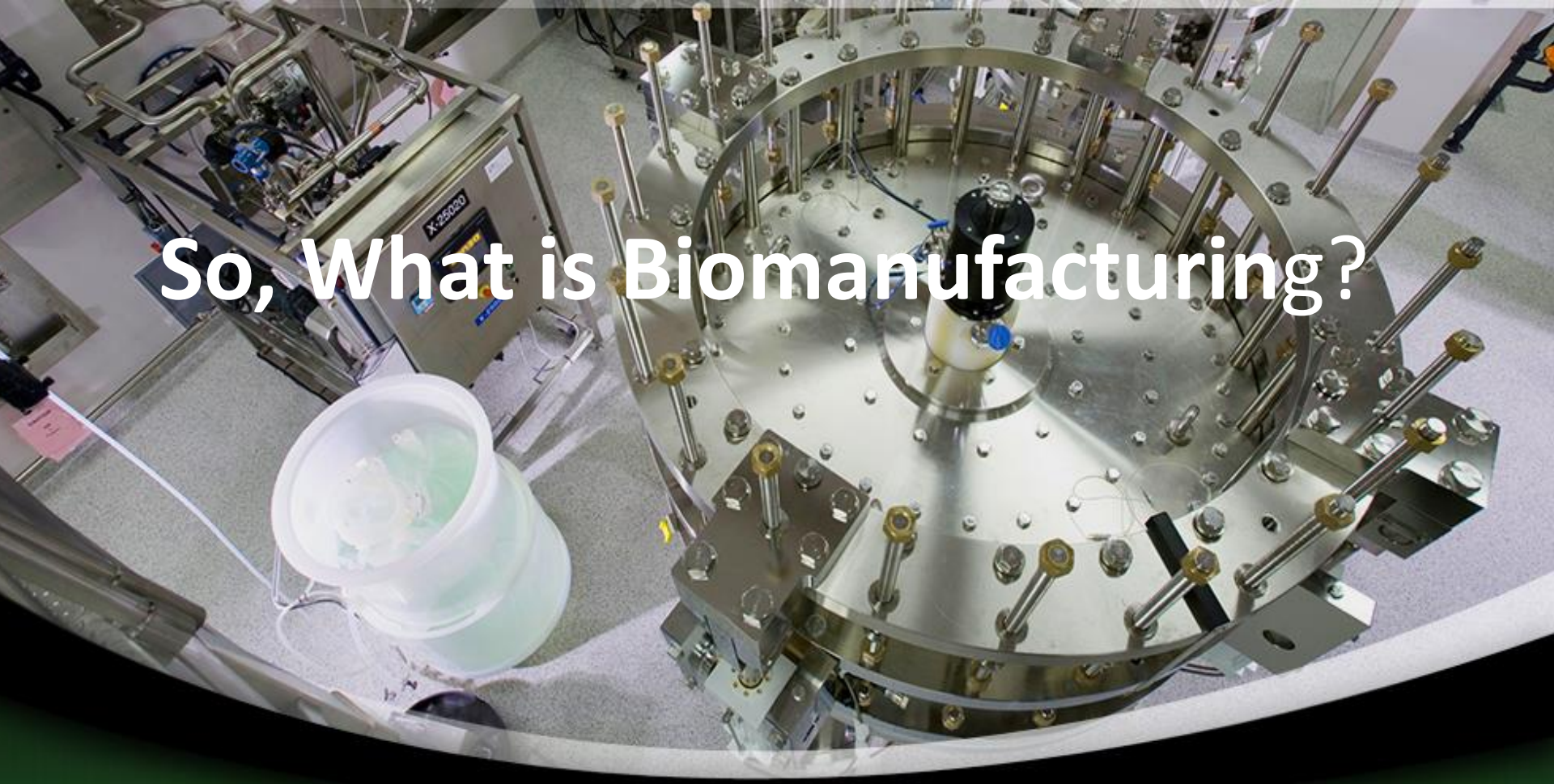


So, What is Biomanufacturing?

Bench Top to Bottle

Facilities in Biopharmaceutical Manufacturing

Competencies/Job and Career Opportunities

NBC²

Basis of the Bioeconomy

Central Dogma: DNA → RNA → Protein

- Discovery Research (DNA Centric)
- Process Development and Biomanufacturing (Protein Centric)

The Drug Discovery, Development and Approval Process for Biopharmaceuticals (Biologics)

DISCOVERY DEVELOPMENT LAUNCH

Testing Phase	Discovery / Preclinical Testing
Test Population	Laboratory and animals studies
Purpose	Assess safety biological activity and formulations
Success Rate	5,000 compounds evaluated
Manufacturin Activities	Cell line construction, Cell banking
Years	6.5
Approximate Cost	$350M

