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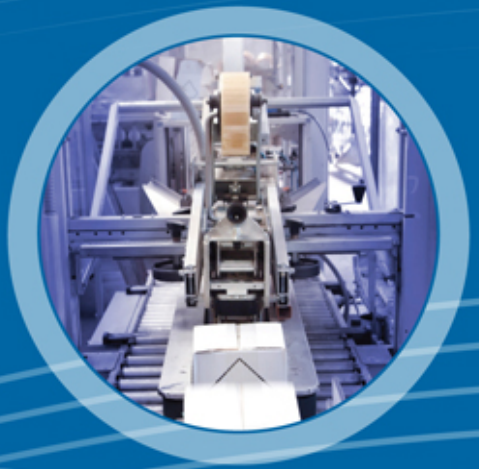
ICH Q7 Chapter 18: Cell Culture / Fermentation



PDA - PIC/S ICH Q7 Training

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When referring to this section

- **The terms ‘Cell Culture and Fermentation (CCF) will be used to refer to ‘Specific Guidance for APIs Manufactured by Cell Culture/Fermentation.’**

- ***Section 18 should not be used as a stand-alone section*** *(18.10)*

Scope reminder

- **ICH Q7 scope of coverage includes cell culture, fermentation, tissue or animal sources including transgenic animals** *(1.3)*
- **This Guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs.** *(1.3)*
- **Early process steps may be subject to GMP but are not covered by ICH Q7**
  - ***Early manufacturing steps are covered by separate guidelines (e.g. establishment of Master Cell Bank ICH Q5D).***
  - ***Phase appropriate GMP (see also Chapter 19) should be applied***

Regulatory Environment

- **Other ICH Guidelines (ICH Q5 series, ICH Q6B)**
  - **Q5A**(R1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin - *1997 – 1999*
  - **Q5B** Quality of Biotechnological Products : Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products – *1995*
  - **Q5C** Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products – *1995*
  - **Q5D** Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products – *1997*
  - **Q5E** Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process – *2004*
  - **Q6B** Specifications: text procedures and acceptance criteria for biotechnological/biological products - *1999*

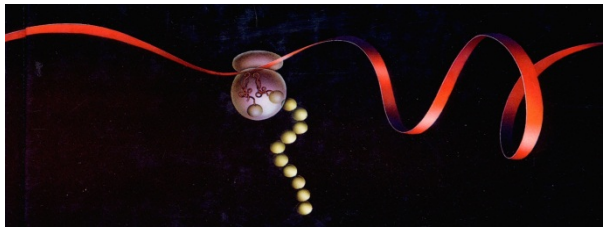
Regulatory Environment (examples)

- **EU**
  - Eudralex Vol 4. ('EU-GMPs'), Part II (GMP for API) linked to Annex 2 (GMP of biologic products)
  - European Pharmacopoeia general monographs
- **US**
  - CBER/CDER - requirements for establishments include CFR 21 Parts 210, 211 and 600
- **Japan**
  - Administrative Notice February 1, 2012 on application of PICs GMP Guide, Part II
  - Notification No. 210 of the MHLW: Standards for Biological Ingredients
  - Minimum Requirements for Biological Products, National Institute of Infectious Diseases, 2006
  - Ministerial Ordinance (No. 136, 'GQP') and enforcement regulation (No. 0922001) for Quality Assurance of Drugs, Quasi-drugs, Cosmetics and Medical Device
  - Ministerial Ordinance (No. 179, 'GMP') and enforcement regulation (No. 0330001) on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs
  - http://www.pmda.go.jp/english/service/regulation.html

Complexity

APIs produced by Cell Culture and Fermentation

- **Difficult to fully characterize**
  - Inherent heterogeneity and size
- **Subject to contamination with potentially infectious agents**
  - Use of biological systems



Biotech (Cell Culture or Fermentation)

