cGMP Considerations in the Manufacturing of Biologics

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CONSULTING • DEVELOPING • MANUFACTURING

Any questions are welcome and encouraged, they can be asked by e-mailing:

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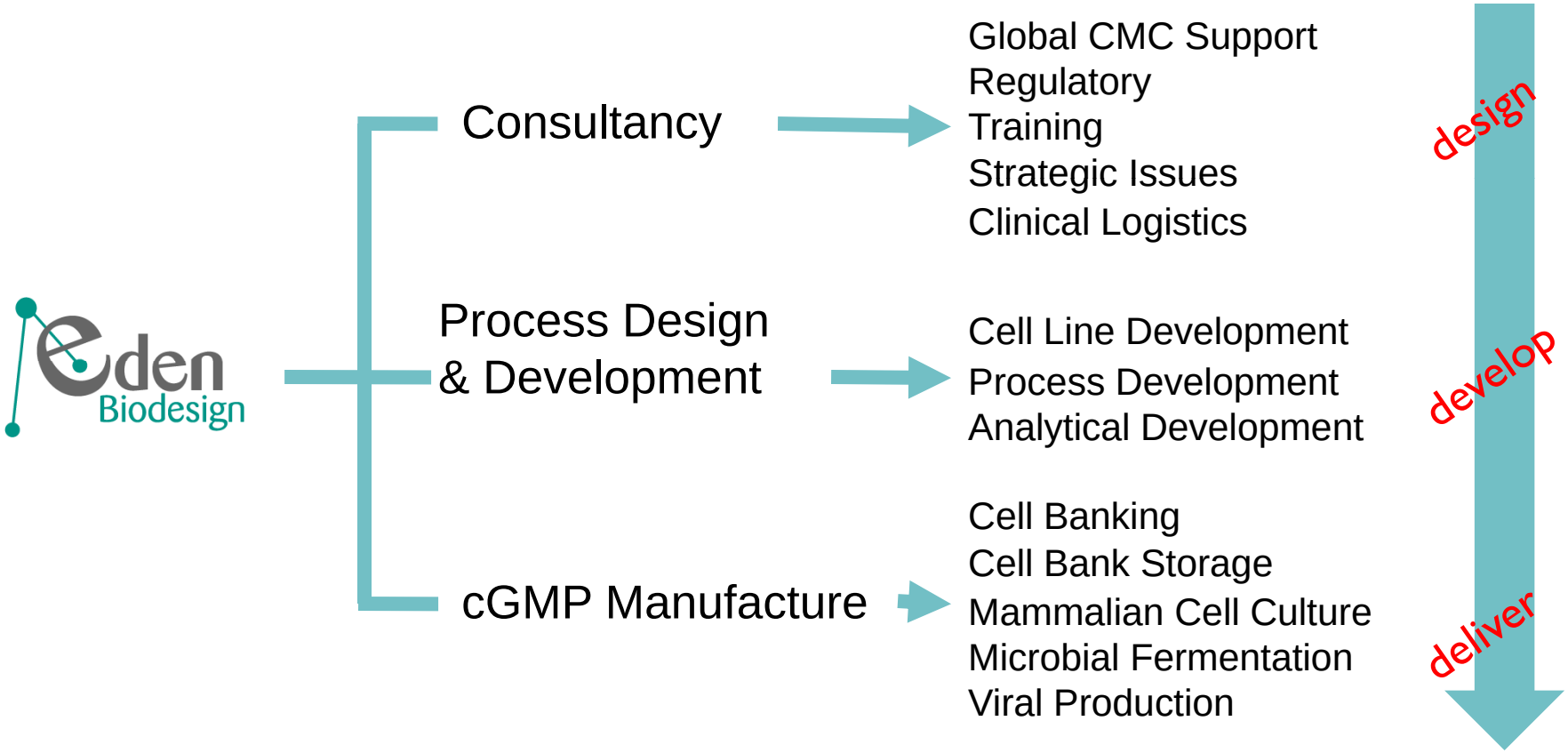
Eden Biodesign

"Designing and developing valuable new medicines by the application of good science from day one"