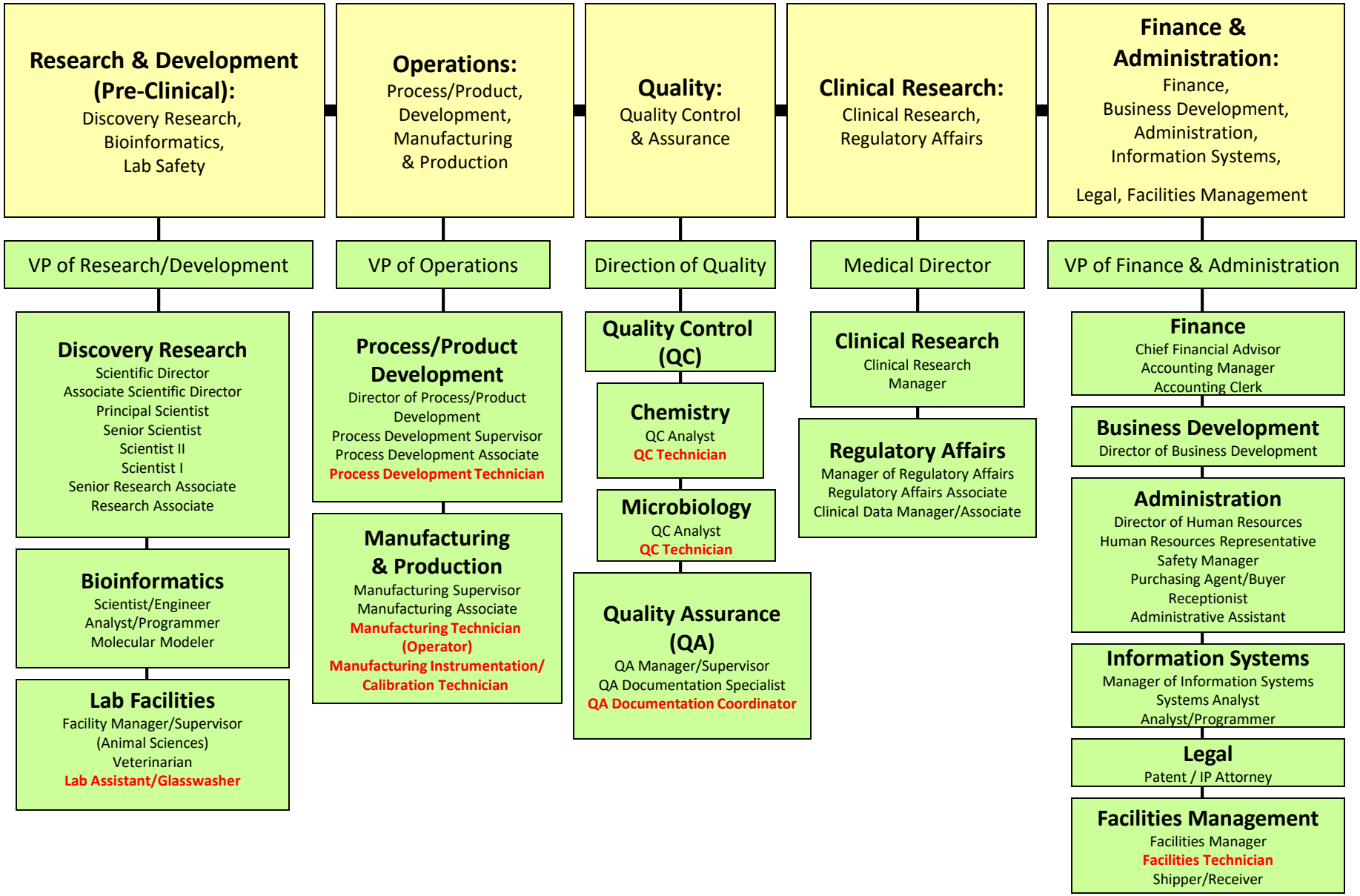
File IND at FDA

Clinical Trials		
Phase I	Phase II	Phase III
20 to 100 healthy volunteers	100 to 500 patient volunteers	1,000 to 5,000 patient volunteers
Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use
5 enter trials		
Process development, assay development, process optimization, scale-up, cGMP manufacture		
1.5	2	3.5
$70M	$100M	$200M

File NDA at FDA

File application	Phase IV
Review process / approval	Additional post-marketing testing required by FDA
1 approved	
Commercial manufacture	
1.5	=15
$80M	= $1B