- **Cells or organisms which have been modified by recombinant DNA techniques, hybridomas, etc.** *(18.11)*
- **APIs produced that are normally high molecular weight substances (proteins, polypeptides)** *(18.11)*
- **If APIs produced are low molecular weight compounds, generally the controls for classical fermentation are utilised** *(18.11)*

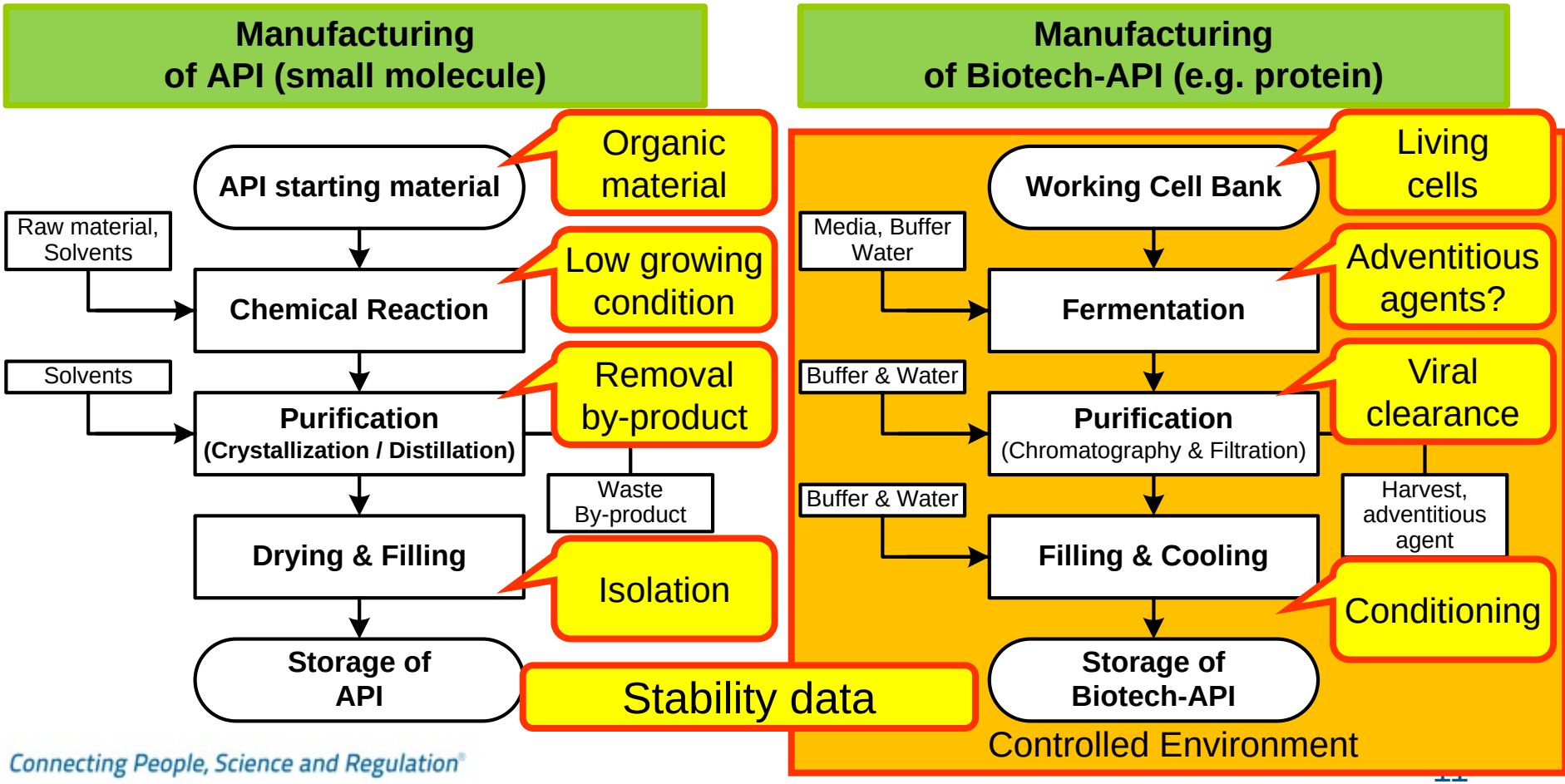
Aim

- **Can we demonstrate that our manufacturing process and facility is appropriately to protect the patient?**

