# Good Manufacturing Practice

An Introduction
to
Regulatory Compliance
in
Biopharmaceutical Manufacturing

Instructor: Dr. Steve Oh Kah Weng



# Introduction to the Course

- The Instructor
- Course Objectives
- Course Timetable

# Day 1 Topics

- Drug Development
- GMP/QA Concepts
- GMP Regulations
- Standard Operating Procedures
- Validation Concepts
- Validation of Systems



# Biopharmaceuticals

Biopharmaceuticals - biomolecules with therapeutic value

>80 biopharmaceuticals in general medical use

benefiting >60 million patients worldwide

global market value >US$12 billion

| Drug name | Manufacturer | Disease |
|---|---|---|
| Epogen (rh EPO) | Amgen | Anaemia |
| Novolin (rh insulin) | Novo Nordisk | Diabetes |
| Remicide | Centocor | Cancer (Crohn's disease) |

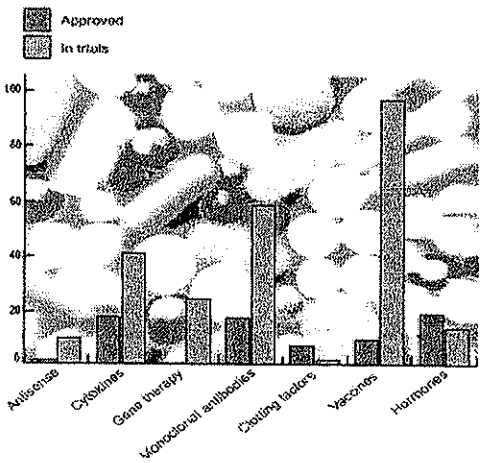
## Biopharmaceuticals - approved or in clinical trials

Nature Biotechnology 2000

> 500 biopharmaceuticals undergoing clinical trials

major product categories (in order of predominance):

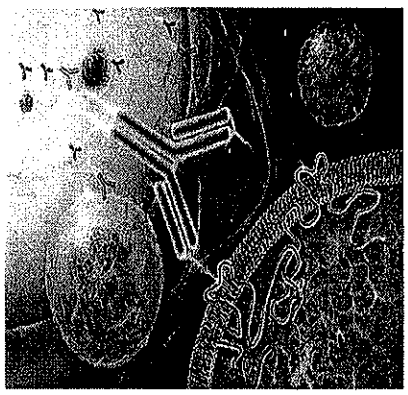
- vaccines
- monoclonal antibodies (MAbs)
- cytokines

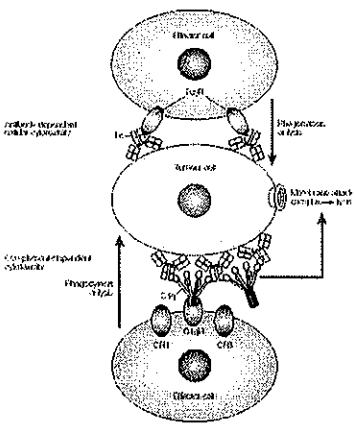





pasteurisation.

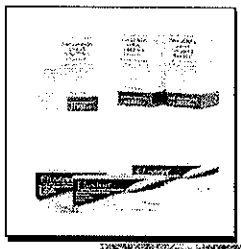
## Antibodies targeting protein on cell surface & effector functions

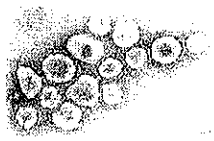




# Viral vaccines

- Polio (1968)
- Influenza (annually)
- Hepatitis (in development)
- HIV (in development)
- SARS ?

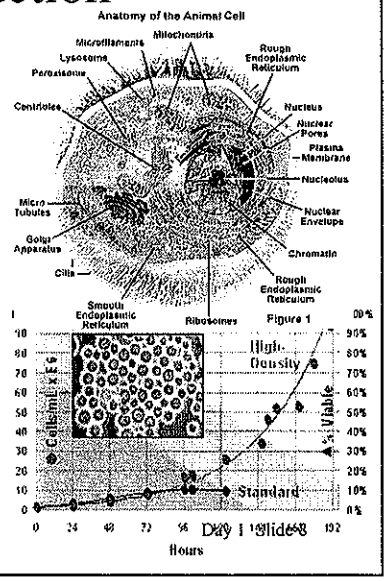





# Cell lines for Recombinant Protein Production

- **CHO**, Chinese Hamster Ovary – recombinant proteins
- **Hybridomas** – monoclonal antibodies
- **HEK293**, Human embryonic kidney - recombinant proteins and viruses
- **Insect cells** – recombinant proteins and viruses
- **PerC6 (new)** - adenoviruses, gene therapy



# Exhibit 1:
# Product Development Stages

| | | | | | | |
|---|---|---|---|---|---|---|
| *Product Concept* | Basic Research | | | | | |
| *Development* | Strategic Plan | Product/Process Development | | | | |
| *Lab/Animal Studies* | Short-term Efficacy | Full-scale Efficacy & Toxicity | | | | |
| *QA/Regulatory Work* | | GLP Audits | IND Preparation & Approval | ***Validation of Processes and Test Methods*** | | NDA Preparation |
| *Clinical Studies Under GCP* | | | | Phase I | Phase II | Phase III |
| *Manufacturing Scale* | Bench-top Process | Pilot Plant | GMP Pilot Plant Manufacture for Clinical Trials | | | Full-scale GMP Manufacturing Plant |
| *Project Time Frames* | 1 - 3 years | 0.5 - 2 years | | 3 - 5 years | | |
| *Development Cost Estimates* | $0.5 - 5 million | $5 - 50 million | | $10 - 100 million | | |

→ Animal | - Human



## The Protein Production Challenge

### Shortage in protein manufacturing capacity

**Number of protein therapeutics in clinical development increasing rapidly**

**Unexpected recent success of monoclonal antibodies (MAbs)**

(i) numerous disappointments with MAbs in the 1980s and early 1990s

(ii) MAbs often used for chronic illnesses → long-term treatment

(iii) dosing for MAbs (10-1000) times > 1st generation therapeutic proteins (eg., Genentech needs over 200kg/yr Rituxin (MAb) but Amgen needs only 2kg/yr Epogen to meet demands, even though the patient population for Epogen is > 6 times greater than that for Rituxin)

(iv) industry unprepared to handle >270 MAb products currently in pipeline (eg., if 50-60 new MAb product approvals in next 6-7 years, an estimated 5-6 fold increase in cell culture capacity is required)

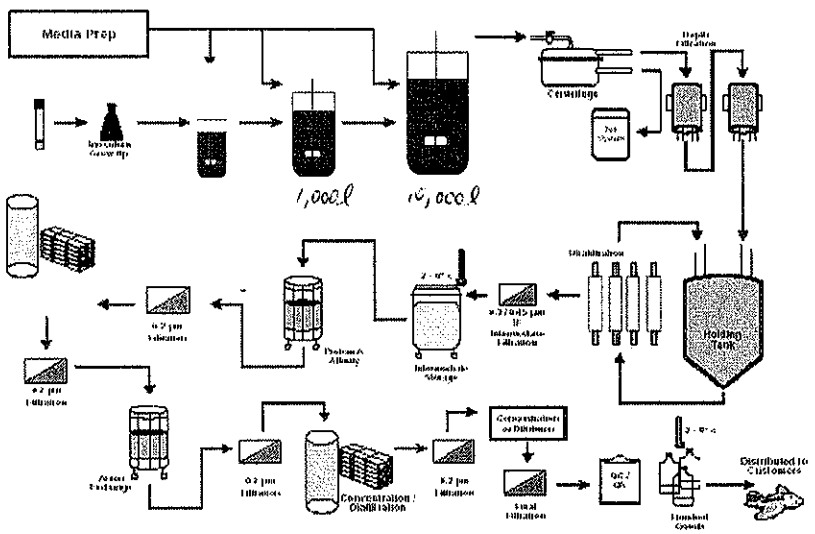
# The Protein Production Challenge

Immunex's **Enbrel** Case Study
(Immunex acquired by Amgen for almost US$17 billion in Dec 2001)

- rec TNFR-IgG fragment fusion protein produced in CHO cells
  TNF Receptor linked to Fc portion of human IgG. Binds to the common inflammatory agent TNF
- 1st biotech drug approved by FDA for treatment of rheumatoid arthritis (RA)---Nov 1998
- demand for Enbrel >> supply (limited manufacturing capacity)
  long waiting list to get on Enbrel
  (only 75,000 of 1 million potential patients have access to Enbrel)
  ➔ Immunex estimated to lose >US$200 million in Enbrel sales/year
  ➔ patients turning to alternative / newer drugs for treatment of RA



## BioManufacturing Process Flow Diagram





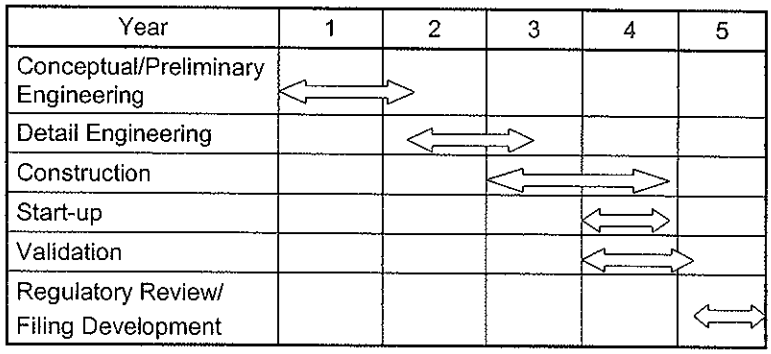

– Cleanliness important to prevent cross-contamination to product

# Biopharmaceutical Production

Long lead time in designing, constructing and validating a new biomanufacturing facility

---may take 4-5 years from deciding to build to receiving FDA approval

---can cost US$150-450 million to build new plant






# Biopharmaceutical Production

**Contract Manufacturing Organizations (CMOs)**

- More and more companies now turning to CMOs to produce materials for clinical trials and licensed products
  (eg., Immunex's Enbrel is manufactured by Boehringer Ingelheim)
- Some CMOs provide cell line and process development in addition to ensuring product supply
- To reserve capacity, advanced reservations of CMOs often necessary
  (eg., 12-24 months advance booking of popular CMOs)

# Introduction to QA/GMP Concepts

- Quality Assurance in Manufacture
- Good Manufacturing Practice Defined
- The Who and Why of Compliance
- The Consequences of Non-compliance



# Introduction to GMP/QA Concepts

Principles:

1. Quality, safety and effectiveness must be designed and built into the product.
2. Quality cannot be inspected or tested into the finished product.
3. Each step of the manufacturing process must be controlled to maximise the probability of finished product meeting quality & design specs.

GMP compliance is responsibility of whole company

Non-compliance means loss of business, injury or even loss of life.

Cost of product recalls, between $ 1-5 million.

# What is "Quality Assurance" ?

- "Quality" is
  - The Nature of Something, i.e. its Character,
  - Excellence, or Goodness
- "Assurance" is
  - Sureness, or Dependability
  - Confidence, or Security



# Quality Assurance is...

"A means of guaranteeing the excellence, security and dependability of a process (e.g. an experiment, test, observation or report) or its product, by monitoring, validating and certifying the constituent parts of the process, its overall operation and the tests applied to it."

# A Definition of GMP

"GMP is that part of *Quality Assurance* which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the *marketing authorization* or product specification."

EUDRA Volume 4. 1998



# In Other Words...

...The production of articles which are FIT FOR THEIR INTENDED USE...

FDA "Principles of QA", 1996

## Who Must Comply and Why ?

- Manufacturers of biologicals and biotechnology products, as well as synthetic chemicals...
- Intended for the diagnosis, prophylaxis or therapy of human/animal diseases
- Required under the Food and Drug Laws of North America, Europe, Japan, Australasia,
- Also by WHO guidelines to other countries



## GMP Must be Applied...

- To the manufacture of *clinical trial materials*, especially Phase III
- To all licensed products
- Even when split between different companies
- Or when done under contract

# How is GMP Compliance Monitored ?

- Internally by QA Department
- Externally, by Regulatory Authorities:
  - Examining Records and Samples
  - Inspecting Facilities & Operations



# The Consequences of Non-Compliance...

- Denial of product market authorization
- Denial or revocation of establishment license
- Recall of marketed product
- Monetary penalties
- Legal action against Co. executives

# Cost of non-compliance

- Loss of business
- A single product recall can cost $1-5 million
- Final product release is mediated by regulatory authority, not manufacturer
- If authority does not agree with findings of manufacturer, batch may not be issued
- If cost of dose is $1000 and 1 batch may have 100,000, severe strain on small company resource
- Penalties are also imposed for breach of law, e.g.
- In 1999, Abbott Labs was penalised $100 mil for failure to comply with GMP on diagnostic devices.
- In 2000, Wyeth-Ayerst made a $30 mil payment to US gov. and consented to inspections by FDA until 2 manufacturing sites complied to GMP
- 2002, Bayer delayed manufacture of Factor 8 due to non-compliance



# Pause for Thought...

- Any Questions ?
- Any Comments ?
- Coffee ?



# The GMP Regulations

- USA and Canada
- European Union
- Japan
- International Harmonization
  - ➢ WHO and ICH



FDA – food & drug Administration

# The United States

- Food & Drug Act (1906), administered by...
- The Food and Drug Administration
  - ➢ CDER Centre for Drug Evaluation & Research
  - ➢ ***CBER*** Centre for Biologics Evaluation & Research
  - ➢ CDRH Centre for Devices & Radiological Health
- Code of Federal Regulations (CFR)
- Title 21, Parts 210, 211, 600, 820, 11

# USA: 21 CFR 210 & 211

- 210: Current GMP in Manufacturing, Processing, Packing or Holding of Drugs: General
- 211: Current GMP for Finished Pharmaceuticals
  - Latest (slight) Amendments: April, 2002.



# USA: 21 CFR 600, 820 & 11

- 600: Biological Products: General
  - § 600, Subpart B - Establishment Standards
  - § 600.21, 22 - Inspections, Nov. 2000
  - § 606 cGMP, Human Blood and Blood Products
  - § 610 - General Standards for Biologics
- 820: Medical Devices
- 11: Electronic records – applies to all products and GLP and GCP practices. Electronic signatures (April 2000)



GLP – Good Laboratory Practice
GCP – Good Clinical Practice

# Canada

- Food and Drug Act, Part C
- Division 2 - GMP (§ 02.001-02.030)
  - Latest version, June 2001
- PLUS: "Guidelines to GMP" 2002
  - Annex June, 1999 - "Biological Drugs"
- Administered by
  - Therapeutics Product Directorate (TPD)
  - Bureau of Biologics (new)



# The European Union

- EUDRALEX: Rules Governing Medicinal Products - Volume 4, 1998, plus Annexes:
  - 1: Manufacture of Sterile Products
  - 2: Biological Products for Human Use
  - 11: Computerized Systems
  - 13: Investigational Products - REVISED '01
  - 14: Human Blood/Plasma Products
  - 15: Qualification & Validation (2001)
  - 18: GMP for Active Ingredients (2001)

# Japan

- MHW "Ordinances"
  - #31, 1980 - Manufacturing & QC
  - #32, 1980 - Buildings & Facilities
- Amended in 1994 (# 3 & 4)
- Biologicals covered by Ord. #71, 1997
- Amendments of 1999:
  - #16 included recombinant products
  - #57 included prevention of cross-contamination in biological facilities



# International Harmonization

- WHO: Compendium of Guidelines,etc
  - Volume 2, GMP & Inspection...1999

  (very similar to ICH Guidelines, for countries without their own regulations)
- International Conference on Harmonization (ICH) Topic Q7
  - GMP Guide for Active Pharmaceutical Ingredients

  (to reduce re-testing & aid international product distribution; approval in one country should permit sale in other member countries.)

  Issued by Committee for Proprietary Medicinal Products (CPMP) Nov. 2000

# Analyzing the Regulations: Organizational Responsibilities

- Plant Management (Managerial commitment is essential, cannot be delegated downwards)
- Staff (Must be properly trained)
- Quality Control & Assurance (Must work in close collaboration, as 1 unit. Reports to CEO or COO independent of Manufacturing.)



# Senior Management Must:

- Be responsible for GMP compliance
- Establish a QC Unit, separate from Production, with adequate facilities
- Employ an adequate number of suitably qualified staff
- Ensure all staff follow the rules
- Maintain GMP training

## All the Staff Must:

- Understand their responsibilities and their position in the reporting structure
- Have capabilities (education, training, experience) commensurate with their assigned functions
- Maintain their levels of GMP and other training
- Comply with the facility rules



## Consultants

- Must comply with the same rules, governing
  - ➢ Education, training & experience
  - ➢ Clothing & hygiene
  - ➢ Restrictions on movement
  - ➢ Observations of SOPs
  - – Confidentiality & Security

## The QC Unit is Responsible for:

- Testing and approval/rejection of:
  - Raw Materials
  - Packaging & Labeling Components
  - In-process Products
  - FINAL PRODUCTS...
- Whether manufactured in-house or under contract by another company



## Further QC/QA Responsibilities

- Review of production records for errors
  - Ensure all errors have been investigated
- Review & approval of validation protocols
- Review of proposed process changes
  - Determine whether revalidation is required
- Approve or reject all procedures or specifications effecting product *identity, strength, quality and purity*

## Laboratory Controls & Records

- "...Specifications...shall be drafted by the appropriate organizational unit and reviewed and approved by the QC Unit." (21CFR 211.160a)
- "Written procedures shall be established for the review and approval by the QC unit of all drug product production, control and laboratory records..." (211.192a) - revised)



## Quality Assurance System

- "..shall be in place, which requires revalidation whenever there are changes in packaging, component characteristics, formulation, equipment or processes ...that could affect product effectiveness or product characteristics, or whenever changes are observed in product characteristics. (New Sub-part 211.220)

# Another Pause for Thought

- Questions ?
- Comments ?
- Lunch ?





# Standard Operating Procedures

- What are SOPs & Why do we need them ?
- How to write SOPs - a Standard Format
- SOP writing exercise
- Minimum SOP List
- SOP Manual and its maintenance

## There Must be SOPs...

- "The responsibilities and procedures applicable to the QC unit shall be in writing and such written procedures must be followed." (21CFR 211.22d)
- "Training shall be ...in current GMP and written procedures required by these regulations" (211.25a)
- "There shall be written procedures for... process control (211.100a)



## Therefore, an "SOP" is:

- A written description of a process, procedure, organizational responsibility, etc.
- Required by CFR for various GMP activities
- A document which must be followed when performing the described activity
- A "living document" which must be kept up to date

# Why do we need them ?

- Apart from the fact that it's mandatory...
- Using SOPs to control activities means that:
  - There is never a question about "how to do it"
  - Consistency in performance should be assured
  - The process of writing an SOP aids in defining the activity clearly
  - All activities can easily be monitored against the written procedure



# What will SOPs cover ?

- Facility Operation, Cleaning & Maintenance
- Staff Safety & Hygiene Procedures
- Equipment Operation, Calibration, Cleaning & Maintenance
- Animal Care & Handling
- Critical Processes, Procedures, Records in
  - Manufacturing
  - Quality Assurance
  - Quality Control

## How to Write SOPs

- Agree on Critical Subjects
- Use a Standard Format
- Appoint someone to do the First Draft
- Have the Draft Reviewed & Approved
- Issue the SOP and Enter it in the Manual
- Ensure All Modifications are Approved AND Recorded.



## SOP Standard Formats
### 1 - Processes (See Exhibit 2)

- Title
- Purpose
- Materials, Equipment, Safety Gear
- Procedure - start with safety, calibrations
- Readings to be made/controls applied
- Records to be created & kept
- Countersignatures & Labels to be applied

## SOP Standard Formats
### 2- QC Tests (See Exhibit 3)

- Title & Purpose
- Materials, Equipment, Sample handling
- Procedure - start with safety, calibrations
- Readings to be made/Result reported
- Countersignature/result check
- Records to be created, submitted & kept
- Reserve sample storage



## The Minimum List of SOPs - 1

- Organization & Personnel
  - QC Unit set-up & responsibilities
  - Personnel qualifications & responsibilities
  - Consultants
- Buildings, Facilities and Systems
  - Sanitation
  - Maintenance

## The Minimum List of SOPs - 2

- Equipment
  - Cleaning & maintenance
  - Automatic, mechanical & electronic controls
- Control of components & containers, etc.
  - Receiving, handling, testing
  - Rejected components, ID and quarantine
  - Standards for cleaning, sterilization, etc.



## The Minimum List of SOPs - 3

- Production & Process Controls
  - SOP for each manufacturing process
  - Reporting & justifying deviations
  - Change control
  - Equipment ID
  - Sampling & testing of in-process materials
  - Control of microbial contamination
  - Reprocessing

# The Minimum List of SOPs - 4

- Packaging & Labelling Control
  - Materials examination & use criteria
  - Issue of labelling materials
  - Packaging & labelling operations
  - Inspection of final product
- Holding & Distribution
  - Warehousing procedures
  - Distribution procedures



# The Minimum List of SOPs - 5

- Laboratory Controls
  - SOP for specifications, standards, sampling plans, test procedures, OOS investigations
  - Measuring instrument calibration program
  - Preparation, labeling & storage of reagents
  - Stability testing
  - Special tests, e.g pyrogen, sterility
  - Reserve samples
  - Lab animal use and handling

# The Minimum List of SOPs - 6

- Records & Reports
  - System for the creation & maintenance of production, control & distribution records
  - Master production and control records
  - Batch production & control records
  - Record review procedure, investigation of discrepancies
  - Complaint files



# The Minimum List of SOPs - 7

- Returned & Salvaged Products
- *Validation*
  - *Systems validation* eg utilities.
  - *Process validation*
  - *Test methods validation*
- *Contamination*
  - *Control of physical & chemical cross-contamination*

## The SOP Master File

- Is maintained by Quality Assurance
- Contains all versions of any SOP, in date order
- With explanations for the amendment of any SOP
- Must be available for RA inspection
- Sample of a MF Page…in your book. (Exhibit 4)



## An SOP-Writing Exercise

- Using the format given, draft an SOP for a procedure, test, etc. with which you are fully familiar.
- If you do not know one, do an SOP for a household chore, like doing the laundry, making a sandwich…
- Hand in your SOPs after the break.

# Wrap-up on SOPs

- Any further questions ?
- Comments ?
- Time for tea...





# Introduction to Validation

- Definitions of "Validation"
- Validation in Research & Development
- Types of Validation under GMP

# Definition:
# FDA - Process Validation

"Validation means *establishing documented evidence*, which provides a high degree of assurance, that a specific process will consistently produce a product *meeting its predetermined specifications* and quality attributes"

(1987 Guideline on General Principles of Process Validation)



# Definition: EU - All Validation

" Validation is the action of *proving*, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system, *actually leads to the expected result*"

EUDRA Volume 4, 1998

# Definition:
# ICH - Analytical Method Validation

"The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose."

Document Q2A

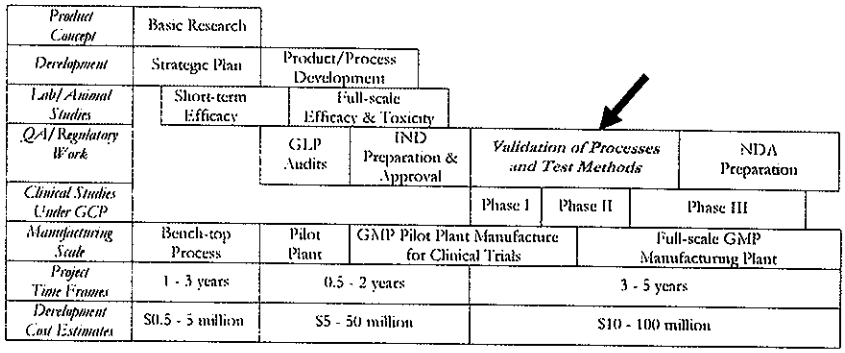


# What This Means To Me...

- All critical activities, which may affect the safety, purity or efficacy of a product, must be properly defined and controlled
- The operation of the system, process or test method produces the required result reliably and reproducibly, and this fact can be well documented as a result of testing the performance

*A Guide to Good Validation Practice*, 2001

# Stages in Drug Development




Validation begins with the analytical test methods!!!



