ICH
harmonisation for better health

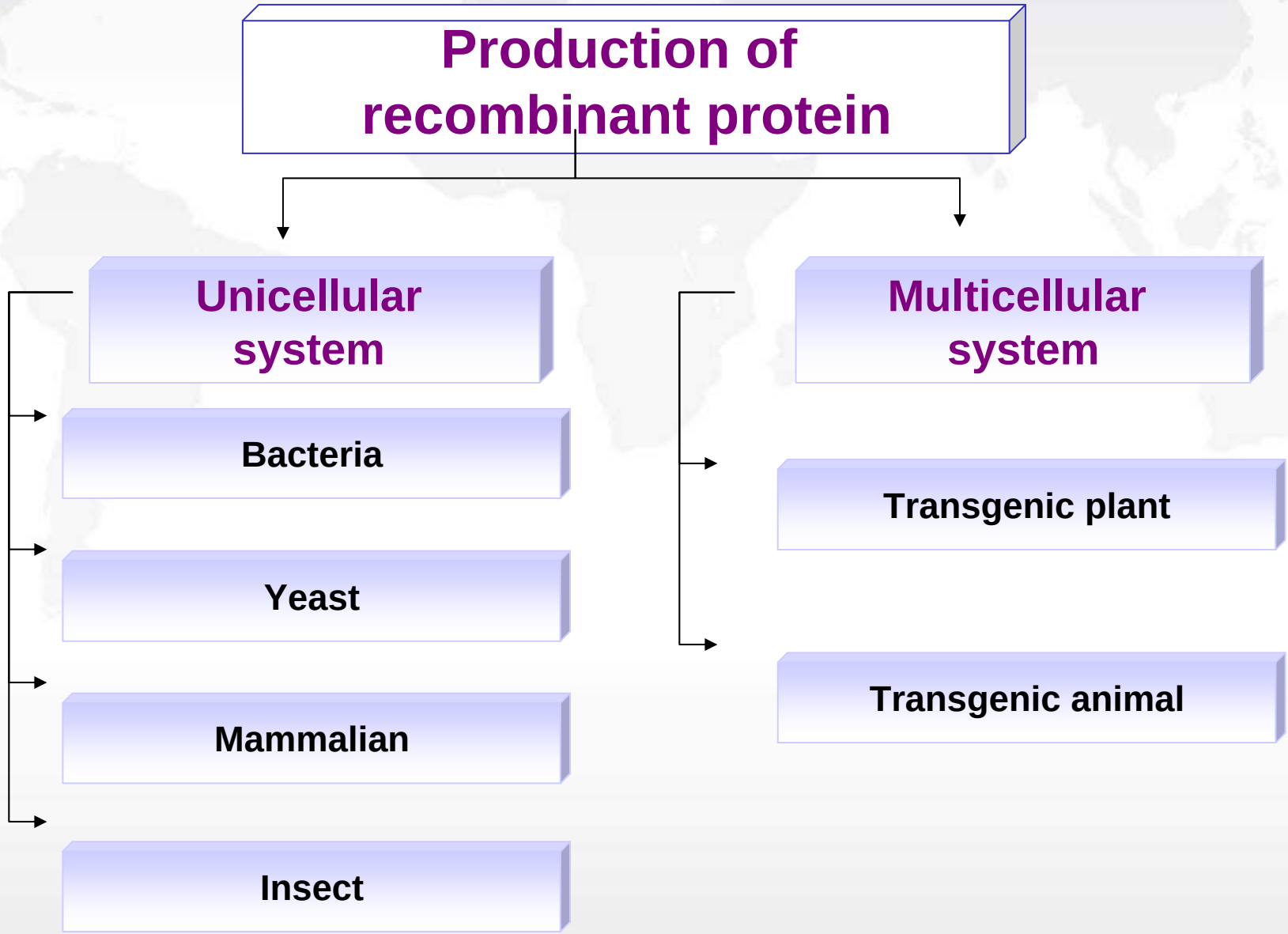
Manufacturing process of biologics

K. Ho
Afssaps, France

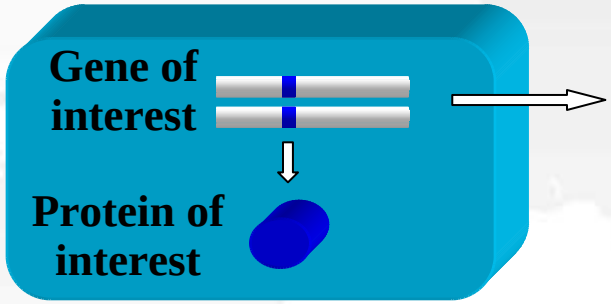
Disclaimer:

- **The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.**

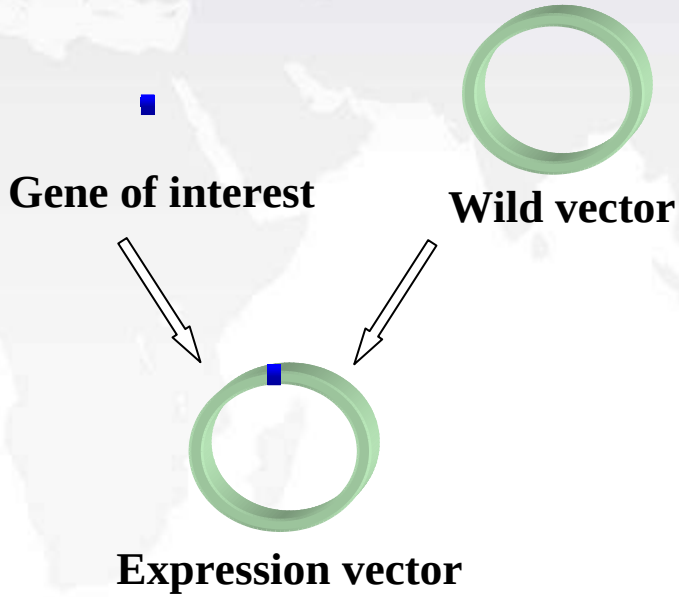
Manufacturing process