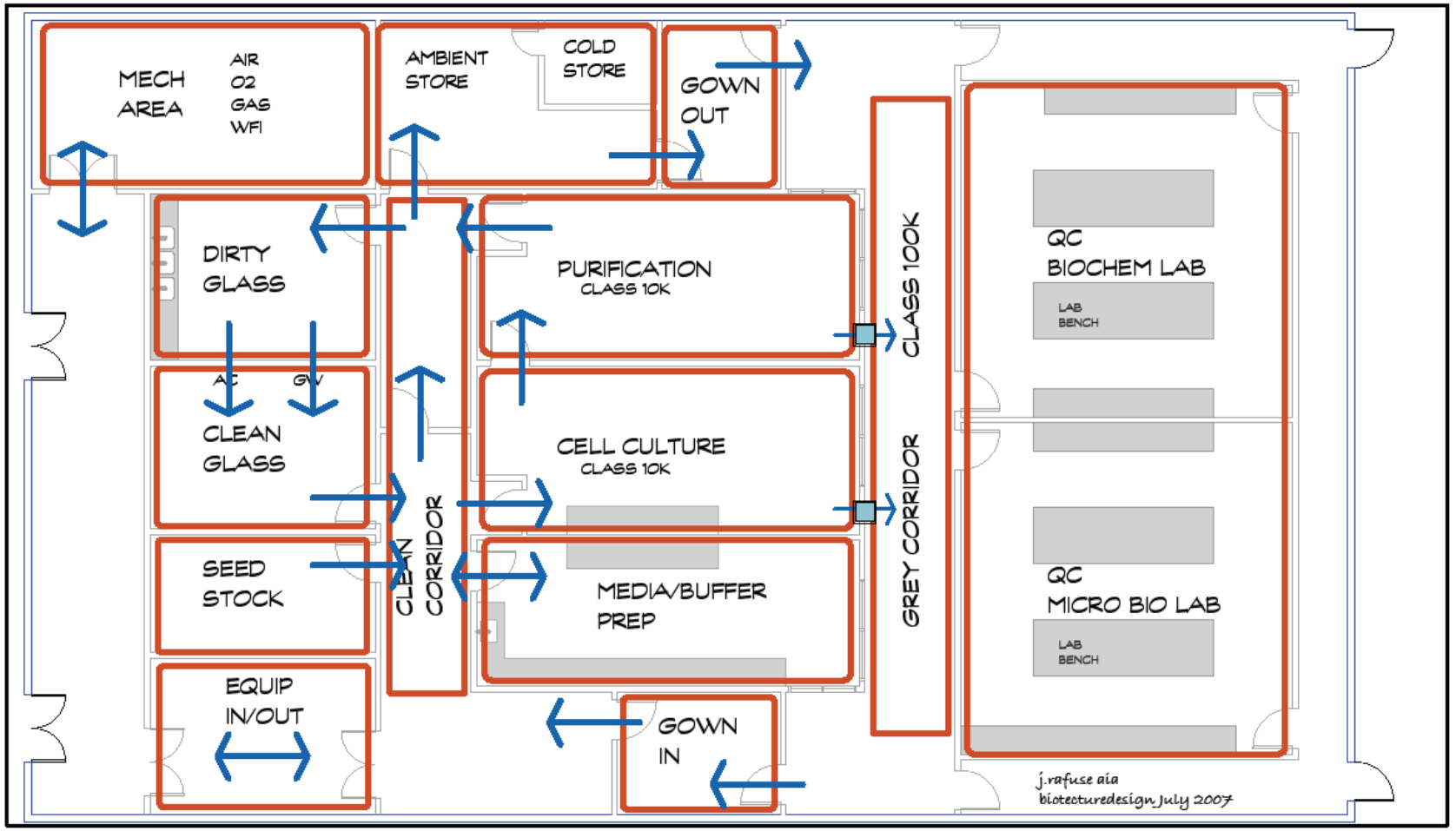
Career Opportunities in Biotechnology/Biomanufacturing



Ten Technician Jobs Anchor Ten Biomanufacturing Departments

- Facilities/Metrology
- Validation
- Environmental Health and Safety (EH&S)
- QA
- Upstream Processing
- Downstream Processing
- QC Microbiology
- QC Biochemistry
- Process Development

Pilot Plant – Overall Flow Plan



320 Corporate Drive Portsmouth, NH 03801	PILOT Process Development Training Facility	OVERALL PLAN FLOW July 4, 2008	JOHN RAFUSE AIA Lab Design + Planning 82 Wagon Wheel Trail Meredith, NH 03253 603-279-2522	A-3

Facilities in Gray Space

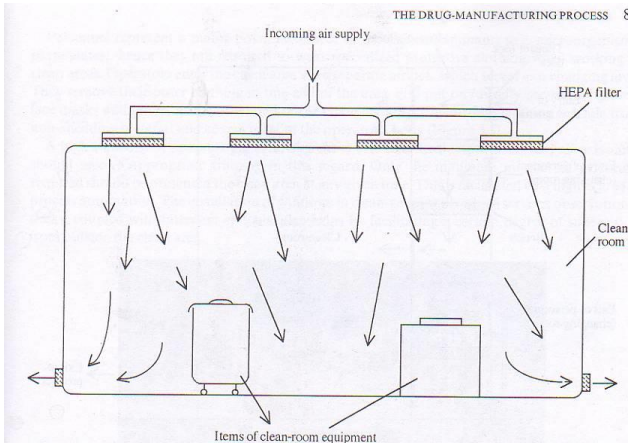
Production Clean Rooms

Cleanrooms are Maintained by Facilities/Metrology Technicians to the Following Specifications

FS209 Cleanroom classification	ISO 14644-1 Cleanroom classification	≥0.5um particles/m3	Viable Microbes (cfu/m3)	Ave Airflow Velocity (fpm)	Air changes/hr
100,000	8	3,520,000	100	5-10	5-48
10,000	7	352,000	10	10-15	60-90
1000	6	35,200	7	25-40	150-240
100	5	3,520	1	40-80	240-480

