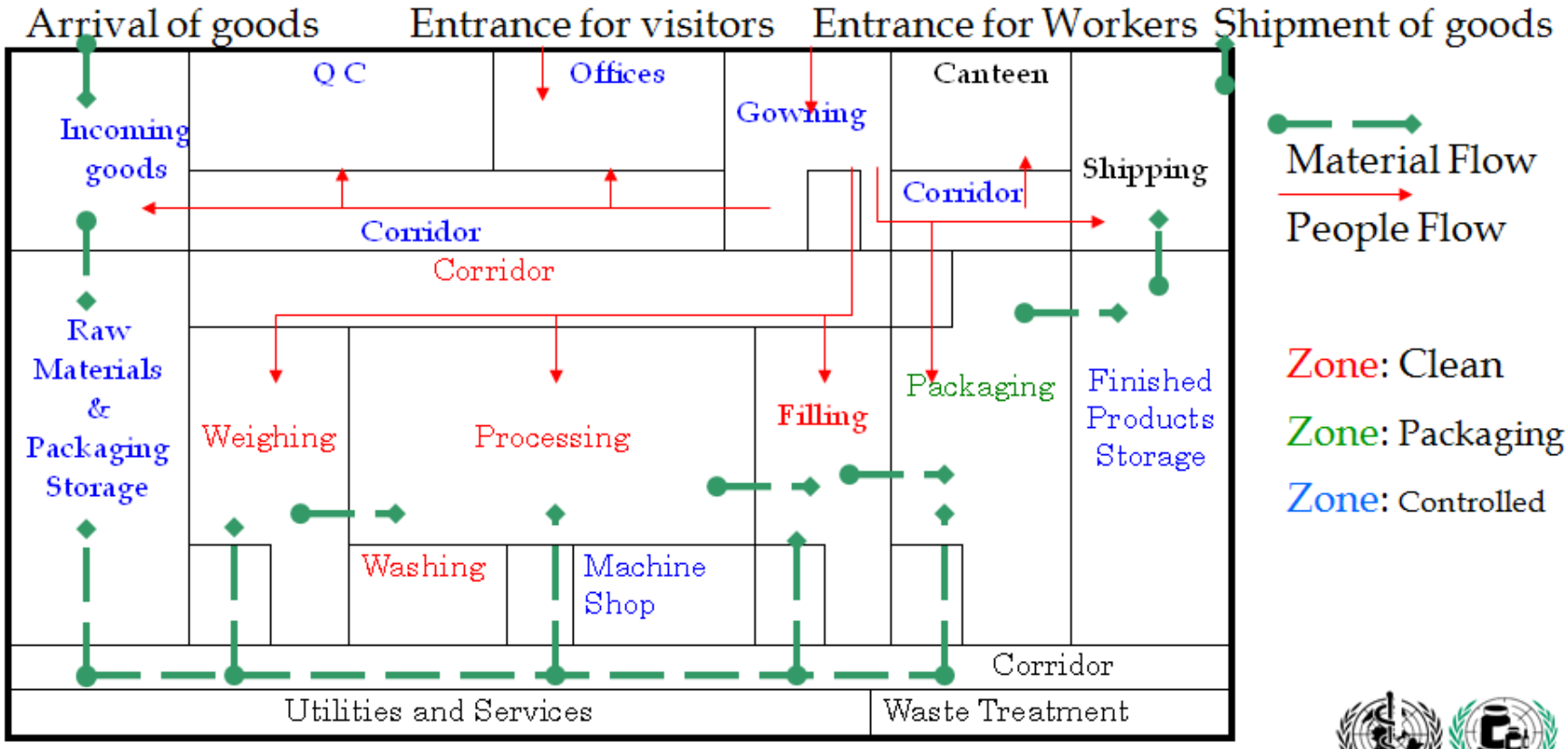
Buildings and Facilities

- Buildings and Facilities must be designed with **adequate size** and **space** for operations.
- There must be a **good flow pattern** for personnel, materials, products and waste materials (helps to eliminate mix-ups and contamination)
- The facility must be easy to clean, and sanitize (surfaces, equipment,..)
- Environmental controls must be in place (lighting, ventilation, air filtration, air heating and cooling clean rooms)

- Utilities must be validated (water systems, plumbing, electrical, …..)