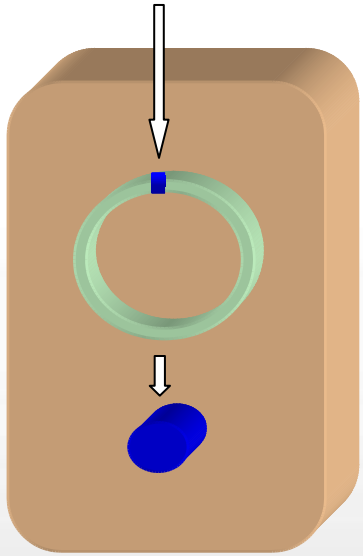


Manufacturing process



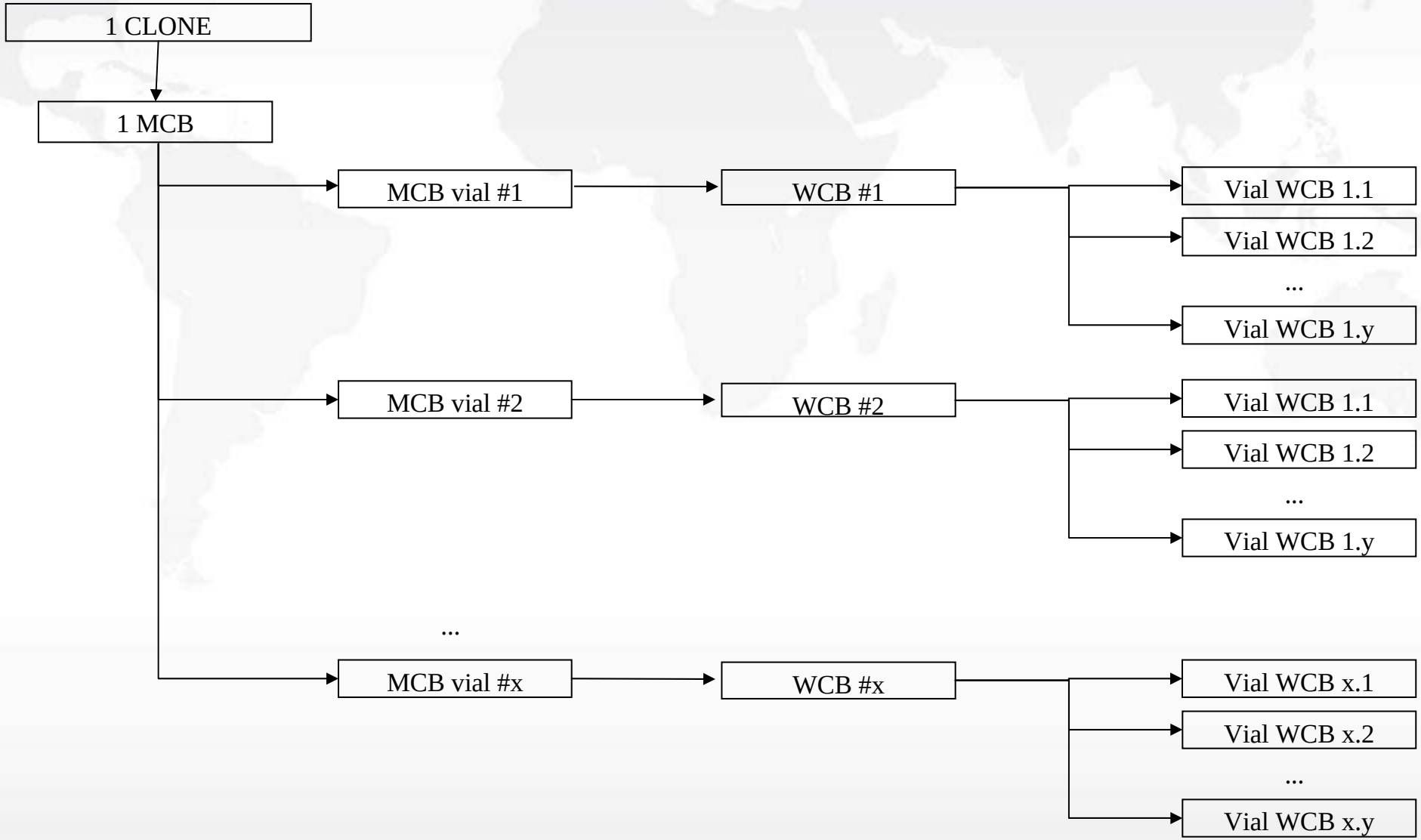
Organism naturally expressing protein of interest





