Promoting the Quality of Medicines Plus

Module I- GMPs General Information

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Focus of Presentation

- What is Good Manufacturing Practices (GMP)
- Objective
- History of GMP
- Basic Principles
- Regulatory Perspective
- Common Elements of GMP
- Key Points & Conclusion

What is Good Manufacturing Practices (GMP)

- Good Manufacturing Practices is part of Quality Assurance which ensures that products are consistently produced and controlled to quality standards appropriate to their intended use

Objective

- To facilitate the compliance

- To enhance consistency in the application of Regulatory Requirements related to;

    - Fabrication and manufacturing
    - Packaging, Labeling and Testing
    - Storage, Distribution and importation

Historical Perspective

- **1848 USA** The US Congress passed the first act prohibiting the sale of adulterated drugs
- **1850's UK** John Postage's efforts to eradicate harmful adulteration
- **1860 UK** An "Act Preventing the Adulteration of Articles of Foods and Drinks" was Published
- **1872 UK** The 1860 Act was amended to include drugs

Historical Perspective

- **1906 USA** The first US Food and Drugs Act was passed by Congress
- **1920 Canada** The Food and Drugs Act
- **1938 USA** 75 people died from using Elixir of Sulfanilamide (Interaction between the drug and the preservative produced toxic effects)
- **1938 USA** The Food and Drugs Act makes it illegal to sell unsafe drug products

Historical Perspective

- **1941 Sulfathiazole disaster**, 300 people died or injured due to phenobarbital contamination. This incident influence the introduction of GMP for drugs.
- **1957 Canada** The first official document on Standards for Manufacture, Control and Distribution of drugs was published
- **1962 USA thalamide tragedy,** the amendment of the US Foods, Drugs and Cosmetics Act (the Kefauver-Harris Amendment) was introduced to ensure that the products are efficacious for their intended use.
- **1963 USA** The FDA published the first cGMP regulations (codified as 21 CFR parts 210 through 226)

Historical Perspective

- **1968 WHO Guidelines** – adopted by the World Health Assembly in 1969
- **1968 PIA (EFTA)** The "Code of Pharmaceutical Manufacturing Practice" of the Pharmaceutical Industries Association (PIA) of the European Free Trade Association (EFTA) was published
- **1969** Europe European Community's GMP Guidelines were published
- **1970 PIC (Europe)** The Pharmaceutical Inspection Convention (PIC) was signed by 12 member countries; Hungary and Romania were also admitted to the Convention (PIC)

Historical Perspective

- **1971 UK** The first GMP Guide (Orange Guide) was published
- **1971 USA** Major revisions of the published cGMP regulation
- **1978 USA** FDA published draft GMPs for LVPs and Medical Devices
- **1979**, the final Good laboratory practices were introduced for conducting non-clinical laboratory studies.
- **1982 Canada** The first edition of the GMP Guidelines was published
- **1982** Tylenol capsules disaster that lead to the introduction of tamper-resistant packaging regulations for all OTC drugs.

Historical Perspective

- **1985 Canada** Second edition of the GMP Guidelines.
- **1986 India,** glycerin adulteration scam happened due to the use of industrial grade instead of pharmaceutical grade.
- **1989 USA,** generic drug scandal (corruption in generic drug approval) that lead to the introduction of generic drug enforcement act.
- **1993 USA vs Barr:** The judge enjoined Barr from conduction of certain operations. The decision reinforces that GMPs can be made by regulation, by industry practice, and by a legal judgment
- **1995 USA** Major revisions of the published GMP regulations

Historical Perspective

- **1996 USA** Proposed amendments for certain requirements for finished pharmaceuticals for: Process Validation; Method Validation; Prevention of Cross Contamination of potentially toxic substances; Adequate testing, Evaluating test discrepancies; and QC to be responsible for Change Control and Revalidation
- **1996 Canada** Fourth edition of the GMP Guidelines
- **1996** Mix-up of co-trimaxazole with Glibenclamide and the company did not recall the product and 12 employees got arrested

Historical Perspective

- **2008 Heparin contamination** (with sulfated chondroitin sulfate), serious injuries and death toll reached to 81. FDA issued guidance document.

- **2008 Apotex Canada,** company had rejected 554 batches of drug products and in-process materials over a two-year period, without keeping records of investigations.

Historical Perspective

Data Integrity:

- Data Integrity violations or data errors can happen in 3 ways:
    - fat finger errors (an accidental lapse by an operator)
    - falsification (a rogue operator who enters false results)
    - fraud (collusion by a number of people).

Basic Principles

- Manufacturing Process should be clearly defined and controlled
- Changes that have impact on Quality should be validated as necessary
- Operators are trained to carry out and document procedures
- Records are made and deviations are investigated and documented

Basic Principles

- Records of manufacture must be maintained to have complete history of batch to be traced and retained
- A system must be available for recall
- Quality defects must be investigated where possible
- GMP Guidelines are not prescriptive but general principles must be observed

Regulatory Perspective

- Why Regulate Drugs?
    - Regulatory mandate to protect public health
    - Highly complex fabrication methods
    - Safety and efficacy depend on how well the manufacturing process in controlled
    - End product testing is insufficient

Regulatory Perspective

- The integration of facilities, systems, procedures and controls, which ensures that products and **consistently** produced to quality standards appropriate to their intended use and as required by the marketing authorization.

Regulatory Perspective

- Why Good Manufacturing Practices?
  - Quality must be built into a drug product
  - Finished product testing is not a guarantee of quality
  - Each step in a fabrication process must be controlled to ensure that the final product meets its specifications

Regulatory Perspective

- Good Manufacturing Practices
  - A common-sense approach for achieving uniform quality on a consistent basis
  - An integrated and flexible tool allowing for optimization of all processes
  - A risk management tool where controls are appropriate for the intended use of the drug
  - Allows alternate means of compliance

Regulatory Perspective

- Guiding Principles in Developing GMP
    - reflect current industry practices
    - be consistent with guidelines issued by other regulatory agencies
    - same requirements for domestically fabricated and imported drugs
    - the guidelines outline what is required; the “how” is left to industry

Common Elements of GMP

- Premises
- Equipment
- Personnel
- Sanitation
- Samples
- Stability
- Records
- Quality Control Department
- Raw Material Testing
- Packaging Material Testing
- Finished Product Testing
- Sterile Products Manufacturing Control

Key Points and Conclusion

- 1905 the jungle by uptown sinclayir
- 1906 pure food and drug act
- 1913 a womb supporter device
- 1935 elixir of sulfanilamide
- 1940 sulfathiazole tinted with phenobarbital
- 1944 Biological products – Batch release
- 1955 Polio vaccine
- 1960 Thalidomide- tragedy
- 1962 Kefauver HARRIS regulation
- 1970 CFR 210-211 implementation

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Premises , Building and Facility

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Focus of Presentation

- General Requirements and Precautions
- Ventilation, Air Filtration, Air Handling and Cooling
- Plumbing and Sewages
- Washing and Toilet Facilities
- Sanitation
- Self-Contained facility
- Key Points & Conclusion

General Requirements and Precautions

General Requirements

- Suitable size and adequate space
- Location to facilitate cleaning, maintenance and proper operation
- Orderly placement of equipment and material to prevent mix-up between different components
- Prevent cross-contamination
- Operation performed in well-designed area
- Flow of material and people

General Requirements and Precautions

Precaution

- Receipt, identification and storage appropriate number of samples and testing
- Holding of rejected material
- Control and storage of several product components
- Manufacturing and processing operations should be performed in a defined area
- The premises are designed in a manner that risk of cross-contamination between product is minimized
- Heating Ventilating and Air Conditioning (HVAC) dust collection and supply of purified water, steam, compressed air, nitrogen for handling in which the drugs are manufactured / packaged and labelled are qualified and are subject to periodic verification

General Requirements and Precautions

Precaution

- Control systems to prevent contamination or mix-up during following procedure
  - Receipt, identification, storage of component and drug products should be controlled before release
  - Holding rejected components, drug product and labeling before disposition
  - Storage of release components and drug product container closure and labeling
  - Storage of in-process material
  - Manufacturing and process operation
  - Packaging and labeling operation
  - Retention sample
  - Storage of drug product after release
  - Control and operation of laboratory
  - No production activities of highly toxic non-pharmaceutical products.

Ventilation , Air filtration, Air handling and Cooling

- Adequate condition shall be provided
- Equipments for adequate control over air pressure, micro-organism, humidity and temperature
- Air filtration system including pre-filters and particulate matter air filters shall be used when appropriate on air supplies to production area. If air is re-circulated to production area measures should be taken to control re-circulation of dust from production
- Area where air contamination occurs during production, there should be adequate exhaust system
- Air handling system for manufacture, processing and packaging of penicillin should be completely separate from those of the drug product for human use

Plumbing/Sewage

- Potable water should be supplied under continuous positive pressure in a plumbing system
- Potable water shall meet the standard of pharmacopeia
- Drain should be adequate size where connected to sewer and shall be provided with an air-break or a device to prevent back siphonage
- Sewage, trash and other refuse shall be disposed off in a safe and sanitary manner

Washing and toilet facilities

- Rest, change, wash-up and toilet facilities are well-separated from production area, sufficiently spacious, well-ventilated and of a type that permits good sanitary practices

Sanitation

- Premises used in the manufacture, processing, packing or holding a drug product shall be maintained in a clean and sanitary condition
- Facility shall be free of infestation of rodents, birds, insects and other vermin
- Written procedure for sanitation should be available to describe detail of cleaning schedules, methods, equipment and material and such procedures must be followed
- Written procedures shall be designed to prevent the contamination of equipment, components or drug products from the agents used for fumigation
- The facility should be maintained in a good state of repair

Self- Contained Facility

- Certain classes of highly sanitizing drugs such as Penicillin and Cephalosporin
- Other classes of highly potent drugs such as potent steroids, cytotoxic or potentially pathogen drugs (e.g.. Live vaccines) for which validated cleaning or inactivation procedures cannot establish (e.g.. The acceptable level of residence is below the limit of detection by the best available analytical methods

Keypoints and Conclusion

- Design qualification
- Flow of material and men
- Contamination and cross contamination
- Separate facility issues
- 246 tribromoanisol (TBA)
- Classification ABCD

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Module III
Equipment's DESIGN, SIZE AND LOCATION

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Focus of Presentation

- Equipment design, size and location
- Equipment construction
- Cleaning and maintenance
- Filters
- Key Points & Conclusion

Equipment , Design , Size and Location

- Equipment part that comes in contact with raw material, in-process drugs and drugs are accessible to cleaning or are removable
- Equipment used in manufacturing shall be appropriate design, adequate size and suitably located
- Tanks used in processing liquid ointments are equipped with fittings that can be dismantle and cleaned
- Equipment should be located at sufficient distance from other equipments and walls to permit cleaning

Equipment Construction

- Contact surfaces not reactive, additive and absorptive
- Contact surfaces do not alter safety, identity, strength, quality or purity
- Contact surfaces are smooth and made of material that is non-toxic, corrosion resistant
- Equipments are capable of withstanding repeated cleaning or sanitizing
- Design is such that the possibility of a lubricant or other maintenance material is not contaminating the drug
- Chain drives and transmission gears should be enclosed or properly covered
- Tanks, hopper and other similar manufacturing equipments are equipped with covers

Cleaning and Maintenance

- Cleaned, maintained, sanitized and/or sterilized at appropriate interval
- Written procedures for cleaning and maintenance should be followed
- Assigned responsibility for cleaning and maintenance equipment
- Describe sufficient detail of method and material used in cleaning
- Removal or obliteration of previous batch identification
- Protection of clean equipment
- Inspection of equipment for cleanliness immediately before use
- Maintain all records

Filters

- Filter should not release fiber into the product.
- The size of the filter has to be specified (0.2 and 0.45 micron).
- The use of an asbestos – containing filter is prohibited.
- Proper calibration of equipment and frequency of change of filters must be established

Key Points and Conclusion

- Calibration (internal & external)
- Auto calibration not acceptable to FDA
- Tolerances of process
- No approval of manufacturing equipment by FDA
- TOC acceptable method for residue detection in cleaning validation

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Module IV Personnel and Sanitation

