction, finish) Qualification status (DQ, IQ, OQ) and reports	Side-by-side comparison with RU facility and buildings; gap analysis **Qualification protocol and report**
Health & Safety assessment	Product-specific waste management plans Contingency plans	
Skill set analysis and training	SOPs and training documentation (product-specific operations, analysis, testing)	Training protocols, assessment results
Analytical method transfer	Analytical method specifications and validation, including in-process quality control	Analytical methods transfer protocol and report
Starting material evaluation	Specifications and additional information on APIs, excipients	

技轉文件需求/ Documentation Required For TOT

Key task	Documentation provided by SU	Transfer documentation
Process transfer: manufacturing and packaging	Reference batches (clinical, dossier, biobatches) Development report (manufacturing process rationale) History of critical analytical data Rationale for specifications Change control documentation Critical manufacturing process parameters Process validation reports Drug master file API validation status and report(s) Product stability data Current master batch manufacturing and packaging records List of all batches produced Deviation reports Investigations, complaints, recalls Annual product review	History of process development at RU Experiences at RU should be recorded for future reference Provisional batch manufacturing document (RU to develop) Provisional batch packaging document (RU to develop) Description of process at RU (narrative, process map, flow chart) **Process validation protocol and report**

Biopharmaceutical Process



國際製藥工程協會/International Society for Pharmaceutical Engineering

Development

Manufacturing of active biopharmaceuticals

ISPE Guide

Biopharmaceutical Process Development and Manufacturing

上游製程/General Upstream Process

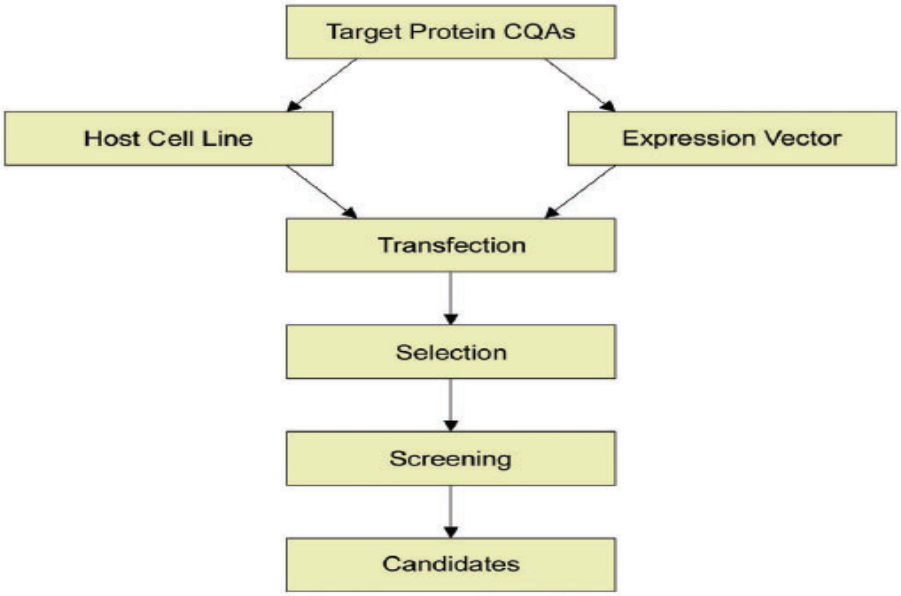
Cell banking

Shake flasks

Bioreactor

Clarification

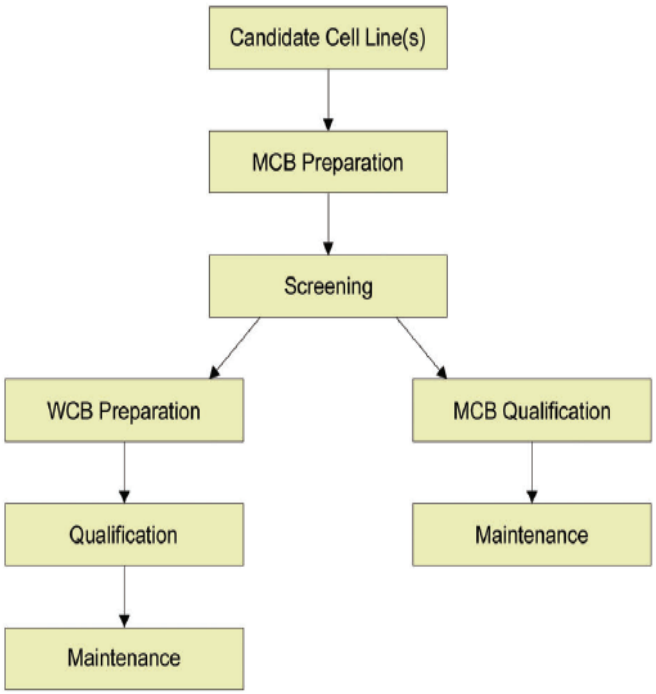
細胞株開發/Cell Line Development



細胞庫製備/Cell Bank Preparation

Cell density

1~2*10 ^{6} cells/ml



法規要求/Regulatory Requirements

- The cell bank preparation should be performed and documented **following GMPs**.

- Regulatory requirements
  - ICH Q5B and Q5D
  - FDA's "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals"
  - Good Laboratory Practice (GLP)
  - ICH Q5A(R1)_Viral Safety Evaluation of Biotechnolog Derived from Cell Lines of Human or Animal Origin,

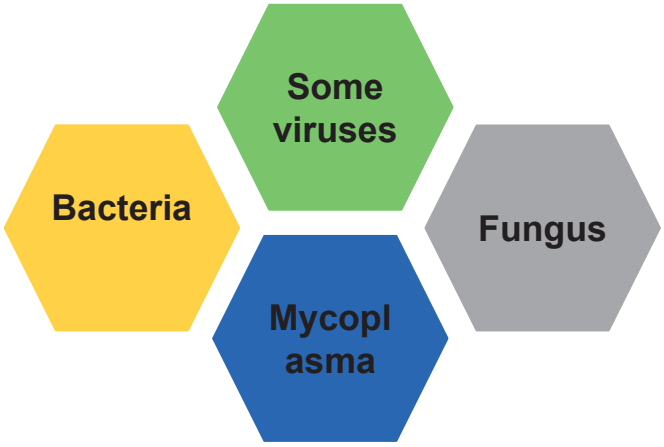
無菌分裝與儲存/Aseptic Fill and Storage

- Aseptic fill procedures and controls
- Validated facilities and equipment
- Suitably trained personnel.
- To store in the **vapor phase** of liquid nitrogen in sealed containers
- To store the split stocks at different locations
- Evidence of the stability and recovery

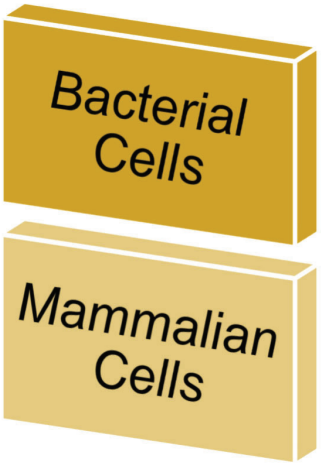
PIC/S_ Annexes 2_人用生物原料藥及產品的製造（**MANUFACTURE OF BIOLOGICAL MEDICINALSUBSTANCES ANDPRODUCTS FOR HUMAN USE)**

細胞庫驗證/Cell Bank Qualification

- MCBs and WCBs should be tested using appropriate tests described in the ICH Q5



發酵槽和生物反應槽/Fermenters and Bioreactors



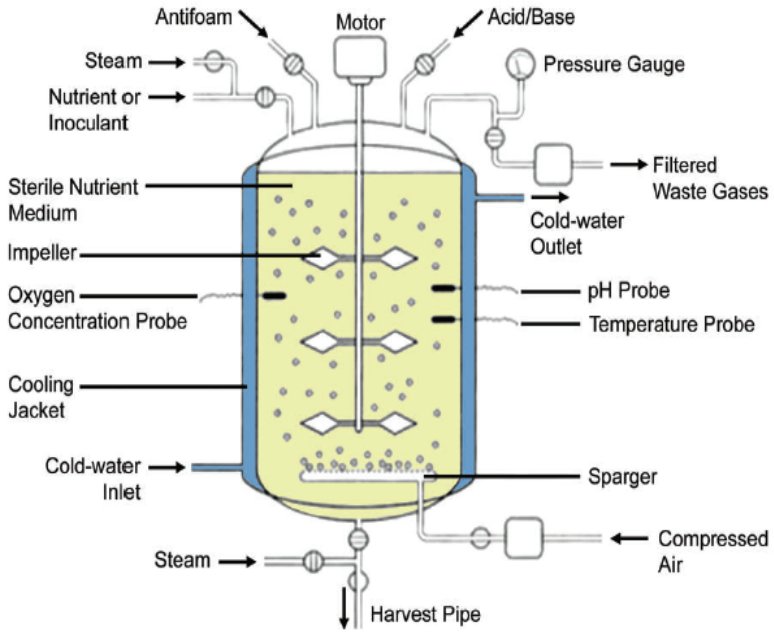
- Controlling the critical parameters to provide optimum conditions for the cell growth and drug substance production.

典型發酵槽/Typical Fermenter

Bioreactors

Additional gases such as O2, CO2

Low shear impellers



兩者差異/Bioreactors VS Fermenters

Type	Bioreactors	Microbial fermenters
Aspect ratio (height to diameter)	1.5:1	3:1
Tank	Stirred tank	Stirred tank
Tank material	high grade stainless steel (316 L) with a Ra (microinch) finish of 25 or less	high grade stainless steel (316 L) with a Ra (microinch) finish of 30 or less
Impeller	A single low shear impeller	Up to 3
Cooling system	Require heating more than cooling	High cooling
Growth rate	Slower	Much faster

培養基/Media Systems

- Two broad categories
  - Dry/powdered
  - Liquid
- Dry/powdered media ingredients are typically used for bacteria, for large scale mammalian cell culture, and for yeast cell lines.

no “clumps” of dry media

澄清流程/Clarification Process

Primary recovery

1.Tangential-Flow Filtration-Microfiltration (TFF-MF),

2. Centrifugation

3. Depth filtration(size exclusion from 0.6 μm to 0.2 μm.).

Removal

bulk of large particles,

whole cells, and/or cell

debris.