# What Needs to be Validated...

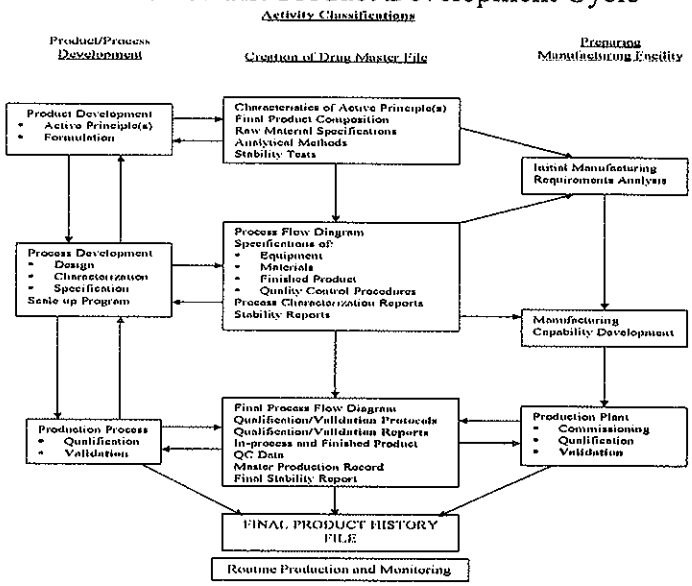
- "All processes where the results cannot subsequently be verified to a high degree of assurance by inspection and test" e.g.viral clearance, sterile filtration
- "Processes that may be responsible for causing variability in product characteristics" e.g. seed preparation, column cleaning
- "Procedures designed to prevent microbial contamination of sterile products" e.g. autoclave sterilization, final filling

# Validation is based upon UNDERSTANDING...

- The science and engineering involved,
- The factors which might affect the performance of the system, process, test,
- The ways in which these factors may be controlled, or...
- In which variability may be minimized..
- Therefore, validation should be in your mind *during development*



## Exhibit 5: The Product Development Cycle



## The Implications of Non-Compliance

- Validation was FDA's #1 Problem in 2001 -
- 15% of all Form 483 Citations
- No process will be approved unless validated
- IND, NDA will be delayed
- Continued non-compliance = Warning Letters, then legal action
- E.g. Abbott, Wyeth, Schering-Plough...



## Validation Master Plan, VMP & Protocols

- Setting up the Master Plan
- Plan Contents (Exhibit 6)
- Organizational Responsibilities

# Setting Up the Master Plan

- Plan may be facility or product-based
- Identify critical systems, processes, tests and prioritize by Risk Analysis
- Define Scope & Set Acceptance Criteria in individual Protocols
- Draw up the Schedule
- Specify Responsibilities & Resources



# Exhibit 6: VMP Contents

- *Introduction*: Covering the basic facts such as location, timing and the definition of the overall scope of the project.
- *Overall Project Description*: This section provides a description of the entire project. If it involves construction, the details of materials, etc. are included here. If it involves systems and processes, the layout of the plant and the interrelationship between elements is included. Product and personnel movements through the plant should also be detailed.
- *Scope:* This section of the VMP defines in general the parts of the facility systems, processes and tests which are to be validated, with the justification for their inclusion in the plan on the basis of the risk analysis or other criteria. Just as importantly, the "Scope" section describes those elements which do not need validation. These latter will be excluded from the validation plan by virtue of the low risk they present to the product, or the fact that they have already been validated and do not need revalidation at this time.
- *Acceptance Criteria*: General criteria to be applied across the whole plan, such as the requirements for commissioning and/or qualification of plant, must be part of the VMP. Quantitative criteria for validation protocols for specific equipment or systems may be spelled out in the VMP. This is not essential, but may be advisable because it places the definition of important criteria earlier in the planning process.
- *Specific issues*: Where particular sections of the overall plan will require greater emphasis and perhaps demand more resources. Validation of computerized systems is a case in point.
- *Project Schedule and Resource Requirements*: A Validation Plan of any magnitude will be best scheduled and controlled by the use of project management techniques and probably by creating the project plan on the computer, using software such as Microsoft "Project".
- *Plan Documentation*: This section should list the complete documentation of the project and describe the format that all plan documents will adopt, in order to ensure conformity across the project and avoid missing reports, etc.
- *Standard Operating Procedures*: This applies to the operation of any system, equipment, process or analytical test which forms part of the plan.

# Risk Analysis

- What Effect does this
  - Process,
  - Procedure,
  - System
  - Test Method, etc. have on the -
- Safety, Purity or Efficacy of the Product ?



# A Formula for Risk Analysis

- Do a numerical list of all process stages
- Assign a "complexity number" to each step
- Multiply "Step #." by "Complexity"
- The highest number has the highest priority
- See Next Slide

# Exhibit 7: Validation Priority Rating Method

| Process Step | Step Order | Step Complexity | Score | Rank |
|---|---|---|---|---|
| Seed Fermentation | 1 | 2 | 2 | 6 |
| Prod. Fermentation | 2 | 4 | 8 | 5 |
| Harvest | 3 | 3 | 9 | 4 |
| Chromatography | 4 | 6 | 24 | 1 |
| Filtration | 5 | 3 | 15 | 2 |
| Final Fill | 6 | 2 | 12 | 3 |

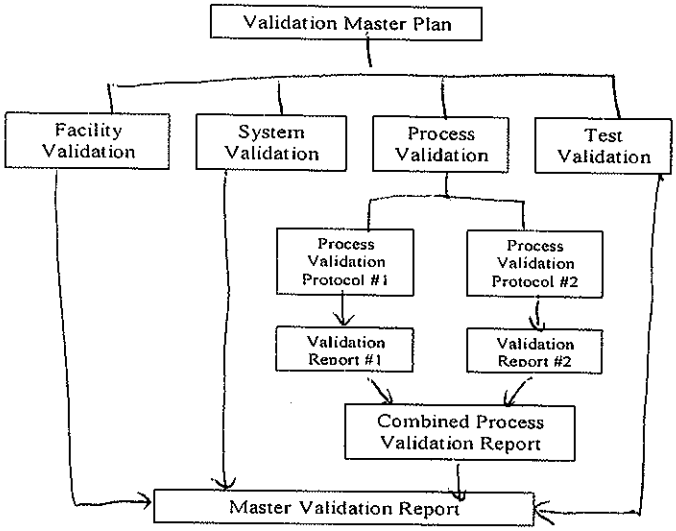


# Unbreakable Rule...

- The Scope of the Validation Project and
- The Criteria for Acceptance of the Validation Data
- Must be Set Before Validation Commences

Virus particle/ load.

Exhibit 8: Derivation of Validation Plan & Protocols






# Validation Protocol

- One document for each validation
- Contents - see Exhibit 8a
- Record-keeping rules must be followed
  - Direct, permanent ink entries
  - Legible, signed, dated and countersigned
  - Printout, etc. permanently attached
  - Corrections must not obscure original entry
  - Special provisions for computerized data, changes to follow audit trial

# Let's Get This Clear...

- Qualification is equipment-based
  - To make sure it is fit for the job
- Validation is process-based
  - To show that the process will yield the product reproducibly under a range of operating conditions that might be encountered in normal working and *under "worst case" conditions.*



# Pre-Validation Qualification of Equipment

- 4 Stages of Qualification:
  - Design, (DQ)
  - Installation, (IQ)
  - Operational (OQ) and
  - Performance (PQ)

# Design Qualification

- The functional and operational specifications of the equipment are laid down by the user, usually based upon manufacturer's specifications

  = Design INPUT
- DQ demonstrates that the equipment, as supplied, meets those specifications

  = Design OUTPUT



# Examples of Equipment

- Incubators – temperature controls
- Biosafety cabinets – Class I, II, or III and air flows
- Bioreactors – pH, DO, temp, mixing, controls, data logging
- Purification columns – pressure drops, run times, flowrates, retention times

## Installation Qualification

- Starts with documentation of DQ
- Checks that the equipment is complete, with all spares, manuals, etc. specified
- Documents that it is installed according to the manufacturer's instructions
- With correct environmental conditions, positioning, electrical, compressed air and other utility requirements



## Operational Qualification

- Starts with full documentation of IQ
- When the equipment is switched on - it works.
- Documents that the equipment operates according to the agreed specifications under normal conditions
- Achieves preset levels of performance (speed, temperature, etc.)

## Performance Qualification

- Follows documentation of OQ
- Is the first stage in actual process validation
- Going from PQ to Validation is a Continuous Process
- The actual manufacturing process is performed with the equipment and reproducibility is confirmed
- Exhaustive testing under a range of conditions will achieve validation.



## How to set up "Worst Cases"

- Ask the question:
- What happens to the yield, purity of the product, or the accuracy of the assay...
- When a factor is changed so that it moves away from its optimum value ?
- How far can it be moved before the result is unacceptable ?

# Some typical examples are:

- **The influence of buffer pH on the purity of an eluted biological from a chromatography column**
- **The result of over-packing an autoclave (steam sterilizer) with goods, so that steam penetration may be reduced.**
- **The effect of using a different analyst to perform a regular test for biopharmaceutical potency, such as an ELISA test. How do the results vary ? This intermediate precision test is a regular part of analytical validations.**
- **The effect of entering incorrect characters into a computer program designed to perform statistical analyses on assembled test data. What results will the program produce?**
- **The effect of adding another person (or a new, relatively untrained person) to the team performing the aseptic filling of a parenteral product which cannot be terminally sterilized. What happens to the air-borne bacterial and particle counts? And to the product?**



# General Validation Round-up

- Any questions or comments on the general concepts of validation ?
- On to consider some particular validation tasks
- Starting with Systems...

## System Validation

- For those systems whose operation is critical in maintaining separation (HVAC or purity (WFI supply) or process integrity (control, monitoring & alarms)
- Go through the 4 stages of Qualification
- Then Validate during Operation...

GMP of Biopharmaceuticals Dr. Steve Oh, NUS, 2003. Day 1 Slide 91

WFI
- water for injection

## W F I is the *"HEART"* of the System!

GMP of Biopharmaceuticals Dr. Steve Oh, NUS, 2003. Day 1 Slide 92

Eg: 10M kg water for 200 kg antibodies

# System Validation Example 1

- For a WFI system:
  - Examine engineering drawings for potential problems (DQ)
  - After IQ and OQ, develop operating and cleaning/sanitization parameters
  - Sampling procedure must be defined
  - SOP is followed and water quality checked frequently at each point of use (POU) - analyze results
  - Observe variations in quality over time



# WFI system

- Blueprint to show all equipment. From water feedpoints to POUs. Detailed drawings (e.g. not drawing water from tap vs. POU!)
- Monitoring equipment at checkpoints for pyrogens (e.g. check conductivity of WFI)
- Piping system – Flow rate > 5ft/s to prevent biofilm formation, deadlegs need periodic draining and flushing.
- Sampling at each purification step e.g ion exchange, filtration, distillation, UV continuously for 4 weeks.
- Validation over 12 months with daily sampling to test seasonal variations and demands on systems.

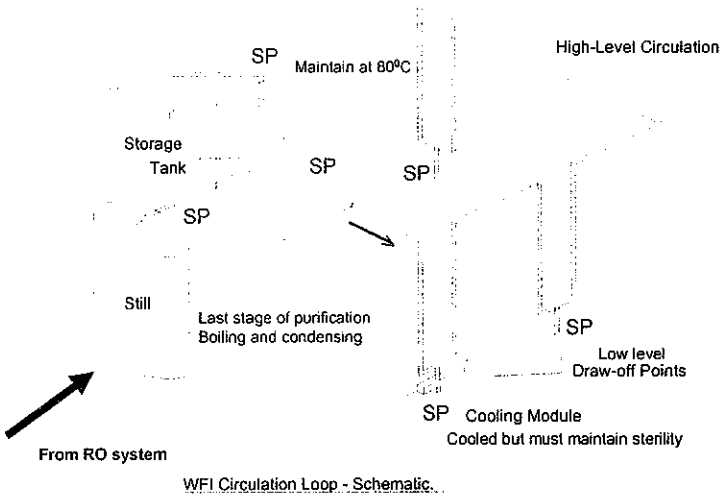
# Quality of WFI, Potable Water

| Product | USP Conductivity (at pH 7 and 25 ° C ) | EP Nitrates / Heavy Metals | USP & EP Total Organic Content (TOC) | (USP Action Limit ) Microbial Count | USP Endotoxin Content |
|---|---|---|---|---|---|
| PUB Water | 250 - 550 | < 0.1 ppm | NA | < 1 cfu / 100 ml | NA |
| Water for Injection | < 1.25 µS/cm | < 0.2 ppm < 0.1 ppm | < 500 µg / L | < 10 cfu / 100 ml | < 0.25 EU / ml |

[Source: Public Utilities Board http://www.pub.gov.sg/water.htm]



## Exhibit 9: Schematic of WFI System




WFI Circulation Loop - Schematic

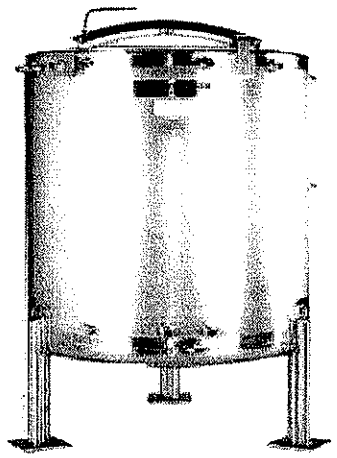
# Storage of WFI

**Storage tanks**

- **Capacity : 200 to 1000 Gallons**
- **Fitted with Ultraviolet light Sterilizer**
- **Recirculation rates : 2 turnovers/h**
- **$H_2O_2$ addition every 24 h to reduce microbial count to 2 cfu/100ml**

**Industrial Practice**

- **5000 gallon storage tank would require a 3.5 gpm capacity Ultraviolet Sterilizer Unit to manage a turnover rate of once/24 hr**





# System Validation Example 2

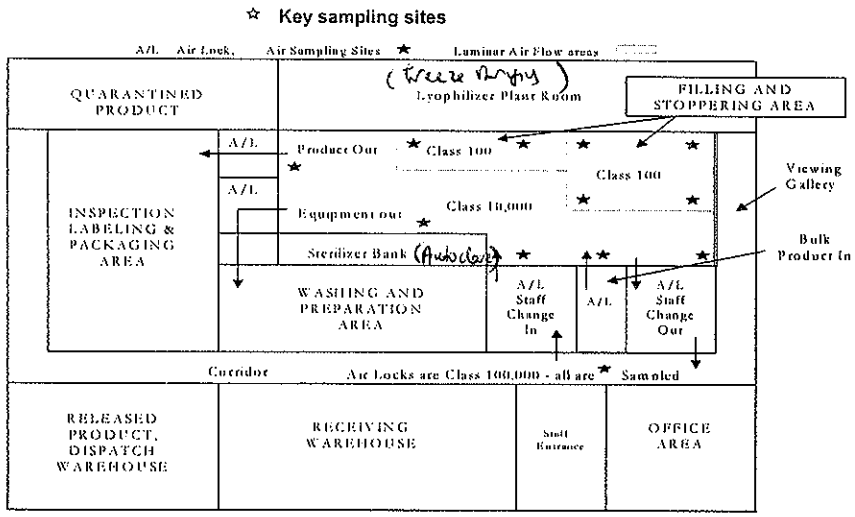
- For a Clean Room system:
  - DQ: Examine engineering drawings & specs
  - IQ and OQ to ensure correct flows & pressure differentials
  - Develop limits for particulate and microbial load under empty and working conditions
  - Define sampling procedures & take samples regularly before, during & after operations
  - Observe variations in quality over time
  - N.B major contaminants from workers!

# Clean Room System

- Design of Class 100, downward airflow must be laminar. Air flows in excess of 70 ft/min, filter setup covering entire area. Need a laminar flow cabinet or custom enclosure.
- Maintain positive pressure (between 0.05" to 0.15" water gauge) to surrounding areas.
- Air sampling with settle plates at sites where products is at risk. Background counts by doors, benches, airlocks. Define Alert and Action levels.
- Good records of pressure and air-flow measurements – continuous monitoring and alarms for failures recorded.



## Exhibit 10: Typical Finishing Plant



# Day 1 Q & A Session

- QA/GMP Concepts
- Regulations
- Organizational Responsibilities
- SOPs
- Validation Concepts
- Equipment Qualification
- System Validation



# Good Night

- Thank you for your attention
- Have a good evening
- See you in the morning...



**Exhibit 1: The Stages in Drug Development**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Product Concept* | Basic Research | | | | | | |
| *Development* | Strategic Plan | Product/Process Development | | | | | |
| *Lab/Animal Studies* | Short-term Efficacy | Full-scale Efficacy & Toxicity | | | | | |
| *QA/Regulatory Work* | | GLP Audits | IND Preparation & Approval | ***Validation of Processes and Test Methods*** | | NDA Preparation | |
| *Clinical Studies Under GCP* | | | | Phase I | Phase II | Phase III | |
| *Manufacturing Scale* | Bench-top Process | Pilot Plant | GMP Pilot Plant Manufacture for Clinical Trials | | | Full-scale GMP Manufacturing Plant | |
| *Project Time Frames* | 1 - 3 years | 0.5 - 2 years | | 3 - 5 years | | | |
| *Development Cost Estimates* | $0.5 - 5 million | $5 - 50 million | | $10 - 100 million | | | |

**Time to Approval = 1-3 years from NDA submission.**

# Exhibit 2: Guide for SOP Form for a Manufacturing Process

## *Company Name* Laboratories Inc.

### Standard Operating Procedure: Master Form

SOP Ref.# _____ Date Originated _____ By: _____

Checked By: _____ Date: _____ Effective: _____

Revised By: _____ Date: _____ Effective: _____

Approved By: _____

Title:

Purpose:

References:

Responsibilities:

Materials:

- Previous Process Stage
- Chemicals
- Equipment

Procedure:

- Safety Precautions
- Special Handling
- Process Stages - Checks
- Samples to be Taken
- Records to be Kept
- Labeling to be Applied

Next Process Stage:

- Storage
- Transport

Counter-signatures required

# Exhibit 3: SOP Form for a QC Test

## *Company Name* Laboratories Inc.

### Standard Operating Procedure: Master Form

SOP Ref.# _____ Date Originated _____ By: _____

Checked By: _____ Date: _____ Effective: _____

Revised By: _____ Date: _____ Effective: _____

Approved By: _____

Title:

Purpose:

References:

Responsibilities:

Materials:

- Sample ID
- Chemicals/reagents/standard preparations
- Equipment

Procedure:

- Safety Precautions
- Special Handling
- Test Description
- Data to be Recorded
- Records to be Kept
- Storage of Reserve Samples

Result Reporting:

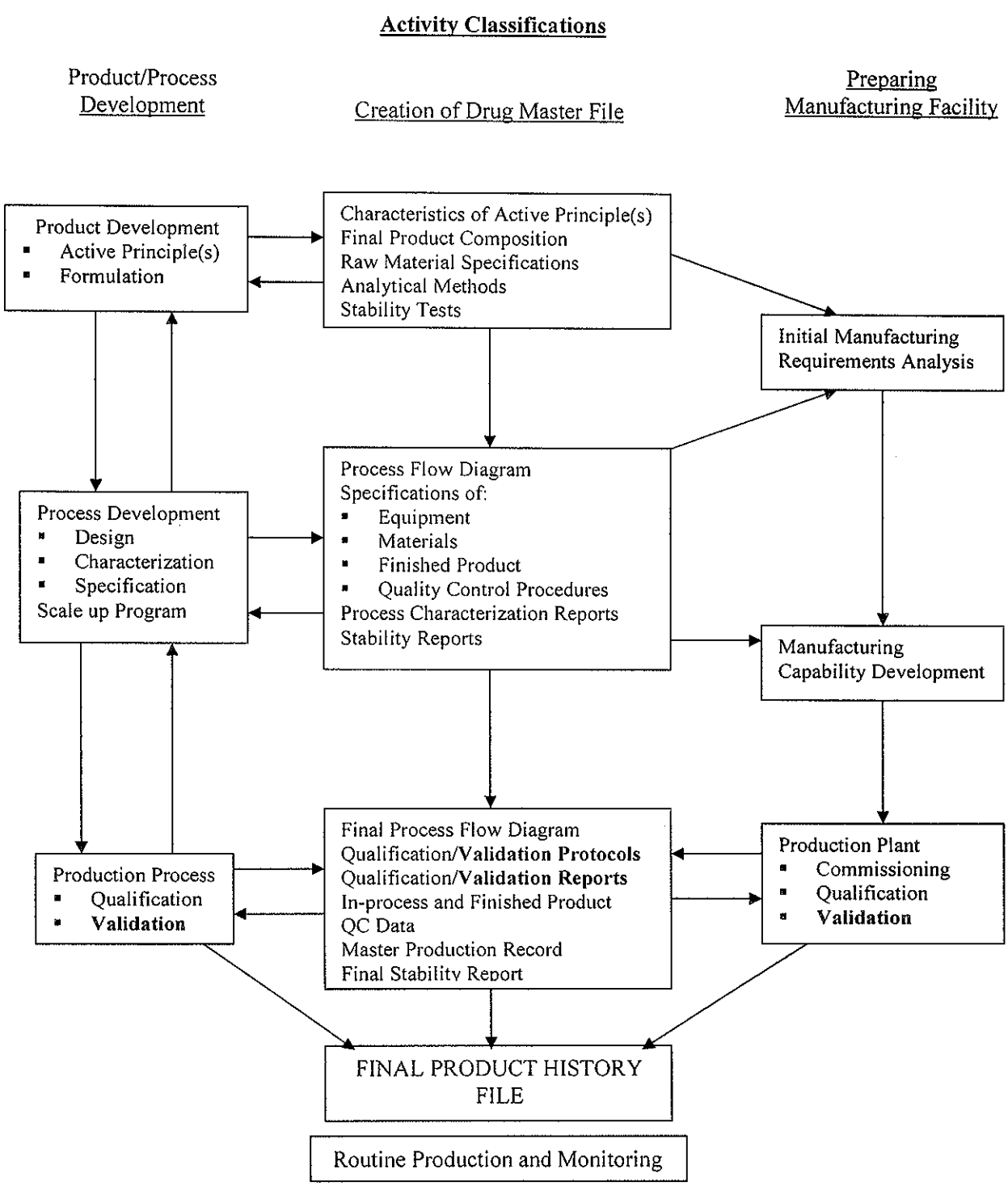
Test Conclusion:

Counter-signatures required:

## Exhibit 4: Suggested Layout for a Master SOP File

| SOP Number | Dept | Original Date | Written By | Subject | Date Mod. | By | Code | Date Mod. | By | Code |
|---|---|---|---|---|---|---|---|---|---|---|
| M99/1-0 | Man | 6/5/99 | DFC | Maintenance of Personnel Files | | | | | | |
| M/99/2-0 | Man | 7/1/99 | DFC | Qualifications for Registered Expert Staff | 1/1/00 | DFC | /2-1 | | | |
| | | | | | | | | | | |
| E99/1-0 | EQ | 5/16/99 | REG | Standardization of pH Meter 1224 | | | | | | |
| | | | | | | | | | | |
| Q99/1-0 | QA | 6/15/99 | MNR | Writing, Approval, Modification and Maintenance of SOPs | 1/15/00<br>5/15/00 | MNR<br>MNR | /1-1<br>/1-2 | 9/15/00 | MNR | /1-3 |
| Q/99/2-0 | QA | 7/1/99 | MNR | Internal Audits and Reports | | | | | | |
| | | | | | | | | | | |
| F99/1-0 | FM | 7/22/99 | NBG | Facility Cleaning Schedules | | | | | | |
| | | | | | | | | | | |
| P99/23-0 | Prod. | 8/1/99 | VRS | Compounding of Product XXX | | | | | | |
| | | | | | | | | | | |
| L99/1-0 | QC | 4/19/99 | AZK | Molecular Weight Determination SDFS-PAGE | 7/1/99 | AZK | /1-1 | | | |
| L99/2-0 | QC | 4/23/99 | AZK | Analysis of Product XXX Stage 2 by Chromatography | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

# Exhibit 5: Process Validation and the Product Development Cycle



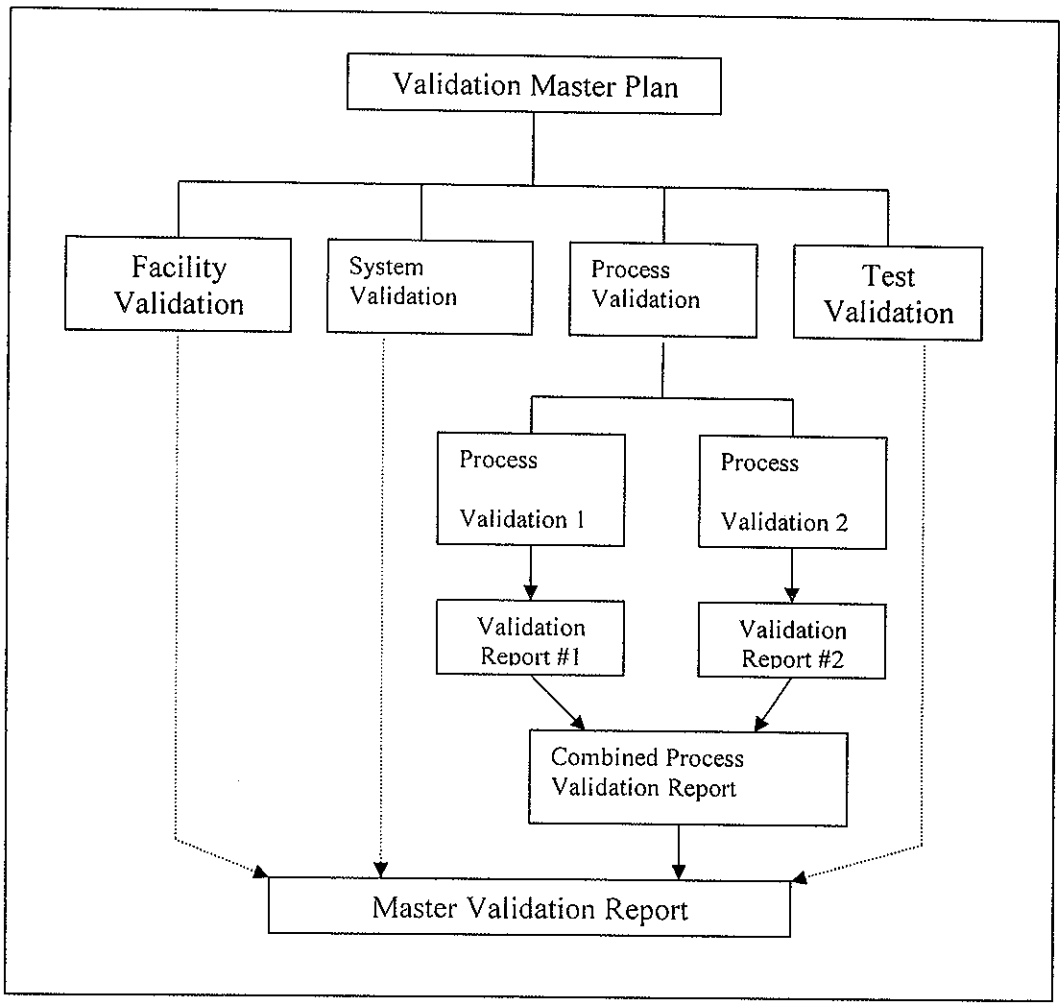
## Exhibit 6: VMP Contents:

- *Introduction*: Covering the basic facts such as location, timing and the definition of the overall scope of the project.
- *Overall Project Description*: This section provides a description of the entire project. If it involves construction, the details of materials, etc. are included here. If it involves systems and processes, the layout of the plant and the interrelationship between elements is included. Product and personnel movements through the plant should also be detailed.
- *Scope:* This section of the VMP defines in general the parts of the facility systems, processes and tests which are to be validated, with the justification for their inclusion in the plan on the basis of the risk analysis or other criteria. Just as importantly, the "Scope" section describes those elements which do not need validation. These latter will be excluded from the validation plan by virtue of the low risk they present to the product, or the fact that they have already been validated and do not need revalidation at this time.
- *Acceptance Criteria.* General criteria to be applied across the whole plan, such as the requirements for commissioning and/or qualification of plant, must be part of the VMP. Quantitative criteria for validation protocols for specific equipment or systems may be spelled out in the VMP. This is not essential, but may be advisable because it places the definition of important criteria earlier in the planning process.
- *Specific issues*: Where particular sections of the overall plan will require greater emphasis and perhaps demand more resources. Validation of computerized systems is a case in point.
- *Project Schedule and Resource Requirements.* A Validation Plan of any magnitude will be best scheduled and controlled by the use of project management techniques and probably by creating the project plan on the computer, using software such as Microsoft "Project".
- *Plan Documentation.* This section should list the complete documentation of the project and describe the format that all plan documents will adopt, in order to ensure conformity across the project and avoid missing reports, etc.
- *Standard Operating Procedures.* This applies to the operation of any system, equipment, process or analytical test which forms part of the plan.