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Focus of Presentation

- Personnel Responsibilities
- Personnel Qualification
- Responsibility of Quality Control Unit
- Sanitation Program
- Health and Hygiene Behavior
- Key Points & Conclusion

Personnel Responsibilities

- Personnel engaged in manufacture, processing, packaging or holding of a drug product shall have clean clothing appropriate for the duties they perform
- Protective apparel such as head, face, hand and arm covering shall be worn as necessary to protect drug product from contamination
- Only personnel authorized by supervisor shall enter those areas of the building and facility designated as ***limited access area***

Personnel Responsibilities

- Personnel shall practice good sanitation and health habit
- Person shown at any time to have an apparent illness or open lesions that may adversely effect the safety or quality of the product should be excluded from direct contact with components of drug until condition is corrected
- All personnel should be instructed to report to supervisor that may have an adverse effect

Personnel Qualification

- Each person engaged in manufacture, processing, packaging or holding of a drug product shall have;
  - Education, training and experience or any combination which enables to perform the assigned function
  - Training shall be in the particular operation
  - Written procedures required by the regulation as they relate to the employees function
  - cGMP training to be conducted by qualified individuals on continual bases with sufficient frequency that employee remains familiar with the GMP requirements

Personnel Qualification

- Each person responsible for supervising the manufacture, processing and packaging or holding the drug product shall have
  - Education, training and experience or any combination which enables to perform the assigned function in such a manner as to provide assurance that drug product has safety, identity, strength, quality and purity that it purports or is represented to possess
  - There should be adequate number of qualified personnel to perform manufacture, processing and packaging or holding of each drug product

Personnel Qualification

- Each person in charge of Quality Control department of a wholesaler should be;
    - qualified by pertinent academic training and experience
    - able to delegate duties and responsibilities to a person who meets the requirements
- Each person responsible for packaging operation should be;
    - qualified by training and experience
    - directly responsible to a person in charge of manufacturing department

Personnel Qualification

- Each person in charge of labeling operations should be;
  - qualified by pertinent academic training and experience
  - delegate their duties and responsibilities to a person who meets the requirements
- Adequate number of personnel with qualification and experience are available on site;
  - Responsibility placed on one individual should not be extensive to present any risk to quality
  - Personnel have their specific duty recorded in a written description with adequate authority to carry out their responsibilities
  - When key personnel are absent qualified personnel are appointed to carry out their duties and functions

Personnel Qualification

- All personnel must be aware of the principle of cGMP and should receive initial and continuing training relevant to their job responsibilities
  - Training is provided by qualified personnel in accordance with the written program
  - Effectiveness of continuing training is periodically accessed
  - Training is provided prior to implementation of new and revised SOPs
  - Record of training are maintained
  - Specific training for personnel working in areas where highly active and toxic material are handled
  - Performance of all personnel is periodically reviewed

Personnel Qualifications

Authorities/Organizations	Requirements
FDA	Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions.
EU	The qualified person shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary science, chemistry, pharmaceutical chemistry and technology, biology.

Personnel Requirements

Authorities/Organizations	Requirements
WHO	Key personnel responsible for supervising the production and quality unit(s) for pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of: (a) chemistry (analytical or organic) or biochemistry; (b) chemical engineering; (c) microbiology; (d) pharmaceutical sciences and technology; (e) pharmacology and toxicology; (f) physiology; (g) other related sciences
PIC	The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience

Personnel Requirements

Authorities/Organizations	Requirements
ICH Q7	There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.
TGA	Personnel having the education, training, experience and skills, or any combination of these elements, that will ensure that staff can perform assigned duties and functions at an acceptable level
MHRA	Same as EU.
INDIA	The manufacture shall be conducted under the direct supervision of competent technical staff with suitable qualifications and practical experience in the relevant dosage and / or active pharmaceutical products.

Personnel Qualification

Authorities/Organization	Requirements
Health Canada	Responsible personnel must hold a Canadian university degree or a degree recognized as equivalent by a Canadian university or Canadian accreditation body in a science related to the work being carried out.
Pakistan	Responsible personnel must hold a degree in Pharmacy with six years experience or Master degree in Chemistry with minimum of ten years of experience

Responsibility of Quality Control Unit

- Quality control unit shall have the responsibility to approve or reject all components, container closure, in-process material, packaging material and drug products
- Quality control unit shall be responsible for approving or rejecting drug products manufactured under contract by another company
- Adequate laboratory facility shall be available to quality control unit
- Quality control unit is responsible for approval or rejecting specifications impacting on the strengths, quality and impurity and all procedures shall be in writing

Sanitation Program

- Each person who manufacture, package and label a drug should have sanitation program implemented under the supervision of qualified personnel
- Sanitation program should include
  - Cleaning procedure for the premises where the drug is manufactured, packaged and tested
  - Cleaning requirement applicable to processing equipment
  - Cleaning interval
  - Disposal procedure for waste
  - Pest control major

Health and Hygiene Behavious

- Each person who manufacture or packages / labels a drug should have
  - Written minimum requirements for health and hygienic behavior
  - Ensure the clean and sanitary manufacturing packaging / labeling of the drug
- No person shall have access to any area where a drug is exposed during manufacturing, packaging / labeling if the person
  - Effected with or is a carrier of disease
  - Or has an open liaison on any exposed surfaces

Key Points and Conclusion

- Role and responsibility of the department/units
- Controlled job description including the designee in case of absence
- Limited of access areas
- Education training and experience or any combination
- GMP training by qualified individuals
- Sanitation program health and hygiene

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Module V
Control of Components (raw material) drug product container & closure

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Focus of Presentation

- General Requirements
- Receipt and storage of untested components, drug product container and closure
- Testing and approval or rejection
- Use of approved components
- Retesting of approved components
- Rejected components
- Drug product container and closure
- Specification and Test Methods
- Storage Conditions
- Key Points & Conclusion

General Requirements

- There shall be written procedure in sufficient details for receipt, identification, storage, handling, sampling and approval or rejection of components and drug product containers and closures
- Component and drug product container and closure shall be at all time be handled and stored in a manner to prevent contamination
- Bagged and boxed components of drug shall be stored off the floor and suitably spaced to prevent cleaning and inspection
- Grouping of container and components of drug products shall be identified with a distinctive code for each lot in each shipment received

Receipt and storage of untested components, drug product container and closure

- Upon receipt and before acceptance, each container or group of containers, drug product container and closure shall be examined at appropriate level.
- Components, drug products and closure shall be stored in quarantine until they have tested and examined which ever appropriate and released

Testing and approval or rejection

- Each lot of the component, drug product, container and closure shall be withheld for use until the lot has been sampled, tested or examined as appropriate
- Represented sample of each shipment shall be collected for testing or examination
- The number of container to be sampled is based upon appropriate criteria such as statistical criteria for component variability, confidence levels, degree of precision and past quality history

Testing and approval or rejection

- Sample shall be collected in accordance with the following procedure
  - Container of component shall be cleaned in a manner to prevent contaminants into the components
  - Container shall be opened, sampled and resealed in a manner designed to prevent contamination of their content
  - Sterile equipment in aseptic sampling technique should be used
  - Sample a component from top, middle and bottom and shall not be composited for testing
  - Container shall be identified by name, lot number, date on which the sample was taken and name of the person collected the sample
  - Container from which sample were taken should be marked that sample have been taken

Testing and approval or rejection

- Sample shall be examined and tested for conformity with written specification
  - Test for purity, strength, identity and quality
  - At least one test shall be conducted to verify the identity of component of each product
  - Container and closure tested for conformance with written specification in lieu of such testing by the manufacturer a certificate of testing may be accepted by the supplier
  - Appropriate components shall be microbiologically examined
  - When component is liable to contamination with filth insect infestation or other extraneous adult trait shall be examined against established specifications for such contaminations
  - Every lot of component should meet written specification of identity, strength and quality and may be approved or released for use. Any lot of material that does not meet such specification should be rejected

Use of approved components

- Component, drug product container and closure approved for use shall be rotated so that the oldest component stop its use first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

Retesting of approved components

- Components, drug product container and closure shall be retested for identity, strength, quality and purity and approved or rejected by Quality Control unit
- As necessary after storage for a long period or after exposure to air, heat and other condition that might adversely effect the component

Rejected components, container and closure

- Rejected component, drug product and container closure shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable

Drug product container and closure

- Drug product, container and closure shall not be reactive, additive or absorptive
- Container closure system shall provide adequate protection against foreseeable external factor
- Container and closure shall be clean and where indicated by nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use
- Standard or specification method of testing and where indicated method of cleaning sterilizing and processing shall be written and followed for product container and closure

Specification and Test Methods

- Each lot or batch of raw material shall be tested against the specification prior to use in the manufacture of a drug
- No lot or batch of raw material shall be used in the manufacture unless that lot or batch comply with the specification of that raw material
- Where any property of raw material is subject to change on storage. No lot or batch of that raw material shall be used in the manufacture of a drug unless the raw material is retested after an appropriate interval

Specification and Test Methods

- When the specification are referred they shall be in writing and shall comply with the published standard
- These specification must be approved by the person in charge of Quality Control department
- Complete confirmatory testing is performed on the first three lots of each raw material received from the vendor and after significant change through the manufacturing process
- Complete confirmatory testing is conducted on a minimum of one lot per year of a raw material received from each vendor with the raw material being selected on a rotational bases

Specification and Test Methods

- The certification of the vendor is important and all documents approved by the quality control department is updated at an appropriate frequency
- Specific identity testing is conducted in all lots of any raw material received on the premises of the person who formulate the raw material in dosage form

Specification and Test Methods

- Transportation and storage should be such that they prevent alteration and potency, purity and physical characteristics

- If a delivery or shipment of a raw material is made up of different batches each batch is considered as separate for the purpose of sampling, testing and release

Storage Conditions

- Condition for transportation and storage should be such to prevent alteration to potency, purity or physical characteristics
- SOP for records for shipping and receiving should be available and contain
  - The type of immediate packaging for the raw material
  - Labeling requirement and storage condition
  - Special precautions or warning
  - Description of how the package raw material is sealed
  - Verification that the material has not been tempered

Key points and conclusion

- Written procedure appropriate storage condition
- Testing and approval procedures
- Confirmatory testing to be performed on first three batches each raw material received from vendor after significant change in the manufacturing process.
- Complete testing on minimum one lot of a year.
- Storage and transportation
- retesting plan

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Module VI – Production and Process Control

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Focus of Presentation

- Written Production and Process Control Procedures
- Charge-in of Components
- Calculation of Yield
- Equipment Identification
- Sampling and Testing of In-process Material and Product
- Time Limitation on Production
- Control of Microbiological Contamination
- Reprocessing
- Key Points & Conclusion

Written Production and Process Control Procedures

- Written procedures to assure that drug products have identity, strength, quality and purity
- Any changes shall be drafted, reviewed and approved by appropriate organizational unit
- All written procedures shall be followed in the execution of the various production and process control function and shall be documented
- Deviation from written procedures shall be recorded and justified

Charge-in of components

- The batch must be formulated with the intent to provide NLT 100/ labelled amount of APIs
- During dispensing if a component is removed from original to another, the contents shall be identified with this information
  - Name or code
  - Control number
  - Weight or measure
  - Batch number, product name, strength and lot number
- Weighing, measuring or subdividing operation of components shall be adequately supervised
- Each container dispensed must be supervised by a second person
- If operation is automated only one person is needed
- Component added to batch must be verified by a second person

Calculation of Yield

- Actual yields and percentage of theoretical yield should be determined at appropriate phases of
  - Manufacturing
  - Processing
  - Packaging
  - Holding

  And verified by second person
- Equipment identification
  - All equipment used in manufacturing, processing must be identified at all time
  - Code or distinctive ID number must be recorded
- Sampling
  - Written procedures shall be established and followed for in-process control and test
  - Examination should be conducted on appropriate number of samples for in-process test

Calculation of Yield

- Control procedures are established to monitor the output and to validate the performance
- Control procedures shall include but not limited to;
  - Tablet weight variation
  - Disintegration time
  - Assure uniformity and homogeneity
  - Demonstration, time and rate
  - Clarity completion pit
  - Bio burden testing
- Valid in-process and final specifications shall be derived previous acceptable process coverage
- In-process material shall be tested for identity, strength and quality by QC unit for approval or rejection
- Rejected in-process material shall be identified and controlled under a quarantine system designed to prevent their use

Time limitations on Production

- Time limits for the completion of each phase of production shall be established
- Deviation from established time limits are acceptable if it does not compromise the quality
- Deviation shall be justified and documented

Control of Microbiological Contamination

- Appropriate procedures are required to prevent objectionable microorganism in drug products not required to be sterile

- Appropriate procedures are required to prevent microbiological contamination of drug products purporting to be sterile

Reprocessing

- Written procedure should be established
- Procedures must be validated
- Re-processed batches should conform with all standards and subjected to stability testing
- Reprocessing shall not perform without review and approval of quality control unit

Key Points and Conclusion

- BMR and BPR accuracy authenticity and data integrity.
- Calculation of yield and reconciliation of packaging material and finished Product.
- In process testing and its frequency and authenticity.
- Time limitation of production.
- Reprocessing and Reworking .