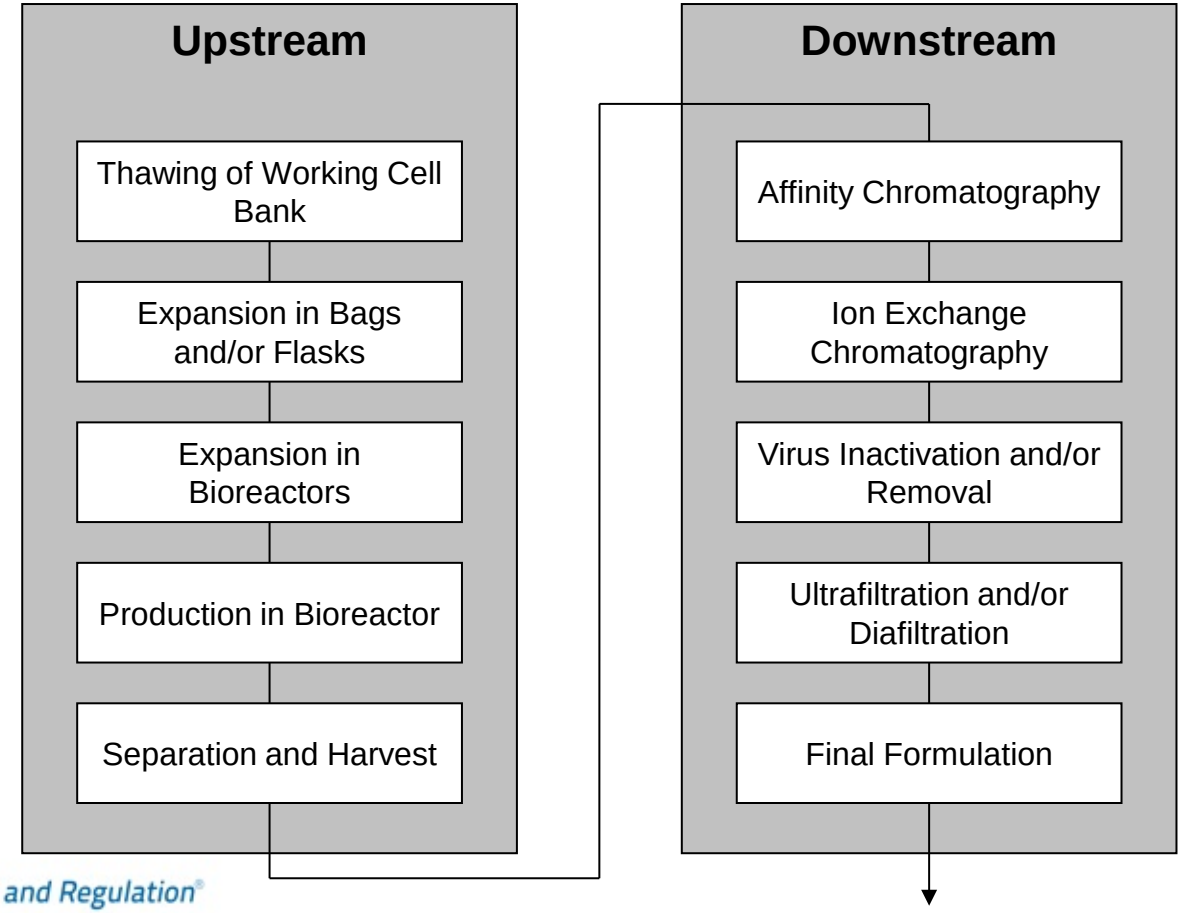
Potential Concerns on

- **Are the regulatory requirements addressed adequately?**
- **Are the cleanliness zones appropriate?**
- **Is the material flow and personnel flow between the segregated areas, connections, appropriate?**