Secondary clarification

Colloids

Lipids

DNA-RNA

Residual cells

Other particles

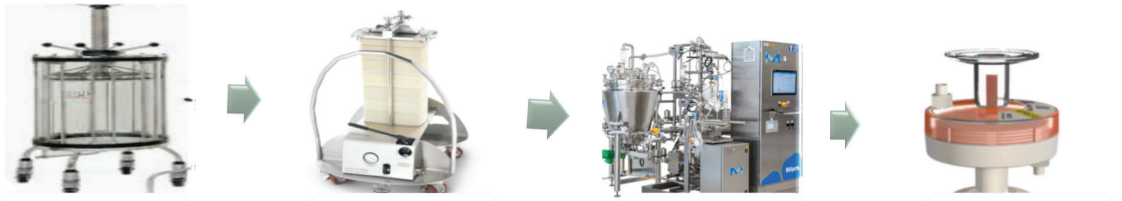
* (depth filtration designed_

reduce the bioburden)

離心目的/Purpose Of Centrifugation

Desired product recovery	Liquid clarity	Removal of cells when production of protein is extracellular
Collection of cells when the product is intra-cellular	Removal of cell debris in lysate clarification	Recovery of inclusion bodies

下游製程流程/General Downstream Process

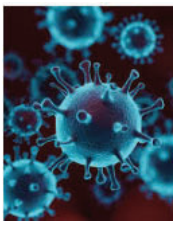


Chromatography → Viral clearance → Tangential Flow Filtration (TFF) → *Final Filtration*

下游製程目的/Purpose Of Downstream Processing

- Removal of
  - Host cell proteins
  - DNA
  - Endotoxins
  - Aggregates

- Viral clearance
- Conjugation for covalent linking of different biomolecules
- Concentration and formulation of the product in a stable form to a specified product titer

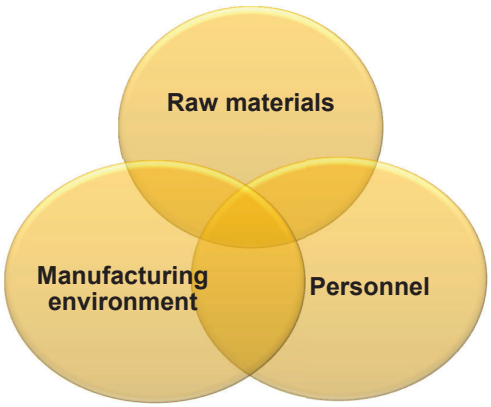


過濾目的/Goal of Filtration

- **Clarification of precipitates**
- **Bioburden reduction**
- **Concentration and diafiltration**
- **Virus removal**
- **Final product filtration**

負荷菌管控/Bioburden Control

- Filtration can provide additional assurance of bioburden control.
- Endotoxin created by the bioburden prior to filtration can impact product quality
- Only reliance on filtration alone to control bioburden is not advisable.



減菌/Bioburden Reduction

Filter Pore Size	Microorganism to be removed
0.22 µm	**Bacteria** *Brevundimonas diminuta* *Pseudomonas aeruginosa* Bacteriophage (Air Filtration
0.45 µm	**Bacteria** *Escherichia coli* *Leuconostoc oenos* *Pediococcus damnosus* *Lactobacillus hilgardii* *Oenococcus oeni*

層析/Chromatography

- To purify target product proteins from other proteins and non-protein species

Size Exclusion Chromatography (SEC)

- Called gel filtration
- Separates proteins by size.

Adsorption Chromatography

- Proteins have extremely complex surface properties that can be manipulated in a controlled manner by altering their environment.

病毒去活化方法/Methods of Viruses inactivation

Held below a PH of 4.0 for one hour

- Low PH
- Heat
- UV light exposure
- A variety of buffer solutions

清除病毒/Virus Clearance

- Virus filters are designed to retain viruses in the range of 18 nm to 30 nm with virus reductions in the range of 3 to > 6 log.
- **Log Reduction Value (LRV)**

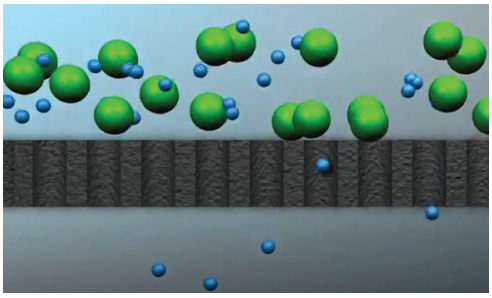
LRV = log (ViCi / VfCf) , Vi = Initial volume
Ci= Initial viral concentration , Vf= Final volume
Cf= Final viral concentration

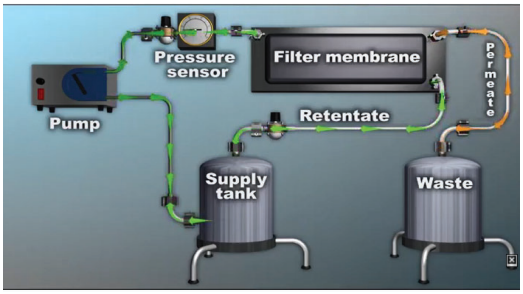
濃縮與透析/Concentration and Diafiltration

- Downstream operations may use an ultrafiltration step to concentrate an intermediate product
- Diafiltration(or buffer exchange step) can be used to remove salts and other low molecular weight impurities.

切向流過濾 /Tangential Flow Filtration (TFF)

- The final principal step ,Tangential Flow Filtration (TFF) or ultrafiltration, which designed to exchange the buffering solution and/or adjust the concentration of the protein target.





安定劑/Stabilization Of The Target Protein

Sucrose
蔗糖

Sorbitol
山梨醇

緩衝液配置與儲存/Buffer Preparation and Storage

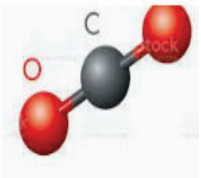
- Should be prepared, filtered using a sterilizing grade filter and stored in a manner to **control bio-burden**.

- **Conductivity or pH meters** to provide real-time verification .

半製品儲存/DS Storage

- The container should not interact with or adsorb the target.

- EMA/410/01 rev. 3 compliance (TSE/BSE certificate)
- To avoid intrusion of CO2 into the container, resulting in PH drift.

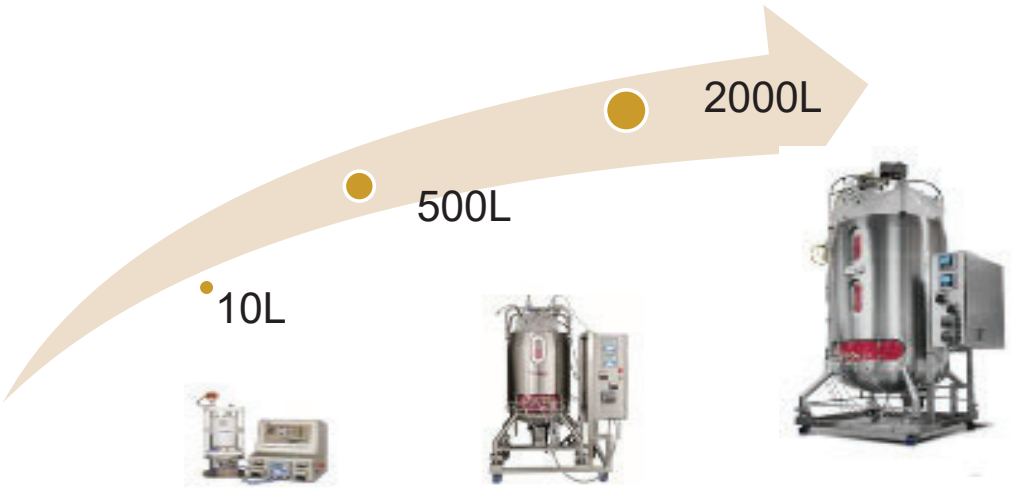


Take a break

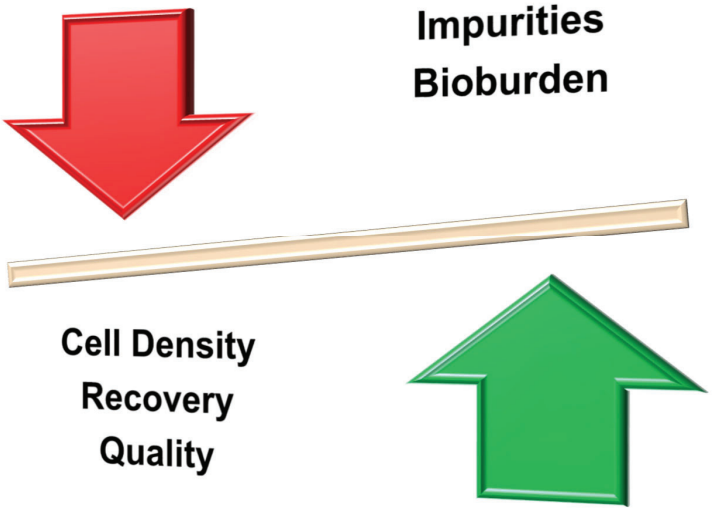
Scale Up Considerations (Upstream/Downstream)

放大的定義/Definition of Scale Up

- Scale-up is an organized and documented process of defining operations to produce a product at a scale larger than the current operation



期望/Expectation



不純物/Impurities

Process-related		
Host cell DNA	Host cell proteins	insulin, anti-foam, residual Protein A