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Module VII- Quality Control/Laboratory Control

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Focus of Presentation

- General requirements
- Quality Control department
- Laboratory Control
- Testing and Release for Distribution
- Special Testing Requirements
- Reserve Samples
- Key Points & Conclusion

General Requirements

- The establishment of specifications, standards, sampling plans, pest procedures or other laboratory controls are required including any changes which should be reviewed and approved by Quality Control unit
- Laboratory controls shall include the establishment of scientifically justified standards and procedures to confirm identity, strength, quality and purity
- An appropriate written specification with acceptable limits of each lot
- Conformance to the written specification with representative and properly identified samples

Quality Control Department

- There has to be Quality Control Department on the premises of manufacturer, packager, labeler (wholesaler) distributor and importer
- QC department shall be a distinct organization unit report to management independently
- QC department has access to adequate facilities, trained personnel and equipment to fulfill its duties and responsibilities
- Approved written procedures shall be available for sampling, inspecting and testing of raw material, in-process, bulk and finished products
- No material is used in manufacturing, packaging or labelling unless that material is approved by QC department

Laboratory Control

- Establishment of specification, standard, sample plans, test procedures, other lab control mechanism are all included in laboratory control
- Laboratory control shall include:
  - Confirmatory of written specification of each lot
  - Sample shall be representative and adequately identified
  - Description of testing procedures used
  - Conformance to written procedures and specifications
  - Conformance to written sampling procedures
  - Calibration of instruments, apparatus, gauges and recording devices

Testing and Release for Distribution

- Each batch of drug product must conform to the final specification including identity and strength prior to release
- Each batch of drug product is required to be free of objectionable microorganism
- Written procedures for sampling and testing should be followed
- Acceptance criteria to assure that the batches of drug product meets each appropriate specification with statistical quality control criteria
- Accuracy, sensitivity, specificity and reproducibility of test method should be established and documented
- Drug products failing to meet established standards or specification shall be rejected

Special Testing Requirements

- These special testing requirements are products such as those purporting to be sterile and/or pyrogenic-free or ophthalmic ointment or inhaler or controlled-release dosage form. In such situation some additional/special testing are needed

Reserve Samples

- Each lot of the finished product as well as active ingredients is required to be retained as reserve sample
- At least twice the quantity necessary for all testing specification are required
- Reserve samples shall be retained for one year after the expiration date of the last lot

Key Points and Conclusion

- Quality control department vs Quality control laboratory.
- Testing and release for distribution .
- Retention sample room
- Chemical room.
- Laboratory information file.
- Log book

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Module VIII- Packaging Material , Labeling and Testing

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Focus of Presentation

- Material examination and usage criteria
- Labeling Issuance
- Packaging and Labeling Operations
- Temper-evident Packaging
- Drug Product Inspection
- Expiry Dating
- Key Points & Conclusion

Material Examination and Usage Criteria

- Written procedures in sufficient detail for receipt, identification, storage, handling, sampling, examination and/or testing of labeling and packaging material
- Appropriate written specification may be approved and released for use
- Material that do not meet specification shall be rejected
- Records shall be maintained for each shipment received of each different label and packaging material

Material Examination and Usage Criteria

- Labels and other labeling material for each different product shall be stored separately and access to these material shall be limited to authorized person
- Obsolete and outdated label and packaging material shall be destroyed
- If cut label is used, packaging and labeling operations shall include special control
- Use visual inspection if electronic equipment are not available and conduct a 100% examination for correct labeling

Labeling Issuance

- Strict control shall be exercised for labeling issued for use in drug product
- Careful examination for identity and conformity to the labeling specified in the batch production record
- There should be reconciliation of the quantities of the labels issued
- Any discrepancies shall be investigated
- Returned labels shall be maintained and stored in a manner to prevent mix-up
- Procedures shall be written in sufficient detail and shall be properly followed for the issuance of label

Packaging and Labelling Issuance

- There shall be written procedure designed to assure correct labeling and packaging material
- Prevention of mix-up and cross-contamination by physical separation from operation
- Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quality of content and lot number
- Examination of packaging and labeling material before packaging operation

Temper-Evident Packaging

- There is a regulatory requirement for temper-evident packaging of OTC drug products to improve the security and assure safety and effectiveness
- OTC drug products (except a dermatological, dentifrice, insulin or lozenge product) for retail sales that is not packaged in a temper-resistant package or not properly labelled will be considered adulterated or misbranded
- A temper-evident package may involve an immediate container and closure system or secondary container or carton system or any combination of system to provide package integrity

Drug Product Inspection

- Packaged and labeled products shall be examined during finishing operation to provide assurance that container and packages in the lot have the correct label

- A represented sample of unit shall be collected at the completion of finishing operation and shall be visually examined for correct labeling

- Results of these examinations shall be recorded in the batch production or control records

Expiry Dating

- To assure that a drug product meets applicable standards of identity, strength, quality and purity at the time of use. It shall bear an expiry date based on stability data

- Expiry dates shall be related to any storage condition stated on the label

- If drug product is to be reconstituted at the time of dispensing its label shall bear expiration information for both reconstituted and un-reconstituted product

Key Points and Conclusion

- Sampling and testing of primary packaging
- Class D for primary packaging operation
- Labeling reconciliation
- Expiry date (month and year)
- Temper evident packaging
- Major mistakes

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Module IX- Finished Product Testing

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Focus of Presentation

- Control and Distribution of Record
- Number of Batches Approved or Rejected
- Complaints, Recalls, Return or Salvaged drug Product
- Equipment Cleaning and Use Log
- Records of Container Closure System and Labeling
- Master Production, Batch Production
- Laboratory,Distribution,Complaint Files
- Key Points & Conclusion

Requirements

- Each lot or batch of a drug shall prior to its availability for sale be tested against the specifications for that drug .
- No lot or batch of a drug shall be available for sale unless it complies with the specification for that drug.
- Finished product test complement the controls employee during the manufacturing process

Requirements

- It is the responsibility of each manufacturer, packager, labeler, distributer and importer to have adequate specification and test method that will ensure that each drugs sold is save and meet the standard under which it is represented.

- The written specifications contain the description of the drug in dosage form. This description includes all properties and qualities including physical characteristics and identity.

Requirements

- The test may be carried out by the distributer or by their contracted testing laboratories when a written agreement is emplace.

- Any lot of batch of a drug that does not comply with specification is quarantined pending final disposition and should not made available for sale.

Specifications

- Specifications are equal to or exceed recognized standard as listed in pharmacopoeia.
- Test methods should be validated and the result of such validation studies are documented.
- Method transfer studies are conducted when applicable.
- All test should be performed according to the approved specifications.

Key Points and Conclusion

- Approved specification
- Testing of drug product
- Batch Release
- Method Validation

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Module X- Records and Reports

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Focus of Presentation

- General requirement
- Equipment, cleaning and use log
- Component of drug product, container closure and labeling record
- Master production and control record
- Batch production and control record
- Production record
- Laboratory record
- Distribution record
- Complaint file
- Key Points & Conclusion

General Requirement

- Any production, control or distribution record is required to be maintained and shall be retained for at least one year after the expiry date of the batch
- Record shall be maintained for all components of the drug products, container closures and labeling for at least one year after the expiry date
- All records required shall be readily available for authorized inspection. These records can be photocopied or reproduced by other means. Records may be retained either as original record or as true copies such as photocopies, micro-film, etc.

General Requirements

- Records required shall be maintained so that data can be used for evaluation at least annually.
- Written procedures shall be established for the review of representative number of batches whether approved or rejected
- A review of complaints, recalls, returned or salvaged drug products should be conducted

Equipment Cleaning & Use Log

- A written record of Major Equipment and cleaning & maintenance shall be included in individual with date time batch number, etc.
- If equipment is dedicated to manufacture one product then equipment logs are not required provided batches follow numerical order and are in sequence.
- In case of dedicated equipment, the cleaning & maintenance record shall be part of batch records.
- Entries in the log shall be in chorological order.

Component , Drug Product Container Closure & Labeling Record

- The identity & quality of each shipment of each lot of components drug product container closure & labelling, the name of the supplier & code number, date of receipt.
- The results of any test or examination performed and conclusion derived.
- An individual inventory record of each component reconciliation of use of each lot.
- Documentation of the examination & review of labels & labelling for conformity.

Master production & control record

- Master product ion & drug control record of each product shall be prepared dated & signed by one person &checked by second person.

- Proper written procedure for master production & control record.

Batch Production and Control Record

- Batch productions & control records must be prepared for each of the drug produced and shall include complete information.

Production Record Review

- All drug product, production & control record including packaging & labelling shall be reviewed and approved to establish the compliance.

- Any discrepancy including yield or failure to the batch to meet any specification should be thoroughly investigated.

- Written records of investigation shall be maintained.

Laboratory Records

- Laboratory records shall include complete data right from all tests necessary to ensure compliance with established specifications and standards including examination and Assays.
- Complete records shall be maintained for any modification of an established method employed in testing.
- Complete records shall be maintained for any testing & standardization of reference standards, reagents & standard solution.

Laboratory Records

- Complete records shall be maintained for the periodic calibration of apparatus, instruments & recording devices etc.

- Complete records shall be maintained for all stability performed.

Distribution Records

- All distribution record, name, strength, dosage form, name of consignee, date, quantity shipped, Lot or control number shall be maintained.

Complaint File

- Written procedure for handling complaint shall be established and followed to determine complaint.

- Complaint represent possible failure for specification or serious adverse reaction.

- A written record o f each complaint shall be maintained at least one year after the date that complaint was received or which ever is longer.

Returned Drug Products

- The returned drug product shall be identified.

- If the condition of returned drug product, its container, carton or labelling damaged as a result of storage and shipping cast doubt on safety identity strength quality & purity. The returned drug products shall be destroyed.

- A drug product may be reprocessed provided the subsequent drug product meets appropriate standards of safety identity strength quality or purity.

Drug Product Salvaging

- Drug products subjected to improper storage conditions or subjected to improper condition of storage due to natural disaster like (fire, flood) shall not be salvaged.

- Records including name, lot number, disposition shall be maintained.

Key Points and Conclusion

- Documentation Control
- BMR / BPR
- Equipment Clearance log
- Complaints Records
- Recall reconciliation
- No lose Papers
- Data Integrity

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Module XI- Stability Studies

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Abbreviations

API	Active Pharmaceutical Ingredient
EoI	Expression of Interest
FDC	Fixed-Dose Combination
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization
MA	Marketing Authorization
DRA	Drug Regulatory Authority

Purple → emphasis Green → WHO Blue → ICH

Applicable Guidelines

- WHO „Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms”
- WHO working document QAS/05.146- Stability Studies in a Global Environment.
- ICH guidelines Q1A-Q1F. Stability testing of new APIs and FPPs has been harmonized at global level.

Applicable Guidelines

- WHO „Guideline on Submission of Documentation for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs) Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis. Annex 4. Stability requirements for variations and changes to prequalified FPPs (draft)

- Supplement 2 [for use from July 2005 (CPH25)] Extension of the WHO List of Stable (not easily degradable ARV) APIs. Further potential APIs are e.g., amodiaquine, mefloquine, and so on.

Subjects for Discussion

1. Essential ICH definitions
2. Interchangeability of FPPs
3. Planning stability studies and reporting results
4. Stability testing of APIs
5. Stability testing of FPPs
6. Evaluation of stability results
7. Key points

Stability Studies

Essential ICH Definitions

Selected Definitions

- Re-test date

  The date after which samples of an API should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given FPP.