## Exhibit 7: Priority Ranking Method

| Process Stage | Stage Order | Stage Complexity | Score | Rank |
|---|---|---|---|---|
| Seed Fermentation | 1 | 2 | 2 | **6** |
| Production Fermentation | 2 | 4 | 8 | **5** |
| Harvest | 3 | 3 | 9 | **4** |
| Chromatography | 4 | 6 | 24 | **1** |
| Filtration | 5 | 3 | 15 | **2** |
| Final Fill | 6 | 2 | 12 | **3** |

## Exhibit 8: Derivation of the Validation Master Plan and Protocols



## Exhibit 8a: Validation Protocol Contents List

1. **Title**: (e.g. "Validation of Gel Chromatographic Process, Step XX of Product YY")
2. **Purpose or Introduction**: In this section, any particular concerns about the process to be validated can be addressed as an introduction to the particular validation tests which will be used.
3. **References**: This is an optional section which can provide the sources of additional information, such as published papers, SOPs, Guidelines and Regulations.
4. **Scope**: Here are described the activities to which the validation does and does not apply. This can be used to place this protocol in perspective with others.
5. **Responsibility**: The person or department responsible for the performance of the protocol. Often, several departments can be involved. This section should spell out clearly what activities each is responsible for. Wherever possible, team members should be named, with their responsibilities listed beside their names.
6. **Protocol**: This will have sections for:
   - 6.1 Preliminary operations (include instrument calibration)
   - 6.2 Installation qualification
   - 6.3 Operational qualification
   - 6.4 Performance qualification
   - 6.5 Worst case testing
   - 6.6 Data recording
   - 6.7 Data analysis
   - 6.8 Deviation reports
7. **Acceptance Criteria:** The validation is only considered complete when acceptance criteria have been met. These should be stated as a range of values or as minimum and maximum acceptable values.
8. **Documentation:** This section should state how events cited in the protocol are to be documented, reviewed and approved. It may also contain references to data collection forms and certificates of e.g. calibration.

## Exhibit 9: WFI System

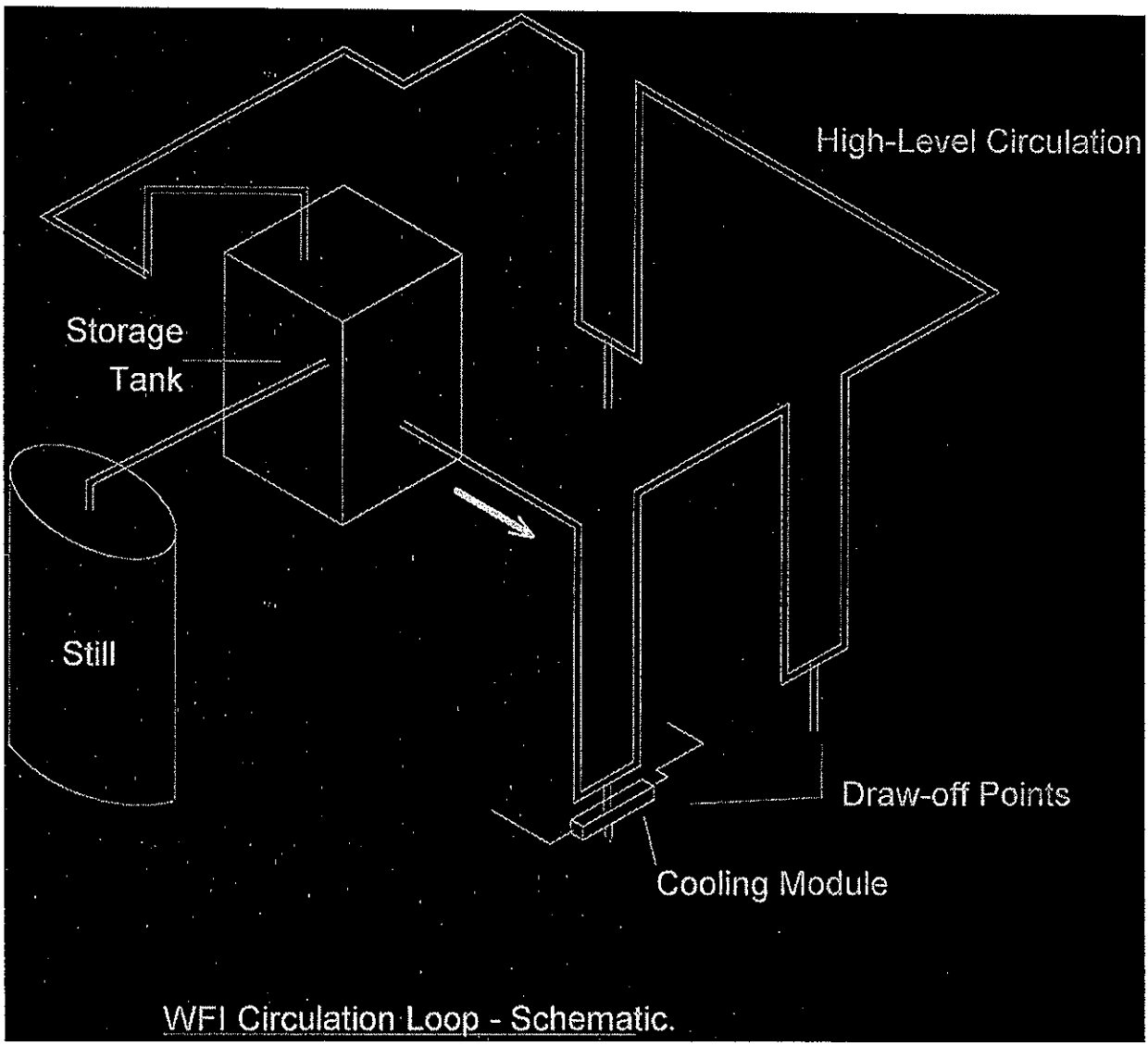
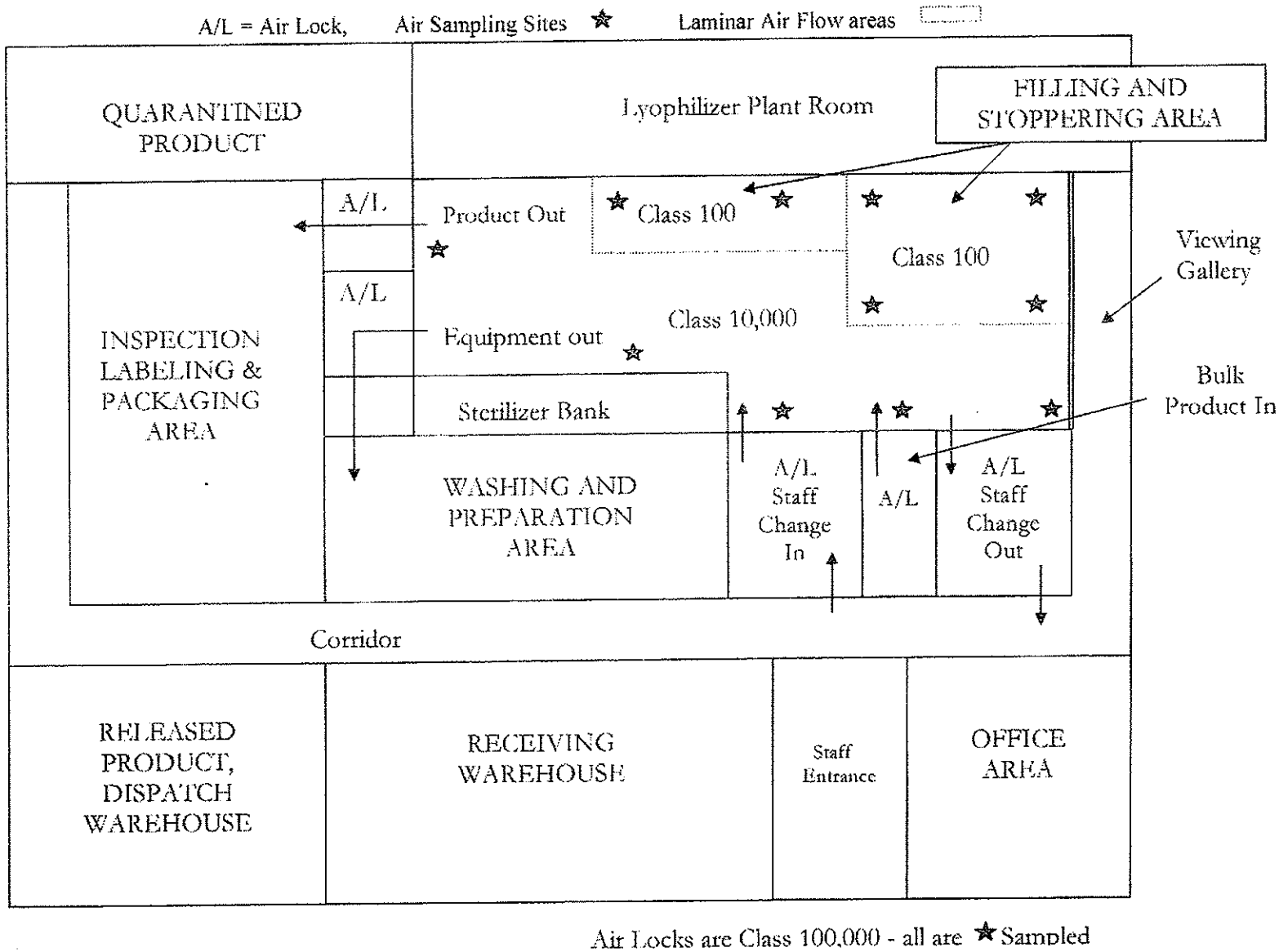


**Exhibit 10: Typical Finishing & Packaging Plant, with CleanRoom Set-up**



# Good Manufacturing Practice

Regulatory Compliance
in
Biopharmaceutical Manufacturing

Day 2

Instructor: Dr. Steve Oh Kah Weng



# Day 2 Topics

- Any Overnight Questions ?
- Validation of
  - Cleaning & Steaming Processes
  - Manufacturing Processes
  - Computerized Systems
- GMP-Compliant Design & Operation
  - Facilities, Space and material flows
  - Equipment, Housekeeping, etc.
- Quality Control
  - Warehousing, Raw materials, Packaging
  - Production and Process controls
  - Packaging, labeling, holding & distribution

## Yesterday's Topics...

- Questions ?
- Comments ?



## Validation involving Process Equipment & Pipework

- Process Equipment and Piped Systems must be Qualified, then
- The procedures involved in *running them* must be Validated, i.e.,
- Clean-in-place systems
- Sterilize-in-place systems

# Introduction

The FDA's Guidelines for the Inspection of the Validation of Cleaning Processes states the following expectations:

- Firms should have written general procedures (i.e. SOPs) on how cleaning processes will be validated. The general validation procedures should address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.
- Firms should prepare specific written validation protocols which should address sampling procedures, and analytical methods to be used, including the sensitivity of those methods.
- A final validation report should be prepared which is approved by management and which states whether or not the cleaning process is valid. The data should support a conclusion that residues have been reduced to an "acceptable level."



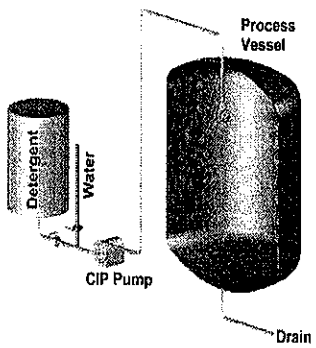
# Introduction

## What is CIP (clean-in-place)?

- permanently installed systems

- deliver, heat and recirculate the flush, wash and rinse solutions

- for controlled periods of time, at the desired temperatures and concentration.



## Introduction

- Until a CIP is validated, the plant should not be used for a multiplicity of products.
- FDA states that "Equipment must be 'visibly' clean between batches of same product.
- But this may be a short sighted, as carry-over of contaminants may affect downstream processes.



## Qualification of Fixed Systems

- DQ: Ensure that the layout and specification of all components is as specified,
  - Including CIP/SIP components
  - All wetted surfaces are non-contaminating
  - The design minimizes the chance of dirt build-up
  - Means of sampling inaccessible areas are provided

# What are we cleaning ?

- Mineral deposits
- Proteins, lipids left on surface
- Fermentation residues
- Types of detergents: Acidic / Alkaline
- Aim: eliminate cross contamination and assure reliably clean equipment.

pH probe cleaned with enzymatic cleaner

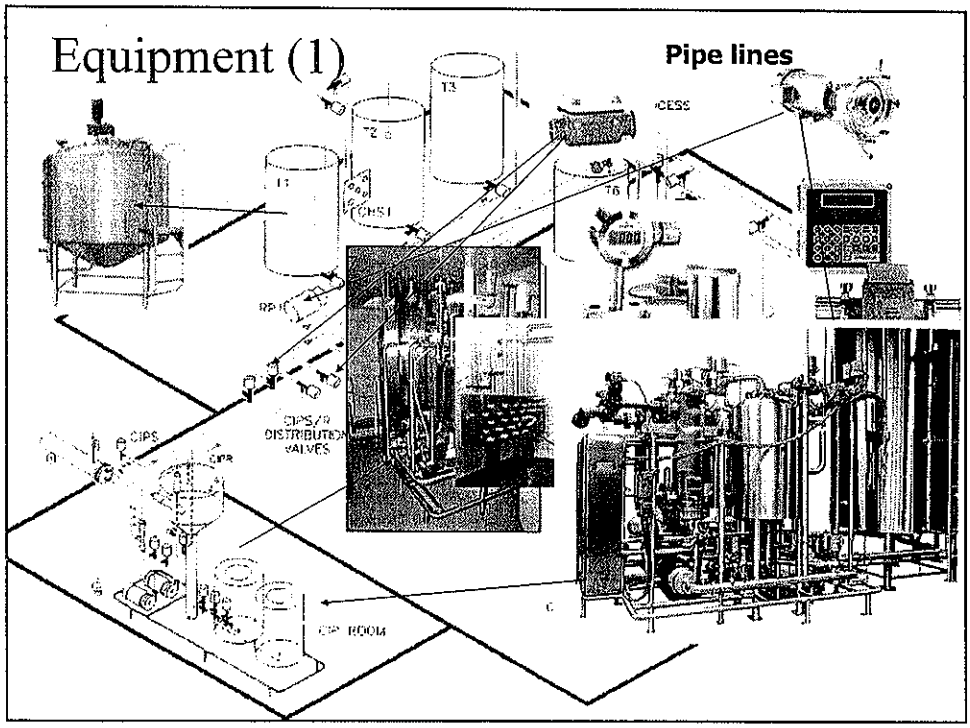







# Equipment to be CIPed/SIPed

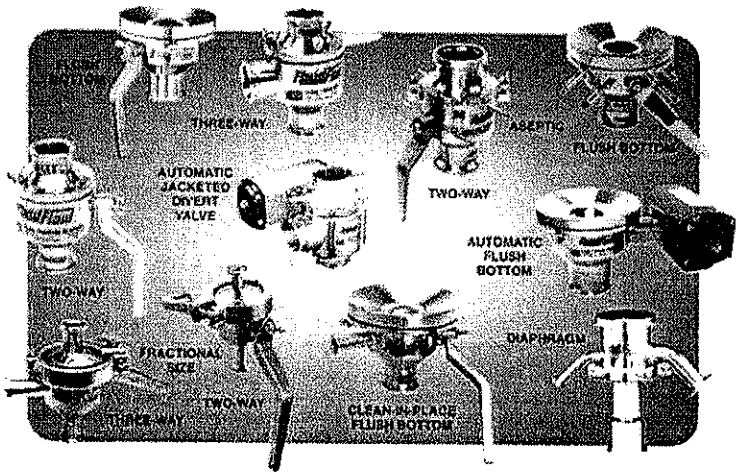
- Vessels, tanks, and containers
- Mixing and preparation tanks
- Containers
- Piping systems
- In-line machinery
- Other process equipment




## Qualification of Fixed Systems (2)

- IQ: Ensure that welding, other types of connection, pipe-run slopes, drains, etc. are according to design
- Minimize risk of stagnant rinse or condensate water being left
- OQ: Check for leaks, correct flows, smooth operation of valves, control systems (including computerized controls)

# Various types of valves



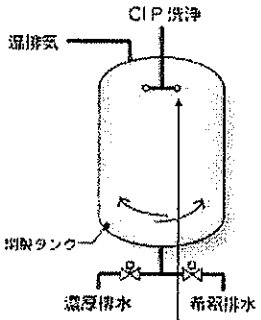



# CIP Validation

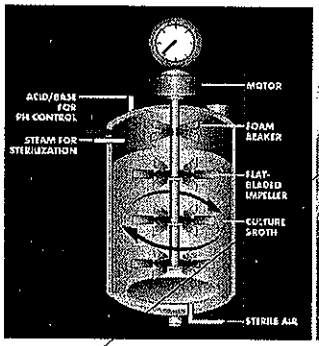
- Planning the validation program
- Define the cleaning load
  - Equipment single or multi-use ?
  - Make an inventory of expected contaminants
    - Solubility in water - other solvents ?
    - Liable to cake ? Dried on ? (e.g., heat-inactivated first ?)
  - Define what cleaning solutions can be used
- Create a cleaning process (or several)

# Equipment (2)

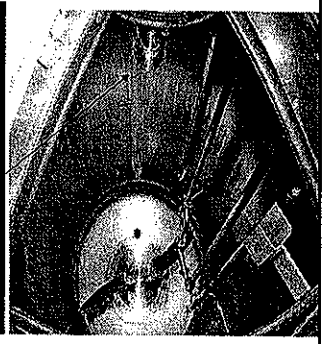
CIPable Tank



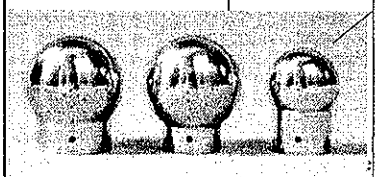

Bioreactor



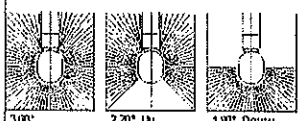

Spray Ball in fermentor

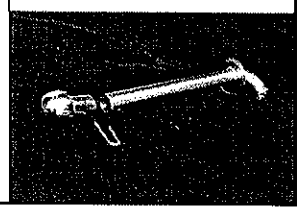


Spray Balls



Spray Patterns



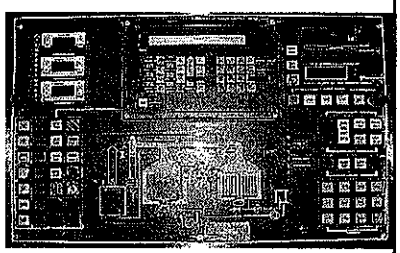



# CIP process

- Automated process !
- Controller typically a PLC
- Time based or Volume based
- Variables include:
  - Time
  - Volume
  - Flow
  - Temperature
  - Pressure
  - Conductivity



Control panel



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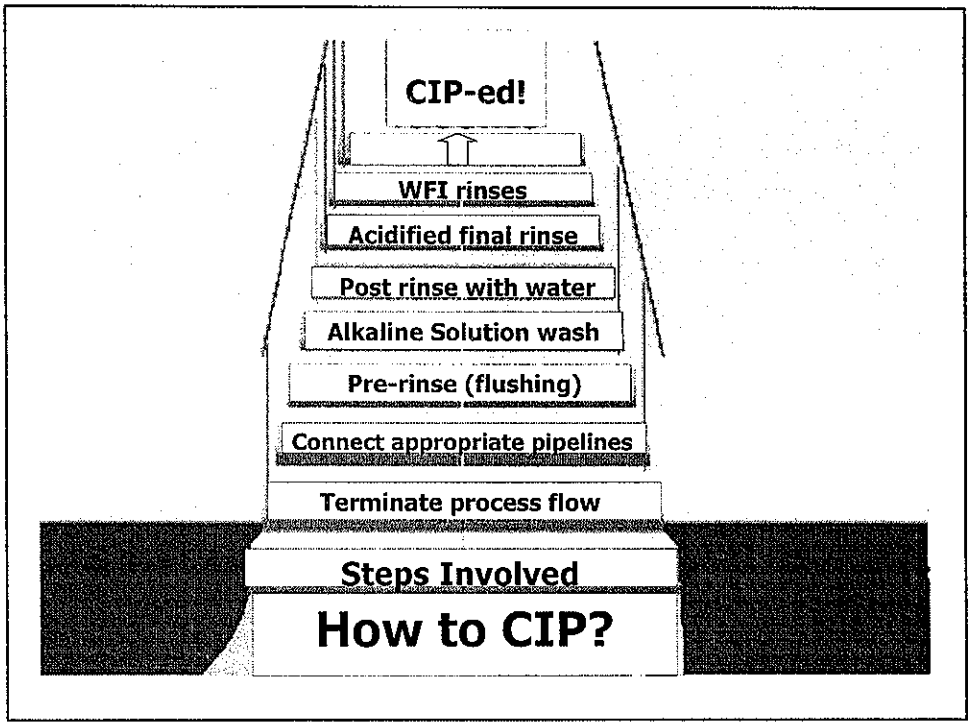



## Cleaning Process Factors

- Nature of the equipment
- Temperature of the cleaning solutions
- Nature of final rinse (WFI ?)
- How to determine adequate cleaning ?
  - By inspection ?
  - Chemical or biological analysis, both ?
  - Of rinse solution, swab eluent ?
- Limits of detection of analytical methods

## CIP Validation (2)

- Defined program is installed on CIP equipment...
- OQ: the program is run to determine that the equipment produces the required cleaning conditions (concentration, temperature, volume, pressure, cycle times)
- PQ starts with runs on normally-used equipment and testing of samples, according to SOP



## CIP Validation (3)

- Points to consider on Sampling & Testing
  - Ensure all problem areas are sampled, e.g. ancillary valves must be disassembled
  - Sampling should be responsibility of QA member to avoid bias of sampling
  - Specify size of sampling area
  - Swabs are better than rinse "It is what's left in that counts, not what's rinsed out"
  - The sensitivity & specificity of the test method must ensure that dangerous levels of any contaminant can be detected, e.g. endotoxins
  - Remember to test for cleaning agents as well
  - All analytical methods must be validated

# Sensitivity of Analytical Methods

- Current analytical methods are very sensitive
- Limits set on each identified contaminant should be realistic
- Based upon sound scientific principles
- Taking into account the potential toxicity of the contaminant or its effect on later downstream processing.
- Limits may be calculated based upon the minimum toxic dose plus a safety factor
- Or the size of the batch to be processed
- Or the lowest quantity known to produce a clinical effect
- Or the lowest level than can be achieved by cleaning
- All related to a fixed surface area of the equipment being cleaned.
- Special attention should be paid to "pockets".