- Recently acquired now part of Watson Pharmaceuticals, Inc. (NYSE: WPI
- Provides complete range of Biopharmaceutical Product Development and Manufacturing Services
  - Investigational Medicinal Product License
    - Granted by MHRA March 2007
- Consultancy for Biopharmaceutical Development and Regulatory aspects

Eden Biodesign

An unusual breadth and depth of services supported by considerable drug development experience and expertise



Eden Biodesign Maintains a Globally Integrated Biopharmaceutical Network

Research Triangle Park, NC
North American HQ

Liverpool, UK
Global HQ & cGMP Operations

Clients on six of seven continents

● *Client Assignments* ★ *Eden Presence* ● *Strategic Partners*

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- Regulations
- Challenges with manufacturing biologics
  - Process considerations
- Facility considerations
  - Environmental standards
- Cleaning
- Equipment considerations
- Validation
- Raw Materials
- Quality Management Systems & Training
- Release by the QP

Regulations & Guidance

- EU GMPs
  - Annex 1 Manufacture of Sterile Medicinal Products
  - Annex 2 - Manufacture of Biological Medicinal Products for Human Use
  - Annex 13 - Manufacture of Investigational Medicinal Products

- EU Directives
  - Directive 2001/20/EC Clinical Trials Directive
  - Directive 2003/94/EC GMP Directive
  - Directive 2004/23/EC Tissues and Cells Directive

- FDA
  - 21 CFR Parts 210, 211 cGMP in Manufacturing, Processing, Packing, Holding of Drugs, Finished Pharmaceuticals
  - 21 CFR Parts 600, 601, 610 Biological Products
  - 21 CFR Part 11 Electronic Records, Electronic Signatures
  - FDA Guidelines (includes ICH guidelines)
    - Characterisation & qualification of cell substrates & other biological starting materials use in the production….
  - Pharmaceutical Quality for the 21stCentury –A Risk-Based Approach

Useful web links:

http://www.mhra.gov.uk http://www.fda.gov http://www.ich.org

Challenges with Manufacturing Biologics

- Biological starting materials
  - ill-defined, inherently variable, potentially unstable and viable or infectious!
  - Need product protection, operator protection and environmental protection
    - Balancing these needs can be challenging

- Processes
  - Cultivation stages are complex, variable, and low yielding
  - Purification steps are long, complex and conducive to growth of viable contaminants
  - Final formulation require aseptic or sterile processing

- Product
  - difficult to characterize and inherent variability
  - Reliance on in-process controls

The PROCESS is the **DETERMINANT OF QUALITY**

A biological product = product AND the process

Process Requirements

- Documented
  - Registered process for marketed products
  - Product Specification File for clinical products