- Shelf life

  (expiration dating period, conformance period)

The time period during which an API or a FPP is expected to remain within the approved shelf-life specification, provided that it is stored under the conditions defined on the container label.

Selected Definitions

- Formal stability studies
  Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of an API or the shelf life of a FPP.

- Stress testing – forced degradation (API)
  Studies undertaken to elucidate the intrinsic stability of the API. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

- Stress testing – forced degradation (FPP)
  Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photostability testing (see ICH Q1B) and compatibility testing on APIs with each other in FDCs and API(s) with excipients during formulation development.

Selected Definitions

- Primary batch

  A batch of an API or FPP used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of an API should be at least a pilot scale batch. For a FPP, two of the three batches should be at least pilot scale batch, and the third batch a production batch.

- Commitment batches

  Production batches of a drug substance or drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application

Selected Definitions

- Pilot (scale) batch

  A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch.
  (For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.)

- Production (scale) batch

  A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

Selected Definitions

- Supporting data

  Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf life, and the label storage statements. Such data include;

1. stability data on early synthetic route batches of API, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing;
2. Information regarding test results on containers; and
3. other scientific rationales.

Selected Definitions

- Specification - Release
  The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

- Specification - Shelf life
  The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an API throughout its re-test period, or that anFPP should meet throughout its shelf life.

- Mass balance
  The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Interchangeability

Stability Equivalence

Interchangeability (IC)

Interchangeability (IC) of multisource FPPs = (Essential similarity with innovator FPP) =

Pharmaceutical equivalence (PE) + Bioequivalence (BE)

$$IC = PE + BE$$

Pharmaceutical Equivalence

- FPPs meet same or comparable standards (pharmacopoeia, marketing authorization)
    - Same API (chemical and physical equivalence)
    - Same dosage form and route of administration
    - Same strength
    - Comparable labeling
- WHO-GMP(batch-to-batch uniformity of quality)
- **STABILITY EQUIVALENCE**

High-Risk APIS FPPS

- Reference standard/comparator is not available for:
  - Pharmaceutical (stability) equivalence studies
  - Bioequivalence studies
- APIs and FPPs are not official in the internationally used major pharmacopoeias
- WHO guides/SOPs apply to multisource FPPs. ICH guides should be used for evaluation.
- Require particular attention by national DRA as regards assessment of applications for marketing authorization

Low-Risk Apis

1. Certificate of suitability (DRA)
2. Drug Master File
   - Open part (APPLICANT)
   - Closed part (DRA)
3. Pharmacopeia monograph
   - Literature evidence of stability
   - Synthesis impurities are controlled by monograph (toxicology of additional impurities)
   - Class1 solvents excluded, class2 solvents controlled
4. FPP is registered in the ICH region

Planning Stability Studies and Reporting Results

Annex 3: Model Stability Protocol and Report of API

Stability Protocol and Report

1. Batches tested
2. General information
3. Container/closure system
4. Literature and supporting data
5. Stability-indicating analytical methods
6. Testing plan
7. Test parameters
8. Test results
9. Other requirements (post-approval commitments)
10. Conclusions

Result sheets must bear date and responsible person signature / QA approval

Illustrative data of API stability batches

Batch number			
Date of manufacture			
Site of manufacture			
Batch size (kg)			
Primary packing materials			
Date of initial analysis			

The batches should be representative of the manufacturing process and should be manufactured from different batches of key intermediates

Illustrative data of capsule/tablet stability batches

Batch number			
Date of manufacture			
Site of manufacture			
Batch size (kg)			
Batch size (number of units)			
Primary packing materials			
Date of initial analysis			
Batch number of the API			

The batches should be representative of the manufacturing process and should be manufactured from different batches of APIs.

Stability Testing API

- Stress Testing *(forced ddegradation)*
- Regulatory stability testing

ICH Guidelines on Stress Testing

Standard	Title and reference
ICH Q1A(R2)	Stability Testing of New Drug Substances and Products (the parent guideline)
ICH Q1B	Photostability Testing of New Drug Substances and Products
ICH Q2B	Validation of Analytical Procedures: Methodology
ICH Q3A(R)	Impurities in New Drug Substances
ICH Q3B(R)	Impurities in New Drug Products

Forced Degradation Tests

- To identify potential degradants (degradation pathways) of the API and assess if they can be formed during manufacture or storage of the FPP (intrinsic stability of the API).
- To validate the stability indicating power of the analytical procedures.
- To identify stability-affecting factors such as ambient temperature, humidity and light and to select packing materials, which protect the FPP against such effects.
- No standard method for testing.

Prequalification Experience

Results	Comments
Deceptive	Degradation level is good (<15%) but no relevant degradants are observed
Predictive	Degradation level is good (<15%) and at least one or all relevant degradants are observed
Useless	Between 15 and 100% degradation but no relevant degradants observed

Requirement for Predictive Stress Conditions

Recommendations in Supplement 2:

- Should lead to the degradation of the main compound, but not more than 5-15%.
- Should lead to a good predictability of degradation pathways (i.e., a low probability of "drastic" or "false" degradation)
- Should be conducted for no longer than three months.

Stress Testing of API in Solution

Storage conditions	Testing period*
pH ± 2, room temperature	2 weeks
pH ± 7, room temperature	2 weeks
pH ± 10-12, room temperature	2 weeks
H_2O_2, 0.1-2% at neutral pH, room temperature	24 hours
* Storage times given or 5-15% degradation, whatever comes first	

Regulatory or Formal Stability Testing

Storage temperature (°C)	Relative humidity (%)	Minimum time period covered by data at submission (months)
Accelerated: 40±2	75±5	6
Intermediate: 30±2	65±5	12
Long term: 25±2	60±5	12 (6)

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CLEANING VALIDATION

Dr Rizwan Mahmood

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After completing this session we'll come to know :

- Definition
- Purpose
- Cleaning mechanisms
- Cleaning agents
- Cleaning Methods
- Cleaning parameters
- Cleaning continuum
- Grouping strategies
- Worst Case considerations

- Acceptance criteria
- Sampling Methods
- Analytical Methods
- Hold time studies

Purpose

- Product integrity
- Cross contamination
- Microbial integrity
- Product impurity
- Batch integrity
- Equipment reuse
- Regulatory issues

Cleaning Validation

- The chemistry of contaminant removal :
- Solubility
- Wetting
- Emulsification
- Dispersion
- Hydrolysis
- Oxidation
- Physical removal
- Antimicrobial action

Cleaning Mechanisms

- Solubility :
- Solubility involves the dissolution of one chemical (the contaminant) in a liquid solvent.
- For example, salts may be soluble in water, and certain organic actives may be soluble in acetone or methanol.
- One of the primary cleaning mechanisms to be considered during design phase.

- Rate of solubility, Insoluble form, Soluble – Insoluble species

Cleaning Validation

- Wetting :
- Wetting involves the displacement of one fluid from a solid surface by another fluid. Wetting can be improved by the addition of surfactants.
- It improve penetration of the cleaning solution into cracks and crevices, which are usually difficult-to clean locations.

Cleaning Validation

Emulsification :

Breaking up an insoluble liquid residue into smaller droplets and then suspending those droplets throughout the water.
Emulsion = Mechanical energy + Surfactants / Polymers.

- Emulsions are thermodynamically unstable (say, 5 to 10 mins.).
- Redeposition of the cleaned residue back onto the equipment surfaces.
- Agitation should be continued till the time to discharge the cleaning solution to the drain.

Cleaning Mechanisms

Dispersion :

- Dispersion is similar to emulsification, except that it involves
- the wetting and deaggregation of solid particles and then the subsequent suspension of those particles in water.

More important in dry product manufacturing.

Hydrolysis :

- This involves the cleavage of certain bonds in an organic molecule.

The resultant hydrolyzed residues must either be water soluble or solubilized at the pH of the cleaning solution.

Cleaning Mechanisms

Oxidation :

This involves the cleavage of various organic bonds, such as carbon-carbon bonds, by the action of a strong oxidizing agent.

Large Non-polar Mol. ⟶ Smaller more polar Mol.

Antimicrobial Action :

Mechanisms that may kill organisms but leave behind nonviable microbial residues.

Special type of mechanism, sterilization, disinfection.

Cleaning Mechanisms

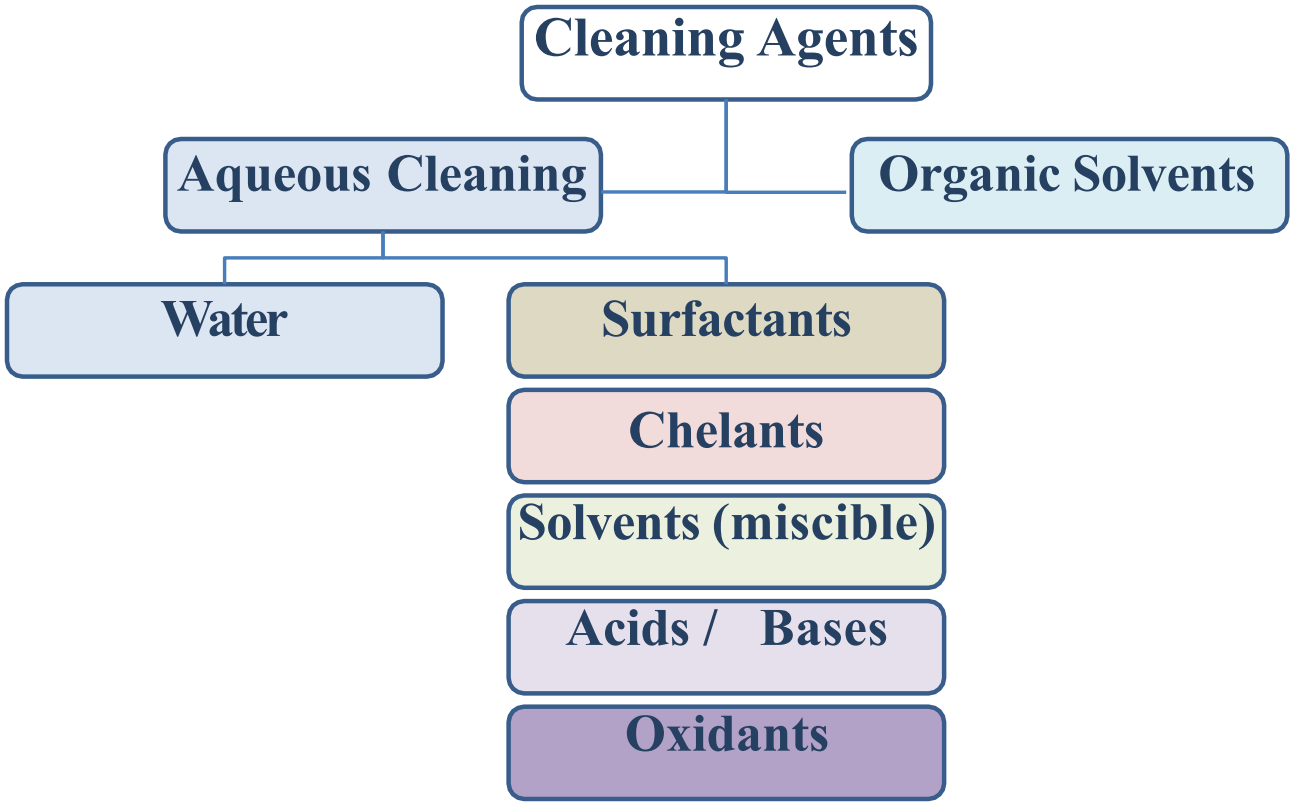
Physical Removal:

Cleaning by some mechanical force. the objective is to physically displace the residue.

Pressurized water + Scrubbing

In real life situation, more than one cleaning mechanisms are being used.