Facilities: General Cleanroom Design

- HEPA filters in ceiling
- Exhaust vents on floor
- Seamless and rounded floor to wall junctions
- Readily accessible corners
- Floors, walls, and ceilings constructed of smooth hard surfaces that can be easily cleaned
- Limited equipment, fixtures and personnel
- Layout of equipment to optimize comfort and movement of operators
- Pressure Differentials between rooms
- Airlocks to control air balance



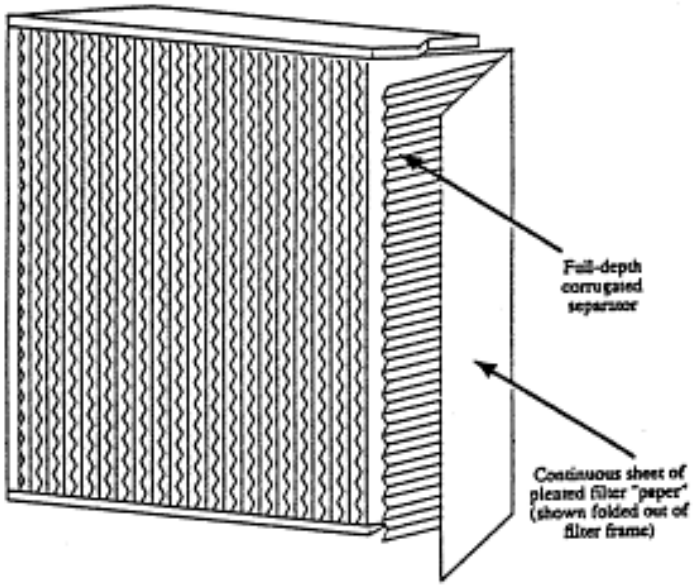
Facilities: HEPA Filters

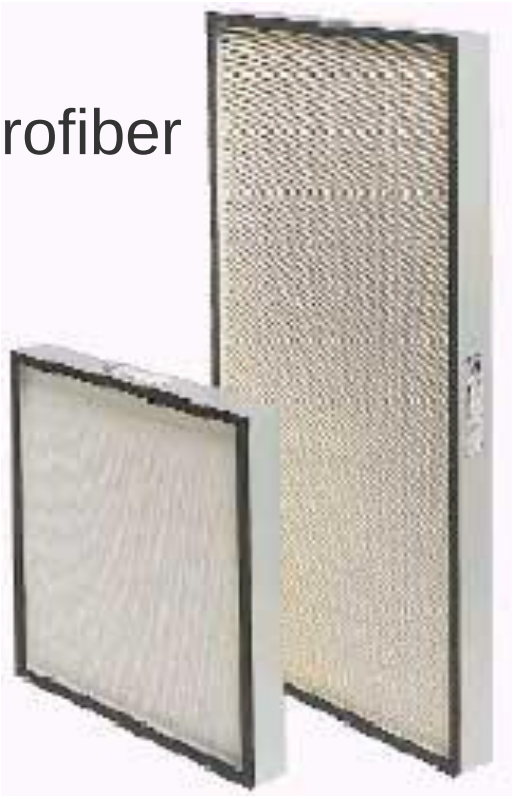
High Efficiency Particulate Air

Minimum particle collection efficiency:
99.97% for 0.3µm diameter particles.

Disposable

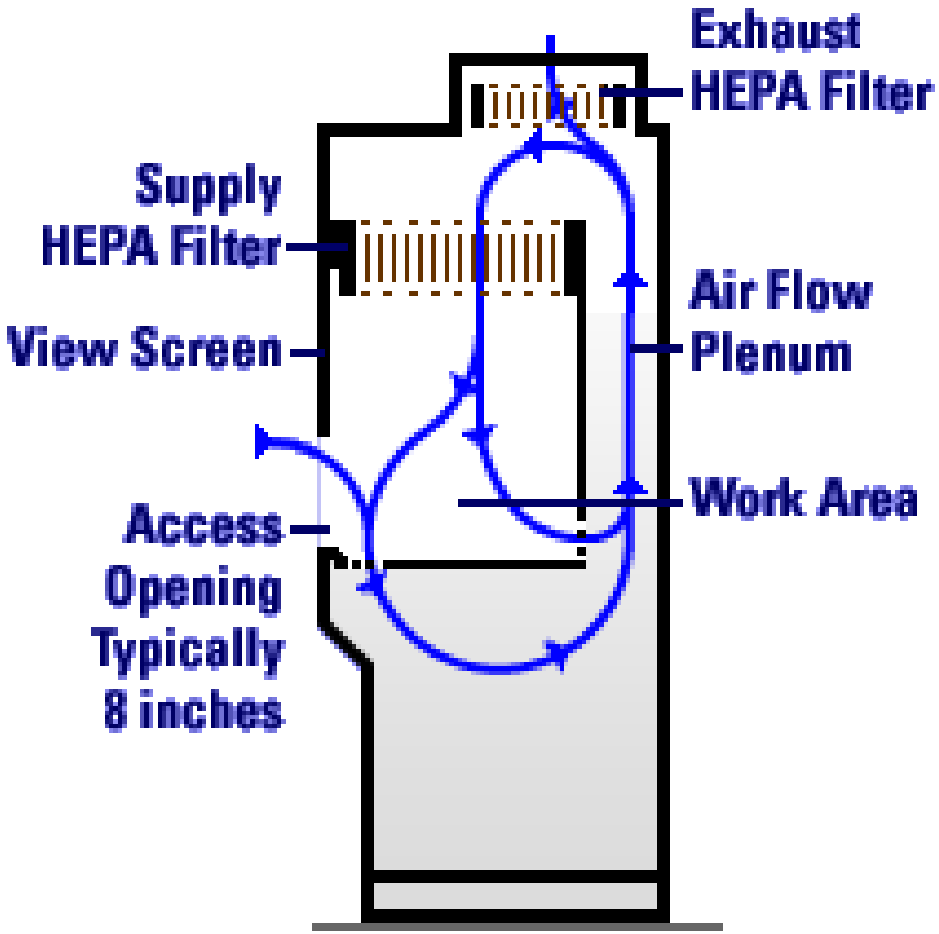
Filter made of pleated borosilicate glass microfiber