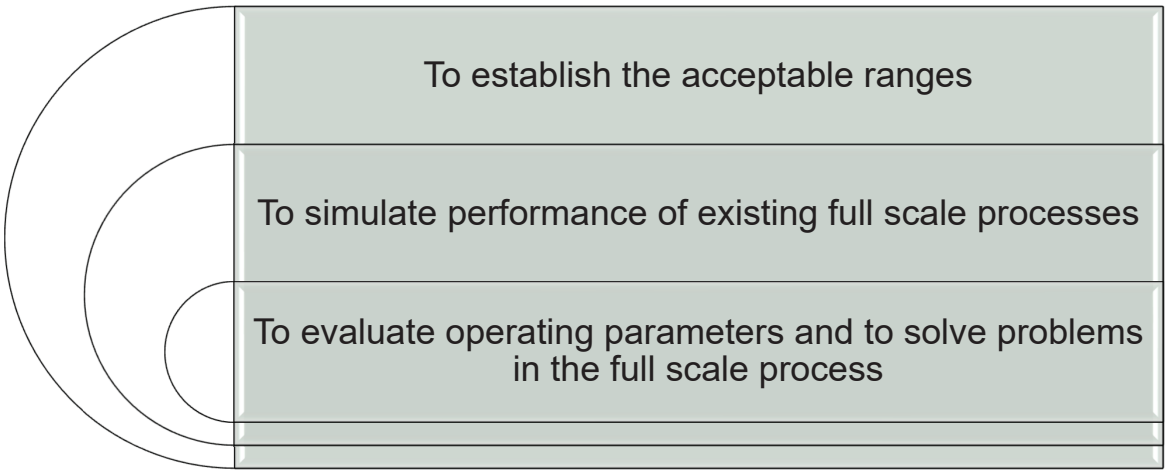
Product-related		
Aggregates	Fragments	Charge variants

品質是經由設計/Quality by Design (QbD)

- ICH Q8(R2)
- *"A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."*

	Process Step	Risk of Impact to Product Quality Attributes	Risk of Impact to Key Process Attributes
1	Seed Culture expansion in disposable shake flasks and/or bags	Low	*High*
2	Seed Culture expansion in bioreactors	Low	*High*
3	Production bioreactor	*High*	*High*
4	Harvest: centrifugation and depth filtration	Low	*High*

實驗室規模/Laboratory Scale Model Systems



常見的顧慮/General Considerations

- Increasing the scale of each unit operation rather than by increasing the number of units.
- Cost of the overall process(Resin)
- The amount of production time (holding times)
- Lack of commercially available equipment of adequate capacity(Membrane Area)
- Steps that are not easily scalable

degradation

solvent

可能會發生的問題/Potential Issues Caused

Cell cultures (fungal fermentations)	• Shear effects • Bubble effects
Fermentation	• Oxygen transfer limitations • Heat removal
Chromatography	• Specific protein binding • Superficial velocities
Ultrafiltration	• Flux rate • Membrane geometry

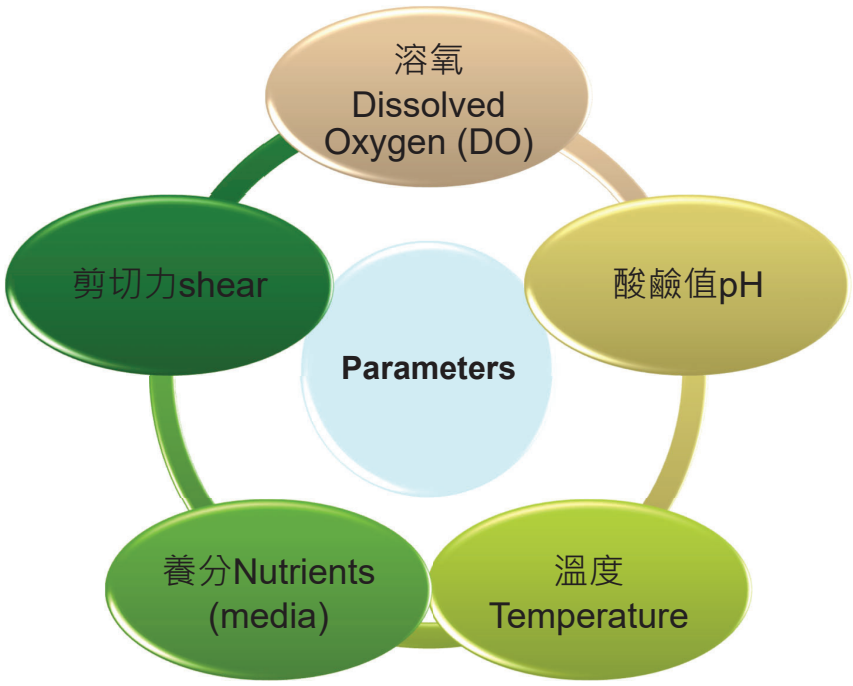
細胞培養/Cell Cultures

- Shake flasks
- Disposable bags
- Stainless steel fermenters
- Bioreactors

接種目的/Goal Of Inoculum Preparation

- **Inoculum Preparation**
  - To minimize the time spent and capital cost in the production reactor
  - Additional inoculum steps are usually added.

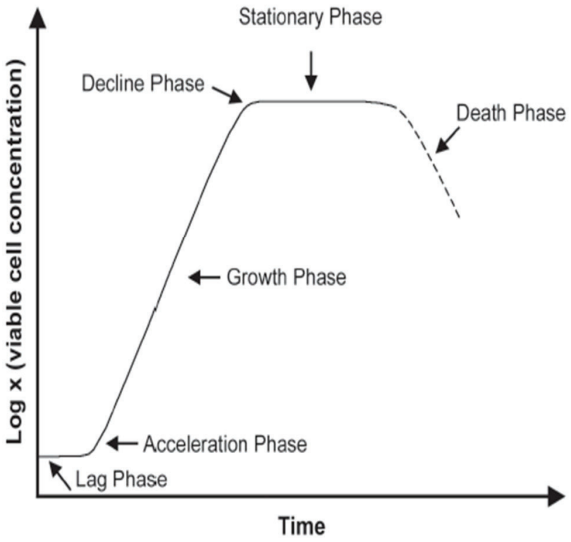
關鍵參數/Critical Parameters



細胞生長條件/Conditions For The Cell Growth

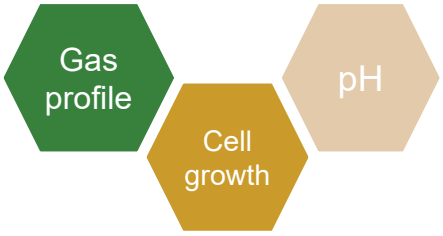
- Temperature
- pH
- Nutrient availability
  - Energy sources
  - Essential amino acids
  - Growth factors

Figure 10.2: Typical Growth Curve for a Batch System

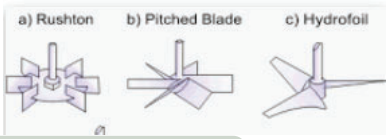


評估氧氣需求/Assessment of Oxygen Requirements

- The oxygen requirements of a cultured organism can be assessed at the laboratory scale by using different shaker rotational speeds in multiple experiments.
  - Oxygen transfer rate氧氣傳輸速率
  - Shaker speed振盪器的速度
  - Shaker rotary action stroke diameter振盪器旋轉動作衝程直徑



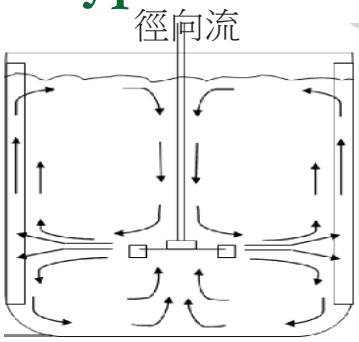
攪拌器/Agitator



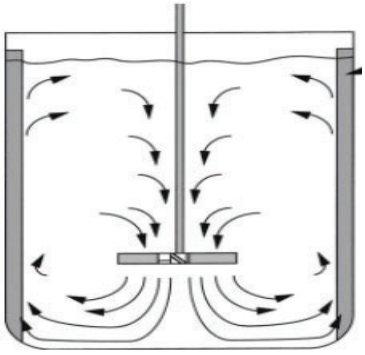
- Maintains the cells in suspension
- Facilitates heat and mass (substrate) transfer.
- Maintained high nutrient levels(soluble in water)
- ***Agitator (Impeller) Types***
  - Radial flow
  - Axial flow
  - Pitched blade

葉輪的選擇/Chosen Impeller Type

Radial flow → High shear → Microbial culture



Axial flow/Pitched blade → Low shear → Cell culture



氧氣傳輸因素/Factors for Oxygen Transfer

- Oxygen is relatively insoluble in water (about 10 mg/L) and should be supplied continuously to the culture.
  - Fermenter dimensions反應槽尺寸
  - Agitator type and dimensions攪拌器類型和尺寸
  - Power input (which is a function of agitator (impeller) type and speed as well as volumetric gas flow rate) 電源輸入(攪拌器葉輪的類型和速度以及氣體體積流量的函數)

◆ Oxygen transfer rate, OTR=Kla(C *- C)

◆ C* is the saturation concentration of oxygen in the liquid, 液體中氧氣的飽和濃度

◆ C is the actual oxygen concentration, 實際氧氣濃度

亨利定律(Henry's Law)
液體溶氧量與氧氣在氣相之氣體分壓成正比。P=KC
P為氣體壓力，
C為摩耳濃度，
K為特定常數的定值

分佈器設計/Sparger Design

- Introducing air into fermenter/bioreactor.
- A single pipe with multiple holes can be used at larger scale.
- Smaller bubbles into the culture broth and can result in a higher constant volumetric O2 transfer rate.