Cleaning Agents



Cleaning Parameters

- *Time*
- *Action*
- *Cleaning chemistry*
- *Concentration*
- *Temperature*
- *Mixing / flow / turbulence*
- *Water quality*
- *Rinsing*

Risk Classfications

Low Risk Drugs . . . . . High Risk Drugs
Highly Characterized . . . . . Poorly Characterized
Sterile . . . . . Non-Sterile
Solid Formulations . . . . . Liquid Formulations
Soluble . . . . . Insoluble
Single Product Facility . . . . . Multiple Product Facility
Campaigned Production . . . . . Non-Campaigned Production
Simple Equipment Train . . . . . Complex Equipment Train

Grouping Strategies

- "Grouping" is the concept of demonstrating that certain elements of cleaning are of a similar type and selecting one (or more) representative object(s) on which to conduct the Cleaning Validation (*Cleaning Process Qualification*).
- Product grouping :
- Same manufacturing equipment being used
- Same cleaning SOPs being followed
- Similar formulations
- Similar risk / therapeutic group
- Equipment grouping, Cleaning method grouping, Cleaning agent grouping etc.

Acceptance criteria

Visual clean criteria :

- GMPs require inspection for visual cleanness before manufacture.

Key items to consider :

- Angle of view
- Distance from equipment surface
- Lighting conditions
- Viewer's knowledge
- Surface usually must be dry

Visual aids :

- Additional lighting / Magnifying glass / Mirror / Fiber-optic scope / UV light

Acceptance criteria

Chemical residue limits (Therapeutically or Toxicologically safe criteria) :

- **Therapeutic dose based criteria**
  - Most suitable for drug product (finished product) manufacturing facility.
- **Toxicological criteria**
  - Most suitable for active drug (API) manufacturing facility.
  - Where cleaning agents are used (other than water).
- **10 PPM criteria**
  - CGMP requirement widely applicable.

Selection of Worst – Case Product for Cleaning

- The least soluble product produced on a particular equipment or process. This product is then used to validate cleaning for that process / equipment.
- Most toxic product

Limit Setting (Non dedicated equipment)

- The residue limit can be calculated according to
- Dose Percent: No more than 0.1% of a dose
- Weight Percent: No more than 0.001% (10 ppm)
- Visually Clean

Product Contact Sites (Dedicated Equipment):

- Visual inspection

Non-Direct Contact Surfaces

- Minimum requirement is visually clean.

Non-Product Contact Sites:

- Visual inspection

Approach

Initial Data Gathering:

- List of Product manufacturing & filled in equipment.
- Equipment & cleaning Procedure assessment.
- Critical area to be cleaned.
- Selection of marker product for Matrix.

ASSESSMENT OF EQUIPMENT

- **EQUIPMENT**
- Product Contact parts.
- Non Product contact parts.
- Indirect Product contact parts.
- The cleaning validation of equipment will be restricted to product contact parts only
- Non dedicated equipments are covered

- **PRODUCTS**
- List of products is prepared
- Cleaning SOP is ensured

Validation process

Matrix Approach:

- Select a Marker compound

Sampling procedure

- According to the cleaning validation protocol.
- Visual inspection
- Surface swabs – quantitative method
- Rinse analysis – quantitative method

Testing

- As per validated analytical method.

Acceptance Criteria

- **Organoleptic Assessment:**
- Equipment should be visually cleaned and odor free.

Calculation of the Maximum Allowable CarryOver (MACO)

For the calculation by considering 0.1 % Safety factor

$$\text{Limit (mg)} = \frac{\text{Daily therapeutic dose of product A in mg}}{1000} \times \frac{\text{Min. Batch Size of Product B (in mg)}}{\text{Max. daily therapeutic dose of product B in (mg)}}$$

Where,

Product A – Product manufactured before cleaning

Product B – Next Product after cleaning

For Considering 10 ppm as acceptance criteria.

The quantity equivalent to 10 mg/L of the batch size is considered as the acceptance criteria for the acceptance criteria as 10 ppm.

Calculation of acceptance criteria

Calculation of acceptance criteria for swab samples

Active Ingredient Residue (For Non-dedicated equipment): Acceptance criteria based on the following rationale for swab samples :

Calculation [Applicable to all items of common equipment in product train].

$$\text{Limit (PPM)} = \text{MACO} \times \frac{1000}{C} \times \frac{D}{V}$$

Where,

C – the Cumulative surface area of the equipment used (in cm^2).

V – Volume of solvent used to dispense swab.

1000 – Multiplication factor to convert the value in mcg from mg.

D – Swabbed Surface Area in cm^2 .

Calculation of acceptance criteria for Rinse samples

Active Ingredient Residue (For Non-dedicated equipment): Acceptance criteria based on the following rationale for rinse samples:

Calculation [Applicable to all items of common equipment in product train].

$$\text{Limit (PPM)} = \text{MACO} \times \frac{1000}{C} \times \frac{1}{V}$$

Where,

C – the Cumulative surface area of the equipment used (in cm^2).

V – Volume of solvent used for the rinse of the same in mL per cm^2 of Equipment.

1000 – Multiplication factor to convert the value in mcg from mg.

Calculation of recovery factor :

% Recovery shall not be less than 75% unless otherwise specified and justified in the individual protocol of analytical method validation.

Recovery factor shall be calculated as follows:

$$\text{Recovery factor} = \frac{100}{\%\ \text{Recovery}}$$

- **LIMITS FOR SWABS / RINSE:**
- MACO: Maximum allowable carryover is acceptable transferred amount from the investigated product previous.
- MAXCONC: General limit for maximum allowed concentration (ppm) of previous substance in the next batch
- MBS minimum batch size for the next products where MACO can end up

Take the calculated MACO for the product and divide this number by the total internal surface area of the total product processing system, i.e. preparation and holding vessels + pipework + filling machine. This figure is the amount of residue allowed throughout the entire process, the assumption being that there is even distribution of product residue throughout the process equipment.

- The allowed residue in the entire process = MACO / total surface area

= 50.0 mg / 7500 cm^2

= 0.0067 mg / cm^2 (MACO / cm^2)

This value is then multiplied by the area to be swabbed to give the allowed limit per swab sample.

If swabbing a 5 cm x 5 cm (25 cm^2) surface area and placing the swab in 25.0 ml of swabbing solution then the following applies:

$$\text{Limit for swab sample} = \frac{\text{MACO / cm}^2 \times \text{Swab Area}}{\text{Volume of Swab Solution}}$$

$$= \frac{0.0067 \text{ mg / cm}^2 \times 25 \text{ cm}^2}{25.0 \text{ ml}} = 0.0067 \text{ mg / mL (6.7 µg/ml or ppm per swab)}$$

In this case, swab sample results for 25 cm^2 must be ≤ 6.7 µg / mL of active to prove that the cleaning process is satisfactory.

Acceptance criteria

Safety Factors :

Approach	Approach Typically Applicable To
0.1 to 0.01	Topical products
0.01 to 0.001	Oral products
0.001 to 0.0001	Parenterals, opthalmic products
0.0001 to 0.00001	Research, investigational products

Acceptance criteria

Microbiological criteria :

- Internal specifications
- Official specifications: e.g. USP <1111>, "Microbial Examination of nonsterile Products: Acceptance criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use"

Adminstration route	Total aerobic count (cfu/g or cfu/mL)	Total combined yeasts/molds count (cfu/g or cfu/mL)
Nonaqueous oral	10^3	10^2
Aqueous oral	10^2	10
Most topicals	10^2	10

Sampling Methods

The sampling procedure refers to the method of collecting the residues from the surface so that they can be measured.

Types	Advantages	Limitations
Swabs & Wipes	Dissolves & physically removes sample, adaptable to wide variety of area	May introduce fibers, technique dependent, hard-to-reach areas
Rinse	Easy, quick, non-intrusive, large surface area	Limited information about actual surface cleanliness
Direct Surface	Rapid, non-invasive, economical	Some techniques not widely developed

Sampling Methods

- **Swab sampling techniques:**

(1) One of the **most widely used technique** for chemical and microbial sampling.
(2) Swabs are being wet with solvent aiding **solubilization and physical removal** of surface residues.
(3) Results are **technique dependent**.

Microbial swab (sterile)

Chemical swabs (*Texwipe*)

Cotton wipes

Sampling Methods

Swab sampling techniques:

(5) Generally **1 swab sample per location** is adequate.

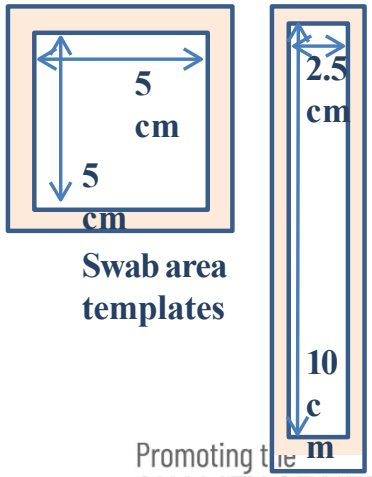
(6) Multiple swabs can be taken to **improve surface recovery**.

(7) Typical swabbed per site varies from 25 cm^2 to 100 cm^2. There is **no *"magic"* number**.

(8) PTFE(polytetrafluoroethylene)(chemically inert) **templates** may be used for accurate swabbing area.

(9) "Difficult to clean" equipment surfaces shall be identified and sampled.

(10) Representative surfaces of **different materials** should be sampled.



Swab area templates

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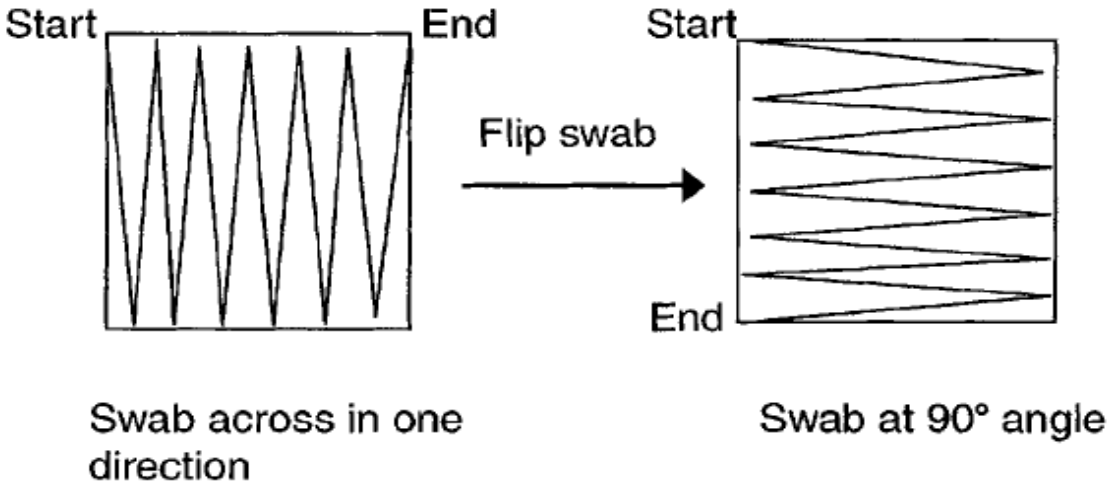
Sampling Methods

Swab sampling techniques:

(11)Wiping should be **unidirectional** at a time. **Parallel strokes** should be employed to cover entire swab area.



Courtesy: Validated Cleaning Technologies for Pharmaceutical Manufacturing, D. A. LeBlanc

Sampling Methods

Swab sampling techniques:

Example of "Difficult to clean" locations of an RMG:

Courtesy: Rapid mixer granulator, Kevin.

The design aspect of the equipment should be considered to identify "difficult to clean" locations.

Sampling Methods

Determination rinse volume:

Example :

$$\text{Rinse vol. for Equipment A} = \frac{0.63\ \text{mg}/\ \text{cm}^2 \times 1760\ \text{cm}^2}{10\ \mu\text{g}/\ \text{mL}}$$

$$= 110.9\ \text{L} \quad \text{(considering mg/L = PPM)}$$

$$\text{Rinse vol. for Equipment B} = \frac{0.63\ \text{mg}/\ \text{cm}^2 \times 810\ \text{cm}^2}{10\ \mu\text{g}/\ \text{mL}}$$

$$= 51.0\ \text{L}$$

Analytical Methods

- **Specific vs non-specific methods:**

(1) A non-specific assay may detect a variety of residues.

(2) A specific assay may quantify any anticipated residue.

(3) It is essential to correlate the results from a specific method to the results from other non-specific methods that might be used for routine monitoring of cleaning effectiveness.