Genetically modified organism expressing protein of interest

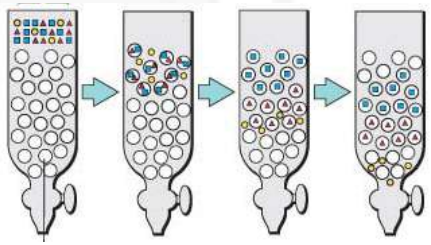
Manufacturing process



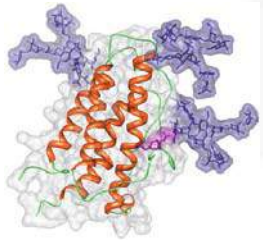
Manufacturing process

Cell bank

Fermentation



Purification

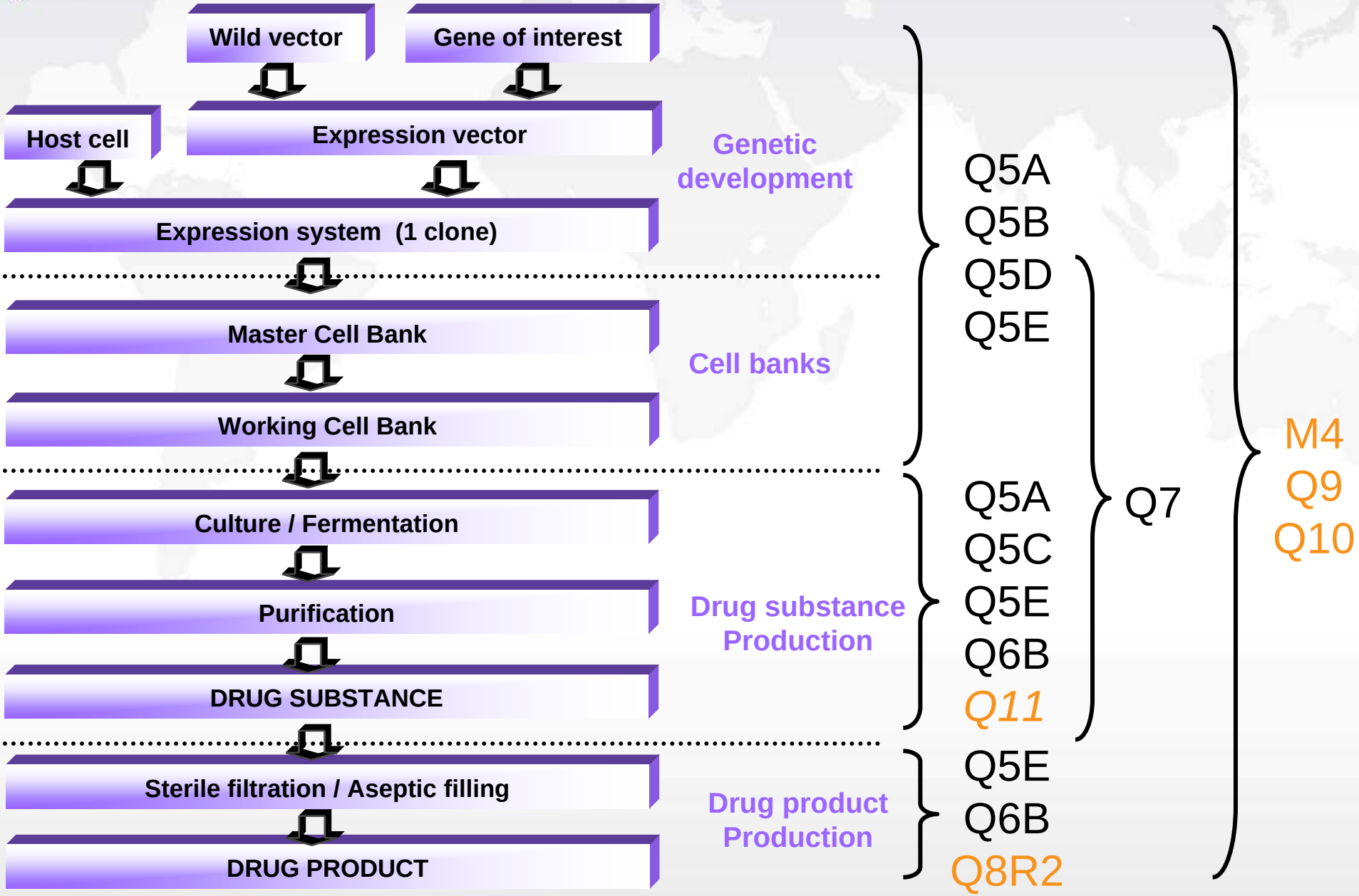


Purified protein

ICH documents for biologics

- **Q5 A: Viral Safety**
- **Q5 B: Genetic Stability**
- **Q5 C: Product Stability**
- **Q5 D: Cell Substrates**
- **Q5 E: Comparability**
- **Q6 B: Specification**
- **M4 / M2: CTD / e-CTD**
- **Q7: GMP for APIs**
- **Q8: Pharmaceutical development**
- **Q9: Quality Risk Management**
- **Q10: Pharmaceutical quality system**
- **Q11: Development and Manufacture of Drug Substances**

Typical biotech manufacturing process



Description of Manufacturing Process and Process Controls (ICH M4)

- **Description:**
  - Applicant's commitment for the manufacture of the drug substance.
  - Manufacturing process and process controls.
  - Typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions.
- **Batch(es) and scale definition:**
  - Explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.