三種放大的方法/Three Scale-up Methods

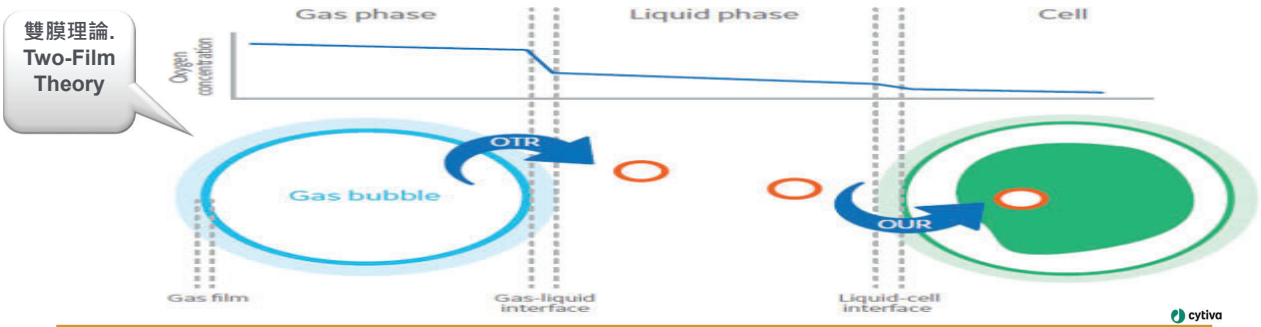
- Constant volumetric oxygen transfer rate, kLa
  固定體積氧氣傳輸速率
- Constant impeller tip speed (πNdi)
  固定葉輪葉尖速度
- Constant volumetric power input Pg/V
  固定體積功率輸入(**cell cultures**)

Tip Speed = π × D × N
π= 3.14
Di = impeller diameter
N = impeller speed

Pg/V=(Np *ρ* N^3*d^5)/V
*N*p =impeller power number,
ρ =density
N=agitation speed
d =the impeller outer diameter
V =the vessel's full working volume

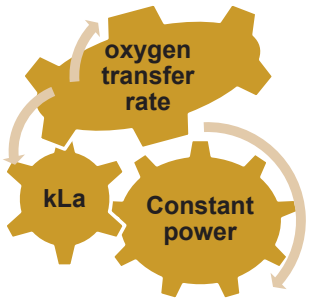
傳值係數/ Oxygen Mass Transfer Coefficient (Kla)

- kLa = kL × a, An indication of the oxygen transfer efficiency in the culture medium. 表示培養基中氧氣的傳輸效率。
  - kLa is the mass transfer coefficient from the gas to liquid phase, given in sec^{-1}• kLa是從氣相到液相的傳值係數，以秒1為單位
  - kL = liquid side mass transfer coefficient 液體側傳值係數
  - a = bubble surface (available for diffusion) 氣泡表面



發酵槽放大/ Scale-up Of Fermentation

- Constant power per volume and geometric similarity was used for scale-up of fermentation processes.
- keep constant…….
  - Tank height to diameter ratio,桶槽高度與直徑之比
  - Impeller to tank diameter ratio,葉輪與桶槽直徑之比
  - Impeller geometry葉輪幾何形狀



剪切力敏感產品/Shear-sensitive Product

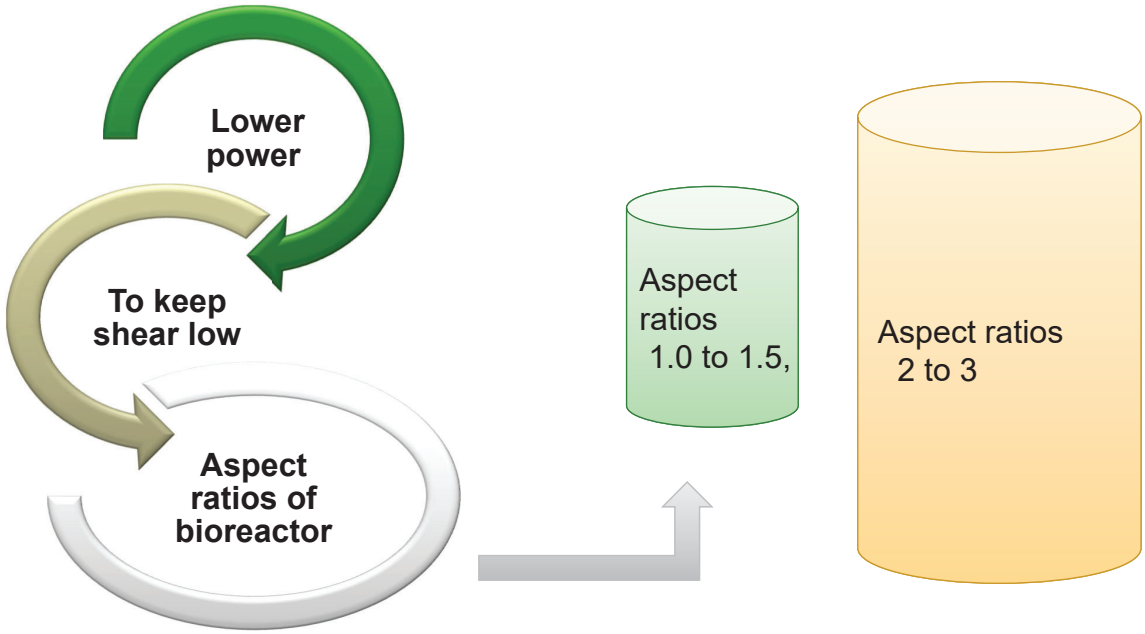
- When cell cultures or fermentations are sensitive to shear, the shear of an agitator should be kept constant by scaling based on constant impeller tip speed (π NDi).
  - 1. Calculate the impeller tip speed for the large scale to match the smaller scale 計算大批量的葉輪葉尖速度，以符合較小批量
  - 2. Calculate the expected large scale kLa with that tip speed 運用該葉尖速度計算預期大批量的kLa
  - 3. Adjust the oxygen/gas ratio and head pressure to make meet the kLa of the smaller scale 調整氧氣/氣體比率和頭壓，使其符合較小批量的kLa

$$\pi N_1 D_{i1} = \pi N_2 D_{i2}$$

$$Pg/V=(Np * \rho * N^3 * d^5)/V$$

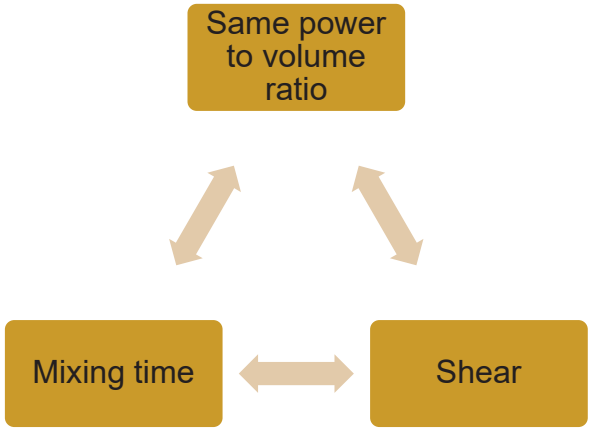
$$k_L a = K' \left(\frac{P_g}{V} \right)^{\alpha} v_g^{\beta}$$

哺乳類細胞/Mammalian cell

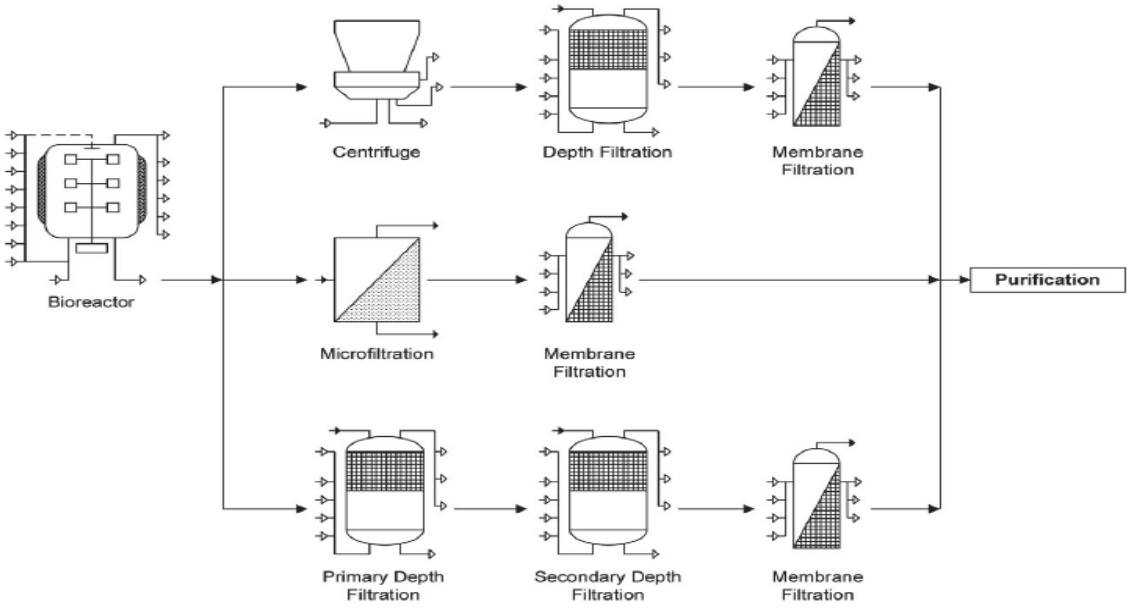


混合時間與剪切力/Mixing Time VS Shear Limitations

- Mixing time increases with scale-up and can be difficult to maintain without exceeding cell shear limitations.



典型的收穫和澄清策略/Typical Harvest And Clarification Strategies

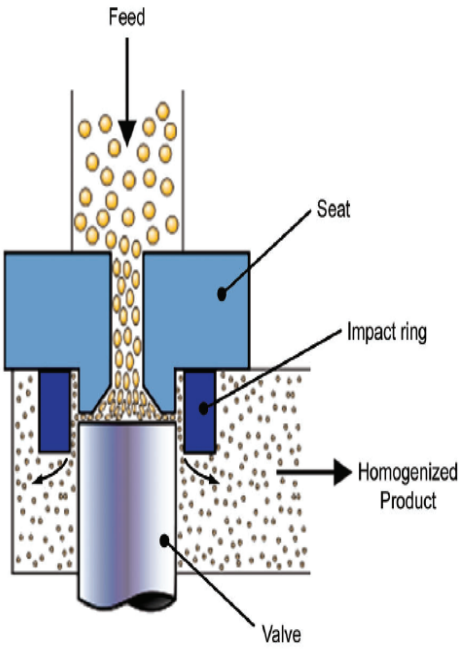


第一道回收/Primary Recovery

- **Centrifugation**
  - The objective of centrifugation scale up is to achieve the desired product recovery and/or liquid clarity.
- **Homogenization**
  - Physical cell lysis with processing equipment (usually for bacterial cells) is performed between 2°C to 8°C and to break cell walls
  - High-pressure homogenization is a commonly used cell lysis technique for recovering intracellular target proteins

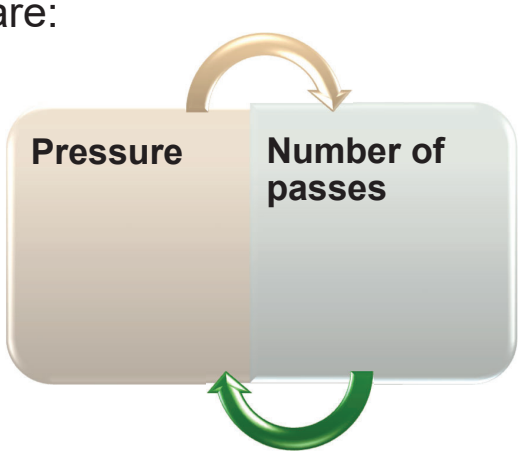
均質作用/Homogenization

- High pressure 5,000 to 30,000 psi (300 to 2000 bar)
- Same type of valve manufacturer is required for laboratory and large scale.