HPLC

pH meter

Analytical Methods

Specific Test Methods	Non-Specific Test Methods
UV/Visible Spectrophotometry Near Infrared Spectrophotometry (NIR) **High Performance Liquid Chromatography (HPLC)** Mid Infrared Spectrophotometry (MIR) Atomic Absorption Capillary Zone Electrophoresis Enzyme Linked Immunosorbant Assay (ELISA)	**Total Organic Carbon (TOC)** **pH** Titration **Conductivity** Gravimetric

Analytical Methods

The analytical methods used for testing cleaning samples must be validated for [ICH Q2 (R1)]:

- Limit of Detection (LOD)
- Limit of Quantification (LOQ)
- Specificity
- Accuracy
- Repeatability
- Precision
- Range
- Linearity
- Recovery

Analytical Methods

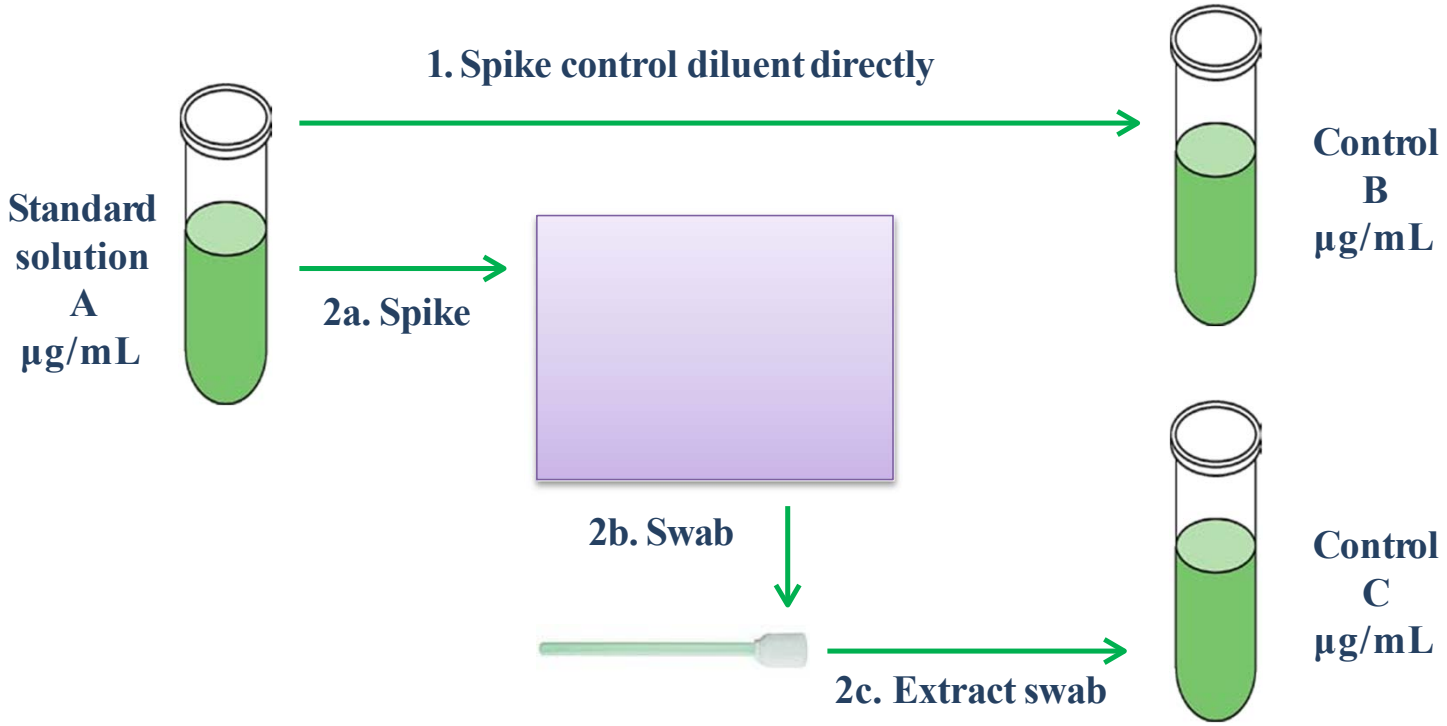
Recovery studies :

Procedure :

- Allow to dry
- Remove in swab or simulated rinse procedure
- For swab, desorb
- Analyze sample
- Compare to expected 100% value

Analytical Methods

Swab recovery schematic :



Revalidation of cleaning procedure

Revalidation of cleaning procedure is required if any of the following occur and revalidation of cleaning procedure shall be performed on a minimum of three cleaning cycles.

Modification of cleaning procedure / Surface area of product contact parts of the equipment or any modification to the equipment which has got a direct bearing on product contact parts.

Change in cleaning procedure.

Change in the analytical method for determination of residue.

Major non-traceable contamination occurrence.

Failure during cleaning verification/validation.

Monitor the validation status for cleaning during new product introduction.

In case of microbial analysis results of swab samples or rinse samples, no need to wait for the release of results.

Summary

- Cleaning validation is extremely important for the safety of products and to demonstrate cross contamination
- Cleaning SOPs must be available
- Cleaning validation protocol to be prepared, duly signed by QC, production, R&D and approved by QA
- Responsibility of production and QA to ensure cleaning validation
- Review mechanism for cleaning validation must exist
- Training on cleaning SOPs must be ensured
- Final report to be signed by stakeholders duly approved by Quality head

Thank You

Promoting the Quality of Medicines Plus

Introduction to HVAC & Cross Contamination

Nadeem Ahmed

30th June 2020

USAID FROM THE AMERICAN PEOPLE

usp

Cross-Contamination Definition

WHO Quality Assurance of Pharmaceuticals

Contamination of a starting material, intermediate product or finished product with another starting material or product during production

Risk of Cross-Contamination can be minimized

1) Adequate Design of Premises
2) Quality Control Laboratory
3) Personnel Organization
4) Adequate movement of RM, Bulk & Products
5) Adequate Procedure for Personnel Movement
6) Equipment
7) Proper handling & timely maintenance of Equipment
8) Validated Cleaning Procedures
9) Correct Air Pressure cascade & HVAC System
10) Quality Risk Management (ICH Q9)

Facility Design

- Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.
- Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage
- Premises should be designed and equipped so as to afford maximum protection against the entry of insects
- Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- Rest rooms and canteen should be separate from manufacturing and control areas.

Facility Design

- Warehouse Receiving and dispatch bays should be separated and protect materials and products from the weather.
- Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel.
- Segregation should be provided for the storage of rejected, recalled, or returned materials or products.
- Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas

Facility Design

- In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and separate facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins)
- Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection
- Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination.

Quality Control Laboratory

- Quality control laboratories should be separated from production areas.

- Quality control laboratory should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

Personnel Organization

- Cross-contamination should be avoided by taking appropriate personnel organizational measures.
- The firm should have a defined organization represented in a chart.
- The responsibilities placed on any one individual should not be so extensive as to incur any risk to quality

Raw Materials

- Sampling facilities should be designed to prevent cross-contamination by other materials, products and the environment
- Sampling from large containers of starting material or bulk products can present difficulties. Whenever possible, this work should be carried out in a separate, closed cubicle within the warehouse, to reduce the risk of contamination (e.g. by dust) of either the sample or the materials remaining in the container, or of cross-contamination.
- The weighing/Dispensing of raw materials should be carried out in separate weighing areas designed for that use, for example with provisions for dust control.

Bulk & In-Process Controls

- Intermediate and bulk products should be kept under appropriate conditions.
- Finished products should be held in quarantine until their final release.
- The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination)

Personnel Movement

- Personnel entering changing rooms should follow the changing and washing as per written procedure designed to minimize the contamination in clean area
- All personnel involved in Sensitizing Beta Lactam and non-penicillin beta lactam operations should be tested for sensitivity.

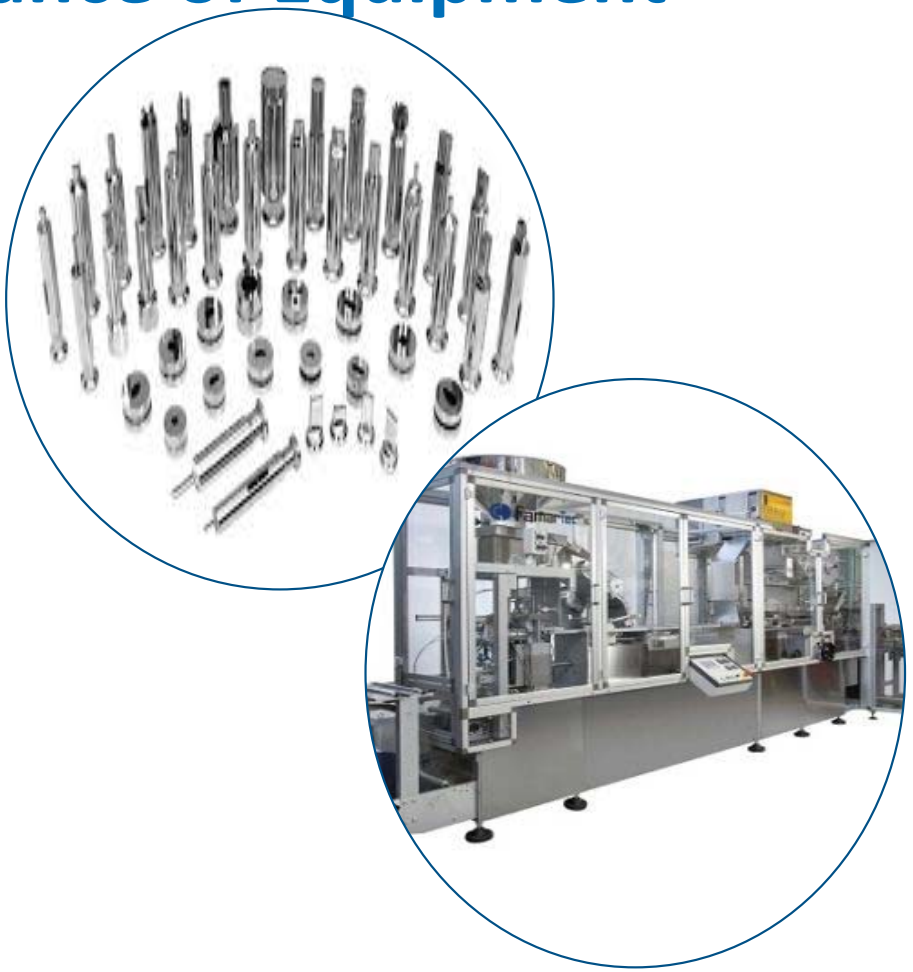
Equipment

- The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination.

- Non-dedicated equipment should be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.