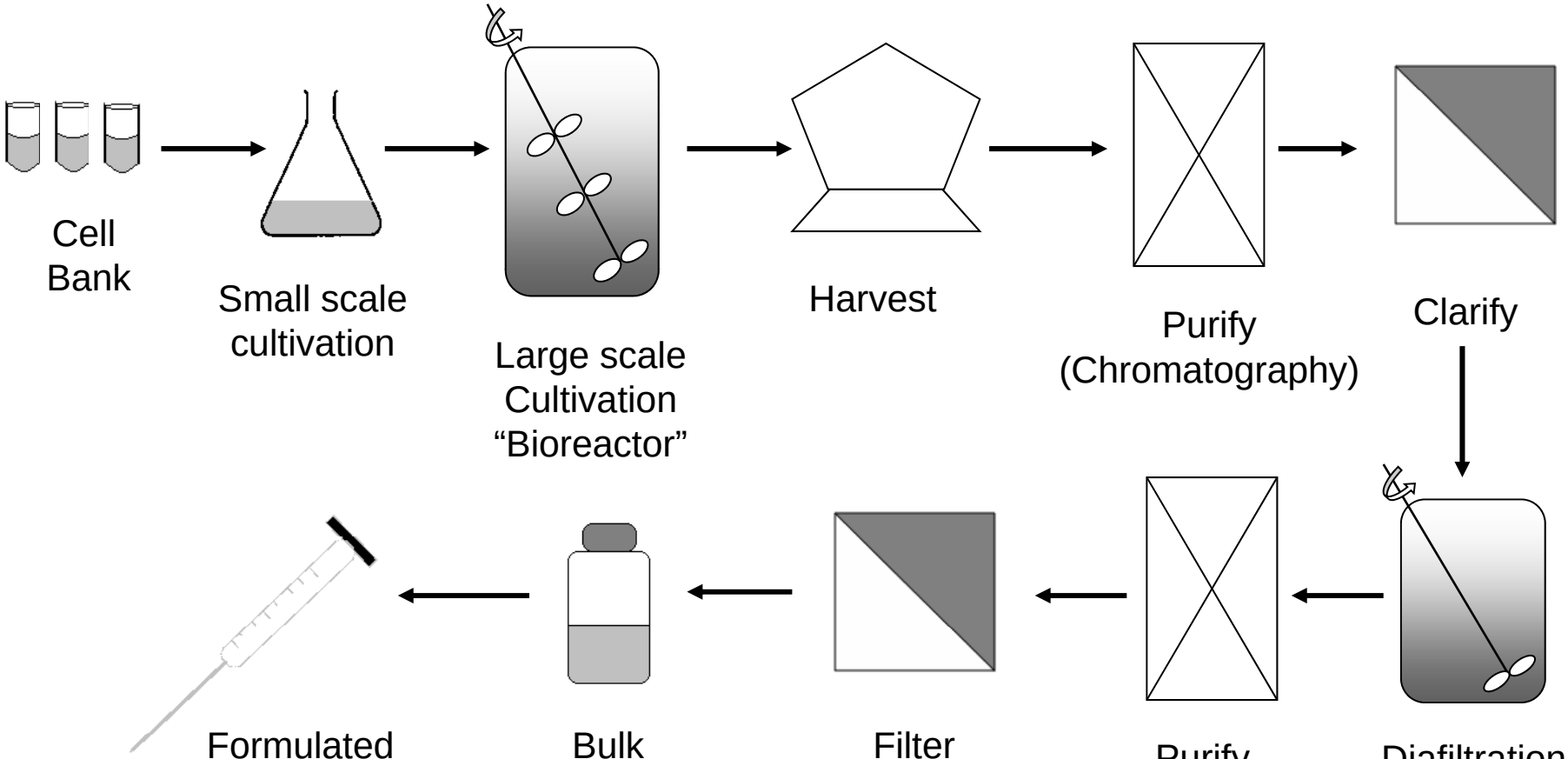
- Process must be
  - Well developed and defined clearly
  - Robust
  - Perform consistently

- Batch Manufacturing Records
  - Process steps clearly defined
  - Operator entries to record key information
    - Batch numbers of raw materials
    - Weights
    - Manufacturing Area
    - In-process control data
    - Times and dates

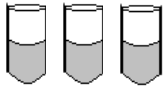
Biological Products

- Cell Banks
  - Master Cell Banks
  - Working Cell Banks
  - Master Virus Seed Stocks
  - Working Virus Seed Stocks
- Drug Substance
  - Bulk formulated drug substance
- Drug Product
  - Injectable
  - Infusion

Live Virus Gene Therapy Product



Cell Banks

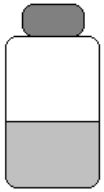


- **Quantity of microbial, animal or plant cells**
- **Produced to ensure consistency of starting materials for processing**
- **Master and Working Cell Banks**
  - **Processed in local grade A environment**
  - **Uniform composition**
  - **Adequately characterised**
    - **Full testing for Master Cell Banks**
    - **Reduced testing for Working Cell Banks**
  - **Segregated storage (liquid nitrogen, -80°C) to maintain these characteristics**
    - **Temperature control and monitoring**
    - **Procedures and back-ups in place for emergencies**
    - **Second site storage**

For example
- **Origin**
- **Identity**
- **Safety**
- **Purity**
- **Free of bacteria, fungi & mycoplasmas**