關鍵製程參數/Critical Process Parameter

Two CPP values (ranges) that should be specified from development studies are:



- Optimize Cell Disruption 優化細胞分裂
  - Controlling the pressure, 控制壓力
  - Residence time,停留時間
  - Valve tension,瓣膜張力
  - Shear force剪切力

注意事項/Points To Consider

Large temperature increases

Target protein integrity

Post-valve heat exchanger

+

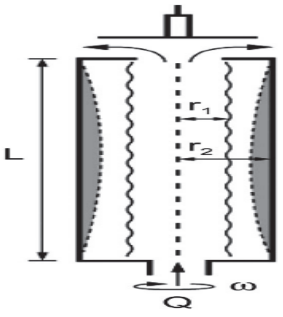
Feed should be chilled

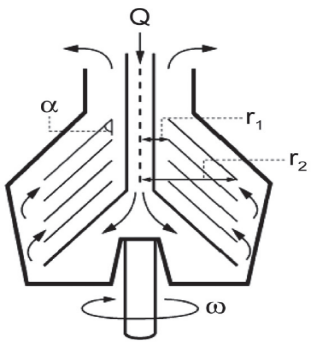
=

Homogenizer

離心機種類/ Types of Centrifuge

Type	Application
Tubular Bowl Centrifuge	Microbial cells, mammalian cells, and most microbial cell debris
Disk-stack Centrifuge	Removing cells and can partially recover microbial cell debris and protein precipitates very short residence time
Ultracentrifuge	Very high velocities (~ 70000 rpm) Separation of cell Debris from viruses, collecting very fine protein particles and purify RNA polymerase





Σ 理論/Σ theory

- Scaling up a centrifugation step is most often accomplished using Σ theory.

$$Qc1/\Sigma 1 = Qc2/\Sigma 2$$

  - Qc = vt Σ
  - Qc = volumetric flow rate of centrifuge離心機的體積流量
  - vt = setting velocity設定速度
  - Σ values for a particular centrifuge can be obtained from the manufacturer由廠商提供

可能的產率損失/Potential Loss Of Product

- Several purification steps are usually needed and each purification step can introduce potential loss of product, due to

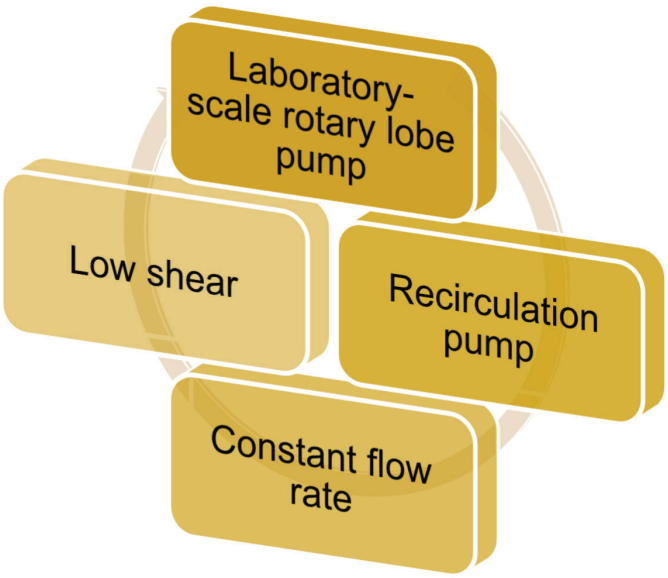
  - Less than ideal separations
  - System hold-up
  - Equipment failure

濾膜選擇/Membrane Selection

- The smallest module representative of a scaled down version of a large scale manufacturing system, which has similar:
  - Flow paths lengths
  - Membrane type
  - Channels

- Capacity= Volume per filter area (L/m^2)
- Flowrate =Volume per time per area ($L/m^2/hr$ = LMH)

建議/Suggestions



深層過濾器/Depth Filtration

- Removal of materials found in upstream, Viral clearance or sterile filtration and remove particles by size exclusion from 0.6 µm to 0.2 µm. Some depth filters are charged.
- Screening study criteria:

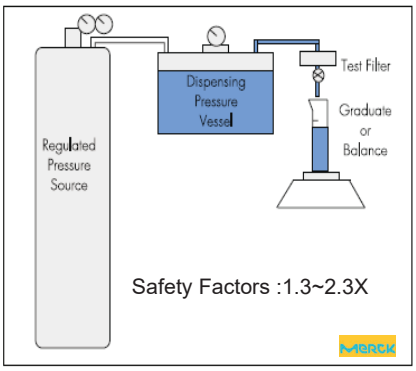
Filter capacity(evaluation can be performed by measuring the **volume filtered** Versus **time** at **constant operating pressure.)**

Filtrate quality determined by filtrate turbidity

Target protein mass balance

Robustness regarding variation in feed characteristics such as % solids and feed turbidity

Constant Pressure: Vmax

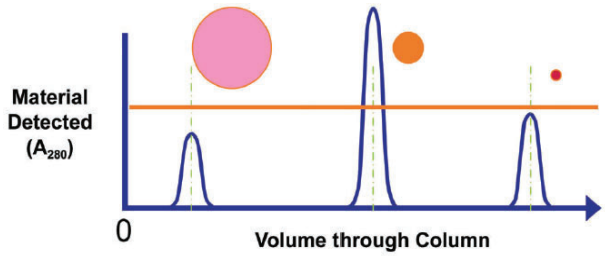


層析開發步驟/Development Of Chromatography

- Selection of resin, buffers
- Elution conditions (for bind-and-elute chromatography)
- Selection of ranges for product loading
- Selection flow rate

粒徑篩析層析法/Size Exclusion Chromatography(SEC)

- SEC columns are typically very large with product loading volume of concentrated product being around 5% of the column volume.
- Bed heights of SEC columns can be as long as 100 cm to provide the residence time to cleanly separate the various species.



吸附層析法/Adsorption Chromatography

Ion Exchange (IEX) Chromatography

離子交換(陰陽)

Hydrophobic Interaction Chromatography (HIC)

疏水性層析法

Reverse Phase Chromatography (RPC)

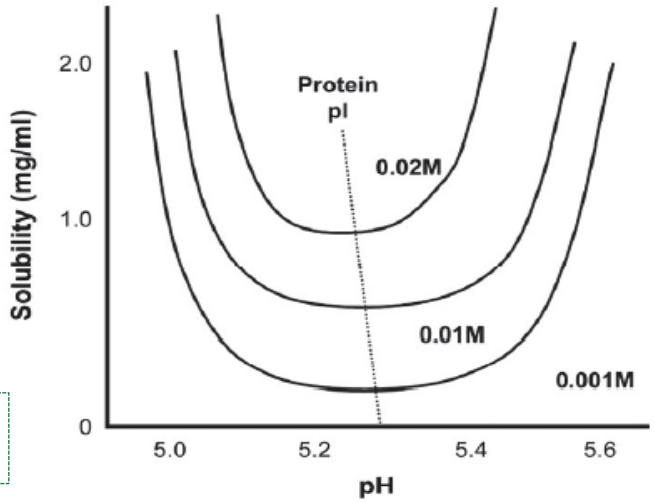
逆向層析

Affinity Chromatography

親和層析

蛋白質的溶解度/ Protein Solubility

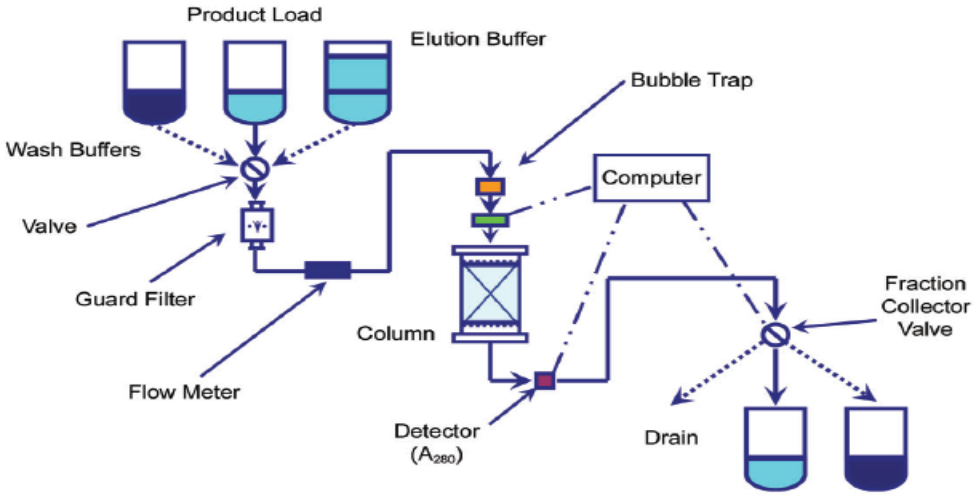
- Protein solubility can be controlled by
  - pH
  - Salt concentrations
  - Temperature