http://people.deas.harvard.edu/~jones/lab_arch/nano_facilities/hepa.gif

Biological Safety Cabinets
Class 100



Facilities:
Pressure Differentials

- Used to maintain airflow in the direction of higher cleanliness to adjacent less clean areas
- A minimum of 10-15 Pascals should be maintained between the aseptic area and an adjacent room with a different clean room classifications (doors open)

Facilities: Airlocks

Permit the passage of objects and people into a clean room.

Consists of two airtight doors in series which do not open simultaneously.

Spray down materials with 70% IPA before placing in the airlock

http://news.thomasnet.com/images/large/451/451402.jpg

ISOPROPYL ALCOHOL

- Powerful disinfectant and antiseptic
- Mode of action: denatures proteins, dissolves lipids and can lead to cell membrane disintegration
- Effectively kills bacteria and fungi
- What is not killed by IPA?
- Why are aqueous solutions are preferred?

Gowning Certification

INCORRECT

Biopharmaceutical Manufacturing
QC Microbiology

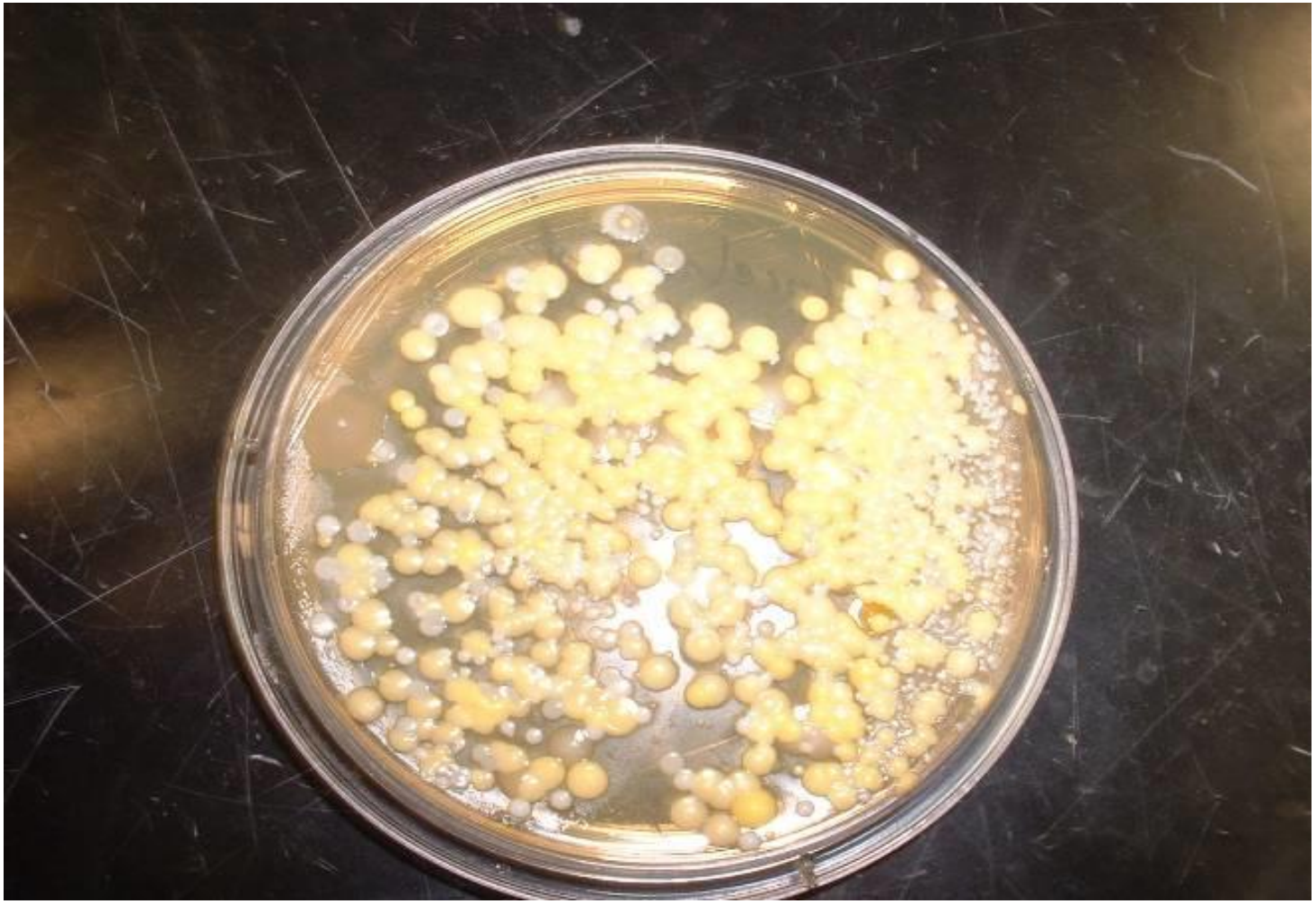
A significant portion of the cGMP regulations pertain to the quality control laboratories including the QC Microbiology Unit which carries out microbiological testing of the product and the microbiological control of site utilities and environment. The principal functions of this unit are: Environmental Monitoring, Microbiological Testing and ID, and the Cell Culture Collection.