- **EU requirement to cGMP; US can be non-GMP**

Drug Substance

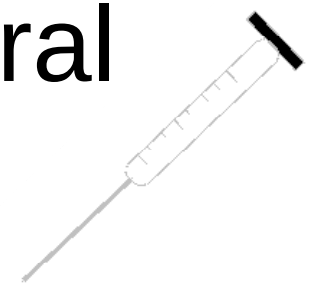


- **Typically low bioburden product**

- **Cell culture typically aseptic processing**
  - **Operators qualified in aseptic techniques**
  - **Local Grade A environment**
    - **Biological safety cabinets**
  - **Closed systems (bioreactors) with sterilise-in-place capability**
  - **Isolator technology where needed**

- **Low bioburden processing during purification**
  - **Mix of closed systems, local grade A environment and open processing in grade C or greater**
  - **Buffers made using HPW or WFI & filtered 0.2μm prior to use**
  - **Final filtration step through 0.2 μm in grade A environment**

Drug Product - parenteral



- **Sterile product**

- **Grade A environment within grade B background**
  - **Operators qualified in**
    - **aseptic techniques**
    - **Gowning**
  - **Isolators**
  - **Validation of sterilisation processes**
    - **Autoclave**
    - **Gamma irradiation**
    - **Sterilisation in place**
    - **Hydrogen peroxide gassing**

Facility

- **Controlled environment to ensure**
  - Product protection – ensuring the quality of the medicine to be safe and efficacious
  - Operator safety
  - Containment

- **Achieved through**
  - **Design features**
    - **Process, equipment and personnel flows**
    - **Separate Entry (Clean) and Exits (dirty) corridors**
  - **Engineering controls**
    - **HVAC air filtration**
    - **air pressure differentials**
  - **Policies and procedures**
    - **Segregation**
    - **Cleaning regimes**
  - **Training**
    - **operator training and discipline**

Facility continued

- **Single vs Multi-product**
  - Single-product – only one product produced
  - Multi-product – more than one product
    - Campaign manufacture
    - Simultaneous multiple manufacture

- **Dedicated facility & equipment for live organisms**
  - Closed systems where possible

- **Controls for preventing cross contamination**
  - No recirculation of air for areas where live organisms are handled
  - Pressure cascades within the rooms
  - Cleaning between batches
    - Caustic and acid washes
    - Rinse water and swab analyses for equipment
    - Validated cleaning cycles
    - Cleaning-in-place
  - Environmental monitoring to show product clearance
  - Line clearance procedures between batches

- **Waste Handling**
  - Capped drains for liquid waste
  - Effluent streams to include chemical kill before discharge
  - Contaminated consumables through autoclave to decontaminate
  - Waste product autoclaved to deactivate

Facility continued

- **Cleaning**
  - Detailed in SOP
  - At least 2 disinfectants
    - Rotated to prevent organisms developing resistance
  - Surface cleaning using 70% alcohol
  - Cleaning at the end of each day
    - Floors, equipment
  - Changeover cleans
    - Floors, ceilings, all surfaces, inside equipment
    - Environmental monitoring data to confirm cleanliness

Clean Room Classifications

- Requirements
  - 10-15Pa air pressure differentials between areas of different classifications
  - More than 20 air changes per hour
- Differences between EU and US requirements
  - Particulate monitoring
    - EU - at rest and in operation (see Orange Guide)
    - US - in operation
- Gowning requirements change for the different classifications

EU Classification	US Equivalent
A	100 (ISO 5)
No grade equivalent	1,000 (ISO 6)
B	10,000 (ISO 7)
C	100,000 (ISO 8)
D	no equivalent