Description of Manufacturing Process and Process Controls (ICH M4)

- **Cell culture and harvest:**
  - Flow diagram
    - From the Working Cell Bank up to the last harvesting operation.
    - Include all steps (i.e. unit operations) and intermediates.
    - Relevant information for each stage (eg PDL, volumes, times…)
    - Critical steps and critical intermediates with specifications
  - A description of each process step
    - include for example, scale; culture media and other additives; major equipment and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria
    - Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions
    - Criteria for rejection of harvests and premature termination of the culture
    - Single harvest production
    - Multiple harvest production

    …

Description of Manufacturing Process and Process Controls (ICH M4)

- **Purification and modification reactions**
  - Flow diagram
    - From the crude harvest(s) up to the step preceding filling of the drug substance.
    - All steps and intermediates and relevant information for each stage (e.g.,volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate…)
    - Critical steps with specifications
  - A description of each process step :
    - Information on, for example, scale, buffers and other reagents, and materials, conditions of use and reuse
    - Process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates.
    - Reprocessing procedures
    - Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions

Description of Manufacturing Process and Process Controls (ICH M4)

- **Filling, storage and transportation (shipping)**
  - A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided.
  - The container closure system(s) used for storage of the drug substance and storage and shipping conditions for the drug substance should be described.

Derivation and characterisation of cell substrates (ICH Q5D)

Guidance for

- Derivation of cells
- Cell bank preparation
- Cell bank characterisation

Derivation and characterisation of cell substrates (ICH Q5D)

- **Derivation of the cell substrate**
  - Origin, source and history of the cell substrate
    - Research & development information: published data, historical data from source laboratory, and experimental data
    - Characteristics of the cell substrate: species, strain, genotypic and phenotypic characteristics, generation level, pathogenicity, toxin production, biohazard…
    - Biological purity: exposure to infectious agents (contact with biological constituent?)
  - Generation of the cell substrate
    - Procedure(s) used to obtained the cell substrate (transfection, selection…)

Derivation and characterisation of cell substrates (ICH Q5D)

- **Cell bank preparation**
  - Cell Banking system
    - Two-tiered system: most common approach
    - MCB: directly derived from an initial clone
    - WCB: prepared from 1 or more vial of MCB
  - Cell banking procedures

- **Cell bank characterisation**
  - Identity
    - Phenotypic and/or genotypic characteristics
    - Performed on MCB and/or WCB
  - Purity
    - Free from adventitious contaminants

Derivation and characterisation of cell substrates (ICH Q5D)

- **Cell substrate stability**
  - 2 concerns:
    - Consistent production of the intended product and retention of production capacity during storage under defined conditions.
    - Stability during cultivation for production, at least two time points should be examined:
      - one using cells which have received a minimal number of subcultivations,
      - another using cells at or beyond the limit of *in vitro* cell age for production (LIVCA)
        - Based on production cells expanded under pilot or commercial scale
        - Expansion of cells from the WCB; cells from the MCB could be used with appropriate justification.
        - Commonly performed once for each product marketing application.
  - Evaluation of the cell substrate
    - Consistency of the coding sequence at LIVCA for production use or beyond
    - By nucleic acid testing or product analysis
    - Other specific traits (e.g. morphological characteristics, growth characteristics, biochemical markers, immunological markers, productivity of the desired product…)

Derivation and characterisation of cell substrates (ICH Q5D)

- **Banked cell stability under defined storage conditions:**
  - usually generated during production of clinical trial material (cell viability after reconstitution)
  - A proposal for monitoring of banked cell stability should be provided.
  - If the viability of the cell substrate is not significantly decreased, generally no further testing of the MCB or WCB is considered necessary

Genetic stability (ICH Q5B)

ISSUE : potential mutations on the expression system

RATIONALE

Evaluation of integrity of expression construct

- Nucleic acid analysis
- Protein analysis

Viral Safety (Q5A)

ISSUE : Known and Unknown viral contaminant

RATIONALE

3 Complementary Approaches

- CELL LINES / RAW MATERIALS
- PRODUCT TESTING AT APPROPRIATE STAGES
- PROCESS CAPACITY TO CLEAR INFECTIOUS VIRUSES

Viral Safety (Q5A)