Proper Handling & Maintenance of Equipment

- When equipment maintenance is carried out within a clean area, clean instruments and tools should be used, and the area should be cleaned again, where appropriate, before processing recommences.
- Develop planned preventive maintenance programs for equipment and of the recording system



Validated Cleaning Procedures

- Documented evidence should be available that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing toxicology and equipment size
- The objective of cleaning validation is to prove that the equipment is consistently cleaned of product, detergent and microbial residues to an acceptable level, to prevent possible contamination and cross-contamination

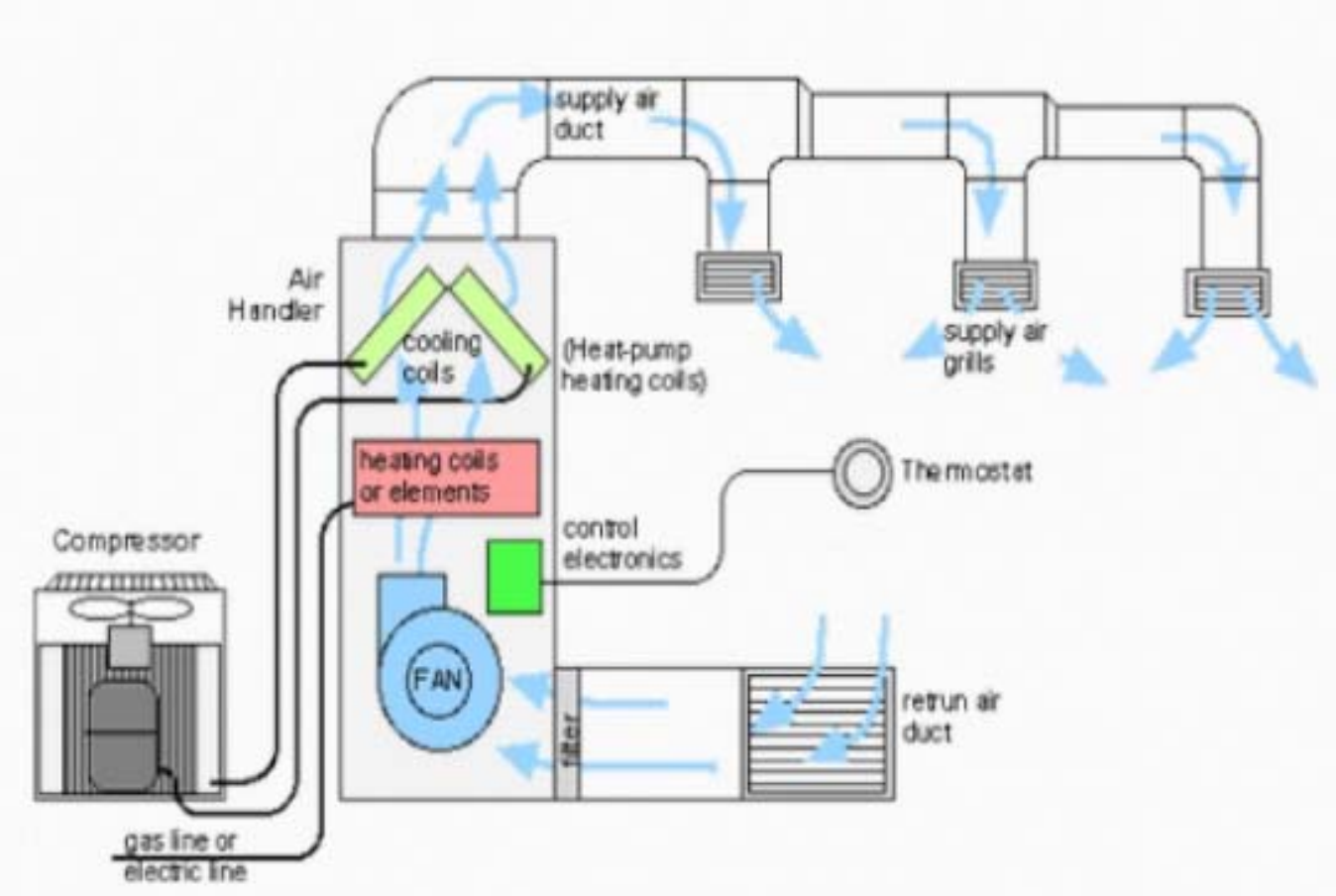
HVAC System

What is HVAC?

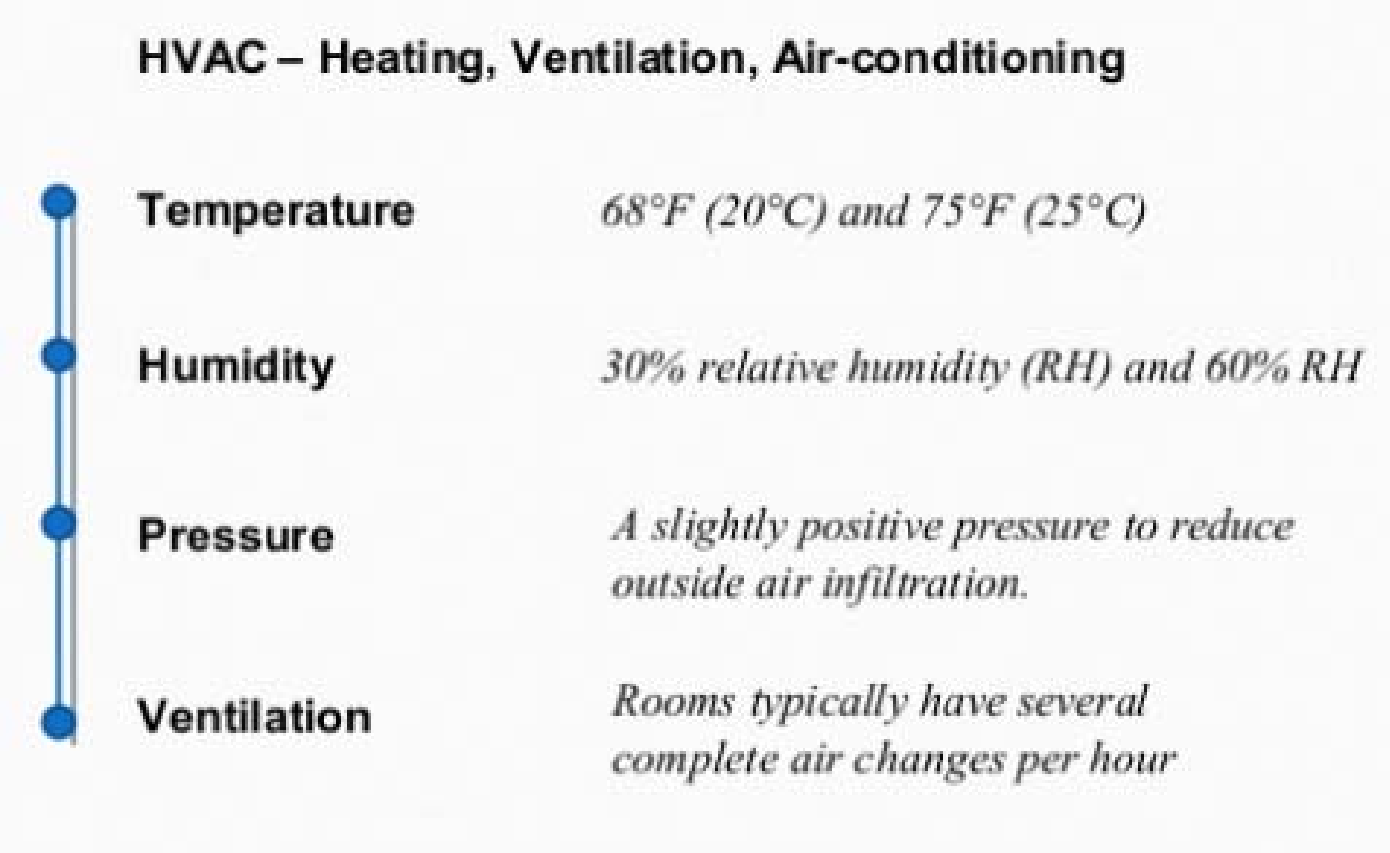
H – Heating

V – Ventilation

AC – Air Conditioning



HVAC System


HVAC – Heating, Ventilation, Air-conditioning
Temperature
68°F (20°C) and 75°F (25°C)
Humidity
30% relative humidity (RH) and 60% RH
Pressure
A slightly positive pressure to reduce outside air infiltration.
Ventilation
Rooms typically have several complete air changes per hour

What HVAC Cannot Do?

1) HVAC cannot clean up the surfaces of a Contaminated Places, Room or Equipment
2) HVAC cannot compensate for personnel who do not follow procedures

Airlocks

Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock:

- *cascade airlock*: higher pressure on one side of the airlock and lower pressure on the other
- *sink airlock*: lower pressure inside the airlock and higher pressure on both outer sides
- *bubble airlock*: higher pressure inside the airlock and lower pressure on both outer sides

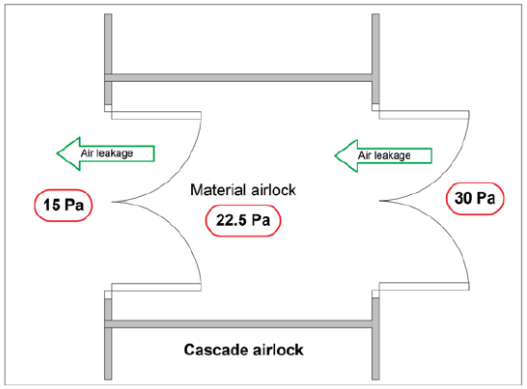
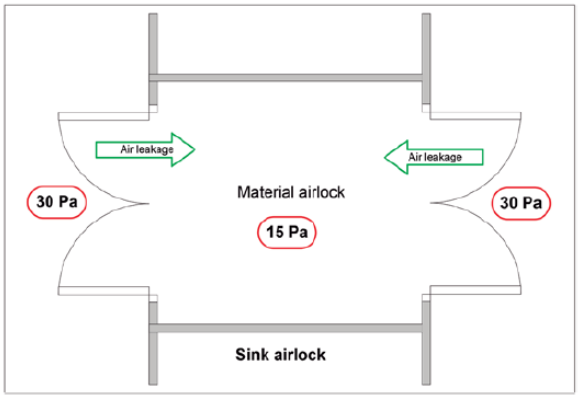
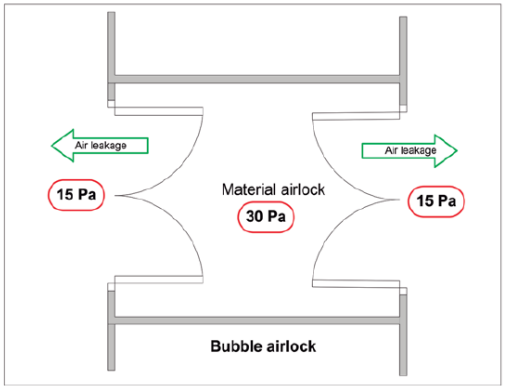


Image of room pressure gauge indicating colour-coded normal, alert & action parameters





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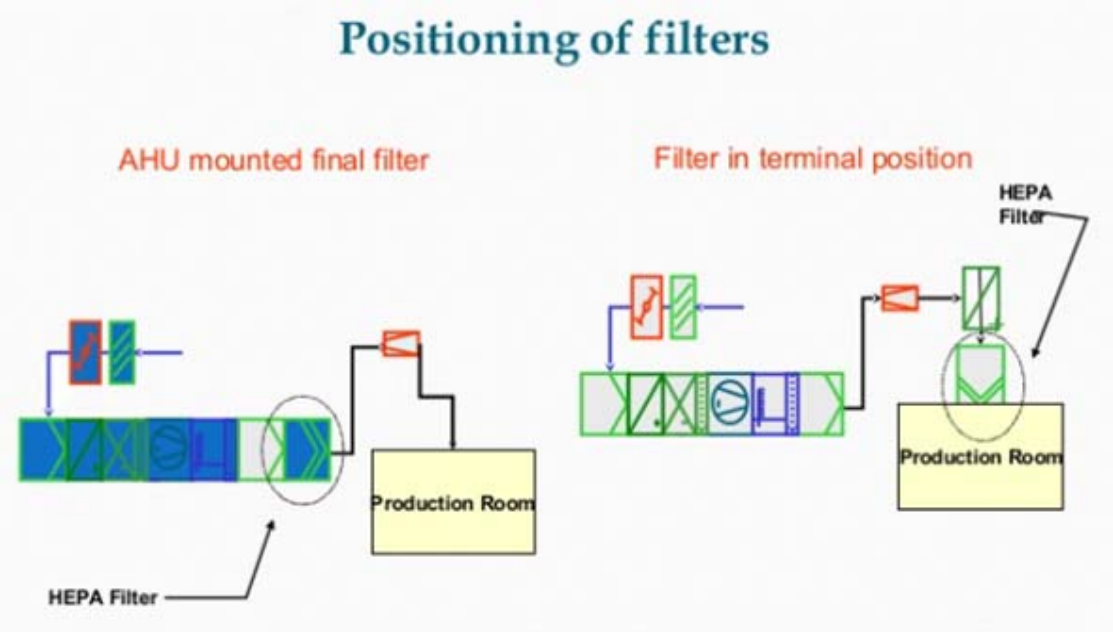
HEPA Filters