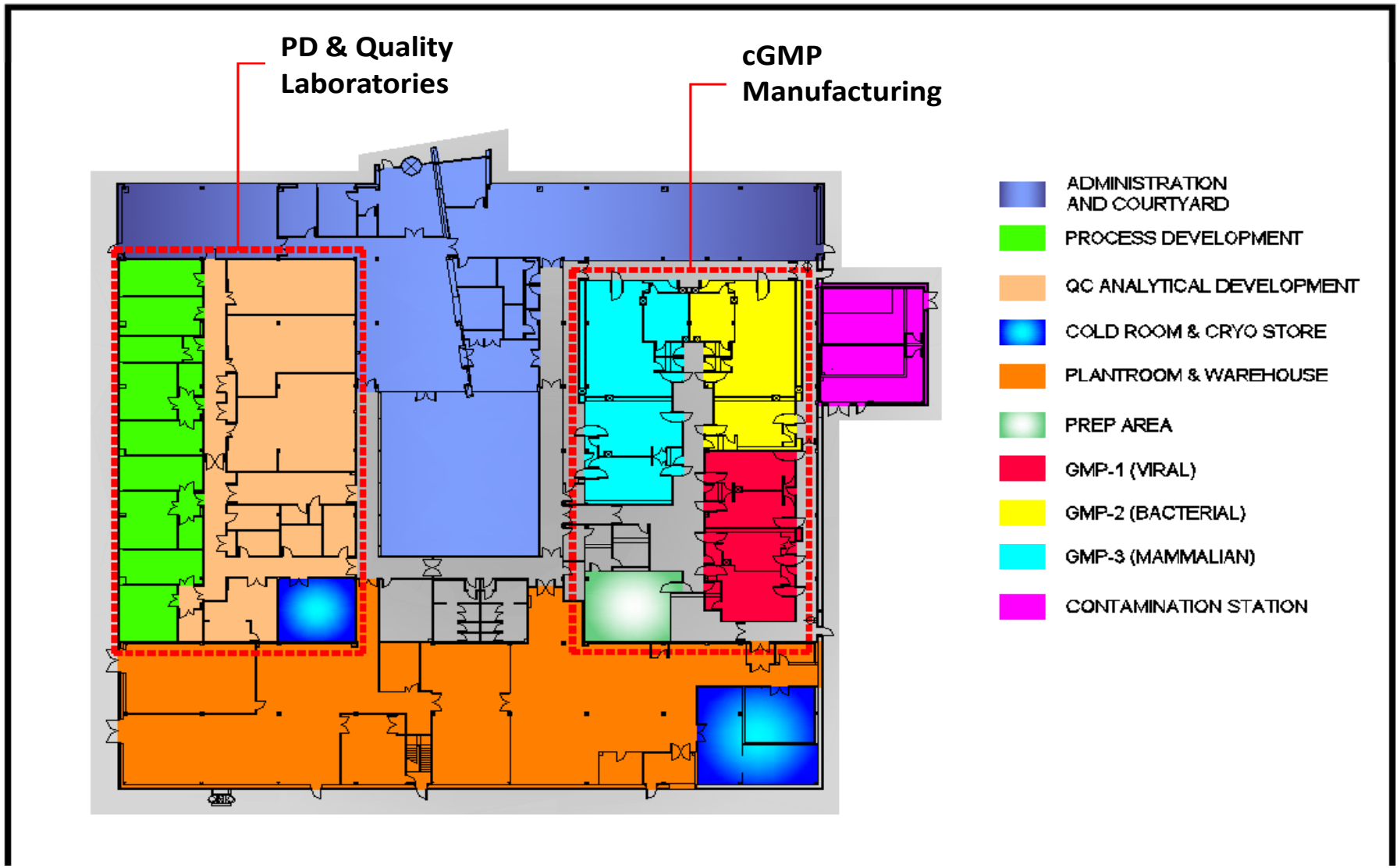
Case Study: Eden Biodesign

- **Multi-product facility**
  - 3 segregated production areas dedicated for
    - Mammalian products
    - Microbial products
    - Viral technologies

- **Design**
  - Unidirectional flow of people, materials & waste
  - 8 separate HVAC systems
  - Negative sinks in each viral suite
  - Isolator technology
  - High reliance on disposable technology

- **Procedural control for personnel entry to prevent cross contamination**

Eden Biodesign Multi-product Facility



Equipment

- Maintained and calibrated
  - Maintenance appraisal
    - Maintenance tests
    - Calibration methods
    - Frequency
- Logbooks
  - Record usage and maintenance
- Real time performance monitoring to ensure constantly meeting temperature requirements
  - Storage facilities – freezers, fridges, cold stores
  - Critical process equipment - incubators
- Status labelled
- Disposables
  - Avoids cleaning verification and validation

Validation

- Facility validation
  - Performance qualification of the HVAC system
    - Are environmental controls maintained in operation?
    - Qualify the manufacturing room for the number of personnel that will be working in the room
    - Identify routine monitoring regimes
      - Location of environmental plates
      - Which operations?