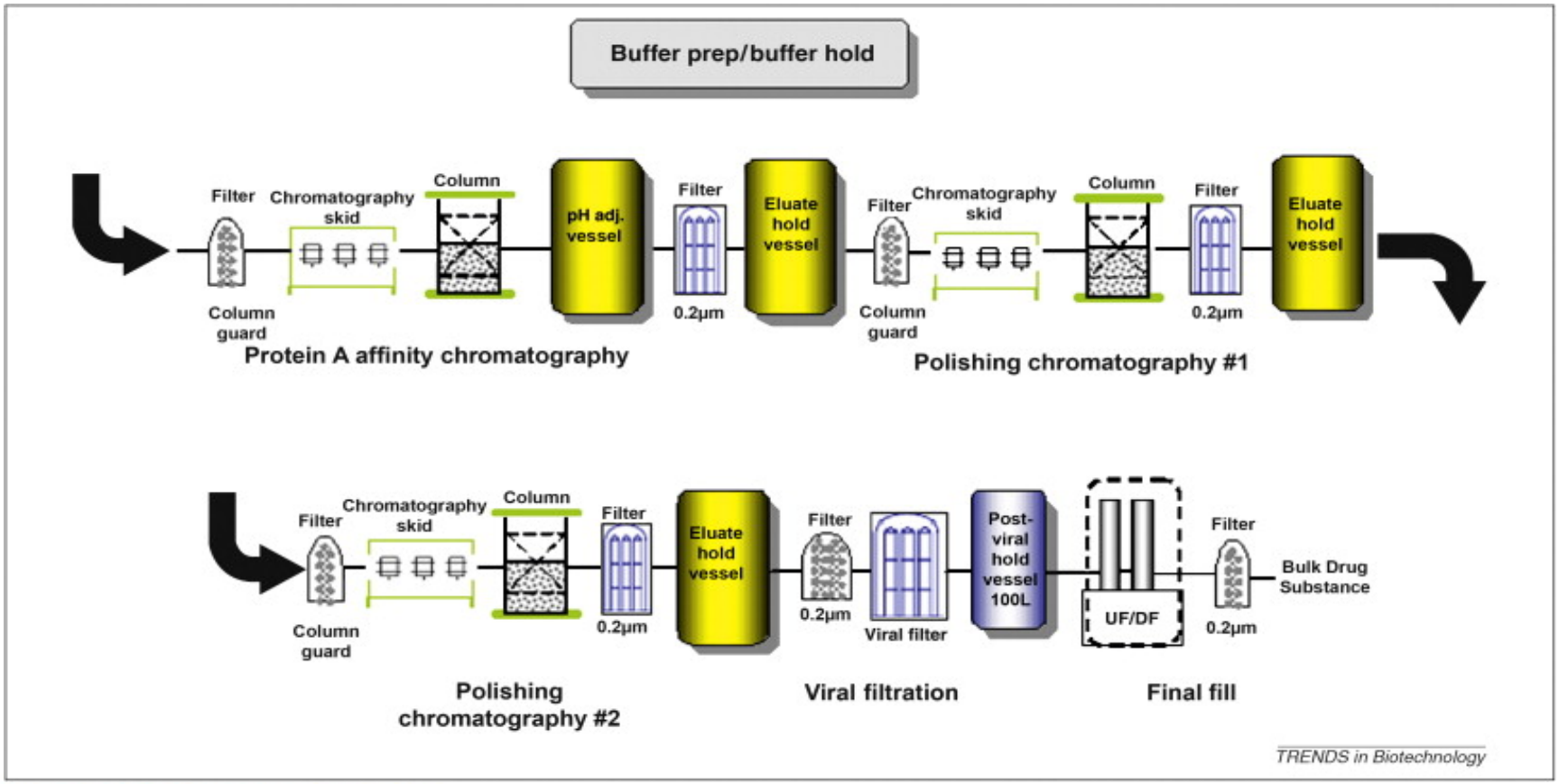
In the scope of ICH Q7: What makes a Biotech Process different ?