- **Cell Lines / Raw Materials**
  - MCB
    - Presence of latent or persistent virus infection, endogenous retrovirus
  - Introduction of adventitious virus during production
    - Contaminated biological reagents, excipients…
- **Product Testing At Appropriate Stages**
  - Cell line : MCB, WCB, End production(+)
    - Retroviruses & endogenous viruses: Infectivity, EM, Rev trancrp, specific tests…
    - Non-endogenous viruses: In-vitro (cells), in-vivo (mouse, eggs…), antibody production tests, others
  - Unprocessed bulk
    - 3 lots
    - And ongoing : case by case

Viral Safety (Q5A)

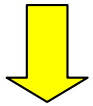
- **Process capacity to clear infectious viruses**
  - To assess steps for elimination / inactivation
  - Spiking : reduction of virus infectivity
  - Choice of viruses relevant viruses and model viruses (specific and non-specific)
  - Rationale for viral clearance : based on results for cell banks (A to E) and unprocessed bulk
  - **Purified bulk testing on at leaset 3 lots at pilot-plant scale or commercial scale,** except for case A (ie no virus detected in cells)

A New Vision of Pharmaceutical Quality

- **ICH July 2003**
  - ‘Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science’
  - Q8 : Pharmaceutical Development (Step 5)
  - Q9 : Quality Risk Management (Step 4)
  - Q10 : Pharmaceutical Quality System (Step 4)
  - Q8/Q9/Q10 – Questions & Answers (Step 5)

‘New Quality Vision’ Expectations

- Enhanced drug substance and drug product development
- Quality Risk Management
- Pharmaceutical Quality System



- Lower risk operation
- Innovation
- Continual improvement
- Optimized change management process
- Potential for flexible approaches?

ICH Q8 – Pharmaceutical development Part I

- **Objective:**
  - Description of 3.2.P.2 – Pharmaceutical development
  - Opportunity to present knowledge gained through the application of scientific approaches and quality risk management
  - Demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches

- **Scope:**
  - 3.2.P.2 – Pharmaceutical development
  - Does not apply to DP during clinical research

ICH Q8 – Pharmaceutical development Part II (Annex)

- **Elements of Q8 - Part II:**
  - Clarification of key concepts outlined in the core guideline.
  - describes the principles of quality by design (QbD).
- **Approaches to Pharmaceutical development**
  - Approach to, and extent of, development can also vary and should be outlined in the submission.
  - Applicant might choose either:
    - an empirical approach or
    - a more systematic approach to product development, or
    - a combination of both
- **A greater understanding of the product and its manufacturing process:**
  - can create a basis for more flexible regulatory approaches.
  - degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application.

ICH Q9 – Quality Risk Management

- **Application by manufacturers :**
  - optional
  - can be applied in:
    - manufacturing environment
    - pharmaceutical development
    - preparation of the quality part of marketing authorisation dossiers.

- **Application to the regulatory authorities:**
  - pharmaceutical assessment of the quality part of the marketing authorisation dossier,
  - GMP inspections
  - handling of suspected quality defects.

  …

ICH Q10 – Pharmaceutical Quality System

- **Designed for the entire product lifecycle: beyond current expectations.**
- **Optional**
- **Should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.**

Perspectives: Q11

- **Guidance on S.2.2 to S.2.6.**
  - S.2.6: Process development (same principles as Q8)
  - But also
  - S.2.2 Description of Manufacturing /Process Controls
  - S.2.3 Control of Materials
  - S.2.4 Controls of Critical Steps and Intermediates
  - S.2.5 Process Validation and/or Evaluation
- **Applicable to « Traditional » and «Enhanced » approach**
- **Common guidance for NCE and BIO**

Adapted from P. Zorzi, CASSS Barcelona, March 2011

Perspectives: Q11

- **Q11 Key areas**
  - Manufacturing process development
  - Description of manuf. process /process controls
  - Selection of starting materials /sources materials
  - Control strategy
  - Process validation/evaluation
  - Lifecycle management

Adapted from P. Zorzi, CASSS Barcelona, March 2011

ICH
harmonisation for better health

Thank You!