# Final Validation of Cleaning Procedures

- Must test the efficacy of the set procedure under any abnormal conditions which might be met in practice, e.g.:
  - Low detergent concentration
  - Low temperature
  - Low pressure in spray heads
  - Shorter treatment times.
  - High residual deposition

## A Warning on Cleaning

- Recleaning and retesting equipment that fails analytical tests after the first cycle
- IS NOT VALIDATION
- You cannot test into compliance - if the first test fails, the cleaning method must be redesigned.
- Failure during routine operations must be investigated and, if necessary, the procedure changed and re-validated.



## Sterilize-in-Place Systems

- For static sterile plant, e.g. bioreactors
- Equipment connected by rigid stainless-steel or flexible Teflon-lined piping
- Are usually built on-site (unless skidded)
  - Employing steam pressure up to 20 psi and corresponding sterilizing temperatures in the 121° to 125°C range.
  - Need a clean-steam generator
  - Must ensure that all air can be removed (Venting to prevent pressure build-up)
  - Must ensure no "dead-ends" or condensate build-up
  - Air introduced on cooling must be through a sterilizing filter that is sterilized in process

## SIP System Qualification

- DQ/IQ is done on the as-built system
- Gauges, thermometers, etc. are calibrated
- System controller is validated
- OQ confirms that all required operating conditions are met, sometimes using multi-point temperature recorders

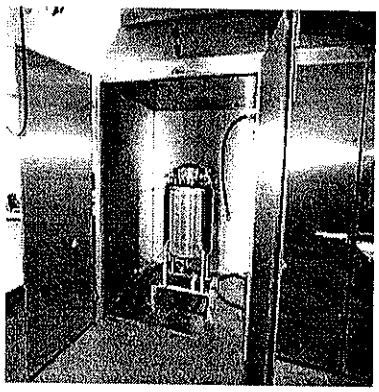


## SIP System Validation

- Program is set and SOP written
- Chemical & biological indicators are placed in problem areas
- SIP is performed under operating conditions
- Worst case testing may involve low steam pressure, shortened cycle time
- Runs with culture medium are the final test

# SIP process

- Aim: Inactivate microbial contaminants
- Sterilizing agent:
  - Clean Steam from dedicated generator
  - Steam pass through a microfilter
  - 20 psi
  - 121 to 125 °C
- Steps:
  - Pressure test
  - Vacuum & repeat
  - Steam sterilization for specified duration
  - Drying/Cooling
  - Pressurization



A SIP unit



# SIP process

- Final evidence of the validity of the sterilization process is achieved by running culture medium through the sterilized set up in imitation of the manufacturing processes
- Then incubating a large number of media samples, or the entire batch for 7 days, to ensure no bacterial growth occurs.
- Regular manufacture of product batches which pass sterility and endotoxin tests after processing in the SIP plant will confirm PQ of the system.
- If sections of the plant are rebuilt or changed, the entire SIP set up must be revalidated.
- Given the critical nature of the SIP procedure, schedule revalidation of the installation at regular intervals.

# Process Validation

- General Principles, Types of Validation
- Fermentors & Bioreactors Control
- Chromatographic Separations
- Transverse-flow Filtration
- Viral Removal
- Sterilizing Filtration
- Aseptic Filling



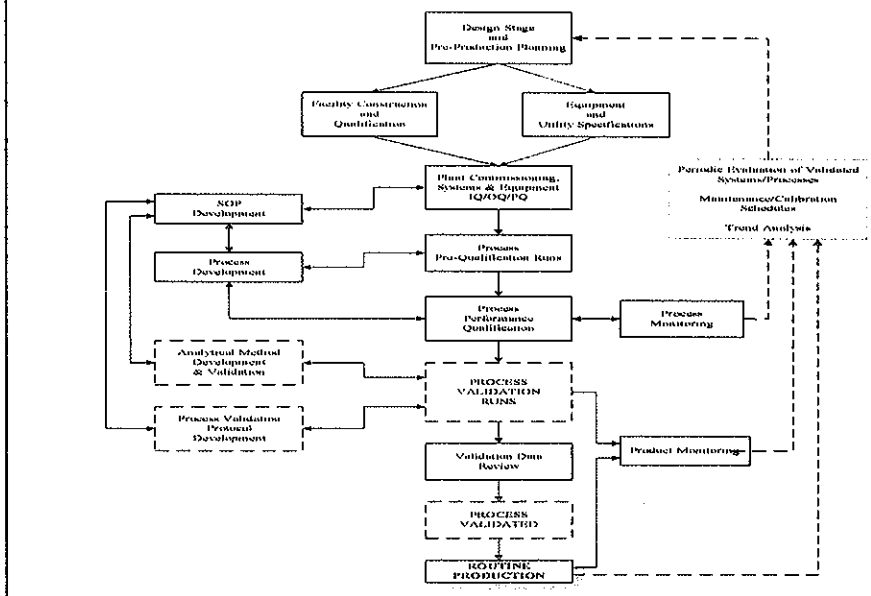
# Types of Validation

- These usually apply to the manufacturing process...
- Prospective Validation (during development stages perform risk analysis)
- Concurrent Validation (during production, on at least 3 consecutive batches)
- Retrospective validation (e.g. for the last 2 years or 50 runs)
- Re-Validation (when processes are changed)

## General Principles of Process Validation

- The objective is to establish confidence that the process delivers product, meeting specifications regularly & reliably
- Prospective Validation is preferred
- The VMP should define what processes are to be validated, based upon risk assessment
- The Validation Protocol should be complete
- Observe the Validation Life Cycle (Ex. 11)





## Principles of Validation (2)

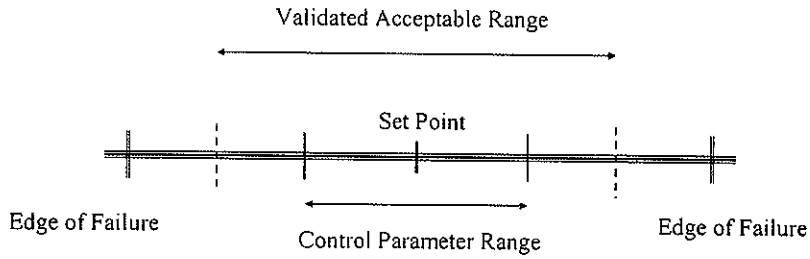
- The results of scaled-down experiments must be able to be applied to full-scale
- Process control parameters should be fixed before validation
- KEY: Ensure that the process does not operate too close to the failure limits of any critical parameter (Exhibit 12)



## Essential Process Validation Steps

- Define the process parameters
- Set the ranges for each parameter within which the process operates satisfactorily
- Decide which must be "tested to failure"
- Perform tests within and outside the set ranges and observe results
- Define operating parameter ranges within those that have been proven acceptable

## Exhibit 12: The Terminology of Process Validation




**Start from inside out,**
**e.g. pH 7.1 set point; control 7-7.2;**
**Alert 6.9 – 7.3; Failure 6.5 to 7.5**



# Pause for Thought...

- Any Questions ?
- Any Comments ?
- Coffee ?



## Process Validation Examples

- Fermentor/Bioreactor Control
- Chromatographic Separations
- Viral Clearance Processes



## Bioreactor/Fermentor Control

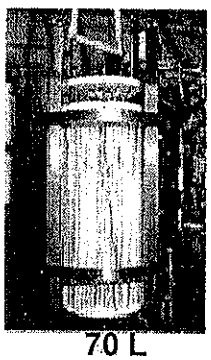
- Involves the validation of the system which controls:
  - CIP/SIP (if done)
  - Run parameters, such as
    - pH
    - Oxygen/$CO_2$ concentration
    - Medium feed (supplements) or perfusion
    - Cell density measurements

# Bioreactor Validation Steps

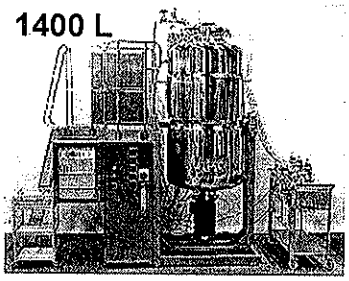
- DQ/IQ usually done by supplier with user
- OQ done during original run-up and perhaps media sterilization runs
- Then, determine the effect of critical parameters on yield and set the ranges
- PQ involves setting run parameters and recording how well the system maintains set values - validation is by product quality
- Seek assistance of engineering staff on controls panels, instruments, etc.



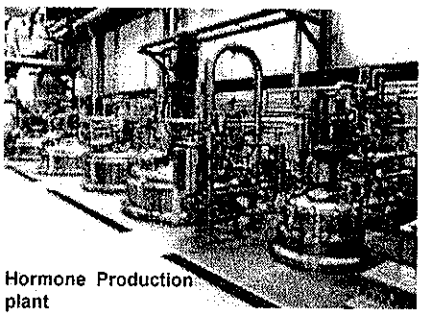
# Bioreactors



70 L



1400 L



Hormone Production plant

Exhibit 13: Control of a Cell Culture Bioreactor

| Process Control Parameters | Process Response Variable |
|---|---|
| Temperature<br>pH<br>Agitation<br>Time<br>Dissolved Oxygen<br>Perfusion rate | Cell Viability<br>Cell Number<br>Generations<br>Product Titer, Concentration<br>Product characteristics<br>Product Stability<br>Impurity Levels. |



# Bioreactors

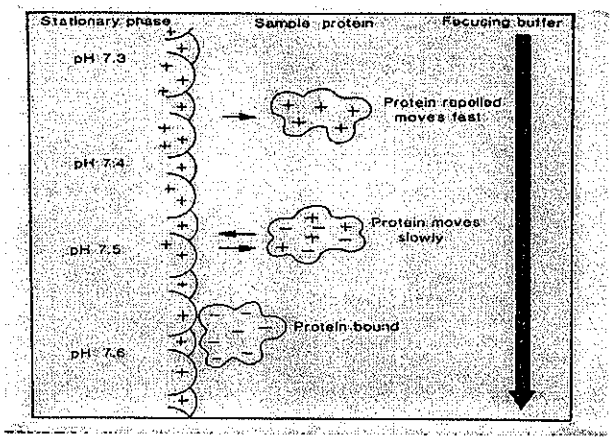
- The probes built into the system, for temperature, pH, gas concentration, etc. measurement, should be calibrated.
- Use calibration standards which can be referred back to national standards.
- The system is then set to provide the desired fermentation cycle and the run is started.
- Continuous records should be taken of all controlled parameters.
- On-line monitoring or the concurrent testing of off-line samples must be performed to confirm the probes readings.

# Bioreactors

- The ultimate aim of the fermentor/bioreactor validation process is determined by product characteristics.
- Effect of varying fermentation conditions upon the cell or product yield must be known.
- Exhibit 13 relates certain process control parameters to process response variables.
- Variables must be controlled so that the product of the bioreactor can be properly processed downstream.
- Validation of this system will document that it can keep the process control parameters within preset limits, satisfy the specifications set for the process response variables and supply the quality and quantity of product.
- It is useful to maintain a validation protocol check list.

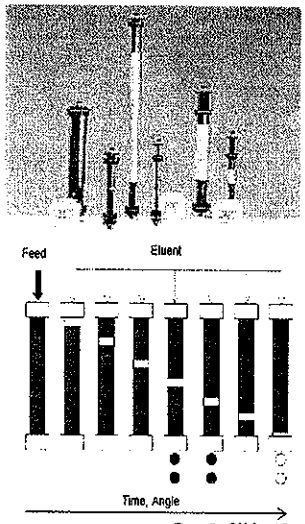


# Principle of operation Chromatography



## Types of Chromatographic Separations

- Ion Exchange, e.g. anion and cation
- Affinity, e.g. Protein A for anibody purification
- Hydrophobic Interaction
- Gel permeation, e.g. size exclusion






## Chromatographic Separations

- Chromatographic processes to concentrate and purify biopharmaceutical products the most common form of bioprocessing.
- Special attention is being paid by the regulatory authorities to the way in which the manufacturer defines and validates each chromatographic step.
- The chromatographic process must be shown to be capable of coping with such variables without jeopardizing the quality of the down-stream product.

## Chromatographic Separations

- Definition of medium and column operation
- SOPs to cover:
  - Column packing & equilibration
  - Sample loading, with load limits
  - Pre-elution wash (if done)
  - Elution of target protein
  - Washing & sanitization
  - Storage conditions, if needed



## Column IQ

- Document the following:
  - Equipment specifications, drawings, manuals
  - Correct utilities & connections
  - Instrumentation set-up, qualification, calibration
  - NB: validated computerized systems ?
  - Medium specification, bed dimensions, volume, maximum flow rate

# Column OQ

- Document the following:
  - Confirm assembly and absence of leaks
  - Confirm correct operation of all valves, monitors, alarms, recorders, data handling
  - Confirm correct packing (measure HETP)
  - Specification for equilibration
    - Buffer and number of column volumes
    - Means of demonstrating correct equilibration
  - Acceptance criteria for medium (specs.)



# Good vs. bad resolution

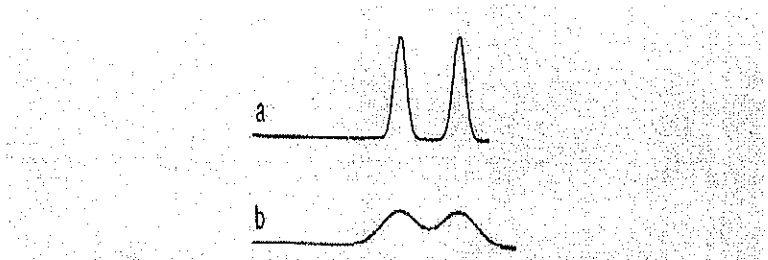



FIGURE 2-11. (a) A chromatogram showing two resolved peaks. (b) Same retention volumes as in a, but wider peaks.

# Column PQ

- Documents results of tests for:
  - Purity and recovery of product
  - Product biological activity, if appropriate
  - Effect of variable feed loads on the above
  - Effect of worst case conditions, such as buffers at the edge of acceptable range of pH, ionic strength
  - Identity and removal of process additives, such as enzymes



# Column PQ (2)

- Nature of leached materials, e.g. Protein A
- Effectiveness of cleaning and sanitization program
- Determine the column life
- NB - if the process step is also used for viral clearance, spiking studies are done on scaled-down columns (see later)
- Validation is finalized by three to five full-scale production runs, all yielding acceptable product - but trending must be done

# Column PQ (3)

- Tests for purity and recovery of the product, including identifying major and minor contaminants, such as host cell proteins, growth medium serum components and endotoxins and setting limits for these
- Creating "worst case" conditions for process, v/v load, buffers, etc.
- Identifying and quantifying the removal of process additives, detergents, enzymes.
- Determining the nature of material that may be leached out of the medium. Limits must be set for these leachates.
- Confirming the effectiveness of the cleaning and sanitization program, especially for the removal of nucleic acids and proteins, bioburden reduction and the absence of contamination of the succeeding run.

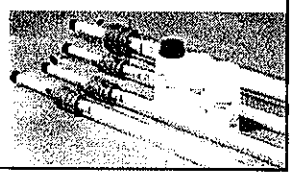


# Column PQ (4)

- Worst-case scenarios : deliberately contaminating small-scale representative columns , omitting the regeneration step after elution of the product , the use of sanitizing solutions at the end of their shelf life, as well as reduced exposure times.
- Microbial counts and endotoxin tests are used to determine efficacy. The sanitization process should produce at least a 90% (1 log) reduction in bacterial colony count.
- Small-scale column "tested to destruction" to determine the "life" of the medium in use, in terms of the number of use/cleaning/ sanitization cycles that can be performed before the medium shows signs of deterioration in structure or performance.

# CIP of Chromatographic Columns

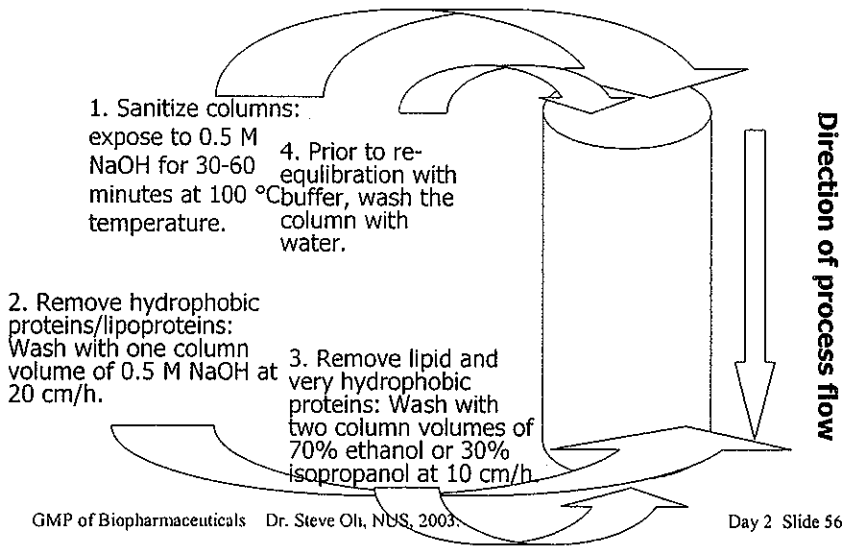
- Chemical stability of the media is essential
- CIP helps to ensure a longer column life and good process economy. Repeated separation cycles ⇒ build-up of contaminants. Specific CIP protocols developed as part of the routine separation process.
- Sanitization (SIP) ⇒ the use of chemical agents to inactivate microbial contaminants in the form of vegetative cells, maintain high level of process hygiene and economy.



Reference: Amersham Biosciences
www.amersham.com



# SIP of Chromatographic Columns



## Concerns for Viral Safety

### (i) Viral Contamination of Cell Cultures

| CONCERN | HISTORY | FUTURE |
|---|---|---|
| Transmission of infectious virus from biopharmaceuticals produced by continuous cell cultures to humans | No known incidences of human infection | Potential exists whenever animal-derived material is used in production |

**Some Undesirable Characteristics of Viruses**

- Can be hard to detect without amplication
- Small in size → removal by filtration can be difficult
- Difficult to inactivate
- Potentially pathogenic

*** Regulatory authorities must be notified in event of contamination



## Concerns for Viral Safety

### (ii) Viral Contamination of Cell Cultures

| Potential Sources of Viral Contamination | |
|---|---|
| ■ MCB/WCB<br>---virus infection<br>---endogenous retrovirus | ■ Introduction of adventitious viruses during production |
| ■ Route of Viral Introduction<br>• Derivation of cell lines from infected animals | ■ Route of Viral Introduction<br>• Use of contaminated reagent (eg., MAb affinity column) |
| ■ Common Routes of Viral Introduction<br>• Use of virus to establish cell line (eg., viral promoters for recombinant gene expression)<br>• Use of contaminated biological reagents (eg., animal serum components)<br>• Contamination during cell and medium handing | |

## Concerns for Viral Safety

## (ii) Viral Contamination of Cell Cultures

---instances reported in 1996

| Virus Detected | Viral Structure | Material Tested/ Product | Possible Source |
|---|---|---|---|
| **Minute Virus of Mice (MVM)** |  | **CHO Unprocessed Bulk (rDNA)** | **Cell Culture Medium** |
| **Epizootic Haemorrhagic Fever Virus** |  | **CHO Unprocessed Bulk (rDNA product)** | **FBS (fetal bovine serum) suspected** |
| **Human Rhinovirus** |  | **BHK Unprocessed Bulk (rDNA product)** | **Unknown** |



## Multi-tiered Approach to Viral Safety

### (i) Limitations of Viral Testing

(1) No single approach can establish product safety

(2) Detection of viruses at low concentrations
---probabilistic event → affected by sample size (statistical effects)

(3) Direct testing methodologies

(a) overly-specific → unable to detect variants of known viruses
(eg., initial hepatitis C screening kits)

(b) rely on identifying expected, known viruses
→ theoretically unable to detect unknown/unsuspected viruses

Examples:

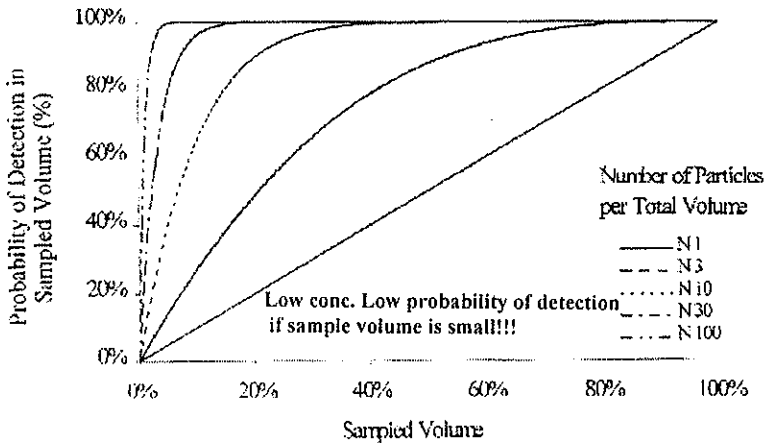
(i) "emerging viruses"---viruses not known previously
---eg., hepatitis G (discovered in 1996)

(ii) "unsuspected viruses"
---viruses not expected to be associated with product
---eg., hepatitis A not known to be bloodborne until early 1990s
→ no screening for hep A virus in plasma products until then

## Multi-tiered Approach to Viral Safety

### (ii) Limitations of Viral Testing

**Effects of Sampling Size on the Probability of Detecting Viruses Present at Varying Concentrations**



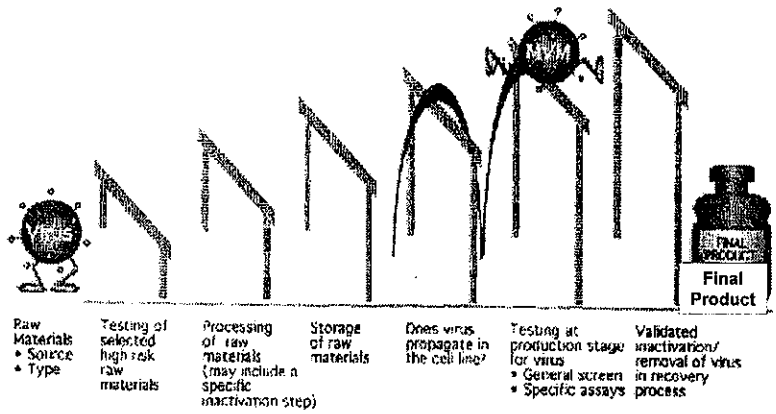



## Multi-tiered Approach to Viral Safety

### (iii) Multi-tiered Barrier Approach to Viral Testing

**Concept of using this approach to prevent product contamination**

---multiple tests conducted at different stages throughout production process
→ minimize chances that virus can escape detection



# Viral Clearance Processes

- Any human/animal sourced material may introduce contamination
  - Human plasma - HIV, Hepatitis B, C
  - Bovine serum - BSE prion
  - Cell lines - endogenous retroviruses
  - Antibody ligands from hybridoma cells
- Potential virus load must be determined, total virus (TV)
- Then a safety factor added ( TV + 6 logs)
- i.e. < 1 virus in 1 million human doses



# Calculation of Virus Load

$$\underline{TV = VC \times (HD/PC)}$$

TV = total virus (in log units)

VC = log virus count/ml of process fluid

HD = human dose (mg, μg protein)

PC = protein concentration in mg or μg/ml in the process fluid

## Viral Clearance Methods

- Filtration
  - Some sterilizing filtration processes may also remove some viruses
- Chromatography (especially IE)
  - Also some other chromatographic processes
- Membrane Adsorption
  - Millipore Intercept™ Q membrane
- Physical/chemical inactivation
  - Beware damage to protein drugs

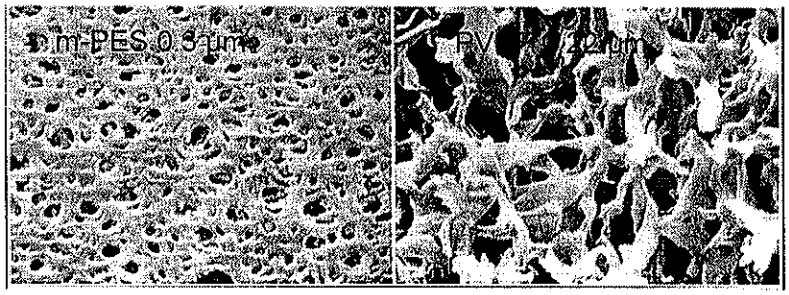


## Viral Clearance Methods

- Should reach levels of virus removal that are considered acceptable, i.e. an overall reduction of at least 12 to 15 log infectivity units.
- It is recommended that at least two different virus removal processes are applied to a product.
- These should employ unrelated methods of viral clearance, e.g. ion-exchange chromatography and detergent inactivation.