Premises

Example of Materials and People Flow



Equipment

- Each piece of equipment must be: **appropriate design** and **size** to facilitate **use, cleaning, and maintenance**.
- Equipment's surfaces and parts **must not interact** with processes or products so not affect **purity**, **strength**, or **quality**.
- **Standard operating procedures (SOP)** must be **written and followed** for proper use, maintenance, and cleaning of each piece of equipment.
- Equipment and computers used in the processes must be **routinely calibrated**, maintained, and validated for accuracy.
- Filters used in the manufacture of injectable drug products **must not** release fibers into such products.

Control of components, containers and closure

- Written procedures describing: identification, storage, handling, sampling, testing, and approval or rejection of all product components, containers, and closures must be maintained and followed.

- Bulk pharmaceutical chemicals, containers, and closures must meet **the required property** (the exact physical and chemical specifications established with the supplier at the time of ordering).

- Raw materials Raw materials are **quarantined** until they are **verified** through sampling and qualitative and quantitative analysis by **quality control unit.**

- **Rejected** components, containers, and closures are **identified** and **controlled** under a **quarantine system** to prevent their use in manufacturing and processing operations.

- Mainly bulk chemicals (APIs) are synthesized in **China and India.** it is important to confirm their **identity** and **purity** with **USP** and **NF** prior to use in finished pharmaceuticals.

Production and Process Controls

- **Written procedures** are required to ensure that drug products have correct **identity**, **strength**, **quality**, and **purity**.
- In-process samples taken from production batches **periodically** for product control.

(*a*) performed by production personnel at the time of operation

(*b*) performed by the quality control laboratory personnel to ensure compliance with all product specifications and batch-to-batch consistency.

If in-process product out the standards ??????

Packaging and Labeling Control

- Written procedures are required for the issuance of labeling and packaging materials.
- Labeling for each variation in drug product— strength, dosage form, or quantity of contents—must be **stored separately** with suitable identification. Outdated labels and other packaging materials must be destroyed. Access to the storage area must be limited to authorized personnel.
- label examination shall be performed by one person and independently verified by a second person.
- Labels must meet the legal requirements for content.
- Each label must contain **expiration dating** and the **production batch** or **lot number** to facilitate product identification.
- Appropriate stability testing used to determine expiration date to assure that a drug product meets applicable standards at the time of use.

- Exception for the requirement are **homeopathic drug** products, **allergenic extracts**, and investigational drugs (**INA**) that meet the standards established during preclinical and clinical studies.

In 1982, several consumers of OTC Tylenol capsules suddenly died of cyanide poisoning. An intensive investigation of the production records showed that this was not the result of a raw materials mix-up during manufacturing. Rather, **tampering apparently** occurred on store shelves.

- A **tamper-evident package** is defined as “one having one or more **indicators or barriers to entry** which, if breached or missing, can reasonably be expected to **provide visible evidence** to consumers that tampering has occurred”. Some ex. Blister/strip pack, seal band for capsule, bottle seal, tape seal and aerosol container

Holding and Distribution

- Written procedures must be established and followed for the holding and distribution of product.
- Finished pharmaceuticals must be **quarantined in storage until released** by **the quality control unit**.
- Products must be stored and shipped under conditions that do not affect product quality.
- The oldest approved stock is distributed first.
- The distribution control system must allow the distribution point of each lot of drug product to be readily determined to facilitate its recall if necessary.

Laboratory controls

are requirements for the establishment of and conformance to: **written specifications**, **standards**, **sampling plans**, **test procedures**.

 The specifications, which apply to each batch of drug product, include:

- **sample size**
- **test intervals**
- **sample storage**
- **stability testing**

special testing requirements for parenteral, ophthalmic , controlled-release products, and radioactive pharmaceuticals.

Records and Reports

The master records of each batch must document that **each step in the production, control, packaging, labeling, and distribution** of the product was accomplished and approved by **the quality control unit**.(must be maintained for **at least a year following the expiration date** of a product batch)

- Equipment cleaning and maintainance logs.
- specifications and lot numbers of product components including, raw materials, drug product container, closure, and labeling records.
- Master production and control records for each batch.
- Batch production and control records.
- Production record review.
- Laboratory records.
- Distribution records. - Complaint files.

Records of **written and oral complaints** regarding a drug product (e.g., product failure, adverse drug experience) must also be maintained, along with information regarding **the internal disposition** of each complaint.

All records must be made available at the time of inspection by FDA officials.

Returned drug products (e.g., from wholesalers) must be identified by lot number and product quality determined through appropriate testing.

Drug products that meet specifications may be **salvaged or reprocessed**.

Those that do not, along with those that have been subjected to improper storage (e.g., extremes in temperature), shall not be returned to the marketplace.