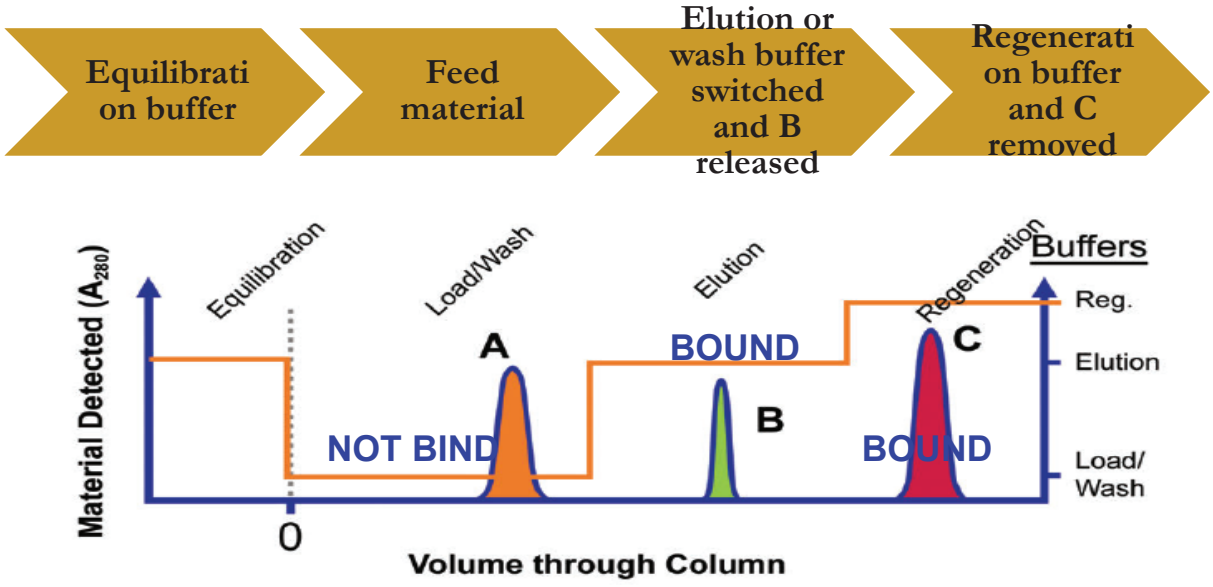
等電點（pI）是蛋白質的淨電荷變為零時溶液的pH值

典型層析操作/Typical Chromatography Operation

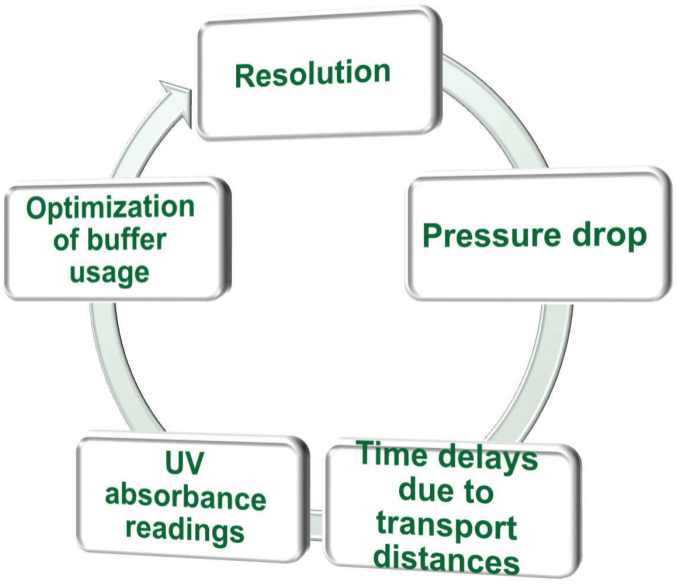
- A typical biopharmaceutical process will have between two and four chromatography steps.



層析光譜/Basic Chromatogram For Adsorption Chromatography



層析設備差異/Chromatography Equipment Considerations



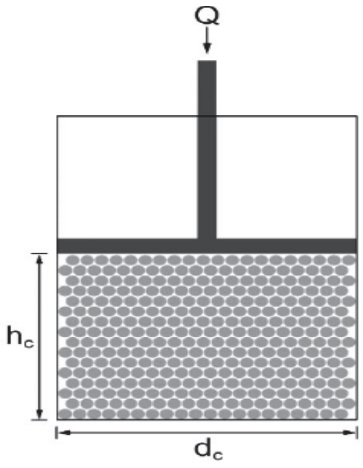
層析放大/Chromatography Scale Up

Achieved by	Increasing the column diameter
	Holding the column height
	Mobile phase linear velocity constant

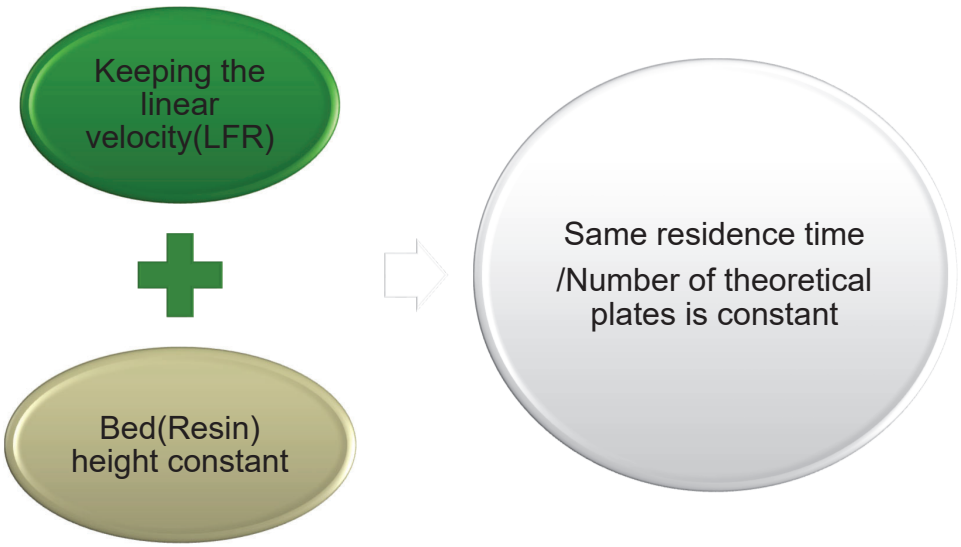
放大常見的方法/A Common Method For Chromatography Scale-up

- By replicating sufficient laboratory-scale columns, each running at optimized operating parameters
- By increasing the column diameter while holding the column height and mobile phase linear velocity constant.

Column Cross-sectional Area = $A_c = \pi d_c^2/4$
Column Volume = $V_c = \pi (d_c^2/4) h_c$



維持管柱高度/Maintain the Bed Height

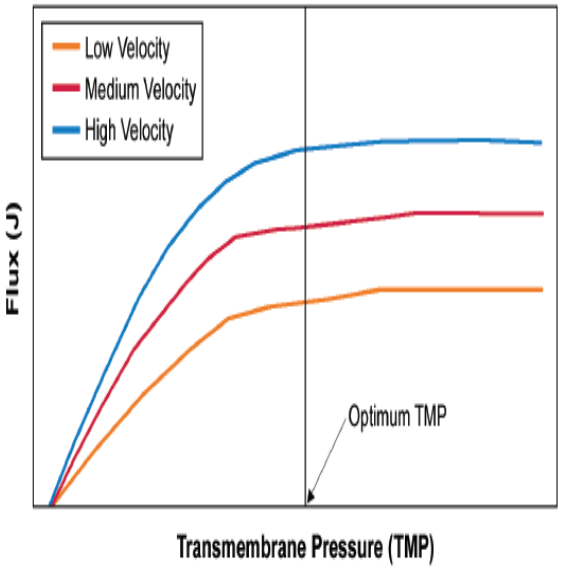


微過濾系統的參數/Parameters for a Microfiltration System

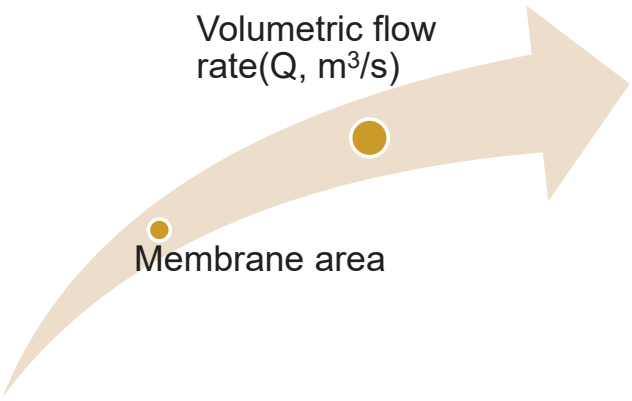
- Data required of scaled-up may be obtained from the membrane manufacturer. Parameters which should be considered include
  - Membrane type
  - Feed characteristics
  - Flux (Liters per square meter per hour,**LMH**) as a function of Transmembrane Pressure (**TMP**) and feed concentration (Cf)
  - % passage of the product of interest
  - Optimal flux as a function of time
  - •Diafiltration buffer

穿膜壓差與流通量/Flux VS TMP

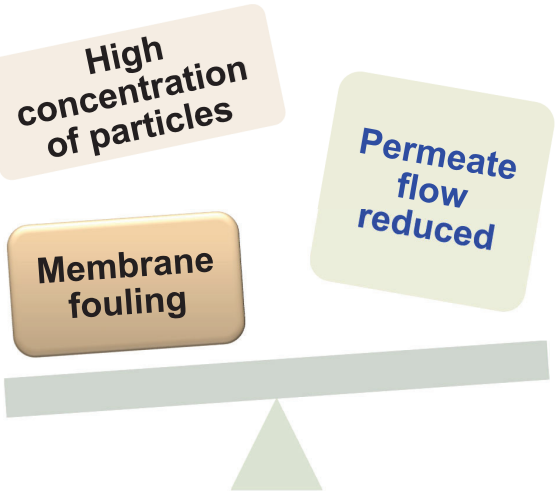
- Process development studies should determine ranges for **Transmembrane Pressure (TMP)** and **crossflow rate** that maximize the permeate **flux(J) (= Qp/Am)**
- The permeate flux determines the amount of membrane area required for the separation.