# Surface Morphology
# Microporous Membranes

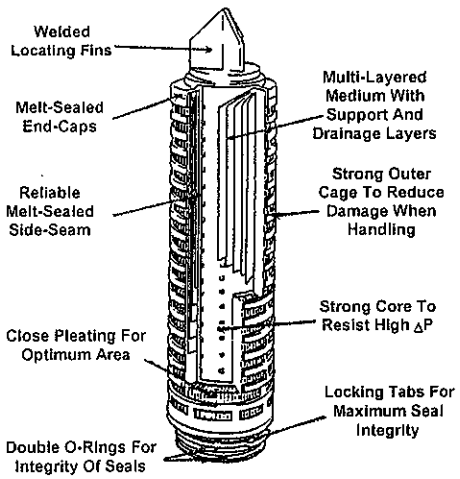
Magnification 10,000X



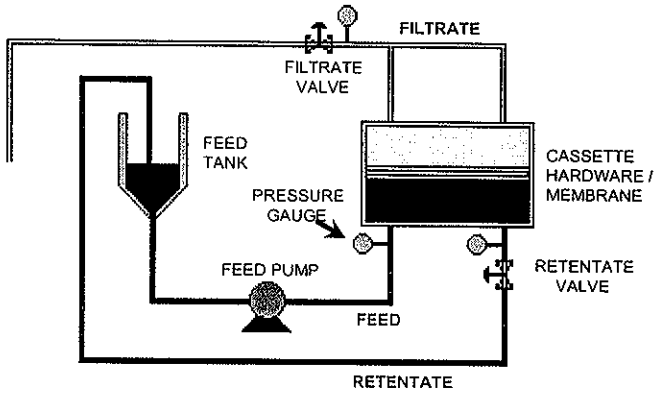

Scale 1 µm



## Typical A/B Sanitary Style Disposable Filter Cartridge

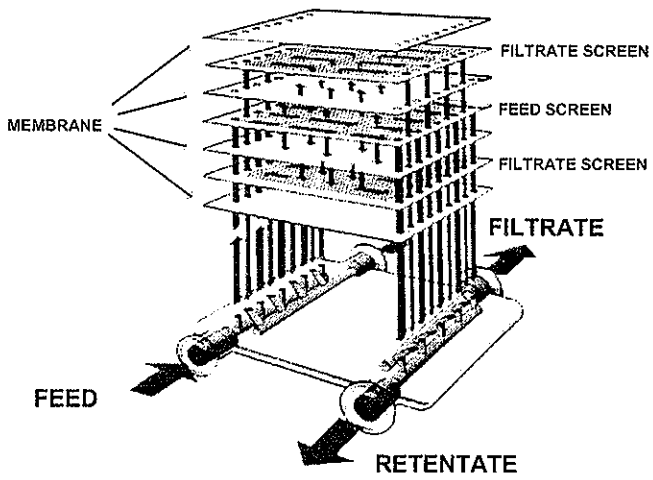


# Tangential Flow Filtration System Configuration






# Cassette Schematic



## Applications of UF / MF TFF

- Concentration
- Diafiltration
  - ➢ Desalting
  - ➢ Buffer Exchange
- Fractionation
- Pyrogen (Endotoxin) Removal
- Virus Reduction
- Cell Harvest
- Clarification



## Spiking Studies

- Small-scale experiments
- Acceptable to Regulatory Agencies
  - ➢ PROVIDED operating conditions are *identical to the full-scale process*
- Filtration & most column processes are easy
- Chemical methods can be proven similar
- Physical inactivation methods more difficult
- NB: "SPIKE" may alter the process fluid

# Viral Clearance Validation

- Exhibit 14 - Worst Case Conditions
  - For different clearance methods
- Exhibit 15: Representative Virus Panel for spiking studies
  - Panel used should become more extensive as product moves through clinical trial phases



## Exhibit 15: Virus Panel

| | | | |
|---|---|---|---|
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| | | | |
| | | | |

## Change Control

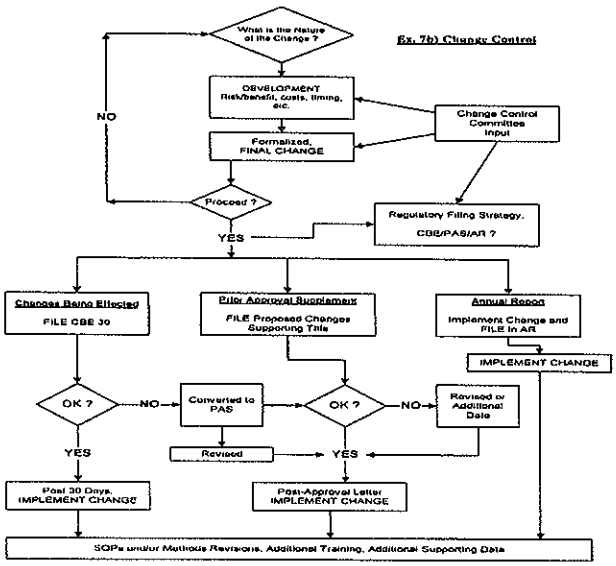
- Revalidation is required:
  - When a system, process or test is changed...
  - To the extent that its outcome may be affected
- "The QA Unit shall be responsible for the review of changes in product, process, equipment or other changes, to determine if and when revalidation is warranted" - FDA



## Change Control (2)

- QA Unit must have written SOPs describing the Change Control System
- All proposed changes must be submitted for review - *before implementation*
- All proposals, the changes that result, and all revalidation data must be fully documented in permanent QA files

# Exhibit 16: Change Control Chart






# Validation Exercise

- Consider one of these processes:
  - Mammalian cell culture in a perfusion bioreactor for MAb production
  - Product concentration by transverse-flow ultra-filtration
  - Sterile filtration of the final bulk
- What are the most critical factors that you would test ?
- How would you define the Worst Case ?

## Process Validation Recap

- Questions ?
- Comments ?
- Lunch ?

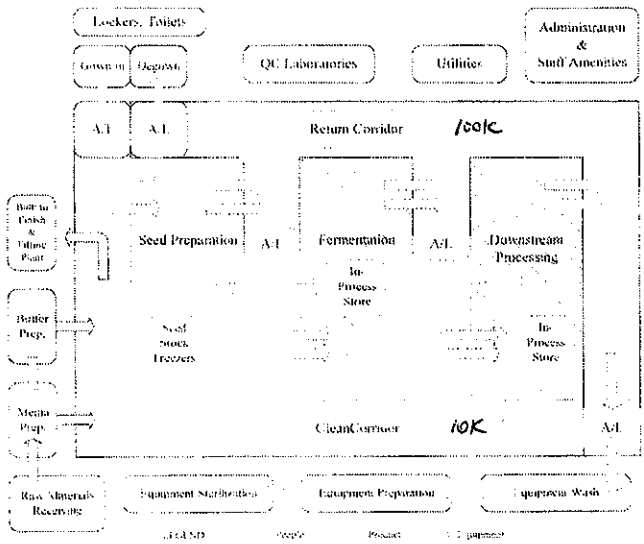




## GMP Aspects of Biological Facility Design

- Adequate separation & isolation of activities & products
- Logical process flow (Exhibit 17)
- Prevention of cross-contamination
- Easy to keep clean and prevent infestations
- Special requirements for aseptic areas
- Separate QC laboratories
- Separate animal facilities

# Exhibit 17: "Bubble Diagram"






# Biologicals Manufacturing Functions

- Cell/microbe seed banking
- Media production
- Upstream processes (culture, expression)
- Product harvesting, capture
- Down-stream processing
- Formulation/stabilization
- Final filtration & filling (lyophilization)
- QC Testing
- Warehousing

## Design Factors to Consider: 1

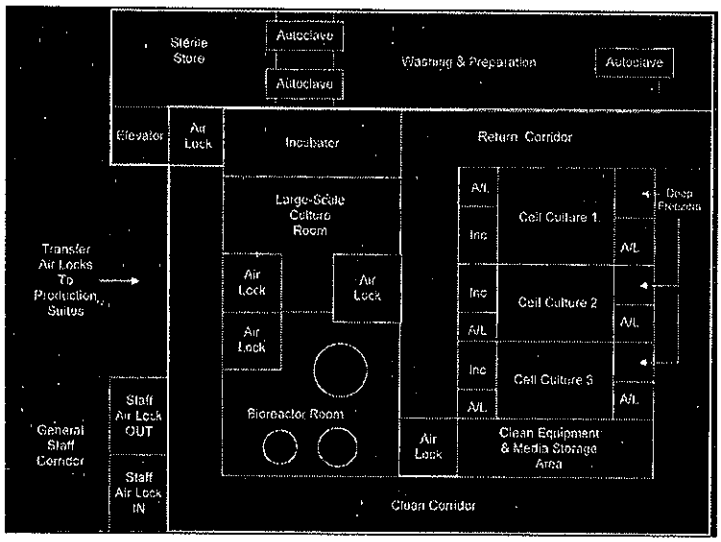
- Media Production Unit
  - Dust control for powders
  - Controlled area for weighing & mixing
  - Closed mixing tanks, bioburden control
  - With validated CIP
  - Sterile filtration unit
  - Means of transporting sterile media
  - Secure quarantine storage of bulk media



## Design Factors to Consider: 2

- Seed Banks & Culture facilities
  - Will need $LN_2$ Storage
  - Will require separate rooms or isolation cabinets to handle seeds
  - Large Bioreactors will be CIP/SIP
  - Utilities needed:
    - Clean Steam
    - WFI
    - Clean Gases
  - Must have Effluent Control

# Exhibit 18: GMP Cell Culture Suite






# Design Factors to Consider: 3

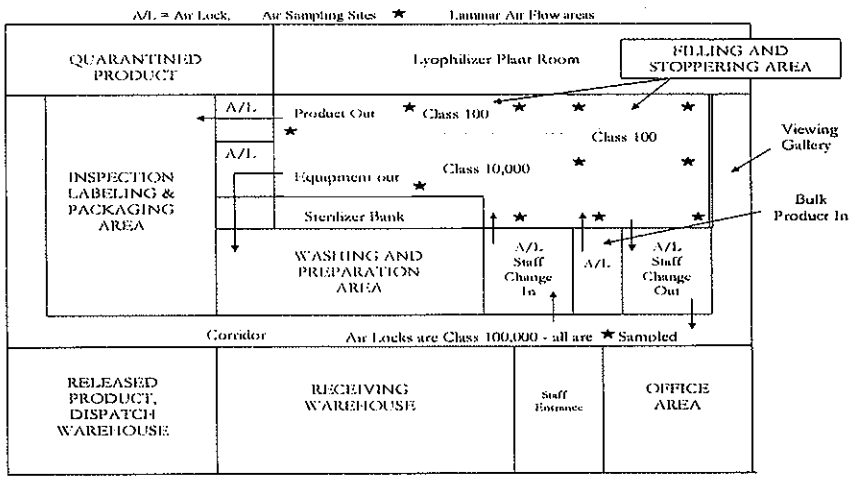
- Down-stream processing units
  - Adequate separation for different products
  - Some major equipment may be CIP
  - Some processes may need refrigeration
  - Adequate storage for media and WIP
  - Chromatographic equipment preferably dedicated, validated clean/sanitize
  - Needs sterile mobile equipment supply, from autoclave(s)

# Design Factors to Consider: 4

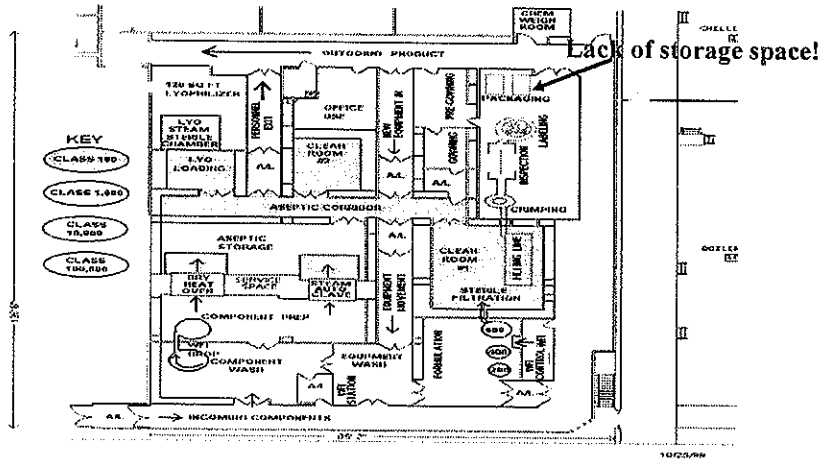
- Final formulation, filtration, filling
  - Separate air supply
  - Needs Class 100 air over filling plant and loading area for lyophilizer
  - Lyophilizer plant room accessible from outside the clean room
  - Adequate quarantine and released storage
  - Under proper conditions.
- Packaging/labelling on release.



## Exhibit 10: Typical Finishing Plant

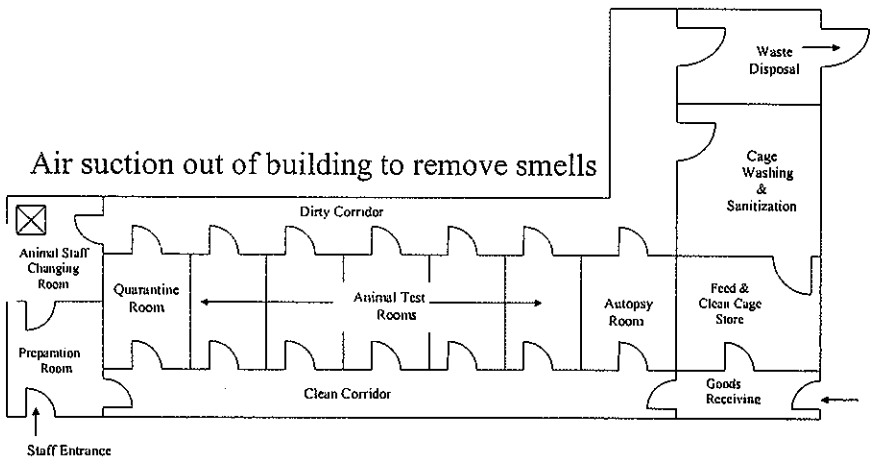


## Aseptic Manufacturing Floor Plan






## Exhibit 19: Animal Test Unit Layout



## Facility Operation under GMP

- Staff Rules
- Cleaning & maintenance
- Specialized systems, e.g. WFI System
- Equipment selection, calibration and maintenance
- Records



## The Facility Rules Must Cover:

- Safety and Security of the people, plant and products
- Movement of staff & visitors
- The wearing of protective clothing, etc.
- Staff personal hygiene & health
- Control of food, drink, smoking, etc.
- Special rules for clean-room operations

## Examples of Methods to Control Cross-Contamination

- Keep your white coat buttoned (Demo gowning)
- Don't sneeze on the plates (!)
- Change clothing between different areas
- Restrict movement of staff from one area to another on the same day
- Any Others ???



## Cleaning & Maintenance

- To be done according to SOPs
- Responsibilities must be clear
- *Cleaning of critical areas must be validated*
- Maintenance of the facility systems/utilities must be documented

## Specialized Systems

- Means those critical to the product's integrity
- Clear responsibility must be documented
- Must be operated and maintained according to SOPs
- Must be regularly checked to confirm they comply with recognized standards & specifications set during validation
- All activities & results must be recorded.



## Equipment

- Proper design, size, location
- Proper construction
- SOP for cleaning & maintenance
- Log must be kept (Exhibit 20)
- Special rules for automatic, mechanical or electronic equipment (21CFR 211.68)
- AND 21CFR 11

## Equipment Calibration

- Best guidelines on calibration are in GLP regulations (21CFR58.63)
  - Measuring equipment must be calibrated using appropriate standards
  - All standards must be supplied with calibration certificates
  - SOPs must describe calibration methods in sufficient detail, *and the person responsible*



## Records - Facility Summary

- All of the following must be maintained:
  - Personnel qualifications, duties & training
  - Facility cleaning, maintenance
  - Equipment cleaning, calibration, maintenance
  - Special systems maintenance, sampling and testing
  - Validation Reports on all critical activities
- Deviations must be investigated & reported

# Break Time

- Questions ?
- Comments?
- Refreshments?





# Quality Control: 1

- Good Warehouse Practice
- Starting (Raw) Materials
- Product Containers & Closures

## Good Warehousing (211.80-94)

- Of Raw Materials & Components…
  - Receipt, storage, handling, labeling (211.80)
  - Inspection & quarantine (211.82)
  - Sampling, testing & approval (211.84)
    - See Exhibit 21a) - Warehouse Labels
  - Stock rotation (211.86)
  - Retesting & handling of rejected materials (211.87)



## All Warehouse Work:

- Must be covered by written SOPs
- All handling and storage must ensure
  - Adequate separation of quarantine & released stock
  - Prevention of contamination
  - Clear identification
  - Inspection on arrival
  - Proper sampling for QC

## Sampling of Received Materials

- Sampling & testing is according to SOPs
- Shipping containers should be cleaned before sampling
- Sampling must not contaminate the remainder of the shipment
- Use sterile equipment and aseptic techniques for pre-sterilized goods
- Samples must be representative
- Must be labelled immediately (Exhibit 21b)



## Testing of Received Materials

- Specifications must exist for all out-sourced materials, components, etc.
- Onus is on the manufacturer, not the supplier, to ensure compliance with specs.
- QC must determine what samples should be taken and what tests should be done, depending upon the reliability of the supplier and the variability of the goods (*supplier/vendor qualification*)

## Typical Testing Requirements:

- For chemicals, intermediate products:
  - Identity, purity, strength & uniformity
  - Media components - growth promotion
- For containers & closures
  - Material identity, quality, critical dimensions
- For pre-sterilized products
  - Packaging integrity, sterilization indicators or certificates



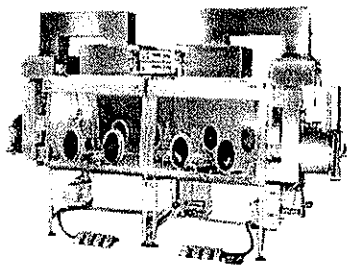
## Product Containers & Closures

- Regulatory specifications: 211.94
  - Non-reactive
  - Provide adequate protection against product degeneration
  - Clean and sterile/pyrogen-free, if required
  - SOPs required for the above procedures
- EU Code requires extra documentation in Section 4.11

# Emerging Packaging Techniques

Barrier Isolation Technique

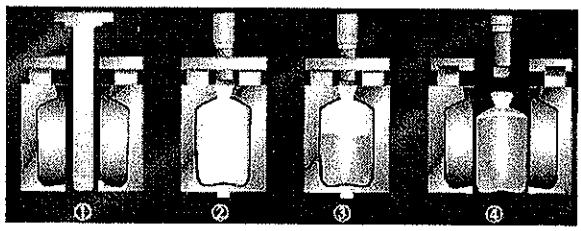
- Closed filling & packaging environment
- Superior to aseptic process





# Emerging Packaging Techniques

Blow-Fill-Seal

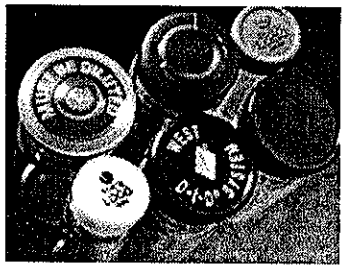



(1) Extrusion of plastic granulate into a parison at 170°C to 220°C
(2) Blow-molding of the parison into a container with sterile air
(3) Aseptic filling of the sterile pharmaceutical solution
(4) Hermetic sealing of the sealed container

# Emerging Packaging Techniques

## Decorative-Identification-Differentiation (DID)

- Innovative packaging
- Enhance product security





# FDA Citation Trends

- No written procedures describing the setup or operation of packaging equipment
- No process validation of filling & packaging/labeling procedures
- No testing of packaging materials
- Failure to maintain packaging control procedures and/or records

# Product Recall Examples

| Mislabeling | | |
|---|---|---|
| Product Name | Colchicine | Anthrax vaccine |
| Manufacturer | Phyne Pharmaceuticals | Bioport |
| Date of recall | 19 Dec 2000 | 3 Feb 2001 |
| Cause | 0.5 mg/ml but actually formulated at 5 mg/ml | Expiry date error |



# Product Recall Examples

| Packaging Defects | | |
|---|---|---|
| Product Name | Cefzil (Ceprozil) | Pulmozyme |
| Manufacturer | Bristol-Myers Squibb Company | Genentech, Inc. |
| Date of recall | 18 Aug 1993 | 20 Apr 2000 |
| Cause | Strips of 500mg packaged and labeled as 250mg | Ampoule leakage |

# Product Recall Examples

| Counterfeit Products | | |
|---|---|---|
| Product Name | Serostim | Epogen |
| Manufacturer | Serono, Inc. | Amgen, Inc. |
| Date of recall | 16 May 2002 | 8 May 2002 |
| Cause | Counterfeit packaging | Counterfeit active ingredient strength and packaging |



# Conclusions

Current Industry Situation

- 30-40% of total product recalls due to labeling/packaging defects
- Lack of effort and control over operations

Improvement

- Will save time and money for manufacturers
- Public will benefit from safer and more reliable drug products

## Facility Design Exercise

- A new facility is to make a virus vaccine, using mammalian cell culture
- The final product is an inactive extract from the whole virus.
- Sketch a "Bubble Diagram" for the main activities that need to be accommodated in this facility



## QC Part 2: Manufacturing Control

- Production and Process Controls
- Packaging and Labeling
- Holding and Distribution
- Batch Production Records

## Production & Process Controls

### #1: Procedures (211.100)

- There shall be written SOPs…"to assure that the products have the characteristics they are represented to possess…"
  - SOPs shall be followed
  - Procedures shall be documented at the time of performance *directly into the BPR*
  - Deviations from the SOP must be recorded and justified
- 600.14 - Biological product deviations



## Record-Keeping Rules

- Permanent Ink
- Directly into the final form
- All measurements, etc, must be checked and counter-signed
- Alterations must not obscure original entry (No "White-out")
- Must be explained and countersigned
- Charts, etc. must be pasted in & signed across join.

