P03: Pharmaceutical supply chain and best practices

E356 Pharmaceutical and Bio-Chem Supply Chain

Diploma in Supply Chain Management (DSCM)

E356 Topic Tree

Pharmaceutical and Bio-chem Supply Chain

- Introduction to Pharma and Bio-chem
- Classification of Dangerous Goods
- Best Practices (GMP/GDP)
- Clinical Supply Chain
- Cold Chain Management

Import, Packaging and Distribution

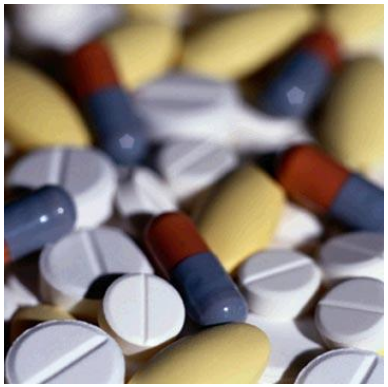
- Import and Distribution of Medical Devices
- Import of Pharmaceutical and Bio-Chem Products
- Local Transportation of Pharmaceutical and Bio Chem Products
- Packaging of Pharmaceutical DG for Air Transport
- Declaration of Pharmaceutical DG for Air Transport

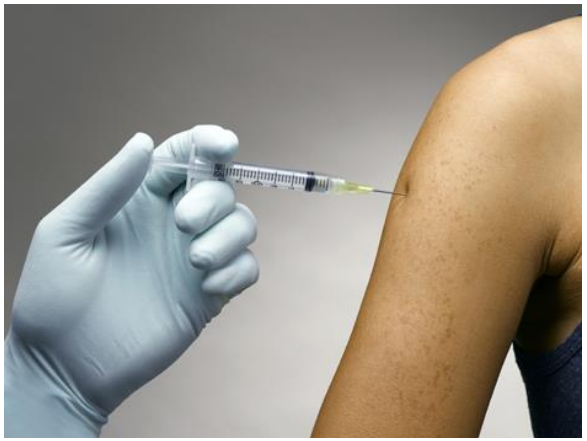
Product Tracing, Recall and Disposal

- Product Tracing
- Drug Recall
- Disposal of Bio-chem Products in Hospital Logistics

Medicine

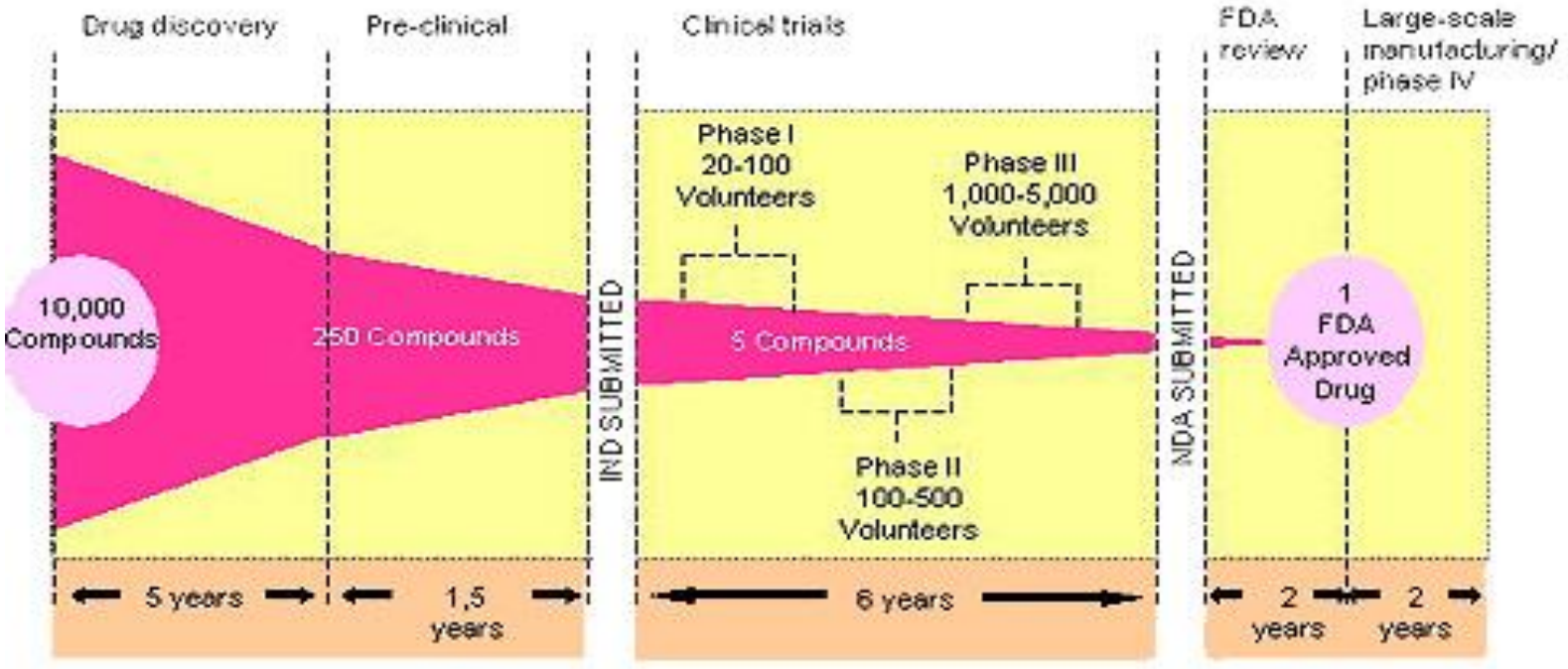
- **A medicine contains an accurate dose of drug in an easy-to-use and easy-to-administer form. For the drug to attain the status of medicine, the following objectives must be attained.**
  - The drug must be shown to be safe
  - The drug must be shown to be effective
  - A process for manufacturing the drug has to be developed, along with controls to assure its quality
  - The drug product has to be developed for clinical studies and as a commercial product