Example for a biotech cell culture MAB process



Example for a biotech cell culture MAB process



Implement QRM: Risk Identification

- **The Hazard**
  Potential growing of adventitious agent
  which may can be neither detected nor removed
- **The Problem**
  Working with cell banks, media and buffer = optimal growth conditions
- **The Control**
  Requirements for a low bioburden during manufacturing

QRM: Levels of Protection

- **Level A: Protection of the patient**
  - Impurities are reduced
  - The adventitious agents and risks for contamination are controlled
  - The Biotech-API (protein) is stabilised
- **Level B: Protection on manufacturing using working cell bank**
  - Key for running the process at all
  - Controlled master cell bank (see ICH Q5D) and working cell banks
- **Level C: Protection of employee and environment**

QRM: Levels of Protection

Protection levels \ Unit operations	Storage of working cell bank	Seed-preparation	Inoculum build up	Fermentation	Harvesting / isolation stage	Purification	"API-Bulk" preparation	Storage / transport
Level A: Protection of the patient						■	■	■
Level B: Protection on manufacturing using working cell bank	■	■	■	■	■			
Level C: Protection of employee and environment	■	■	■	■	■	■	■	■

■ Primary controls needed to control critical to quality attribute

■ Secondary controls needed to control critical to quality attribute

Risk Control of Protection Levels

- **Level A: Protection of patient on manufacturing of the API-Bulk**
  - Sterility of the (drug (medicinal) product) ensured by the quality built in during manufacturing of the API-bulk (low bioburden)
- **Level B: Protection on manufacturing using working cell banks**
  - Ensure that the cells are producing the right product by an adequate level of purity and freedom from contamination (low bioburdon) e.g. controlling the environment (e.g. physical containment)
- **Level C: Protection of employee and environment**
  - By clean room concept, airlocks and gowning the operators and the environment protections is ensured.

Classical Fermentation

- **Processes that use microorganisms that occur in nature or modified by conventional methods** *(18.12)*
- **APIs produced that are normally low molecular weight products such as antibiotics, amino acids, vitamins, carbohydrates** *(18.12)*

Classical Fermentation versus Biotechnology

Level of control

- Where differences exist, ICH Q7 provides flexibility in applying the GMP expectations for these processes
- Q7 tries to address these differences so that GMPs can be applied in an appropriate manner
- In general, greater controls are needed for biotech processes than classical fermentation

Advantages/Disadvantages of bacterial versus mammalian systems

Bacterial	Mammalian
Batch time-hours	Batch time - days
Generation time (20 mins)	Generation time (8 hours)
Endotoxins	No endotoxins
No post translational modifications	Post translational modifications for example glycosylation
No virus	Virus control (adventitious or endogenous)
No Shear	Shear needs to be controlled
Reactor taller	Reactor shorter
More robust less susceptible to contamination	More susceptible to contamination
Scale High (up to 100,000L)	Scale lower (up to 15,000)
Yields High	Yields lower than bacterial
Antifoam used	Pluronic used to reduce shear
Cost of media low	Cost of media High
Need to refold proteins	Proteins folded correctly
Example:E. coli	Example:CHO

Where does GMPs start?

- **Creation of the cell banks should be performed under appropriate controls**
  - ***See ICH Q5 series.***
    This is outside of the scope of ICH Q7!