## Production & Process Controls
### #2: Equipment (211.105)

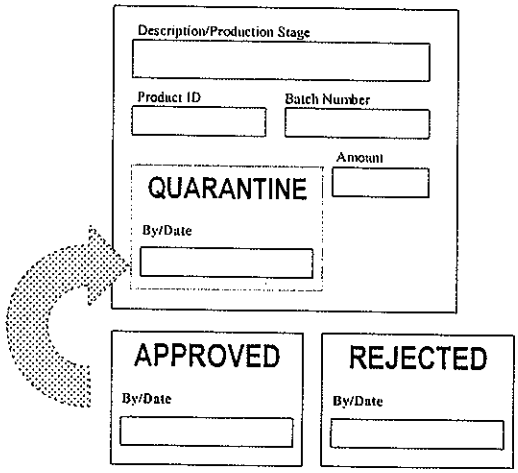
- Equipment must be identified
  - Tanks, pipelines, processing vessels, must be labelled with the product in process
  - All major equipment should be identified with a unique code
- The name of the machine is not enough, unless there is only one in the plant



## Production & Process Controls
### #3: Sampling (211.110)

- Sampling & in-process testing SOPs
  - Sampling methods must be validated
  - Specifications of in-process materials are set so that the final product will conform to the final specifications
- The results of in-process tests are reviewed by QC, which releases the material for further processing (e.g. bulk to filling) (See Exhibit 22)

# Exhibit 22: In-Process Label






# Production & Process Controls
## #4: Sterile Products (211.113)

- Control of microbiological contamination
  - Essential for all biological products
  - All stages of manufacture must be designed so as to minimize bioburden
- Sterilization, de-pyrogenation & aseptic procedures must be according to SOPs and validated
- Competence of the staff is critical

# Validation of Heat-Sterilizing Processes

- Must represent the "real world"
- Using standard load patterns
- Biological challenge essential
- Worst-case situations include:
  - Low temperature
  - Reduced exposure time
  - Over-packing of chamber



# Production & Process Controls
## #5: Aseptic Procedures

- Essential points to consider:
  - Adequate monitoring of environment and air filter checking - full records
  - Full recording of all sterilization runs & other procedures
  - Full training of staff in gowning & aseptic operations
  - Regular monitoring of the staff during operations & retraining of staff who fail tests

## Packaging & Labeling Controls #1: General (211.122)

- SOPs for receipt, identification, storage, handling, sampling & testing of materials
  - Record of use/rejection of each shipment
  - Separate storage of labels for different products
  - Destruction of obsolete, outdated labels
  - No gang-printing
  - Care with use of cut labels



## Packaging & Labeling Controls #2: Handling (211.125)

- Issuance & Return of labels:
  - Must conform to batch production record
  - Must be reconciled according to SOP
  - Unused labels carrying a batch number must be destroyed
  - Returned labeling must be stored so as to prevent mixups
  - Should be properly identified

## Packaging & Labeling Controls
### #3: Operations (211.130)

- A favorite area for citations...
- Points to consider:
  - Prevent mix-ups by spatial separation, dedicated lines
  - Filled containers held in bulk before labelling should be sealed and the bulk container properly identified
  - Lot numbering system should enable the complete history of the lot to be traced



## Packaging & Labeling Controls
### #4: Other (211.134 &137)

- Inspection of finished products
  - To ensure proper filling/sealing
  - To identify contaminants
  - To ensure proper labeling
- Expiry dating
  - Essential for biologicals, based upon validated stability tests
  - Must state storage conditions

## Holding & Distribution
### #1: Warehousing (211.142)

- SOPs will be in place for:
  - Quarantine of unreleased products
  - Storage under conditions which will maintain identity, strength, quality, purity
  - Release procedures under QC control
  - *Shipping conditions must also preserve the product - essential for biologicals*
- Full records of all warehouse activities



## Holding & Distribution
### #2: Distribution procedures (211.150)

- Oldest stock must be shipped first,
  - although with temporary deviations permitted under SOP-defined conditions
- A record system must be in place permitting rapid recall of any shipped materials.
  - If the product is handled by wholesalers, etc. they must have similar systems
  - Shipping temperature recorder advised

## Production/Control Records - 1 (211.188)

- Master Production (& Control) Record (MPR)
  - Production of this document is by SOP
  - Covers all aspects of production & testing
  - Assembled in one document
  - Managed by QA/QC (best if 1 person)
  - Contents shown in Exhibit 23
  - Best stored as a computer document, with adequate security.



## Production/Control Records - 2

- Batch Production/Testing Records (BPR)
  - Each is a dedicated copy of the MPR
  - Printed out by QA when production of a new batch is ordered
  - Should include printed record forms for:
    - Starting materials testing & release
    - Processing stages (See Exhibit 24)
    - Sampling & testing & QC release
    - Packaging & labeling

## Production/Control Records - 3

- Record Review & Discrepancy Investigation (211.192)
- SOPs for:
  - Review by QA of all records of production
  - Thorough investigation of any unexplained discrepancy
  - Preparation of appropriate report, to form part of final version of BPR



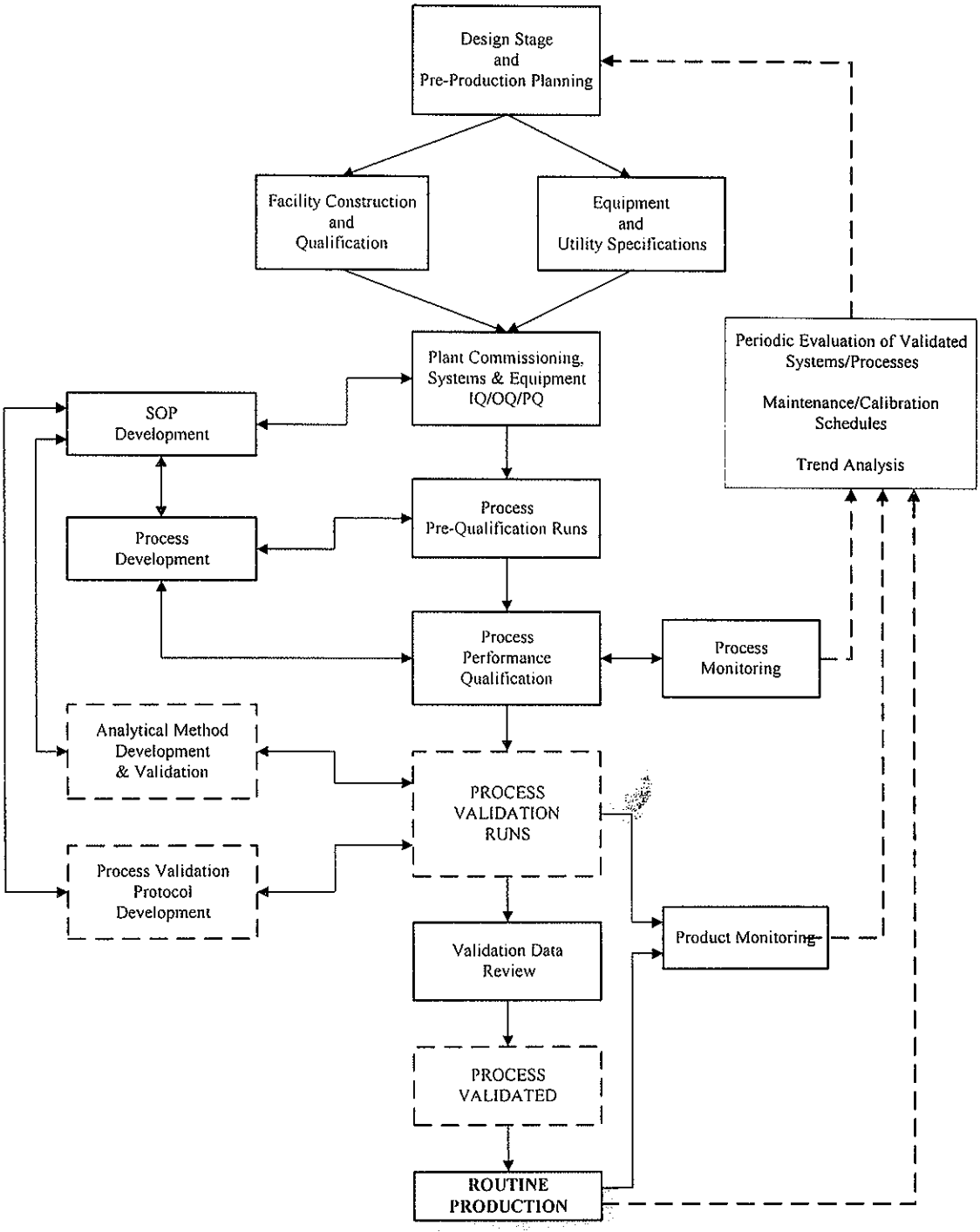
## Day 2 Round-Up

- Cleaning Validation
- Process Validation
- Computerized Systems
- Facility Design & Operation
- GMP in Warehousing
- Production Quality Control (1), warehousing, raw materials and final packaging
- Quality Control (2), Production Process control, packaging & labeling, holding & distribution

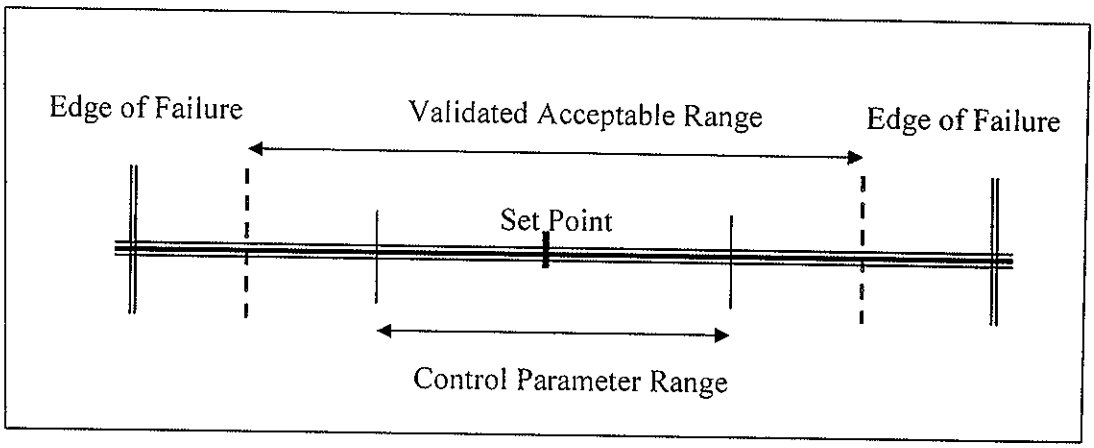
# ***Question and Answer Session***

*Thank you for your attention!*

# Exhibit 11: Process Validation Life Cycle



## Exhibit 12: The Terminology of Process Validation



## Exhibit 13: Control of a Cell Culture Bioreactor

| Process Control Parameter | Process Response Variable |
|---|---|
| Temperature<br>pH<br>Agitation<br>Time<br>Dissolved Oxygen<br>Perfusion Rate | Cell Viability<br>Cell Number<br>Generations<br>Product Titer, Concentration<br>Product Characteristics<br>Product Stability<br>Impurity Levels |

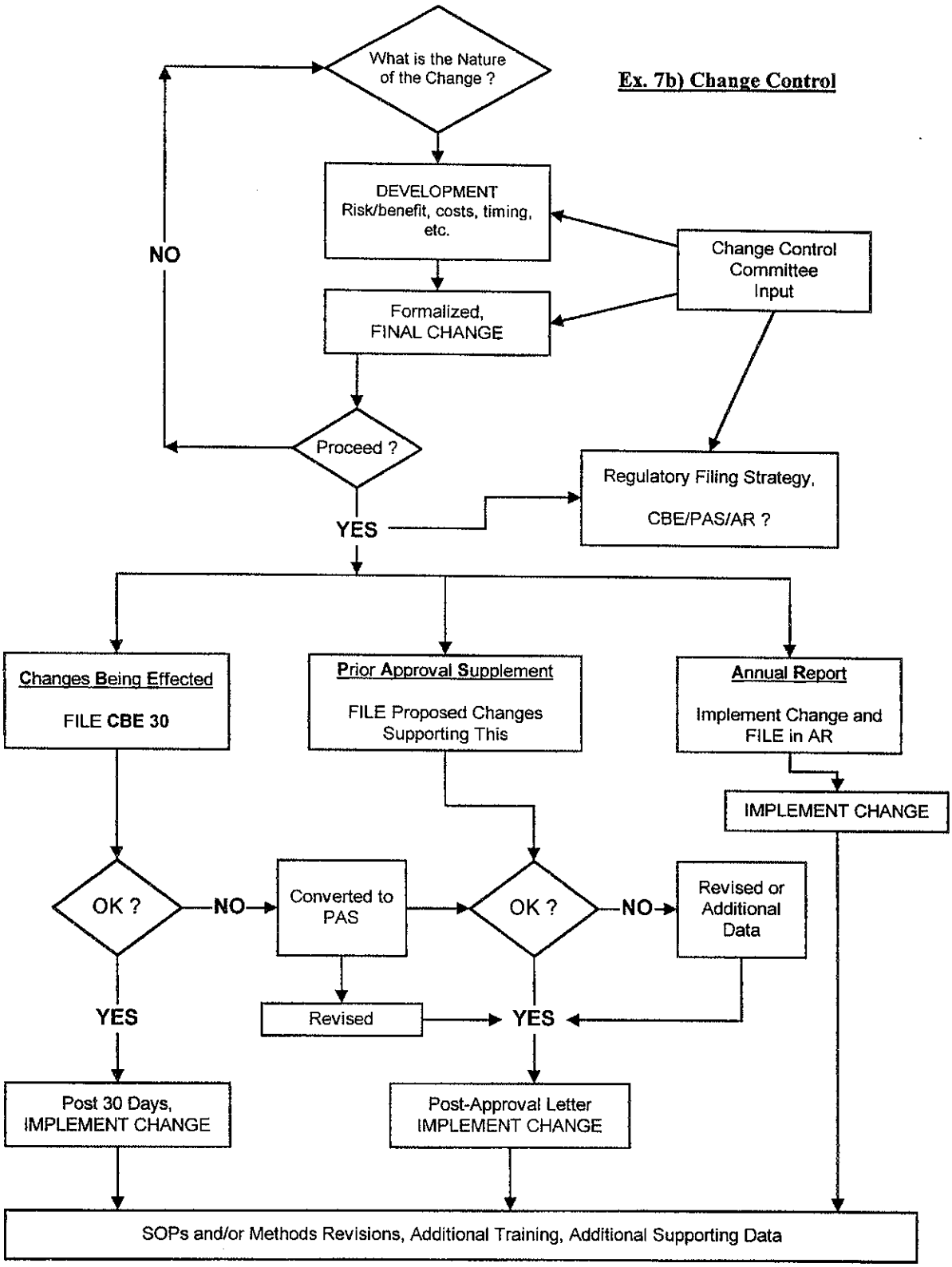
# Exhibit 14: Worst-case Conditions for Viral Clearance Studies

| Virus-Removal Method | Critical Process Variables | Worst-Case Conditions |
|---|---|---|
| Filtration<br>Transverse-flow and Direct | Solution Composition :<br>(protein concentration, pH, ionic strength)<br>Process Conditions:<br>(differential pressure, fluid flux,<br>ratio of volume to filter area) | Highest protein load<br>Highest volume/area ratio |
| Chromatography | Product & Contaminant concentration<br>Buffer composition<br>Flow rates<br>Wash volumes<br>Temperature | In product-binding process, minimum wash volume before elution will cause virus to elute with the product<br>For impurity-binding processes, increase the contaminant/product ratio, or load column with larger volume than used in production.<br>The largest post-load wash will elute virus with product |
| Chemical<br>Inactivation Processes<br>(rarely linear reactions) | Concentration<br>of inactivating agent and product<br>Contact time<br>Temperature<br>Volume or flow rate<br>Other contaminating proteins or stabilizers | Lowest concentration of inactivating agent<br>Shortest exposure time, highest flow rate, etc.<br>Highest concentration of protective proteins/stabilizers<br>For detergent inactivation, use lowest detergent concentration with shortest exposure time and lowest temperature |
| pH Inactivation | Product concentration,<br>pH, Exposure Time | With pH inactivation process, the lower the pH the better, thus the worst case is the pH closest to neutral within the range. |
| Heat Inactivation | Product & Stabilizer concentration<br>Temperature<br>Exposure time | Highest product and stabilizer concentration,<br>Lowest temperature<br>Shortest exposure time. |

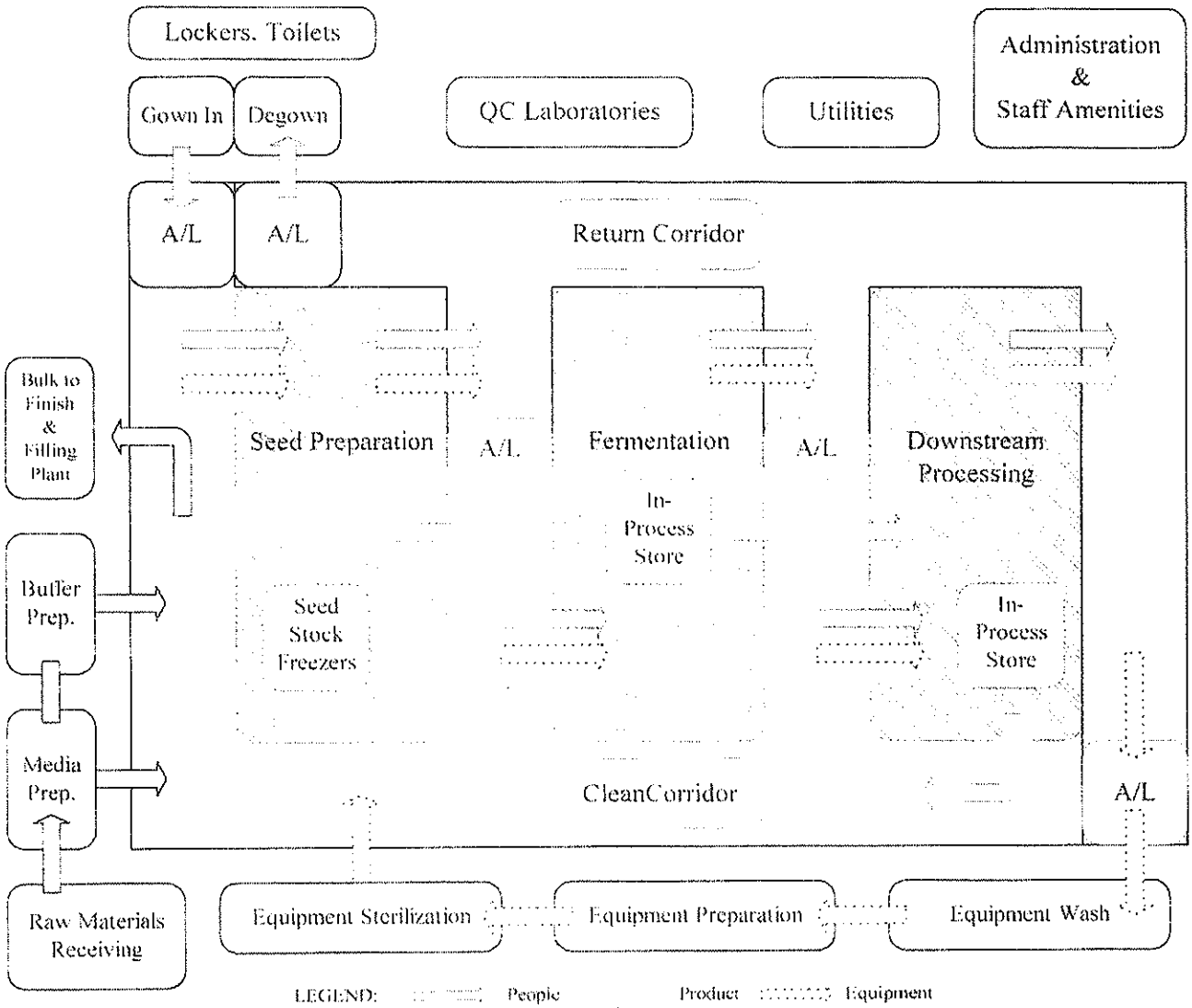
## Exhibit 15: Viruses Commonly used in Clearance Studies

| Family | Virus | Nucleic Acid/ Envelope | Size (nm) & Shape |
|---|---|---|---|
| Herpesviridae | Herpes simplex<br>Pseudorabies | DNA<br>Enveloped | 120-200, spherical |
| Papovaviridae | SV 40 | DNA/No | 40-50, icosahedral |
| Paramxymoviridae | Parainfluenza | RNA/Yes | 150-300, pleomorphic |
| Parvoviridae | Canine, murine, porcine parvoviruses | DNA/No | 18-24, icosahedral |
| Picornaviridae | Poliovirus<br>Hepatitis A<br>Encephalomyocarditis | RNA/No | 25-30, icosahedral |
| Reoviridae | Reovirus 3 | RNA/No | 60-80, spherical |
| Retroviridae | HIV<br>Murine leukemia | RNA/Yes | 80-100, spherical<br>80-110, spherical |
| Rhaboviridae | Vesicular Stomatitis | RNA/Yes | 70 x 175, "bullet" |
| Togaviridae | Bovine Viral Diarrhea<br>Sindbis | RNA/Yes | 60-70, spherical |

## Exhibit 16: Change Control Chart



# Exhibit 17: "Bubble Plan"



# Exhibit 18: Cell Culture Unit

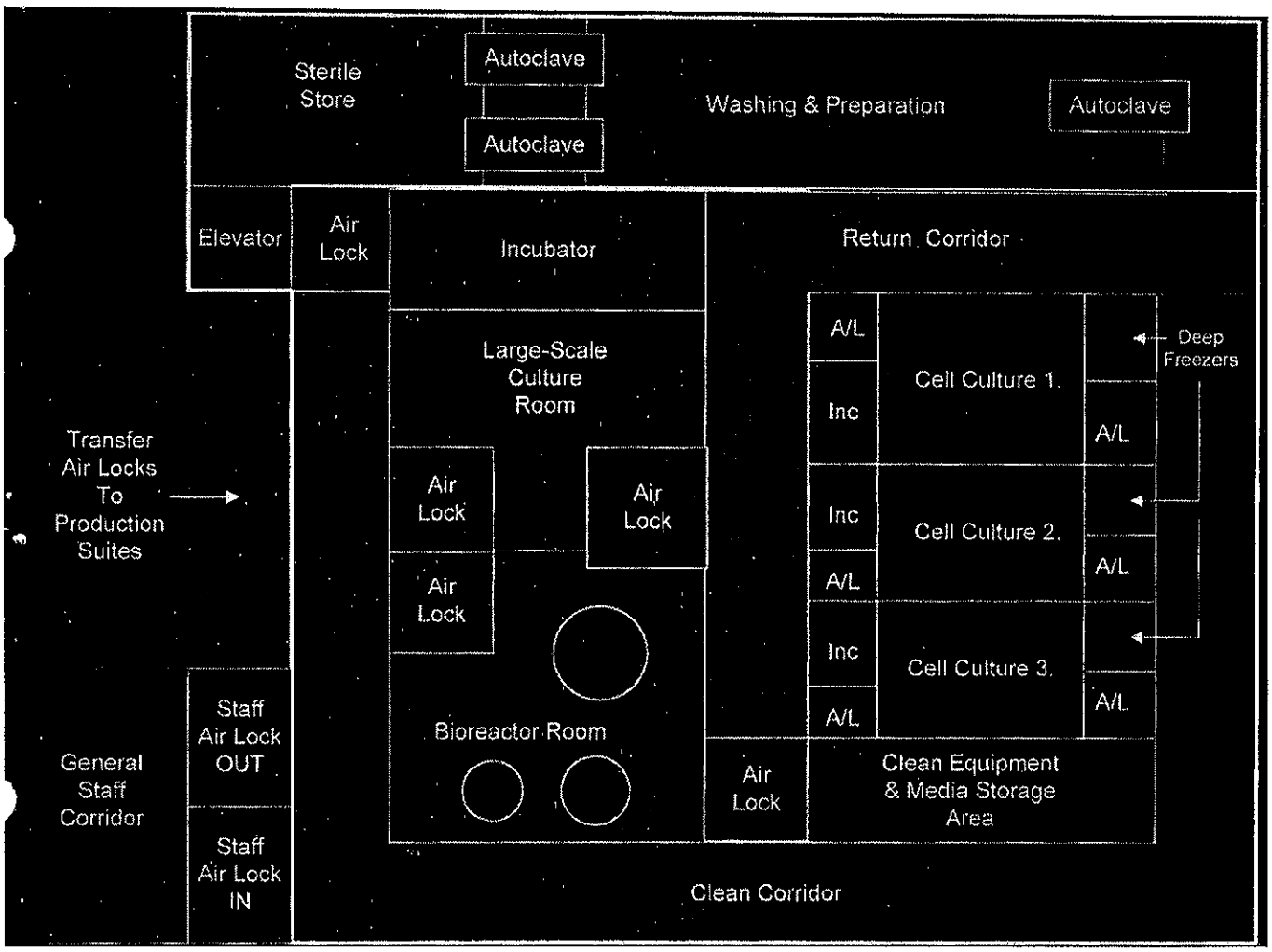
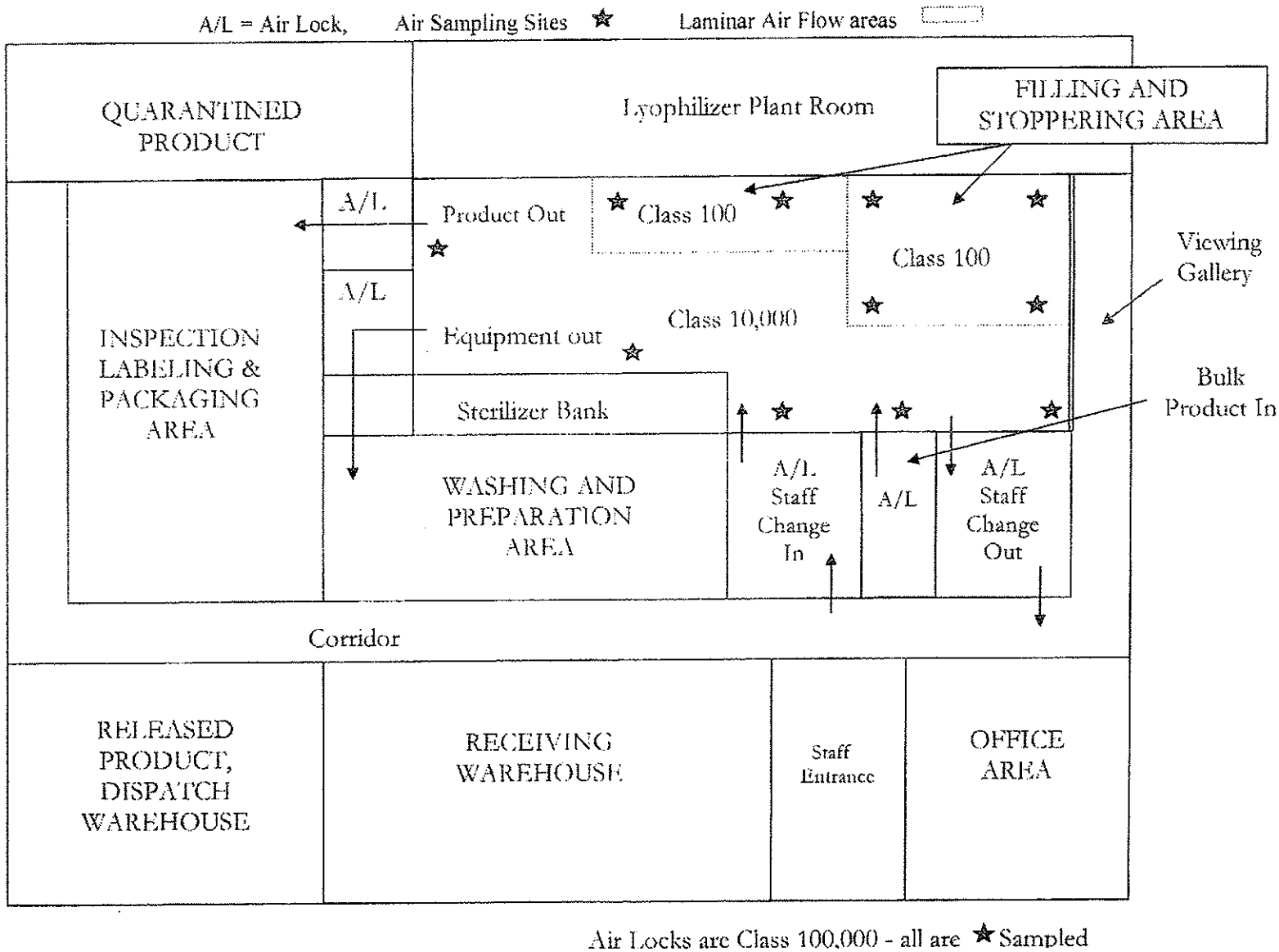