- Equipment Validation
  - User Requirement Specifications
  - Commissioning
  - Installation Qualification
  - Operational Qualification
  - Performance Qualification

Validation continued

- Sterilisation Validation
  - Sterilisation can be achieved by heat, steam, radiation, ethylene oxide
  - Validate loading patterns
  - Use temperature thermocouples and biological indicators

- Revalidation
  - Facility, equipment, systems & processes evaluated to confirm remain valid
  - When a change impacts on the validation status
    - Identified through Change Control
  - Sterilisation processes annually

- Process Validation
  - Phase III and Registration Batches
  - 3 consecutive batches

Raw Materials

- Specifications in place
  - Raw materials
  - Product contact consumables (tubing, filters, disposables)
  - EP and USP grade materials where possible

- Approved suppliers
  - Supplier questionnaires
  - Quality audits
  - Supplier qualification
    - reproducible data for > 3 consecutive lots & QA audit

- Receipt of Goods
  - Controlled access to GMP stores
  - Temperature monitoring or control
  - Segregation of quarantine, released and rejected goods
  - Control of expired stock
  - Release procedures
    - Check product and CoA meet specification
    - Check integrity of pack
  - Inventory records
  - Reconciliation
  - Dispensing & sampling in controlled and clean environment

Raw Materials continued

- Raw Materials of animal origin
  - cell culture media, Foetal Bovine Serum
    - Minimise serum content or eliminate
  - TSE Risk Assessment required for all animal derived materials
  - Compliance with Ph.Eur Monograph 5.2.8 and EMEA/410/01 Rev 2
    - Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human & Veterinary Medicinal Products"
  - Obtain documentation from supplier

- Highly Purified Water
  - Used to manufacture products where biological purity is needed
  - Produced using Reverse Osmosis in combination with ultrafiltration or deionisation
  - Regular analytical and microbial testing of system to ensure meets specifications

- Water For Injections for final formulation of parenterals
  - Produced by distillation
  - Can be bought in

Quality Management Systems

- **Accepted hierarchy**
  - **Policies**
  - **Procedures**
  - **Instructions**
  - **Records**
- **Management of Change – Change Control**
- **Non-conformance reporting (root cause investigations)**
- **Planned Deviations / Temporary Change Controls (Risk assessments)**
- **Corrective and Preventative Actions and Continuous Improvement**
- **Archive (batch related documents, raw material records, calibration records, validation documents, SOP revisions…….)**
- **Complaints procedure**

Quality Management Training

- All staff to have training records
  - Operators
  - Engineering personnel
  - Cleaning personnel
  - Warehouse
  - Quality Control
  - Quality Assurance
- Annual GMP training
- Basic understanding of hygiene and microbiology
- Standard Operating Procedures (SOPs) pertaining to tasks undertaken
- Reviewed annually

Qualified Person

- **All finished products must be certified by QP prior to release for sale or supply to clinical study**