- **ICH Q7 starts with the retrieval of a vial of a cell bank to be used in production**

Cell Culture / Fermentation

- **Applying ICH Q7** *(1.3)*

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

Increasing GMP requirements

- ***Increasing process controls and risk based decisions***
- ***Certain GMP requirements (e.g. documentation) are also applicable in early manufacturing process steps***

Additional Controls necessary

- **In general, greater controls are necessary for these processes, especially to prevent contamination of the intermediate or API**

  - ***Consider in general to control contamination:***
    - ***WCB controls,***
    - ***Manufacturing process controls on fermentation/cell culture***
    - ***Harvesting requirements***
    - ***Isolation stages***
    - ***Purification stages***
    - ***By-products/impurity monitoring and detection (process related and material related)***
    - ***Cleaning and sanitisation***
    - ***Chromatography purification columns and their life cycles***
    - ***Facilities and utilities***
    - ***Control of process materials***

Additional Controls necessary

- **In general, greater controls are necessary for these processes, especially to prevent contamination of the intermediate or API**
  - ***Examples how contamination can be controlled e.g.***
    - ***Product dedicated chromatography columns***
    - ***Single use hoses***
    - ***Buffer media prepared and used within dedicated period***
    - ***Sterilisation filters on air lines to reactors***
    - ***Filters on addition vessels***
    - ***Cerification using media fills***
    - ***….***
    - ***There are a number of strategies used to control/provide assurance against contamination that were not mentioned.***

Additional Controls necessary

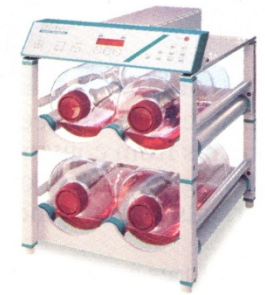
- **Use of classified environments and environmental monitoring programs generally utilized with environmental controls suitable for the process steps**
  - ***Aseptic guidance for drug product (e.g. Annex 1 of the PIC/S GMP) does not apply.***
    - ***However Annex 2 cross references to Annex 1: '..Risk management principles should take into account the principles and guidance in the appropriate sections of Annex 1 when selecting environmental classification cascades and associated controls'...***

Additional Controls necessary

- **Equipment will usually require appropriate bioburden control (e.g. sanitization) between batches**
  - ***This bioburden control is not a sterile operation***
  - ***'Single use systems' should be used only once***
- **In general, processing including reprocessing steps need to be validated** *(12, 14.2)*
- **Water used in the process is often of very high quality (purified water or water for injections (WFI)), depending on the nature of the process and end use of the API**
  - ***As an example see further details: Note for guidance CPMP/QWP/158/01***

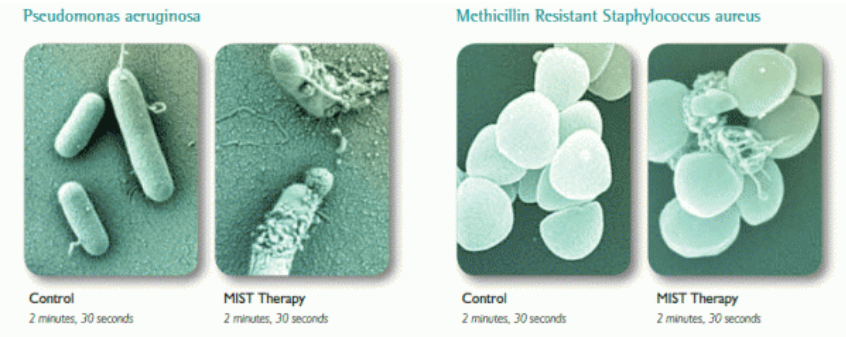
18.1 Typical Process Controls

- **Maintenance of the Working Cell Bank (WCB)**
- **Proper inoculation and expansion of the culture**
- **Control of critical operating parameters during manufacturing**
- **Appropriate process monitoring** *(18.16)*