**Exhibit 10: Typical Finishing & Packaging Plant, with CleanRoom Set-up**



# Aseptic Manufacturing Floor Plan

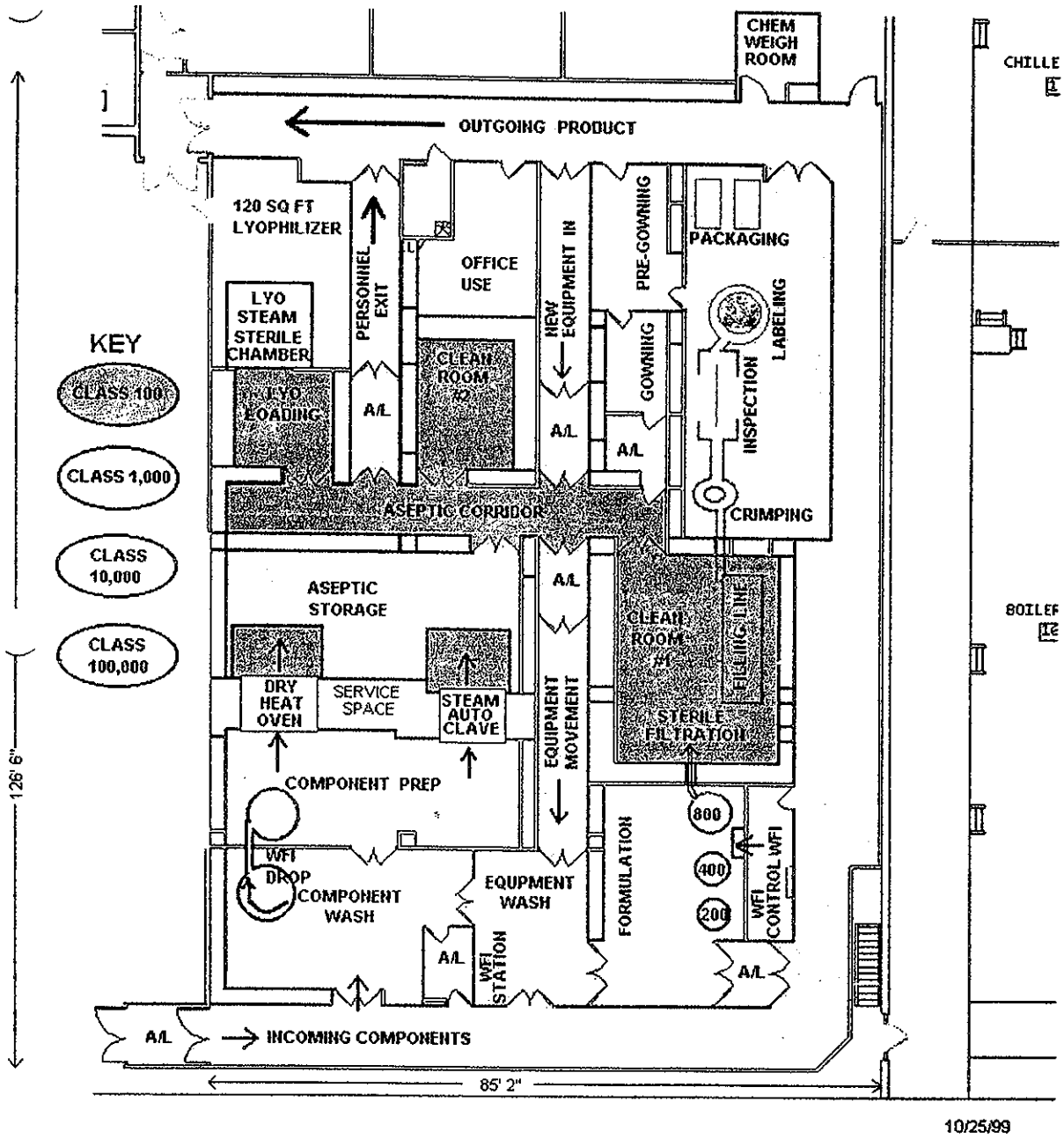
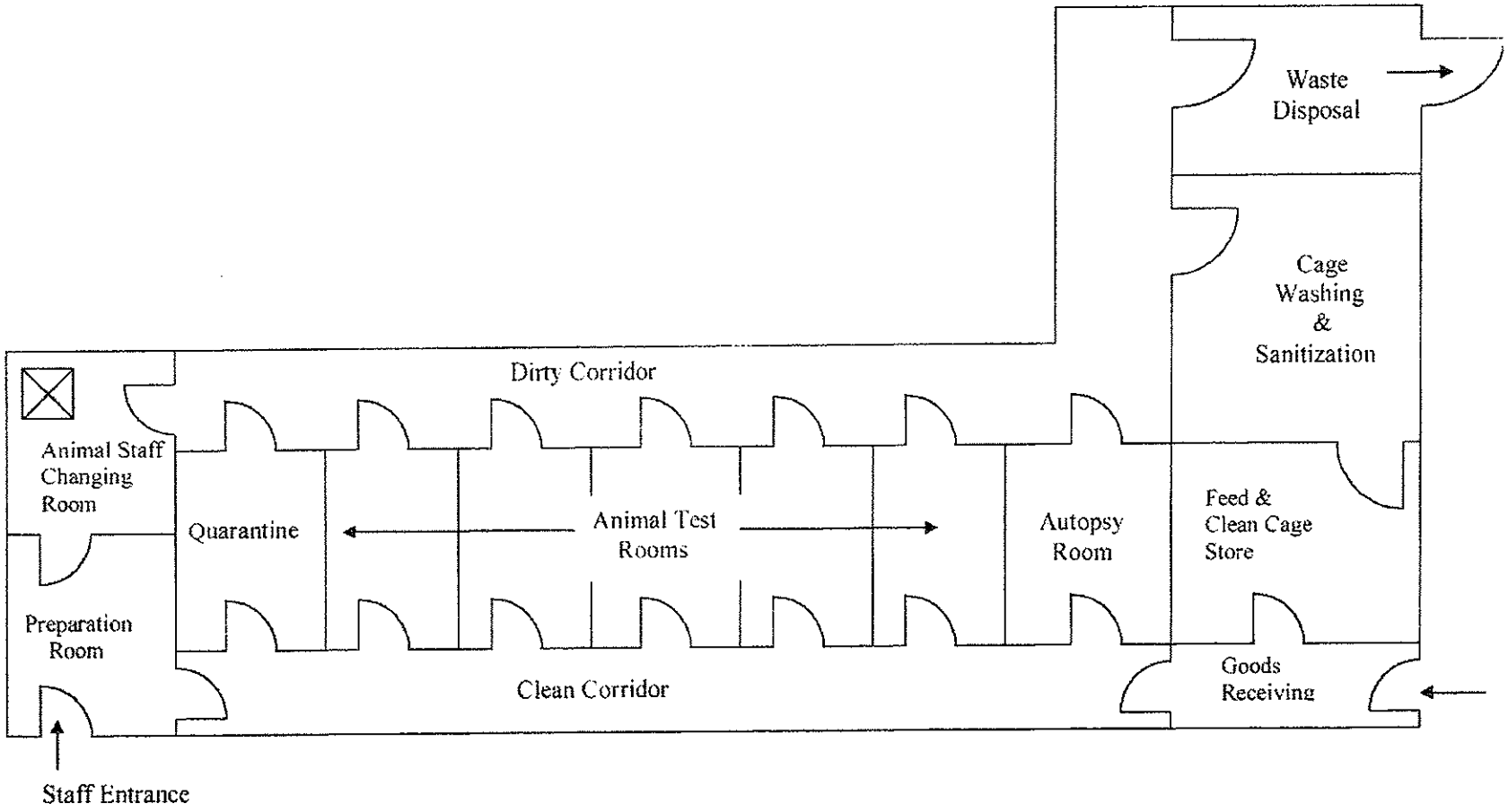


**Exhibit 19: Animal Test Unit Layout**



## Exhibit 20: Equipment Cleaning & Maintenance Log - Specimen Page

**EQUIPMENT CLEANING/MAINTENANCE RECORD** **Page:** 24.1

**Equipment ID:** Westfalia Separator, *Code WS53/2* **SOP Ref:** P/99/585/1-1

**Model #:** GMBJ 1224585 **Location:** Fermentation Suite #2, Blg 53.

**Product(s) Processed:** E.coli fermentation 3-day harvest for Product XXX
DEDICATED EQUIPMENT

| Date of Procedure | Procedure/By | Inspected By | Result |
|---|---|---|---|
| 2/23/99, All day | Initial Set-up/ IQ and OQ A.V. Compton & supplier's Installation staff | J. Varley, Eng QA | Qualified QUALIFIED |
| 3/5/99<br>2.00 pm | Cleaned, STERILIZED IN SITU, Sampled for sterilization validation. Process Validation Run #1 AVC | Validation Team - EVH, Team Leader | Data Acceptable EV Harlan |
| 3/6/99 | Cleaned and sampled AVC | J. Varley | PASSED EVH |
| 3/10/99<br>3.00 pm | Sterilized, sampled and Validation Run #2 AVC | Val. Team: EVH | Data Acceptable EVH |
| 3/10/99 | Cleaned and sampled AVC | J. Varley | PASSED EVH |
| 3/24/99<br>1.30 pm | Sterilized, sampled and Validation Run #3 AVC with George Winston, new operative | Val. Team: EVH | Data Acceptable EVH |
| 3/25/99 | Cleaned and sampled G.W. | AVC & J. Varley | PASSED EVH |
| 4/12/99 | Equipment stripped down for inspection & lubrication, re-assembled and run-up G.Winston | AVC & J. Varley | Equipment Ready, Awaiting Validation Report |
| 4/16/99 | Cleaned and Sampled G.W. | AVC | CLEARED FOR ROUTINE OPERATIONS EVH |

Exhibit 21a): Example of a Warehousing Label

LOT #: _____ Received: _____

Description: _____

Quantity: _____ Sampled: _____

By: _____

STATUS: QUARANTINED Signed: _____

APPROVED Signed: _____

REJECTED Signed: _____

USE BEFORE: _____ Signed: _____

ISSUES

Date: _____ Quantity: _____

Date: _____ Quantity: _____

Date: _____ Quantity: _____

Date: _____ Quantity: _____

Exhibit 21b): Label for Raw Material/Packaging Sample

RAW MATERIAL/PACKAGING SAMPLE

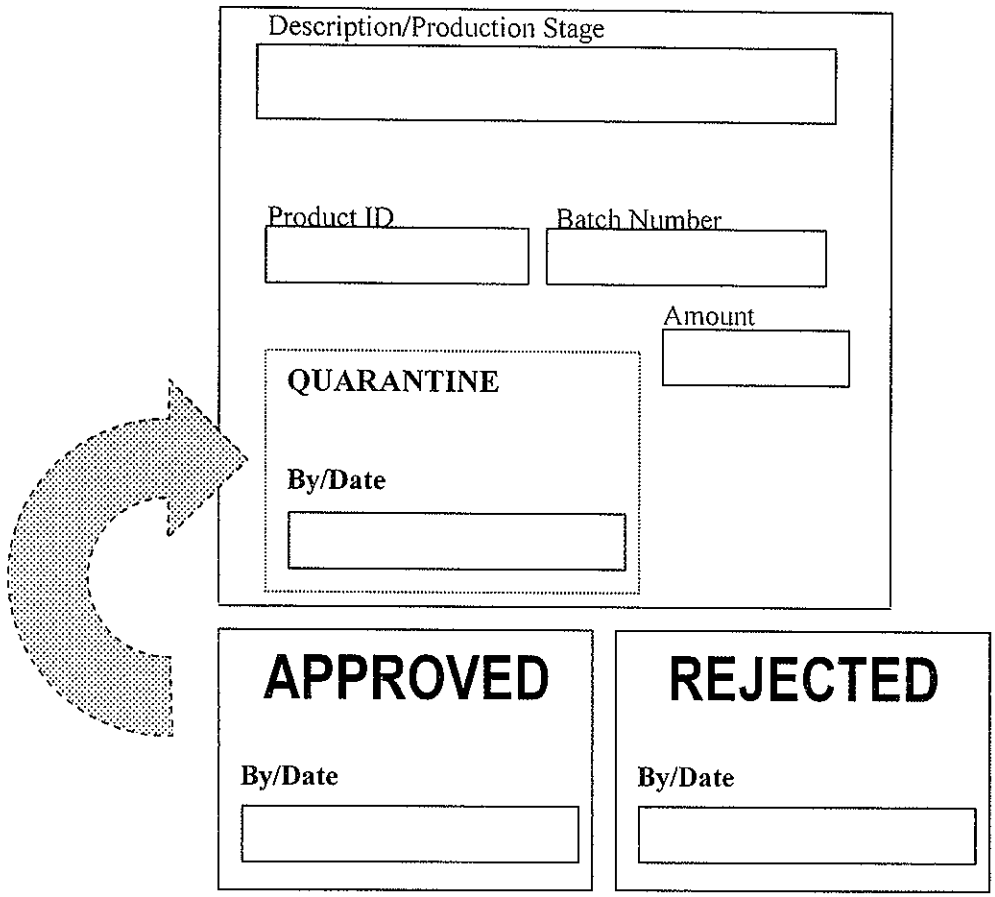
Lot #: _____ Container #: _____

Date Sampled: _____ Sampled From: _____

By: _____ Sample Size: _____

Received, QC: Date: _____ By: _____

Disposition: _____


Description/Production Stage
Product ID
Batch Number
Amount
QUARANTINE
By/Date
APPROVED
By/Date
REJECTED
By/Date

## Exhibit 23: The essential contents of the MPR are:

- Product name and strength and description of the dosage form.
- List of active ingredients, giving proper name or code name sufficient to ensure correct identification, and accurate weight or measure of each, with the same units of measure used for all entries.
- Statement of any calculated excess of any component.
- Statement of theoretical weight or measure at appropriate stages of manufacture.
- Statement of theoretical yield, including permitted maximum and minimum percentages of this, beyond which investigations must be made under §211.192.
- Description of product containers, closures and packaging materials, including a specimen of each label and other labeling, signed and dated by the person(s) responsible for approval of such labeling.
- Complete instructions for the manufacture, in-process and final product sampling and testing procedures with standards and specifications to be met at all stages and any special precautions to be followed, or special notations.

## Exhibit 24: The Contents of the Batch Production Record

- An accurate reproduction of the current MPR , with both production and control sections, checked for accuracy, dated and signed.
- Documentation to confirm that each stage of the process and the control thereof has been correctly performed, using pre-printed forms in duplicate or triplicate onto which the relevant information can be entered. A copy is retained in each operating department, while another accompanies the batch record to the next stage. The processing forms should carry the following information, as appropriate:
  - Batch Number and date of performance of the process or test
  - Description of the process stage, with reference to the MPR and relevant SOPs
  - Identity of individual major equipment and lines used
  - Specific identification of each batch of component or in-process material used
  - Weights and measures of components used in the process
  - Weights and measures of material yielded by the process
  - Any sampling performed during the process and disposition of the samples
  - Results of in-process and laboratory control results
  - Signatures or initials of the responsible operative and supervisor/checker
- For the final processing stages, the BPR forms will include:
  - Description of the product containers and closures
  - Complete labeling control records, including specimens of all labeling used and reconciliation data
  - Report of the inspection of the packaging and labeling area before and after use
  - List of samples taken and their disposition
  - Results of control tests on the final product
  - Results of any visual examination performed (as described in §211.134) to confirm that the correct labeling has been applied.
- In the overall BPR Summary: A calculation of the actual yield of active principle and a statement of the percentage of theoretical yield at appropriate stages of manufacture
- All persons performing and directly supervising or checking each significant step of the manufacturing operation must be clearly identified
- If any investigations are made in accordance with §211.192 - Record review and investigation of discrepancies - a description of the investigation and its results must be included in the BPR.

# GLOSSARY OF BIOTECHNOLOGICAL TERMS

| | |
|---|---|
| **Absorption** | Removal of a particular antibody or antigen from a sample (e.g. of serum) by adding the corresponding antigen or antibody to the sample Compare to Adsorption |
| **Adsorption** | Adherence of molecules in solution or suspension to cells or other molecules – or to solid surfaces, such as chromatography media Compare to Absorption |
| **Adventitious agents** | Acquired, accidental contaminants in a cell line, such as viruses and toxins – often infectious agents. |
| **Affinity** | Attraction between particles or substances – the measure of attraction of one molecule to another, as "affinity of antibodies" |
| **Aseptic** | Sterile, free from bacteria, viruses and other culturable organisms, especially pathogens |
| **Assay** | A technique (test) for measuring a biological response or for determining characteristics such as composition, purity or activity |
| **Attenuated** | "Weakened", as applied to strains of pathogenic bacteria or viruses which can multiply in the host but are not capable of producing the disease. Used as vaccines, they produce a strong immune response, mimicking the natural response to infection.<br>Examples: oral polio, measles, rubella, oral typhoid vaccines. |
| **Backflush** | Washing a column, membrane or filter by reverse flow |
| **Bacteriophage** | Often just "'phage'. Virus that infects bacteria, sometimes used as a vector |
| **Baculovirus** | A virus that replicates only in the cells of Lepidopteran insects (butterflies, moths). Often used in genetically engineered form to express target proteins in insect cell cultures. |
| **BEVS** | *Baculovirus expression vector system* |
| **BFS** | *"Blow-fill-seal"* Method of creating plastic containers and filling and sealing them on the same machine. |
| **BHK** | *Baby Hamster Kidney* - established cell line often used in biotech. production |
| **Bioanalytical methods** | Analytical methods specifically applied to biological molecules |

| | |
|---|---|
| **Bioassay** | Analytical methods using whole animals or living cells to determine and measure the biological activity of a molecule or agent. |
| **Bioburden** | The number of contaminating organisms on or in a certain amount of material before that material has been sterilized. |
| **Biologics** | Products of living organisms used in the prevention or treatment of disease. Other name: "biologicals" |
| **Biomass** | The dry weight estimation of organisms in a given medium |
| **Biopharmaceutical** | A biologic product intended for the treatment of disease, most often applied to products of genetic engineering, e.g. Monoclonal antibodies, receptor-blocking proteins, hormones, peptides, etc. |
| **Bioreactor** | A culture vessel for cells or microorganisms. This name is often reserved for equipment for mammalian or insect cell production. Bioreactors for microbial culture ("fermentation") are usually called "fermentors" |
| **BLA** | *Biologics License Application*. The submission to the FDA for approval to market a biologic or biopharmaceutical. These submissions are handled by the Center for Biologics Evaluation & Research (CBER). Equivalent to an NDA (see) for drugs. |
| **BSE** | *Bovine spongiform encephalitis* – potentially transmissible prion infection of cattle, believed to cause a variant form of Creuzfeld-Jacob disease in man. |
| **Bulk** | Large-volume preparation of a biopharmaceutical as it goes through bioprocessing. It may be called "final bulk" when ready for filling into final containers. |
| **Campaign production** | Continuous production of successive lots of the same biopharmaceutical, before the plant is changed to another product. |
| **CBER** | FDA's *Center for Biologics Evaluation and Research* – enforces biologics regulations |
| **CDC** | USA's *Center for Disease Control* and Prevention in Atlanta, Georgia. |
| **CDER** | FDA's *Center for Drug Evaluation and Research* – enforces regulations on all drugs, including some biologics, like hormones. |
| **CDRH** | FDA's *Center for Devices and Radiological Health* – enforces medical device regulations – including diagnostics. |
| **Cell Lines** | Are established from primary cell cultures and are often "immortalized.", i.e. can replicate indefinitely |
| **CFR** | USA's *Code of Federal Regulations*. Those applying to drugs are found in Title 21, as "21CFR..." |

| | |
|---|---|
| **CFU** | *Colony-forming Units*: a measurement of the number of living organisms in a suspension, derived from the number of colonies formed on a culture plate. |
| **cGMP** | The FDA's term for *Good Manufacturing Practice*, prefixed by the word "Current", to emphasize the need to keep practices up to date. |
| **CHO cells** | *Chinese Hamster Ovary* cell lines, often used in expression systems |
| **CIP** | *"Clean in Place"*, describing systems and methods for cleaning large tanks and other equipment that cannot easily be cleaned by hand without extensive dismantling. |
| **Clarify (clarification)** | To clear liquid of suspended particles by filtration, centrifugation, etc. |
| **Clean Room** | A room in which the concentration of airborne particulate matter is controlled to specific limits to enable the manufacture of sterile or high-purity products. Clean rooms are classified according to the number of particles per specific volume of air permitted to meet specific standards of cleanliness. Contaminants on persons entering the room and all surfaces are also controlled. Also termed "sterile room" |
| **Clearance** | Demonstrated removal of an impurity or potential contaminant (e.g. virus) from a product |
| **CMC** | "*Chemistry, Manufacturing and Controls*" – the section of an IND, BLA or NDA that describes the composition, manufacture and specifications of the product. Will be replaced in 2003 by the ICH "Common Technical Document" |
| **CMO** | *Contract Manufacturing Organization* |
| **Contaminant** | A foreign agent or material that is not introduced as part of the manufacturing process, e.g. air-borne particulates, adventitious organisms |
| **COS, CV-1** | Cell line derived from African Green monkey kidney cells |
| **Cosmid** | An artificially constructed plasmid vector that contains a specific bacteriophage gene |
| **CPMP** | *The Committee for Proprietary Medicinal Products* – the EMEA committee responsible for regulating human medical products in the European Union |
| **CRO** | *Contract research organization*, does R&D and contract testing, e.g. for viral clearance methods – may also do clinical research |
| **Degredation** | Loss or reduction in quality, integrity or character – usually due to a physical or chemical reaction which breaks down a molecule into smaller parts |

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| **Denatured protein** | A protein with unfolded or disordered polypeptide chains, which render the molecule less soluble ands usually non-functional. Sometimes a denatured protein can be re-folded and its function restored. |
| **Desorption** | The opposite of adsorption; the release of adsorbed molecules, particles or cells into the surrounding medium |
| **DIW** | *De-ionized water*, purified by passage through special ion-exchange chromatography columns |
| **DNA Vaccine** | A vaccine containing deoxyribonucleic acids – genes coding for specific proteins are injected and enter the host cells. These then express the target antigen and stimulate an immune response. |
| **Downstream processing** | Manufacturing steps applied to material harvested from the fermentor/bioreactor, usually involving concentration and purification of the target molecule by centrifugation, filtration and chromatography |
| **EBA** | *Expanded-bed Adsorption* – capture of the target molecule from relatively crude harvest streams by upward flow through a column of suspended, dense chromatography beads – the contaminants flow through without clogging the column – may also be termed "**EBC**" – expanded-bed chromatography |
| **ELISA** | *Enzyme-linked immunosorbent assay* – test used to measure antibody or antigen concentration |
| **Eluate** | The separated components recovered from a chromatography column during **"elution"** – the passage of buffer solutions which release or "wash out" absorbed products from the chromatographic medium |
| **Eluent** | The buffer solution used to wash out fractions from a column |
| **EMEA** | The *European Medicines Evaluation Agency* – Europe's "FDA" |
| **Endotoxin** | A lipopolysaccharide (fat/sugar complex) that forms part of the cell wall of certain bacteria. It is released only when the cell is ruptured and can cause septic shock and tissue damage. As it also causes a temperature rise when injected into lab animals, especially rabbits, it is also termed "pyrogen" – "that which causes fire". Biopharmaceutical products for parenteral injection must be endotoxin-free. |
| **EPA** | USA's *Environmental Protection Agency.* |
| ***Escherischia coli*** | Usually known as *"E. coli"* a bacterium normally found in the intestinal tract and widely used in genetic engineering. Often used in recombinant studies. |
| **Eukaryotes** | Complex organisms, usually multi-cellular, whose cells contain nuclei. |

**Exclusion Limit** Term used in size-exclusion chromatography (or "gel filtration") - indicates the smallest size of molecule that is too large to enter the pores of the chromatographic medium

**Expression System** A host organism combined with a genetic vector (such as a virus or a circular DNA molecule called a plasmid) that is loaded with a gene of interest. The expression system provides the means whereby the gene will function in the cell, i.e., the gene will be expressed as a protein.