實現放大的因素/Scale Up Factors For Ultrafiltration



- UF membrane
  - Cassettes卡匣
  - Hollow fibers中空纖維



其他考量/Points To Consider

PROVIDING ADDITIONAL MEMBRANE AREA

Reduce processing time

1.Increase the size of the system

2. Increase Product hold-up

3. Increase Membrane cost

放大的參數需求/Requirements Of Scale Up

UF/DF scale up should maintain the flow path on scale up

- Membrane geometry膜幾何形狀
- Membrane pore size膜孔徑
- Membrane material膜材料
- Channel height or diameter通道高度或直徑
- Channel screen type通道濾網類型

超過濾系統的挑戰/Challenges Of Ultrafiltration Systems

- Temperature control

- Adequate cooling should be provided to prevent product that is recirculated and concentrated, from heating up as a result of mechanical energy from the pump and system friction.

混合設備放大/Mixing Systems Scale Up

Dust hazard	• Weigh booths, dust collars, and local pick-ups (elephant trunks) • Facility layout, and process steps
Dry media size and weight	• More cumbersome to handle and the risk of injury to operators increases significantly
Improve ment	• Drum lifters, platforms with material lifts, pneumatic conveying, and docking/charging systems

Technology Transfer Considerations

技術轉移文件/Technology Transfer Documents

1. *New Product Proposal*
2. *Published Information*
3. *Analytical Methods*
4. *Laboratory Data*
5. *Host Organism Selection and Stability Data*
6. *Development Reports*
7. Process description
8. *Design Space Definition*
9. *Process Timeline*
10. *Process Flow Sheets*
11. *User Requirements*
12. Raw materials description
13. *Equipment Layouts*
14. *History of Clinical Batches*
15. *Piping and Instrumentation Diagrams*
16. *Pilot Scale Batch Records*
17. *GAP Analysis*

產品資訊/Product Information

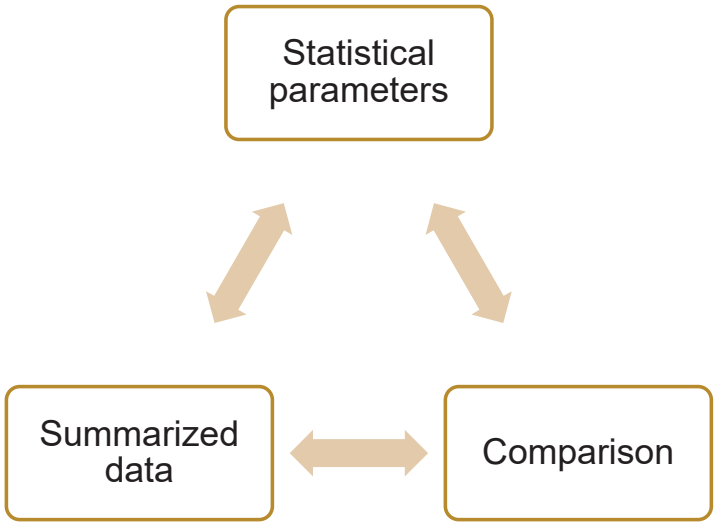
The nature of the bio-molecule
Disease information
The mechanism of action of the molecule.
Host organism
rationale for selection of this host organism
The in vitro age
Culture conditions
Purification techniques
GMO Risk and HAZOP assessments

分析方法/Analytical Methods

- Completed Method
  - The pilot and production scale
  - Practical training of scientists analyzing
- Method development is ongoing
  - Example analytical methods
  - Methods to verify the protein coding sequence
  - Final product characterization methods

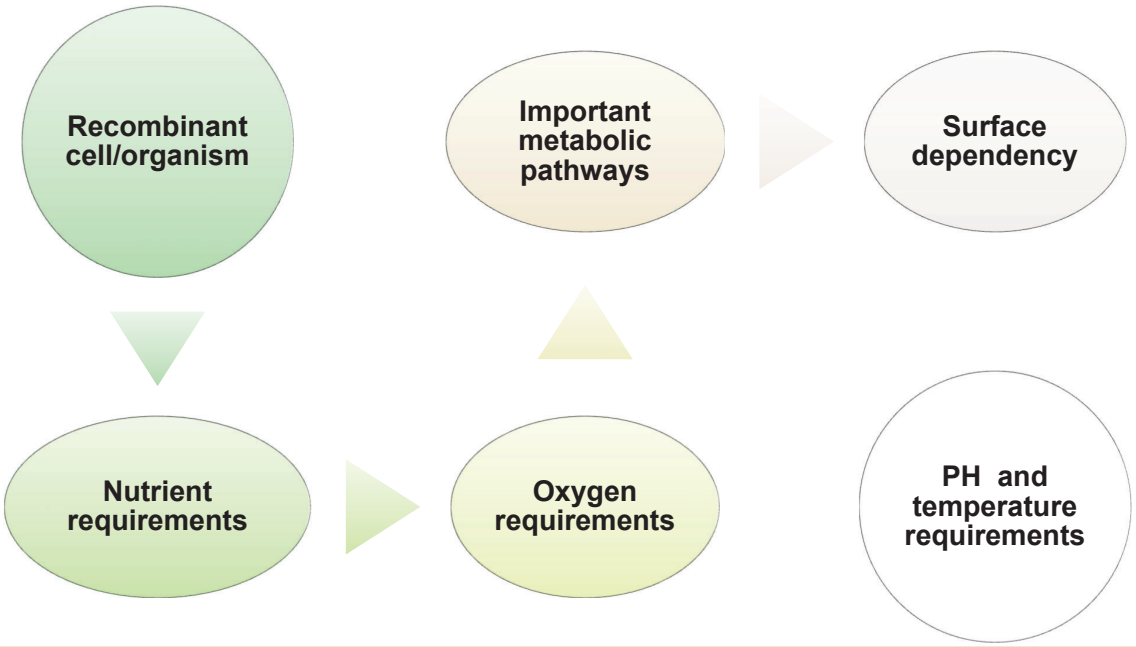
SOPs are correctly interpreted.

實驗數據/Laboratory Data

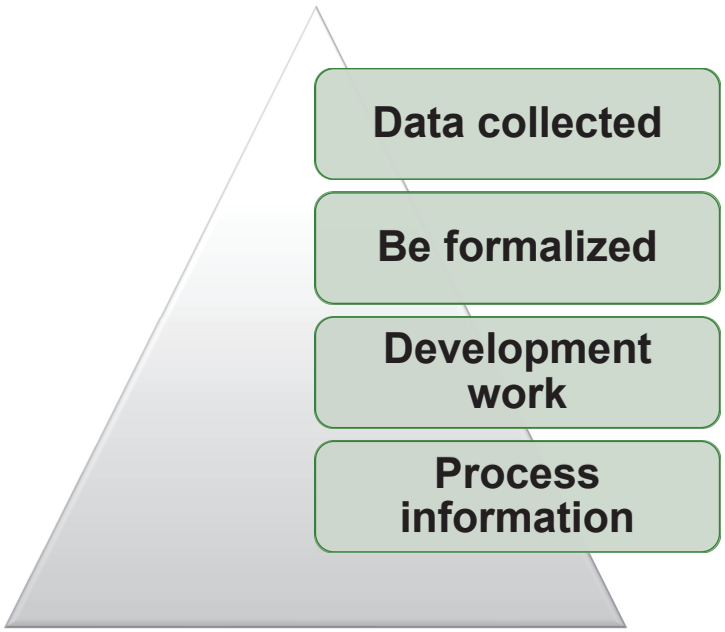


Characteristic	Mean	Standard deviation
Sample Statistics	$\bar{x}$	δ or s.d.

宿主選擇與安定性數據/Host Organism Selection and Stability Data



研發報告/Development Reports



製程描述/Manufacturing Process Description

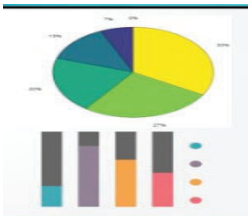
- A list of the CQAs
- The results of any risk assessment studies
- A list of CPPs, Operating ranges for all CPPs
- Each storage step, including volumes of materials involved and length of storage time
- Scale-dependent parameters
- Additional instructions of process scale equipment
- How the process will be operated

製程資訊/Manufacturing Information

- The process description should include information on operations, including:
  - Upstream production steps
  - Harvest and recovery steps
  - Purification steps
  - In-process stability information

設計區間的定義/Design Space Definition

- The design space(ICH Q8(R2)) can be presented as:
  - Two dimensional plots
  - Surface plots of two parameters
  - A set of equations that describe the interaction of the parameters
- Information for the design space should be developed at each step of the process scale-up.



法規建議項目/Criteria Recommended By ICH Q7

- Instructions for maintenance of the cell bank
- Description of proper inoculation and expansion of the culture
- Control of CPPs during fermentation/cell culture
- Process monitoring including cell growth, viability, and productivity
- Bioburden and endotoxin monitoring
- Viral safety concerns as described in ICH Q5A(R1)

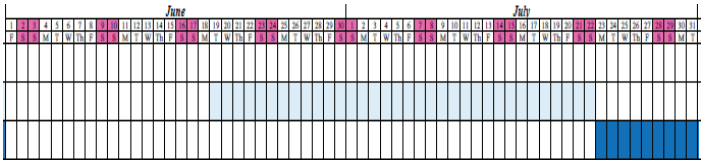
停留的步驟/Hold Steps

- Process material in hold steps should be maintained under identical conditions to those used in laboratory and pilot scale operations.

- Conditions should be described
  - Temperature
  - Agitation
  - Materials of construction
  - Head space

製程時間/Process Timeline

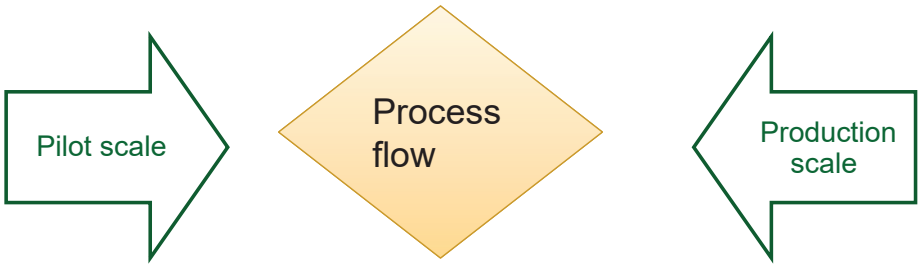
- A detailed timeline should be provided to subsequent process teams
  - Duration of process steps
  - Dependencies of the process steps (e.g., finish to start, start to finish or start to start)
  - Hold steps
  - Duration of hold steps



A gap analysis may be used to compare and comprehend differences between process timelines at the two sites.