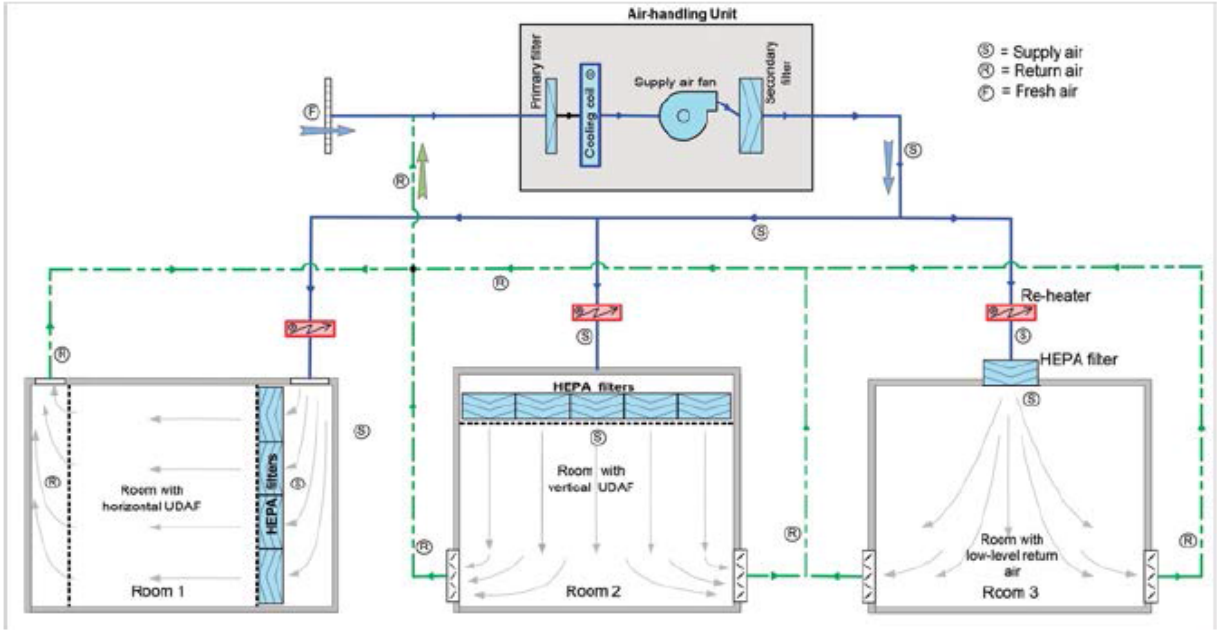
- Install HEPA filters to achieve the desired degree of filtration of air, these filters may be placed in the AHU, or may be installed terminally near the supply grille.



Air Flow Pattern

- Airflow directions should be specified and proven to promote containment and not be adversely affected or obstructed by equipment, utilities, containers or personnel. The location of supply and return or exhaust air grilles should facilitate appropriate airflow directions in an area

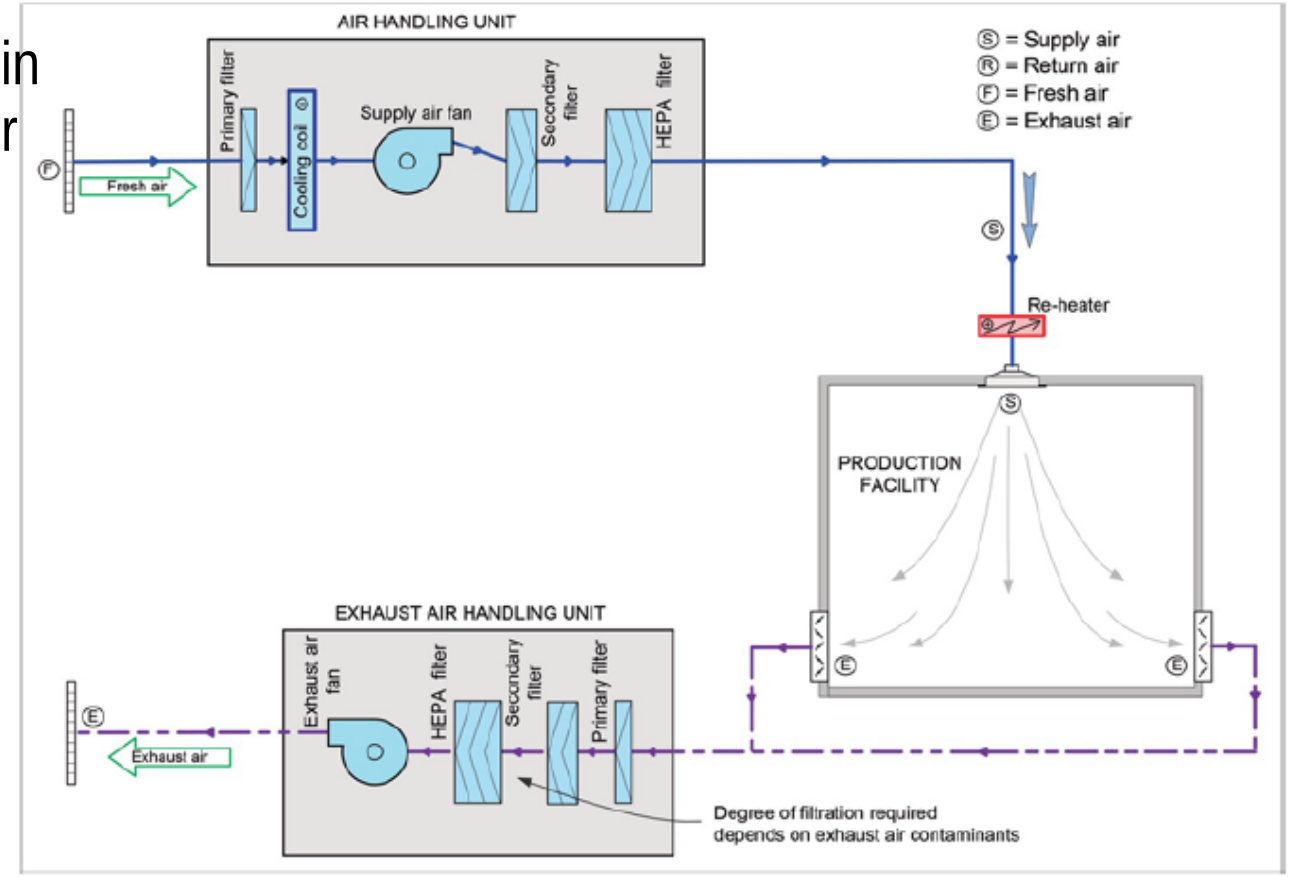
Example of horizontal airflow, vertical flow and turbulent flow



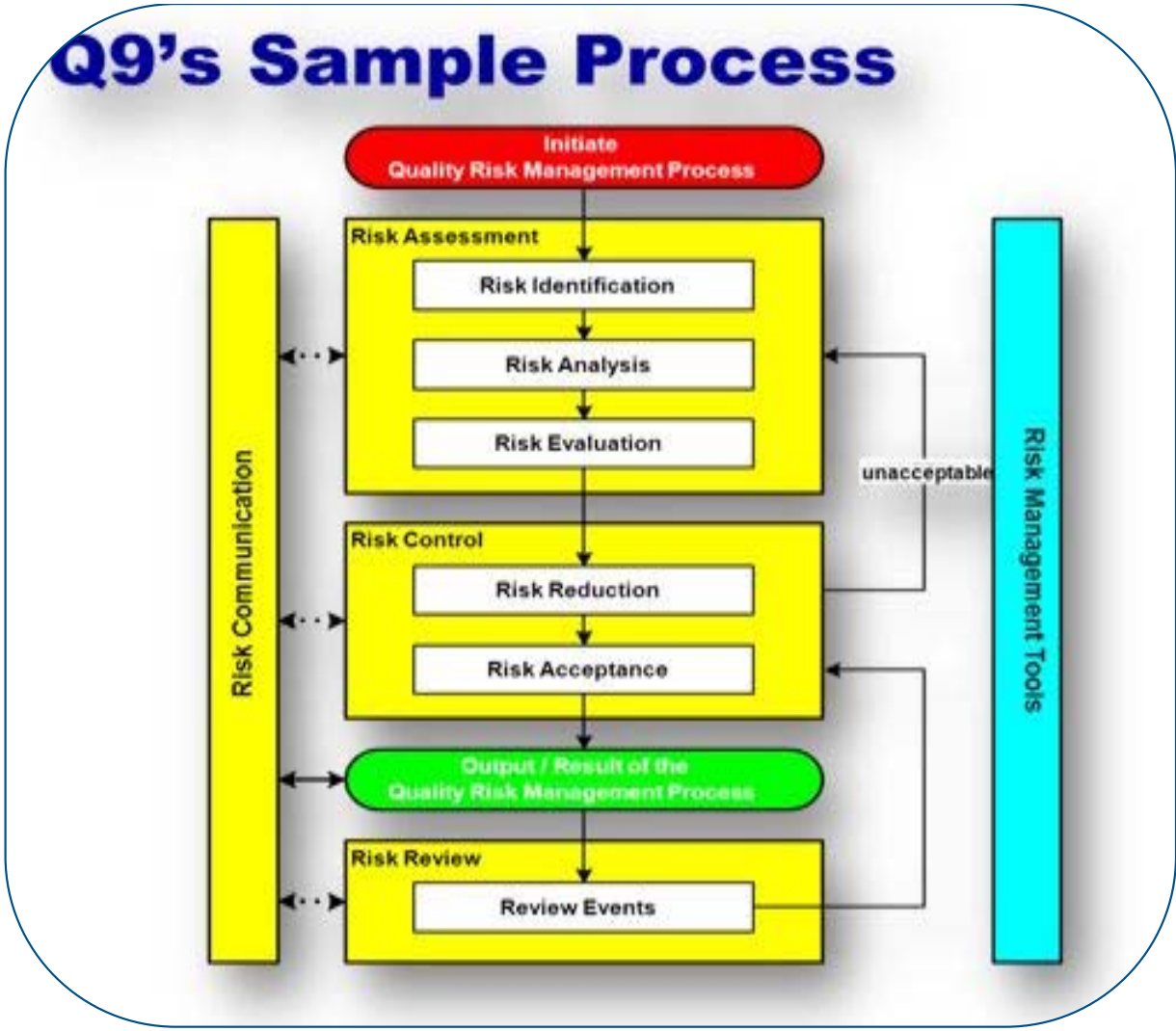
UDAF: unidirectional airflow.

Directions of Fresh Air & Exhaust

- Fresh Air Inlet should not be in close proximity of Exhaust Air Outlet to avoid cross Contamination.



QRM (ICH Q9)


Q9's Sample Process
Initiate
Quality Risk Management Process
Risk Assessment
Risk Identification
Risk Analysis
Risk Evaluation
Risk Control
Risk Reduction
Risk Acceptance
Output / Result of the
Quality Risk Management Process
Risk Review
Review Events
Risk Communication
unacceptable
Risk Management Tools

Thank you

SEPARATE/DEDICATED FACILITIES

Sultan Ghani

REQUIREMENTS

- Separate manufacturing facility is required for penicillin and non-penicillin beta-lactum products.

- The FDA recommends to establish sufficient measures on separation and control in order to avoid cross-contamination risks between;

  - Beta lactam and non-beta lactam products
  - Non-penicillin beta lactams and other non-penicillin beta lactams (cross-reactivity risk)

Continued…

- EU updates GMP to provide better guidance around the need for dedicated facilities and managing the risk of cross-contamination. This need arose from the uncertainty and confusion around the current EU GMPs, which state:

"In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (eg. penicillins) or biological preparations (eg. from live microorganisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. . . "

Continued…

"A more scientific approach based on current available pharmacological and toxicological information is required to establish threshold values to be used as part of the overall Quality Risk Management in shared facilities."

NARCOTICS AND PSYCHOTROPIC DRUGS

- To establish principles for safe practice in the management of controlled drugs in both governmental and private health institutions.
- To provide guidance on all relevant aspects of controlled drugs including ordering, storing, supplying, recording, monitoring and disposing CDs safely.
- To ensure appropriate and convenient access for those patients who need them.
- To ensure compliance with the law of combat of Narcotics and Psychotropic Substances.

VETERINARY PRODUCTS

- The manufacture of premixes for medicated feeding stuffs requires the use of large quantities of vegetable matter which is likely to attract insects and rodents. Premises should be designed, equipped and operated to minimize this risk and should also be subject to a regular pest control programme.

- Because of the large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to avoid cross contamination and facilitate cleaning, for example through the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.

HERBAL PRODUCTS

The procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those employed for conventional pharmaceutical products.

THANK YOU