Drug Discovery to Drug Approval

- **The chart shows the stages of highly regulated drug development.**
- **No matter how potentially effective a drug is, if it is not safe or does not meet acceptable standards of performance and purity, there will be no license to market.**
- **The risk involved with R&D can be costly. Out of 250 drugs that are tested, only five will enter clinical trials, and only one will receive the right to be produced and marketed to the public.**



Life-cycle of a Pharmaceutical Product

In Discovery/Research Phase:

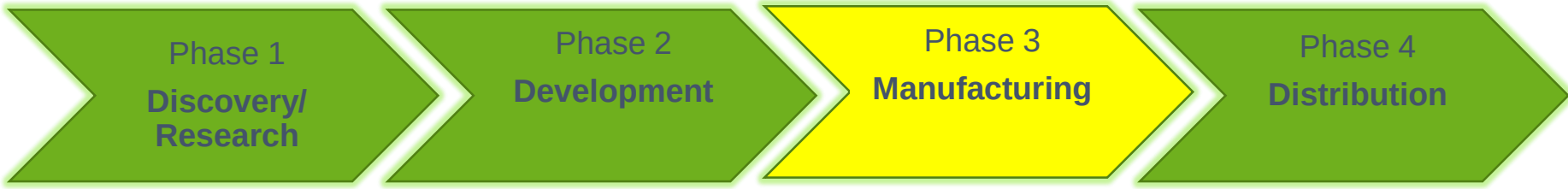
- **The drug discovery phase is initiated after a biological target is identified.**
- **The phase tends to use thousands of more or less random test compounds against therapeutic targets.**
- **It typically takes about 10 years to result in a potential new drug that is registered.**
- **From this point onwards patent protection applies.**

Life-cycle of a Pharmaceutical Product

In Development Phase:

- The potential new drug must then be tested for both safety and efficacy. This involves a variety of trials:
  1) Pre-clinical (on animals) and then
  2) Clinical trials (on humans).
- **Coming up with a chemical or biochemical route to manufacture and an associated manufacturing process.**
- **Submission for regulation approval.**
- **This set of activities typically takes 6–8 years.**

Life-cycle of a Pharmaceutical Product



In Manufacturing Phase:

It can be broadly divided into the following two parts:

- **Primary Manufacturing (manufacturing of API)**

  To produce Bulk Pharmaceutical Chemicals (BPC), also known as Bulk Active Ingredients (AI) or Active Pharmaceutical Ingredients (API) manufacturing.

- **Secondary Manufacturing (from API to finished product)**
  - Finished product manufacturing
  - Packaging
  - Warehousing/holding

Primary Manufacturing
- Active Pharmaceutical Ingredients (API)

- **APIs (or AIs) are bulk pharmaceutical ingredients or bulk pharmaceutical intermediates that would be processed further in the secondary manufacturing processes**
- **API exist as bulk liquid/suspension form or solid (dry powder) form**
- **Packaging and storage of API is critical in ensuring ease of transportation to the next site / secondary manufacturing site for further processing to make the end pharmaceutical product**
- **Examples of raw materials in liquid/suspension form - isopropyl alcohol, ethanol, glycerin, propylene glycol, mineral oil**
- **Example of API in solid form - Antihistamine and decongestant active ingredients such as the bitartrate, maleate, citrate.**

Primary Manufacturing - Active Pharmaceutical Ingredients (API)

The **primary manufacturing process** is characterised by

- long task processing times, often rounded to multiples of shifts
- Multistage processes are operated, considerable inventories are often held between stages
- Delays due to QC checks of an intermediate stage before being approved for use downstream in the process
- Relatively low production volumes
- Need to avoid cross-contamination of products and requirements for validated cleaning and changeovers results in long downtimes between products.

Therefore

- Long production campaigns are the norm, otherwise equipment utilisation is too low.
- Not unusual for 1 year's production of a product to be produced in a single campaign, and the material produced being stored until the next campaign in the following year

Secondary Manufacturing - Final Products

This is concerned with taking the active ingredient produced at the primary site and adding “excipient” inert materials along with further processing and packaging to produce the final products, usually in SKU form.

For example,

A product that is sold in pill form would undergo:

(i) granulation: with addition of all the excipient materials;

(ii) compression: forming the pills;

(iii) coating;

(iv) quality control; and

(v) primary and secondary packaging.