**Expression Vector** A virus, plasmid, cosmid or artificial chromosome that delivers foreign genes to a host. This creates a recombinant organism that will express the desired protein.

**FD&C Act** *Food, Drug and Cosmetic Act* of 1938, the major legislation regulating such products in the United States. It requires companies to prove that their products are safe before marketing them, extends FDA oversight to cosmetics and therapeutic devices, explicitly authorizes factory inspections, requires standards for food, and adds injunctions to previous penalties of seizure and criminal prosecution for violations of related laws.

**FDA** *Food and Drug Administration*

**FDA-483** A form prepared at the conclusion of an inspection (without review by FDA management) citing observations that may constitute violations of law, in the opinion of the inspector. Originally intended to inform companies of possible product adulteration so that prompt corrective action could be taken, 483s now list a host of observations. Form 483s can lead to withholding of product approvals, may come into play in due diligence phases of acquisitions and mergers, and can potentially cost companies money.

**FDAMA** *FDA Modernization Act*, enacted in November 1997, this amends the FD&C Act to improve (facilitate) the regulation of food, drugs, devices, and biological products.

**Fermentor** A large bioreactor used to grow bacteria or fungi in liquid culture.

**Fill-and-finish** The part of a manufacturing process concerned with packaging a product in its final form.

**For-cause inspection** An FDA facility inspection carried out because of specific information such as the results of a sample analysis, observations made during previous inspections, product recall or market withdrawal, consumer of employee complaint, adverse reaction report, or suspicion of fraud. Also, a similar inspection of a clinic or an IRB.

**GCP** *Good clinical practice*; according to 21 CFR Parts 56, 312, and 314, the regulations that govern the actions and environment of those working in clinical testing of drugs and medical devices on human beings.

**Gene therapy** Treats, cures, or prevents disease by changing the expression of a person's genes or inserting genes into the genome. Current gene therapy is primarily experimental, with most human clinical trials only in the research stages, Gene therapy can target somatic (body) or germ (egg and sperm) cells. In somatic gene therapy, the recipient's genome is changed, but the change is not passed along to the next generation. In germ-line gene therapy, the parents' egg and sperm cells are changed with the goal of passing on the changes to their offspring.

**Genetic engineering** Altering the genetic structure of an organism (adding foreign genes, removing native genes, or both) through technological means rather than traditional breeding.

**GLPs** *Good laboratory practices;* according to 21 CFR Part 58, regulations to ensure quality of nonclinical laboratory studies related to safety. All activity is recorded, trained staff uses only established procedures, and records and samples are maintained.

**Glycoproteins** Proteins that contain sugar side chains added as a prosttranslational process; presence of sugar side chains often affects activity and in vivo stability.

**Glycosylation** Adding one or more carbohydrate molecules onto a protein (a *glycoprotein*) after it has been built by the ribosome; a posttranslational modification.

**GMPs** *Good manufacturing practices*; according to 21 CFR Parts 210, 211, 600, 610, and (for devices) 820, current good manufacturing practice (CGMPs) influence the manner in which biopharmaceuticals and other drugs and medical devices are produced. Standard operating procedures must be followed, processes must be validated, equipment must be qualified, and properly trained staff must maintain a clean/sterile environment.

**GRAS** *Generally recognized as safe*, a special status afforded by FDA to ingredients and methods that have a proven, longstanding history of causing no harm to humans or animals.

**Guidance for Industry** The next regulatory level up from a *Points to Consider* (PTC) document (and below official *Code of Federal Regulations* law).

**GXP** All-inclusive term for GCPs, GLPs, and GMPs.

**HEPA filtration** *High-efficiency particulate air* filter used to remove contaminants or to prevent particles from entering a clean room.

**HIC** *Hydrophobic interaction chromatography*, a type of liquid chromatography that makes use of the relative solubility of proteins and matrix materials. Hydrophobic interactions are strongest at high ionic strength, so salt is usually included to increase those levels.

**HPLC** — *High-performance liquid chromatography* or *high-pressure liquid chromatography*; a form of liquid chromatography in which a sample is forced at high pressure through a column that is packed tightly with chromatographic media.

**HVAC** — The *heating, ventilation and air conditioning* systems in a biopharmaceutical production facility.

**Hybridoma** — An immortalized cell line (usually derived by fusing B-lymphocyte cells with myeloma tumor cells) that secretes desirable antibodies.

**ICH** — The *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* a project bringing together the regulatory authorities of Europe, Japan, and the United States with experts from the pharmaceutical industry to discuss scientific and technical aspects of product registration. Its purpose is to recommend ways to harmonize the technical guidelines and requirements for product registration and reduce or obviate the need to duplicate testing during development of new medicines.

**IEC** — *Ion-exchange chromatography*, sometimes abbreviated IEX, a liquid chromatographic technique based on the electrical phenomenon of ion exchange. The amphoteric nature of proteins can be exploited to bind them in cation-exchange (binding positively charged proteins) or anion-exchange (binding negatively charged proteins).

**IND** — The *Investigational New Drug* application, by which a company files a request with FDA for permission to test its experimental drug in patients or healthy human volunteers. This application must be filed for each individual clinical study performed, phases 1-3.

**IRB** — *Institutional review board*, a committee or other group (composed of medical, scientific, and nonscientific members) that is responsible for protecting the rights, safety, and well-being of human subjects participating in clinical trials.

**ISO** — The *International Organization for Standardization*, a worldwide federation of national standards bodies from some 140 countries. ISO is a nongovernmental organization that promotes the standardization and related activities to facilitate the international exchange of goods and services. The organization accredits companies with its generic management system standards, ISO 9000 (for quality) and ISO 14000 (for environmental impact).

**LC/MS systems** — *Liquid chromatography/mass spectrometry* systems, laboratory instruments that combine two popular analytical methods into one piece of equipment.

**LC/MS/MS** Liquid chromatography with tandem mass spectrometry detection; a highly selective bioanalytical method using an atmospheric-pressure ionization triple-quadrupole mass spectrometer to measure the difference in the mass-to-charge ratio of ionized molecules and fragments.

**Ligands** Molecules or ions that chemically bind to certain other molecules or ions. In a binding action, usually the smaller of the two molecules is considered the ligand.

**LMIS** *Laboratory information management system*; computers and software that handle all the data produced by laboratory research and analytical methods.

**MAb** *Monoclonal antibody*; a highly specific, purified antibody that recognizes only a single epitope.

**MALDI-TOF** *Matrix-assisted laser desorption ionization-time of flight* mass spectrometry technique for determining molecular weight. Electrons become excited after laser irradiation, transferring energy into the mixture and causing molecules and ions to be ejected from its surface. Commonly used in proteomic and peptide analyses.

**Master cell banks** Cultures of fully characterized cells are distributed into containers in a single operation, processed together to ensure uniformity, and stored to ensure stability. Cell cultures derived from the master cell bank are used to prepare *working cell banks* for production.

**MedDRA** The *Medical Dictionary for Regulatory Activities* is the global standard medical terminology. Major global regulatory authorities in ICH countries are adopting MedDRA and moving toward requiring its use. FDA has implemented MedDRA within its adverse event reporting system. European authorities are beginning to use MedDRA as a key component of their electronic data base systems.

**Microassays** Assays usually run on very small samples, often using "microplates", and often automated. Microplates can have room for 96, 384, or even 1,536 tiny samples. Microassays measure small quantities of components even when the sample size is large.

**Microcarrier** A microscopic particle (often a 200-μm polymer bead) that supports cell attachment and growth in suspension culture; alternative to microencapsulation. Cells anchor into tiny pores on the beads for protection.

**MSDS** *Material safety data sheets*, documentation (including data describing physical characteristics, toxicity, health effects, first aid, reactivity, storage, disposal, protective equipment, and spill/leak procedures) that provides workers and emergency personnel with the proper procedures for handling or working with a particular substance.

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| **NDA** | The *New Drug Application*, CDER's equivalent of the BLA. It is used for small-molecules and some bio-pharmaceuticals (such as hormones and small peptides), which are regulated by CDER rather than CBER. |
| **NIH** | *National Institutes of Health*, the U.S. government agency that conducts and supports medical research and dissemination of information. One of eight agencies in Public Health Services, which is in turn part of the U.S. Department of Health and Human Services. |
| **NIST** | *National Institutes of Standards and Technology*, a federal agency that develops and certifies standard reference materials for use in various U.S. industry applications. |
| **Optimization** | Determining and implementing process operation at the best possible and most affordable efficiency. |
| **Outsourcing** | Having research or manufacturing done by a contract organization. |
| **PAI** | *Preapproval inspection*; an FDA facility inspection performed in response to a biopharmaceutical company's filing a BLA or NDA. |
| **Parenteral delivery** | Drug delivery by injection; subcutaneous, intramuscular, and intravenous delivery are most common. |
| **PDUFA** | *Prescription Drug User Fee Act* (of 1992). |
| **Pilot plant** | A medium-scale bioprocessing facility used as an intermediate in scaling up processes from the laboratory to commercial production. |
| **Plasmid** | Hereditary material that is not part of a chromosome. Plasmids are circular and self-replicating and found (naturally in bacteria and some yeasts) in the cytoplasm of cells. They can be used as vectors for introducing up to 10,000 base-pairs of foreign DNA into recipient cells. |
| **Polishing** | The final purification step(s) in a biopharmaceutical manufacturing process, usually involving an affinity or other refined chromatography method. Often this step uses the most expensive technique in the process because it handles the smallest amount of material. |
| **Postapproval changes** | Changes (scale-up, for example) made to a biopharmaceutical manufacturing process after the drug has been approved for marketing. |
| **Postmarketing surveillance** | Phase 4 clinical trials, which provide additional details about a product's safety (while the product is on the market) and efficacy and may be used to evaluate formulations, dosages, durations of treatment, medicine interactions, additional indications, and other factors. |

**Preparative chromatography** — Chromatography methods used in manufacturing rather than analytical applications, larger in scale and intended to purify a product; also called *process chromatography*

**Primary recovery** — The early steps in separation and purification of a biopharmaceutical, in which a complex biological solution containing the protein of interest is concentrated and clarified, usually by means of filtration, centrifugation, or extraction (precipitation).

**Prion** — Believed to be the smallest, simplest infectious particle consisting entirely of hydrophobic protein (no nucleic acid, DNA, or RNA), suggested as a possible model for the causal agent of scrapie and related diseases. (Term originally derived from *proteinaceous infectious particle.*)

**Process control** — Management of the many parts of a manufacturing process, usually involving sophisticated computer systems.

**Prokaryotes** — Simple organisms, such as bacteria, with no cell nuclei and only a few cell organelles.

**Protocols** — Documentation (submitted to FDA or other agency in support of regulatory filings) that directs the work performed in an FDA-regulated company. Protocols tell who directs which activities, who approves what, and who is allowed to sign off on materials and products, even where to find specific files and documents – all tying together numerous SOPs.

**PTC** — *Points to Consider* documents are not regulations with the force of law, but are instead guidelines on issues that FDA believes should be considered by regulated industry. These documents are not definitive or all-inclusive. In fact, they are presented as drafts subject to further modification, and readers are invited to submit comments. They acknowledge that processes and associated knowledge change with time. They suggest and recommend procedures that manufacturers should consider during development of new drugs and biologics.

**Pyrogen** — Any fever-inducing (pyrogenic) substance; more specifically, a lipopolysaccharide (the manor constituents of the cell walls of Gram-negative bacteria). The major endogenous pyrogen in mammals is probably interleukin-1, production of which is stimulated by lipopolysaccharide.

**QA/QC** — *Quality assurance/quality control*; the testing, documentation, and enforcement of product quality; a company's department that performs that function, including product release.

**Qualification** — Documenting that a piece of equipment does what it was designed to do, was installed correctly, and continues to operate within specified parameters over time.

**Regulatory affairs** Drug companies must show that their products consistently meet standards set by government agencies. Regulatory affairs departments document those activities, submit proposals, and follow those proposals through completion or approval. RA provides regulatory strategy and sets up meetings with regulatory bodies.

**Robust** Strongly formed or constructed, sturdy; a product or process that doesn't break easily or remains stable and (for a process) reproducible despite physical and chemical stress or varying conditions.

***Saccharomyces cerevisiae*** Brewer's yeast, also the yeast used to leaven bread, was the first and is still the most widely used yeast species in biotechnology. Certain strains are used in the manufacture of alcoholic beverages and fermented foods – and also for expression of genes. Biologically active interferons, for example, have been produced in *S. cerevisiae.*

**Scale-down** To transfer a biopharmaceutical manufacturing process (or section of that process) down to the laboratory scale, usually for validation or other study purposes.

**Scale-up** To transfer a biopharmaceutical manufacturing process from the laboratory scale to a scale at which it is commercially feasible.

***Schizosaccharomyces pombe*** The second most commonly used yeast species in biotechnology, originally used in east Africa to brew millet beer but which is typically unsuitable for other types of fermentation because of the large amount of sulfurous compounds it emits.

**SDS-PAGE** *Sodium dodecyl sulfate-polyacrylamide gel electrophoresis*; The detergent unfolds proteins, aiding in their separation. The analytical separation technique uses a charged gel environment through which molecules of varying sizes and electric charges migrate from one pole to the other. Unlike gel-filtration chromatography, larger molecules move more slowly than smaller molecules because migration rate is not dependent on diffusion into and out of particles.

**SEC** *Size-exclusion chromatography*, gel-filtration or gel-permeation chromatography; an analytical method that uses porous particles to separate molecules of different sizes. Molecules that are smaller than the pore size can enter the particles and therefore have a longer path and longer transit time than larger molecules that cannot enter the particles. SEC can separate biological molecules and help determine the molecular weights and molecular weight distributions of polymers.

**SIP** *Steam-in place*; using steam to clean and sterilize equipment or systems without removing them from their installed location (see CIP).

**Skid** Common term for a complete chromatography system on wheels.

**SMB** *Simulated moving bed*, a method in liquid chromatography of making separations constant rather than a batch process.

**SOPs** — *Standard operating procedures*; detailed (step-by-step), instructions to achieve uniformity in the performance of a specific process or piece of equipment.

**Sparge** — To spray. A sparger is the component of a fermentor that sprays air into the broth.

**Specifications** — Documentation required by regulations that describes in detail (purchasing information, chemical formulas, handling precautions, storage conditions, expiration dates, testing requirements and so on) a raw material, piece of equipment, drug substance, product, or other item.

**Spike** — Adding a known amount of analyte from a laboratory standard, sometimes with something highly reactive (such as a radioactive or fluorescent dye) to act as a tracer. The method is also used with viruses in clearance studies.

**Tangential flow filtration** — A separation method that transfers components of one system (stream) into another. The stream the product is being extracted from crosses the stream that the product is being transferred to multiple times.

**Team Biologics** — A partnership between FDA's Office of Regulatory Affairs (ORA) and CBER to focus on inspection and compliance issues in biologics. Its goal is to ensure the quality and safety of biologic products and resolve inconsistencies.

**TOC analysis** — *Total organic carbon* analysis, an analytical method whereby organic carbon is oxidized to produce CO2, the amount of which produced is directly proportional to the amount of carbon present. Measurement of CO2, as a result, indicates the presence of organic molecules. TOC analysis is used to test pure water and to evaluate and validate cleaning procedures.

**Treatment IND** — An IND that makes a promising new drug available to desperately ill patients as early in the drug development process as possible.

**TSE** — *Transmissible spongiform encephalopathy*, a type of brain disease generally believed to be caused by prions.

**Turnkey system** — A piece of equipment, process train, or manufacturing plant that is delivered to the customer in a ready-to-run condition, specialized for the customer's application, with no additional equipment or modifications required.

**USP** — The *United States Pharmacopeial Convention, Inc.*, which established and disseminates officially recognized standards of quality and authoritative information for the use in the manufacture and testing of drugs, excipients, and raw materials.

**UV-vis** *Ultraviolet-visible* spectroscopy, an analytical method that measures the absorption of light in the 200-750 nm range of the electromagnetic spectrum. It is used in determining protein concentration and is often applied to HPLC detection.

**Vero** An established cell line derived from the kidney of the African green monkey.

**Warning letter** The most serious FDA postaudit (after inspection) letter, notifying a manufacturer of adverse findings and giving it 15 days to reply.

**WFI** *Water for injection*; very pure water suitable for medical uses.

**WHO** The *World Health Organization*, a United Nations organization.

**YAC** *Yeast artificial chromasome*, a vector used to clone DNA fragments up to 100,000 base-pairs long. YACs are constructed from the telomeric, centromeric, and replication sequences of yeast cells.

## 21 CFR PART 11 Vocabulary

**Access security** Determines who is allowed to log on to a system (locally or from the network) and puts mechanisms in place that prevent unauthorized persons from gaining access to the computer system. Some operating systems (such as Mac OSX, Unix or Windows NT) offer configurable access privileges that can be granted or denied to specific users or groups of users. MS-DOS , Windows, Windows 95, and Windows 98 do not have such capability.

**ANDI** *Analytical data interchange*, a generic file format. It was common practice before Part 11 to save information from analytical instruments in this file format. The disadvantage now is that the approach does not allow replaying of data on a different system to yield the same result.

**Audit trail** A computer- generated and time-stamped record of who did what, when. Part 11 requires audit trails to be generated independently of operators. An audit trail must capture all activities related to creating, modifying, and destroying records on a system.

**Black box testing** Software testing from the customer's perspective, without knowledge of the code; testing of the specifications that discover faults of omission.

**CA** *Certificate authority*, a trusted third-party organization that issues digital certificates used to create digital signatures and public-private key pairs. The role of the CA is to guarantee that the people granted the unique certificates are who they claim to be. Usually, that means the CA has an arrangement with a financial institution, such as a credit card company, that provides it with information to confirm an individual's claimed identity. CAs are a critical component in data security and electronic commerce because they guarantee that the two parties exchanging information really are who they claim to be.

**Closed system** An environment in which system access is controlled by persons responsible for the content of the records on the system.

**Data integrity** The validity of data and their relationships. For electronic records to be trustworthy and reliable, the links between raw data, metadata, and results must not be compromised or broken. Without data integrity, it is not possible to regenerate a previous result reliably.

**Data migration** The process of translating data from one system to another when a company replaces the current computing systems with a new one. Part 11 mandates that data migration implementation create accurate and complete copies of the records when they are moved to a new system.

**Digital signature** An electronic signature based on cryptographic methods of originator authentication, computed by using a set of parameters so that the identity of the signer and the integrity of the data can be verified.

**Durable storage device** — A device (a computer component) that holds and retains data. Typically the computer's hard disk or a storage card for a particular instrument.

**Electronic records** — Any combination of text, graphics, data, audio, pictorial, or other information represented in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system. Examples for analytical laboratories include methods for instrument control and data evaluation, calibration tables, original data as captured by the computer, processed data, analysis reports, chromatograms with baselines, log books, and audit trails.

**Electronic signature, digital signature, or e-sig** — According to FDA, an electronic signature is "any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature." A digital signature is an electronic signature "based upon cryptographic methods of originator authentication, computed by using a set of parameters so that the identity of the signer and the integrity of the data can be verified."

**External or remote access** — The ability to log on to a network from a distant location. The system containing data is the host, and the computer at which a user sits is called the remote terminal. Slower data transfer speeds are the only difference between a remote station and a workstation connected directly to the network.

**Hybrid systems** — Combinations electronic and paper records are common in today's analytical labs, in which raw data are recorded electronically to reconstruct the analysis, but the final results are printed and signed on paper. FDA does not prohibit hybrid systems but has expressed some concerns about their usefulness.

**ID parameters** — Set authentication and authorization codes usually related to a user ID and password. The unique set of characters that enables a user to access files, issue commands, or run programs.

**IEEE** — The *Institute of Electrical and Electronic Engineers* that develops standards for computers and the electronics industry.

**LAN** — A *local area network*, one with computers geographically close together (that is, in the same building). Wide-area networks (WANs) have computers farther apart, connected by telephone lines or radio waves.

**Legacy systems** — Hardware and software applications in which a company already invested considerable time and money. Legacy systems typically perform critical operations in companies for many years even though they may no longer use state-of-the-art technology. Replacing legacy systems can be disruptive and therefore requires careful planning and appropriate migration support from the manufacturer.

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| **Metadata** | Include processing parameters and audit trail logs. In chromatography, metadata include integration parameters and calibration tables. Metadata allow reviewers to replay the original result from raw data. Metadata are important for reconstructing a final report from raw data. In chromatography, they include integration parameters and calibration tables. In long division, "1,000 / 5" would be the raw data, the work you had to show on your paper in fourth grade math class would be the metadata and "200" would be your result. |
| **ODBMS** | An *object database management system*, which is specifically designed to manage and store complex objects and their complex relationships; that is, such items are stored as objects rather than as tables or fields. They support modeling and creation of data as objects, allowing for greater flexibility in tracking parent method sets and subcomponents. Such systems may be better than relational database management systems at meeting the data integrity requirements of Part 11. |
| **Open system** | An environment in which system access is not controlled by persons responsible for the content of the electronic records on that system; one with little or no security, authorization, or authentication. |
| **Operational checks** | In a computer system, operational checks extend the concept of controlling user access to ensuring that the steps in the workflow follow the permitted sequence, and the proof of that correct process is linked to a given electronic field. |
| **OS** | The most important program run on a computer, its *operating system* manages all the other programs. All computers must have an OS to run other programs. Operating systems perform basic tasks, such as recognizing input from the keyboard, sending output to the display screen, keeping track of files and directories on the disk, and controlling peripheral devices such as disk drives and printers. For large systems, the OS has even greater responsibilities and powers. It is like a traffic cop, making sure that different programs and users running at the same time do not interfere with each other. The operating system also is responsible for security, ensuring that unauthorized users do not access a system. Microsoft Windows NT, LINUX, Mac OSX and UNIX are operating systems. |
| **RDBMS** | A *relational database management system* stores data in related tables. A relational database is powerful because it doesn't assume how data are related or how they will be extracted from the database. As a result, the same database can be viewed in many different ways. |
| **Security mechanisms or dedicated security mechanisms** | Techniques for ensuring that data stored in a computer cannot be read or compromised. Most security measures involve encryption or passwords. |
| **TCP/IP** | *Transmission control protocol/Internet protocol* language enable devices to exchange information over a network. |

**Time stamp** Part of the audit trail that clearly documents the sequence of events in human terms, helping to authenticate an electronic signature and minimizing the chance of signer repudiation. A local time stamp correlates with the whereabouts of the signer. With client-server data systems used by international companies and records accessed from remote sites (such as on business trips), time stamps that reflect the local time of only the user might make the sequence of actions for an individual record appear inconsistent. For example, the approval by a peer reviewer could be signed at 9:00 am on a chromatographic analysis that was performed at 11:00 am in a different time zone. Local time stamps should probably be supplemented consistently with the time stamp of a remote server, with one stamp clearly labeled as local.

**White box testing** More expensive testing than black box testing, requiring knowledge of the source code; testing of the implementation that discovers faults of commission.