18.1 Typical Process Controls

- **Protecting the intermediate or API from contamination or loss of quality during processing**
- **Monitoring bioburden and endotoxins when appropriate for material and/or process**
- **Appropriate handling and viral clearance steps in place where needed** *(18.16)*
- **Demonstration of impurity removal necessary** *(18.17)*
  - ***e.g. host cell protein, product/process related impurities***



Definition: “Bioburden”

- **“Level and type of microorganisms that can be present in raw materials, API starting materials, intermediates or APIs.**
- **Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.”**

Consider a risk based approach for the need to fully identify organisms, depending on the process steps (early / late) and capability for removal

18.1 Bioburden

- **Make a distinction between normal background isolates and severe contamination which may have an impact on process and/or product quality**
- **Make a distinction between isolates normally encountered and pathogenic organisms**
- **Convey the need to determine the impact on API quality**

  - ***Implement a risk based approach: appropriate procedures to detect contamination and assess the impact on the product (both current and subsequent batches)***

18.2 Cell Bank Maintenance and Record Keeping

- **Access to cell banks should be limited** *(18.20)*
- **Storage conditions should be adequate to maintain viability and prevent contamination** *(18.21)*
- **Records (temperature, use, etc.) should be maintained and reviewed** *(18.22)*
- **Cell banks should be monitored when appropriate (periodic testing)** *(18.23)*

18.3 Cell Culture / Fermentation

- **Where quality of the API could be compromised, transfers should be performed under appropriate conditions (piping, HEPA-filtered air)** *(18.31)*
- **When this isn't a concern (classical fermentation), controls should still be in place to minimize contamination**
  - ***These measures are needed to protect the biological production system and not primarily the patient***

18.3 Cell Culture / Fermentation

- **Personnel should be properly gowned** *(18.32)*

18.3 Cell Culture / Fermentation

- **Critical operating parameters should be monitored. This will depend on the nature of the system and cell substrate used** *(18.33)*
- **For biotech processes, equipment should be sterilized between batches. For classical fermentation, cleaning or sanitization may be sufficient** *(18.34)*
  - ***Equipment will usually require appropriate bioburden control (e.g. sanitization) between batches***
  - ***This bioburden control is not a sterile operation***
- **Media should be appropriately processed** *(18.35)*

18.3 Cell Culture / Fermentation

- **Detecting contamination is an important issue for most biotech processes.** *(18.36)*
- **Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary.** *(18.36)*

◆ ***Appropriate controls should be in please to minimise exposure and risk of contamination***

18.3 Cell Culture / Fermentation

- **Contamination events should be recorded and assessed (deviations)** *(18.37)*
  - ***…in an appropriate time frame. This is depending on the methods available (e.g. rapid versus traditional micro method). Analytical methods must at least be scientifically sound to get accurate results.***
- **Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination** *(18.38)*

18.4 Harvesting,Isolation,Purification

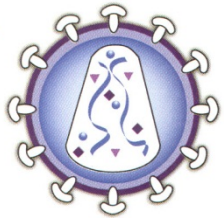
- **Harvesting should be performed in a manner and in an area to minimise cross-contamination** *(18.40)*
- **Product quality should not be compromised during these steps** *(18.41)*
- **Equipment should be properly cleaned, and if needed, sanitised after use** *(18.42)*

18.4 Harvesting,Isolation,Purification

- **During purification, if open systems are used, the environmental quality should be appropriate to preserve product quality***(18.43)*

18.5 Viral Removal / Inactivation

- **These are critical steps and should be performed within their validated parameters** *(18.51)*
- **Precautions (SOPs, equipment, proper segregation) should be in place to separate pre-and post-inactivation activities** *(18.52)*
- **Reference is made to ICH Q5A for additional information** *(18.50)*



- ***Consider applicability if host organisms / cells are receptive to virus contamination and take into account possible unknown viral contaminants***

Specifics from other sections

- **Specific examples from other sections that will be viewed differently in the context of Section 18**

Specifics from other sections

- **Personnel** *(3.2)*
  - "Additional protective apparel, such as head, face, hand and arm coverings, should be worn when necessary, to protect intermediates & APIs from contamination."