製程流程/Process Flow Sheets

- These diagrams can provide operators with a holistic view of a process.
- Parameters should be included
  - Temperature
  - pH
  - Conductivity specifications
  - Volumes of solutions and flow rate specifications



使用者需求/User Requirements

- User requirements for pilot plant equipment should be documented prior to operation of the process
  - Impeller type and size
  - The number of addition ports for feeds
  - Flowrate ranges
  - Number of inlets and outlets
  - Tank volume operating ranges
  - Membrane areas

原物料/Raw Materials

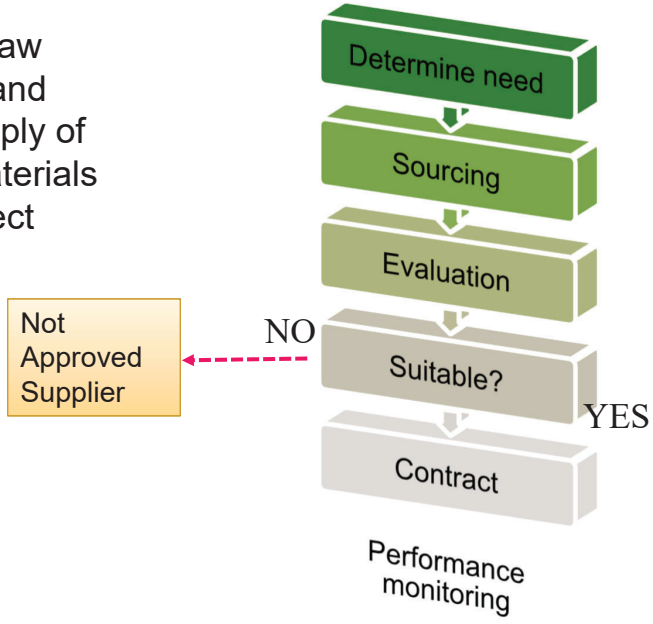
- Be specified at laboratory scale, at the pilot scale, and at the manufacturing scale.
- be classified into:
  - Ingredients
  - Cell lines
  - Culture media
  - Buffers
  - Disposables (e.g., filter membranes and chromatography resins)

Presented in the final product

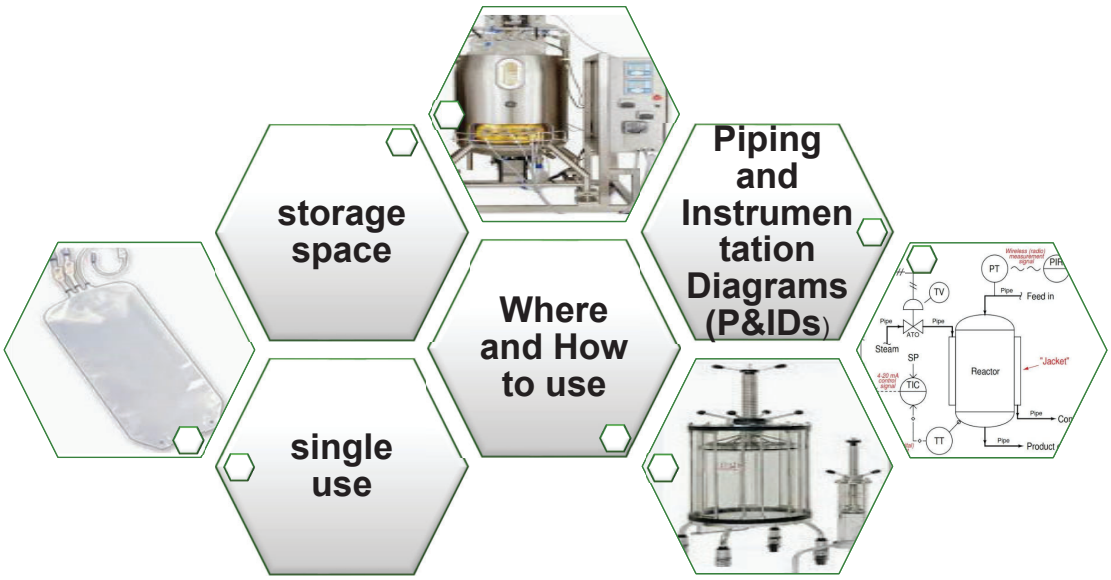
原物料特性/Attributes Of Raw Materials

供應商認可/Supplier Qualification

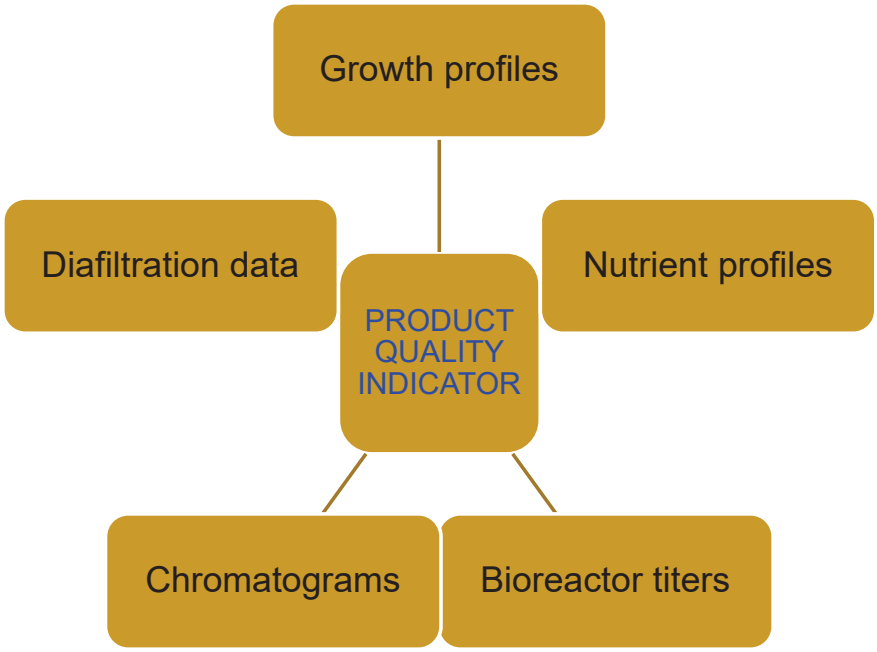
Alternative sources for each raw material should be identified and tested to ensure a steady supply of critical ingredients, as raw materials ingredients variations can affect process performance.



設備配置/Equipment Layouts



歷史數據/History of Batches



先導批次紀錄/Pilot Scale Batch Records

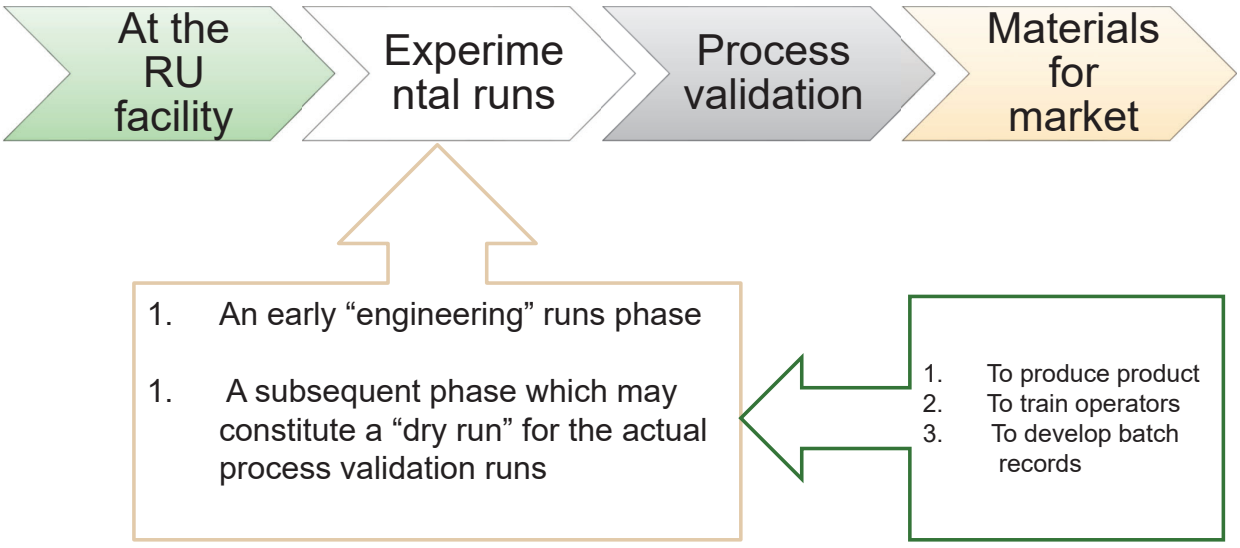
Pilot scale batch records	Should be reviewed prior to development of batch documentation for the production scale
	Provide an additional detail of how the process was operated
	A complete set of executed batch records should be provided
	Should be translated into the language used at the recipient site
	Instructions should be described in the same way

差異分析/GAP Analysis

- The gap analysis can include:
  - Operating parameters/Steps
  - Equipment
  - Raw materials
  - Consumables

The process should be assessed at both sending sites and recipient sites , side by side, to help to identify differences.

規劃製程確效/Planning For Successful Process Validation



委託製造協議/Agreements Of CMO

- Where the transfer is to a third party contract manufacturing organization, confidentiality agreements, and other legal documents should be in place.

美國FDA規範/FDA _ Quality Systems Approach to Pharmaceutical CGMP Regulations

- CONTROL OUTSOURCED OPERATIONS

Under a quality system, the manufacturer should ensure that a contract firm is qualified before signing a contract with that firm

Contractors as extensions of the manufacturer's own facility

重點整理/Key Messages Of TT

- Quality system
- Process Development
- Technology transfer plan
- Team-work
- Communication/Training
- Responsibility agreement
- Comprehensive risk/gap assessment
- Technology transfer documentation

Thank you for your attention!!