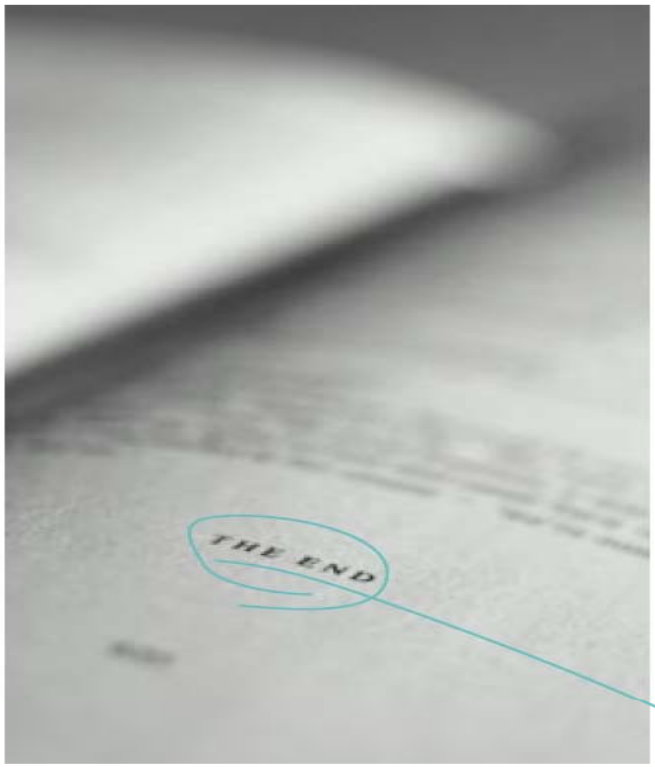
- **To release the product**
  - **Review all batch related data to assure product meets requirements of GMP**
  - **Review batch related documents and data in line with marketing authorisation or IND/CTD for clinical product**
  - **Ensure all non-conformances and planned deviations have been authorised and closed out**

Frequent GMP deficiencies

- Cleaning and maintenance personnel not trained in hygiene and microbiology
- Staff pass from areas with live organisms to other areas without clearly defined contamination procedures
- Waste streams are not segregated
- “Claimed” closed systems are not proven to be closed
- Cleaning and decontamination procedures are not validated
- Specifications for intermediate and bulk biological products are not defined
- The number of generations (doubling, passages) between the cell bank and the finished product is not consistent with the marketing authorisation dossier
- The centrifugation of a live micro-organism containing product is not performed in a contained area
- The acceptance criteria and life span of chromatography resins are not defined
- Investigations into discrepancies or failure of a batch/components to meet specifications are not thorough
- Failure to establish and follow written procedures, and to justify any deviation from written procedures
- Failure to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile

Summary

- Many aspects to consider
- Solid quality management syster imperative to underpin all activities
- Where possible design quality in from the beginning
  - Facility design
  - Develop production processes with end in mind



It's where we prefer to start

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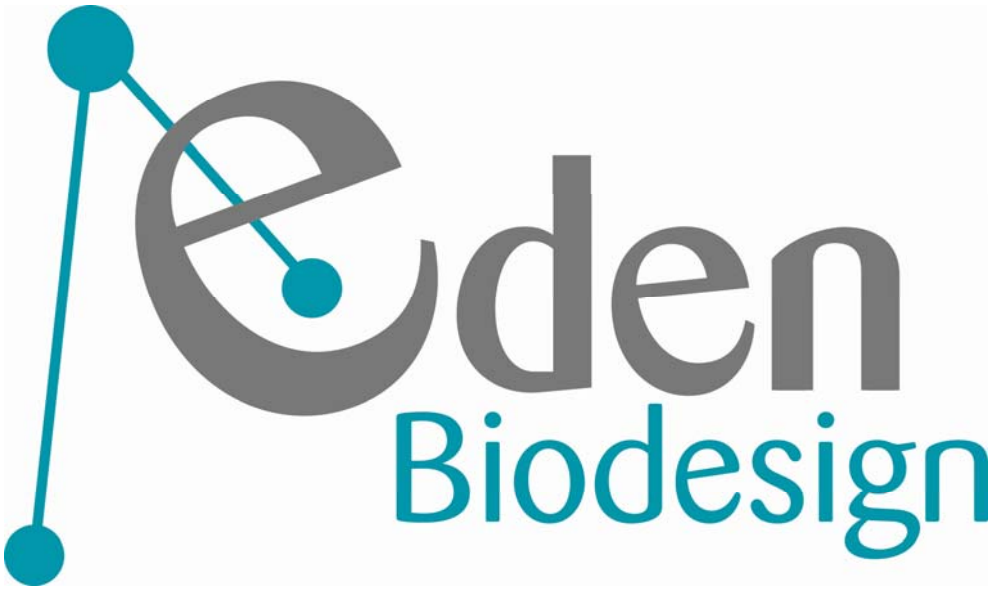
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