◆ ***Pay special attention to e.g. Gowning***

Specifics from other sections

- **Facilities** *(4.1)*
  - "Where microbiological specifications have been established for the intermediate or API, facilities should be designed to limit exposure to objectionable microbiological contaminants as appropriate."

◆ ***Pay special attention to e.g.***
- ***Floors and surfaces (e.g. hard, impervious, easy to clean)***
- ***Personal and material flow (e.g. unidirectional)***

Specifics from other sections

- **Utilities** *(4.2)*
  - "Adequate ventilation and exhaust systems…should be designed to minimize contamination and cross-contamination..."

Pay special attention to e.g.

- ***HEPA filters***
- ***Room classification***
- ***Pressure differentials***

Specifics from other sections

- **Water** *(4.3)*
  - "...appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms/endotoxin should be established."

◆ ***Pay special attention to e.g.***

- ***Physical/ chemical tests***
- ***Total microbial counts***
- ***Endotoxin***

Specifics from other sections

- **Cleaning validation** *(12.7)*
  - ‘In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality.
  - Equipment cleaning / sanitisation studies should address microbial and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API…..”

◆ ***Avoidance of contamination***

a) Bioburden (cross contamination)

b) Products or other materials (carry over)

Specifics from other sections

- **Equipment** *(5.1)*
  - "Closed or contained equipment should be used whenever appropriate."

- ***Pay special attention to e.g.***
  - ***Ensure equipment integrity***
  - ***Single use equipment can be considered***

Specifics from other sections

- **Process validation** *(12)*

  - Documents addressing Biotech needs

Defined principles

- Information in the dossier *(ICH Q11: 7.2)*
- Information for Starting Material or Source Material *(ICH Q11: 5.2.3)*
- Small scale versus large scale *(ICH Q11: 7.2)*
- Limit of in vitro cell age *(ICH Q5B, ICH Q5D)*
- Platform manufacturing *(ICH Q11: 7.2)*
- Full scale validation studies *(ICH Q11: 7.2)*

Frequent Asked Questions

- Life time of column/membranes *(=CPP; ICH Q7 12.51; 18.34)*
- Hold-time *(=CPP: ICH Q7 12.51)*
- Reprocessing *(ICH Q7: 14.2)*
- Pooling of Intermediates *(ICH Q7: 18.14)*
- Selection of batches to be included in validation studies *(ICH Q9: II.6)*
- Impurity clearance *(ICH Q5A, ICH Q6B, ICHQ11: 7.2; ICH Q7: 8.50,11.21,11.22,18.5)*

Key Messages

- **Section 18 should *not be used* as a stand-alone section**
  - Section 18 addresses *additional* issues for Biotech APIs
- **In general, these processes require additional controls not needed for small molecules (e.g. Virus control, where applicable)**
- **Note different level of control for classical fermentation versus biotech processes**

ICH Q7 QaA *Clarification of Uncertainties*

1. Does ICH Q7 expect validation for viral removal/viral inactivation steps for biological/biotechnological products?
2. Do the sections [ICH Q7, 18.14, 18.2] apply to classical fermentation and biotechnology?

ICH Q7 Q&A, 2015

Acknowledgement

- This version represents an update of the 2001/2002 version by ICH Q7 EWG members organised in a joint initiative between PDA and PIC/S developed in 2012
  - Stephan Rönninger (co-chair)
  - Mikael Le Bihan (co-chair)
  - Karl-Heinz Bender
  - Ursula Busse
  - Stephen Hart
  - Norbert Hentschel
  - Volker Lenz
  - Gerog Rössling
  - Greg Orders
  - Karen Walker

  and reviewed in 2014 with input from members of the PIC/S API Expert Circle Co-ordinating Committee, and PDA volunteers. Special thanks to ANSM/France, EDQM and US FDA.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