•**Environmental Monitoring = Monitor non-viable and viable contamination (bioburden) throughout the facility using laser particle counter and microbial air sampler.**

•Microbiological Testing and ID = Gowning certification, air sample processing, production (raw materials, upstream and downstream processing, aseptic fill and finish and storage) and other samples for microbiological contamination (bioburden); ID using Microbial ID System (Biolog, API Strips, PCR, other tests). Use LAL test for endotoxin in WFI water, raw materials and product. Test for mycoplasma in cell cultures (PCR, other tests).

•Cell Culture Collection = Testing and release of cell banks.

INCORRECT



FOREHEAD

ENVIRONMENTAL MONITORING

"In aseptic processing, one of the most important laboratory controls is the environmental monitoring program"

Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing
Current Good Manufacturing Practice, FDA, September 2004

QC Microbiology – Environmental Monitoring

Laser Particle Counter

Air Samplers

Environmental (Air) Monitoring

Particles

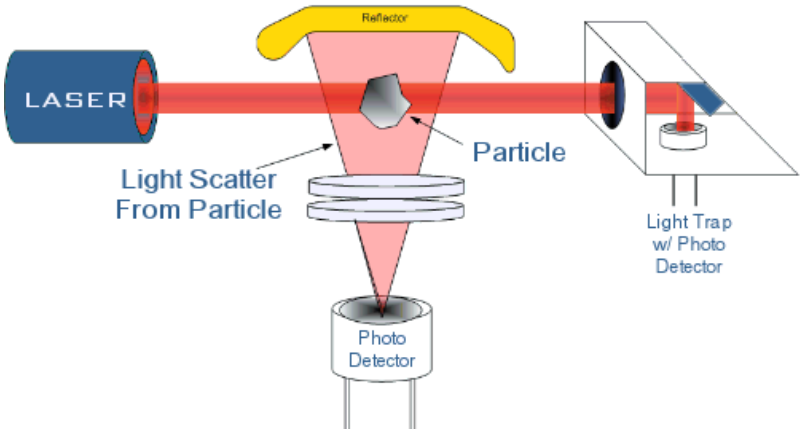
Laser Particle Counter

Viable Microbes (Bioburden)

Microbial Air Sampler

Environmental (Air) Monitoring

Laser Particle Counter (particles/cubic meter)



Microbial Air Sampler (colony forming units/ cubic meter)

www.safety-epa.com/history_mold_air_sampling.htm

Utilities Managed by Facilities/Metrology Technicians

Water*: 200,000 to 300,000 liters of water are used per day in a commercial biopharmaceutical manufacturing facility.

- WFI: sand, diatomaceous earth, charcoal filter, water softener, RO, uv treatment, distillation, and constant circulate in a loop at 80 C degrees. WFI piped to production equipment for CIP and SIP processes and for making media and buffers for production.
- DI and USP water used in QC labs (less pure); chilled potable water used for cooling.

Gasses:

- Air, oxygen, and carbon dioxide to keep cells happy, nitrogen, and helium (to check for leaks in equipment).

HVAC: Heating, ventilation, and air conditioning in clean rooms and gray spaces.

Waste*:

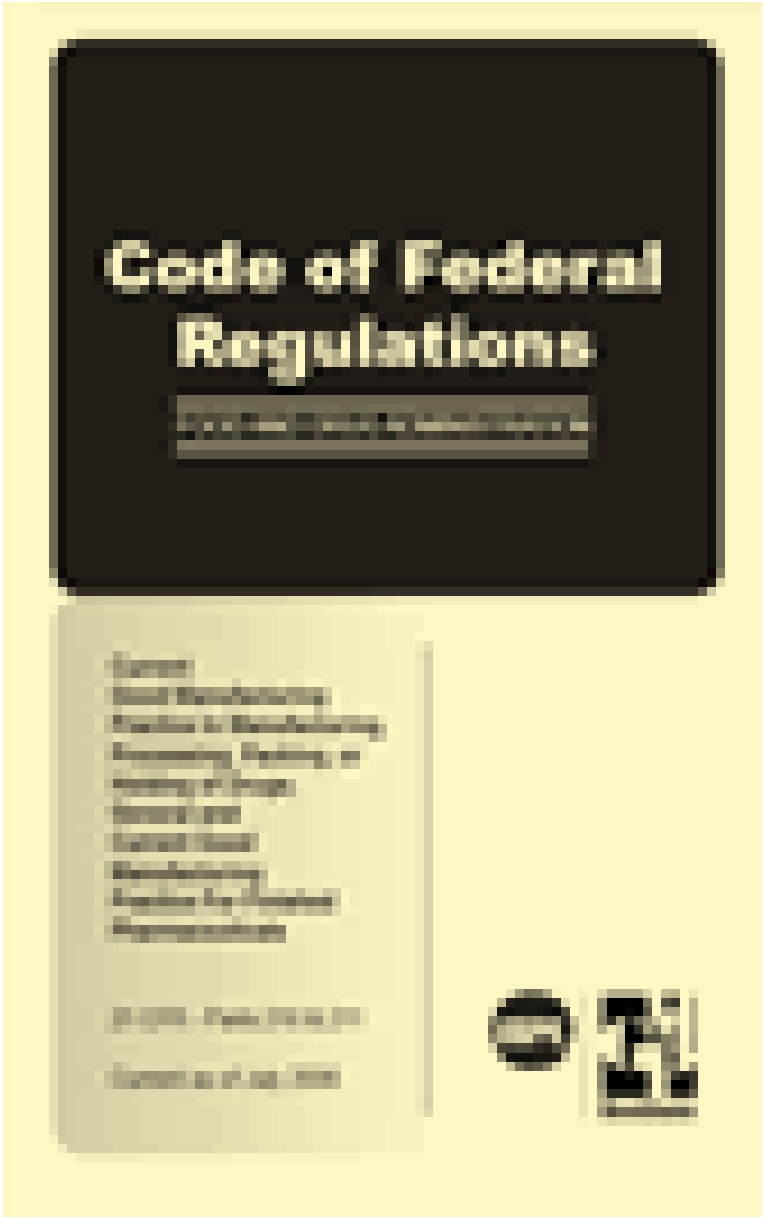
- Cells (sludge) - heat to very high temperatures and to sewer; liquids (media and buffers) treat with base and acid in a series of (three) tanks until neutral pH and to sewer.

*__Piped with 316L stainless dairy piping, triclover clamps, and valves.__

Quality Assurance

“If you didn’t document it, you didn’t do it.”

Quality Assurance



21 CFR Parts 210-211 contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

http://www.21cfrpart11.com/files/library/pred_rules/mcdowall_gmp_annotate.pdf

BIOMANUFACTURING DOCUMENTATION

Assures the product reproducibly meets predetermined specifications

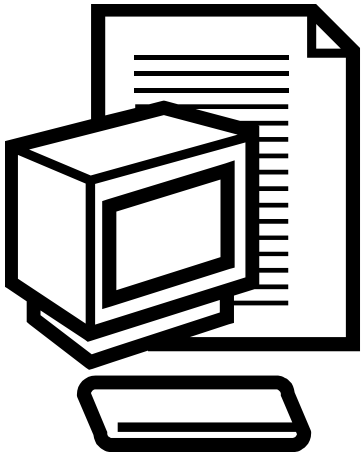
QUALITY ASSURANCE

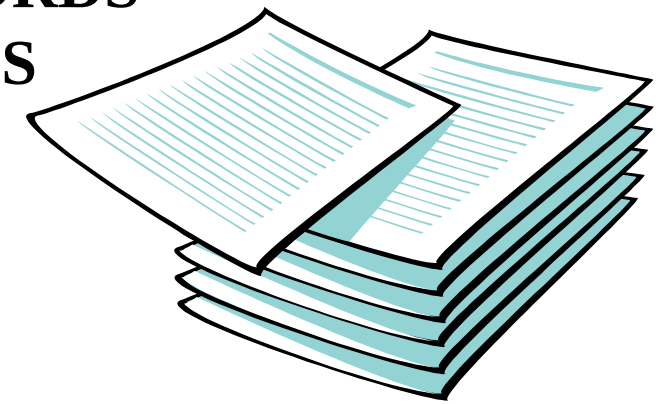
APPROVES ALL DOCUMENTS and MAINTAINS THE FILES