Records for all returned products must be maintained and must include **the date and reasons for the return**; **quantity and lot number** of product returned; **procedures employed for holding**, **testing**, and reprocessing the product; and the product's disposition

Additional cGMP Regulatory Requirements

Inspection of ***Bulk Pharmaceutical Chemicals*** *(product components)* to assure that all required standards for quality are met.

Because the quality of any finished pharmaceutical product depends on the quality of the various components

GMP focuses on all elements of chemical **purity** and **quality**, including following:

- Specifications and analytical methods for components used to detect impurities or chemical residues and limits set.
- critical chemical reaction steps and handling of chemical intermediates

- Quality of water used.
- Solvent handling and recovery systems
- Effect of scale-up of chemical batches on the yield
- Stability studies of bulk pharmaceutical chemical

Biologics

the basic cGMP regulations for biologic products are similar to finished pharmaceuticals , with specific additional mandates

Medical Devices

- devices are approved for marketing when shown to be **safe** and **effective** through premarket approval.

- The regulations for "good manufacturing practice for medical devices" are similar in organizational structure to those for finished pharmaceuticals. They include **personnel**; **buildings**; **equipment**; **control of components**; production and process controls; packaging and labeling; holding, distribution, and installation; device evaluation; and records

- Medical devices are subject to the reporting of adverse events, to recall, and to termination of approval.

Devices covered by cGMP regulations include:

intraocular lenses, hearing aids, intrauterine devices, cardiac pacemakers, clinical chemistry analyzers, catheters, dental X-ray equipment, surgical gloves, condoms, prosthetic hip joints, computed tomography equipment, and wheel-chairs

Objectives

cGMP- Part 4

- Determine the similarity and difference between pharmaceutical manufacturing and extemporaneous compounding

- Describe the various types of packaging containers and their properties.

cGMP and cGCP

- Pharmaceutical **manufacturing** is large-scale production of drugs or drug products for distribution and sale.

- **Compounding** is professional preparation of prescriptions for specific patients as a part of the traditional practice of pharmacy.

The increase in preparing patient-specific medications, due to the following:

1. Many patients need **drug dosages or strengths** that are not commercially available.

2. Many patients need **dosage forms**, such as suppositories, oral liquids, or topical, that are not commercially available.

3. Many patients are **allergic to excipients** in commercially available products.

4. Children’s medications must **be prepared as liquids**, flavored to enhance compliance.

5. Some medications are **not very stable** and require preparation and dispensing every few days; they are not suitable to be manufactured products.

6. Home health and hospice care has resulted in new approaches to pain management and **higher concentrations** and **combinations of drugs** that are now used

Does the compounded drug in community pharmacy have required **quality** and meet standard specifications ?????

To ensure quality compounded products; consequently, many Standards-setting agencies since 1990 tried to establish guidelines for pharmaceutical compounding.

Chapters and monograph related to pharmacy compounding were developed and published in **U.S. Pharmacopeia–National Formulary** (USP-NP). They provide:

a **tested**, uniform **formulation** with valid beyond-use dating (Discard after).

Also, conditions and **practices to prevent harm**, including death, to patients that could possibly result from microbial contamination, excessive bacterial endotoxins, variability in the intended strength and composition, unintended chemical and physical contaminants, and ingredients of inappropriate quality

The **Good Compounding Practices** (GCP) applicable to State-Licensed Pharmacies", developed by the **National Association of Boards of Pharmacy**

(A) General Provisions and Definitions;
(B) Organization and Personnel;
(C) Drug Compounding Facilities;
(D) Equipment;
(E) Control of Components and Drug Product Containers and Closures;
(F) written procedures to ensure that the finished products are of the proper **identity**, **strength**, **quality**, and **purity**, as labeled
(H) Labeling Control of Excess Products; and Records and Reports.

Comparing and contrasting between expiry date of pharmaceutical manufacturing and extemporaneous compounding.

Expiration Date

- The date at which a manufacturer can no longer guarantee the strength or safety of a medication
- Determined by the US Food and Drug Administration
- Based on testing a drug in specific conditions related to storage containers, lighting, temperature, etc.
- Usually the date given in “years” for commercial products

Beyond-Use Date

- The date when the compounded prescription should no longer be used
- Determined by the pharmacy when they fill a prescription
- Based on **the type of drug**, how fast it degrades, **dosage**, **type of container**, **storage conditions**, **prescription length**, the likelihood of contamination
- The dates are generally given in days or months