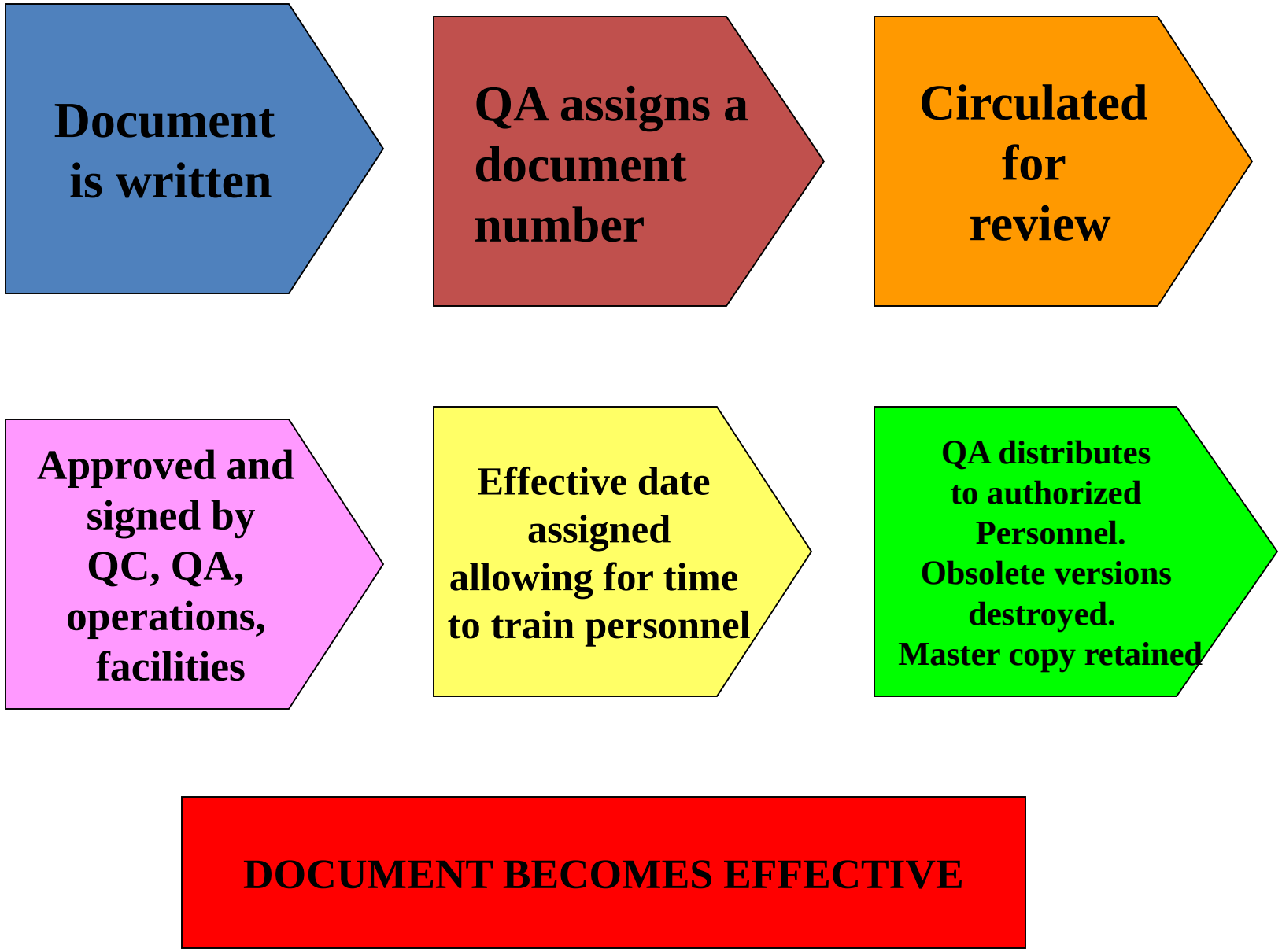
"If you didn't document it, you didn't do it."

TYPES of DOCUMENTS

RAW MATERIAL SPECIFICATIONS
SOPs
MASTER BATCH PRODUCTION RECORDS
PRODUCTION BATCH RECORDS
DEVIATION FORMS
NUMBERING SYSTEM
VALIDATION RECORDS
EQUIPMENT USE and CLEANING LOG BOOKS
COMPONENT, CONTAINER and CLOSURE RECORDS
DISTRIBUTION RECORDS
COMPLAINT FILES






Document is written
QA assigns a document number
Circulated for review
Approved and signed by QC, QA, operations, facilities
Effective date assigned allowing for time to train personnel
QA distributes to authorized Personnel. Obsolete versions destroyed. Master copy retained
DOCUMENT BECOMES EFFECTIVE

SOP: Standard Operating Procedure

Purpose
Scope
Responsibilities
References
Definitions
Precautions
Materials/Equipment
Procedure
Attachments
History

Purpose	Describes why the SOP exists.
Scope	Defines to whom and to what the procedure applies.
Responsibilities	The person or people responsible for performing and updating the SOP. May also include the person responsible for overseeing the activities of the SOP
References	Documents such as manufacturer manuals and other SOPs that were consulted to write the SOP and those that should be consulted to perform the SOP.
Definitions	Describes any words, phrases or abbreviations specific to the SOP Ex:Do not include pH, it is common terminology

Precautions	Describes any hazards associated with the procedure or with materials used in performing the procedure
Materials and Equipment	Any and all materials and/or equipment that are needed to execute the SOP.
Procedure	A step by step description of the procedure organized into subgroups
Attachments	Lists attachments by name and number. Attachments are all documents that are necessary to perform the SOP. Typically includes diagrams and drawings
History	Origin of document and revisions