Secondary packaging

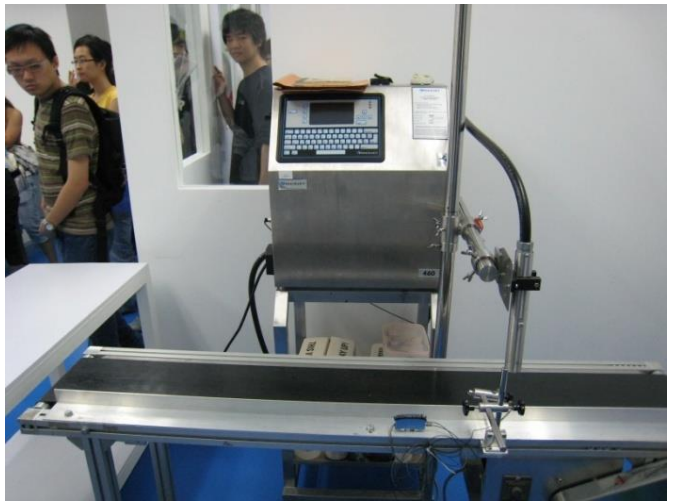
Primary packaging

The primary packaging is the encasement of the drug product in suitable materials to protect the integrity of the drug. E.g. bottles, blister packs etc.

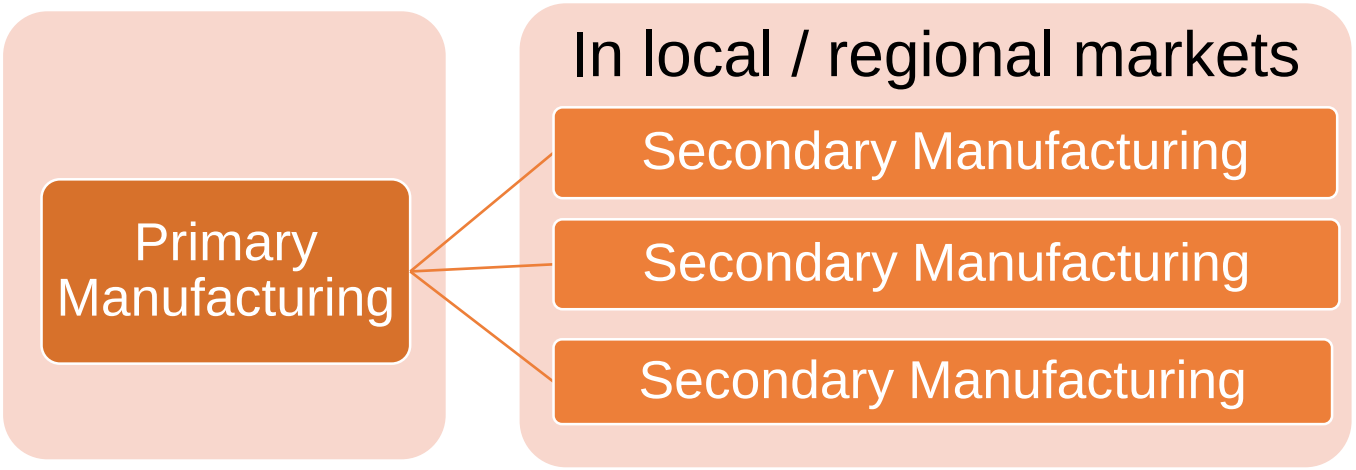
The secondary packaging is the labelling and packing into presentations suitable for patient use and filling into shipping outers reading for transfer to the distribution channel.

Secondary Manufacturing - Value-added services in pharmaceutical storage facility

- **Common services provided with pharmaceutical storage include**
  - Shrink wrapping
  - Emergency response
  - Break bulk repackaging
- **Many value-added services (VAS) are part of secondary manufacturing**
  - Secondary repackaging / redressing
  - Adding instructions insert
  - Changing instructions insert
  - Labeling of vial, bottle or carton
  - Change of insert and carton
  - Inkjet printing of inner bottle
  - Inkjet printing of carton / label



Secondary Manufacturing sites



The secondary manufacturing locations are often geographically separated from the primary manufacturing locations.

This is frequently the outcome of tax and transfer price optimisation within the enterprise. There are often many more secondary manufacturing sites than primary ones, serving local or regional markets.

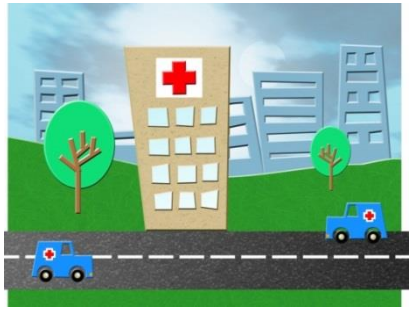
Life-cycle of a Pharmaceutical Product

Phase 1 **Discovery/ Research** → Phase 2 **Development** → Phase 3 **Manufacturing** → Phase 4 **Distribution**

In Distribution Phase:

- **It is the final step to deliver the manufactured goods to consumers.**

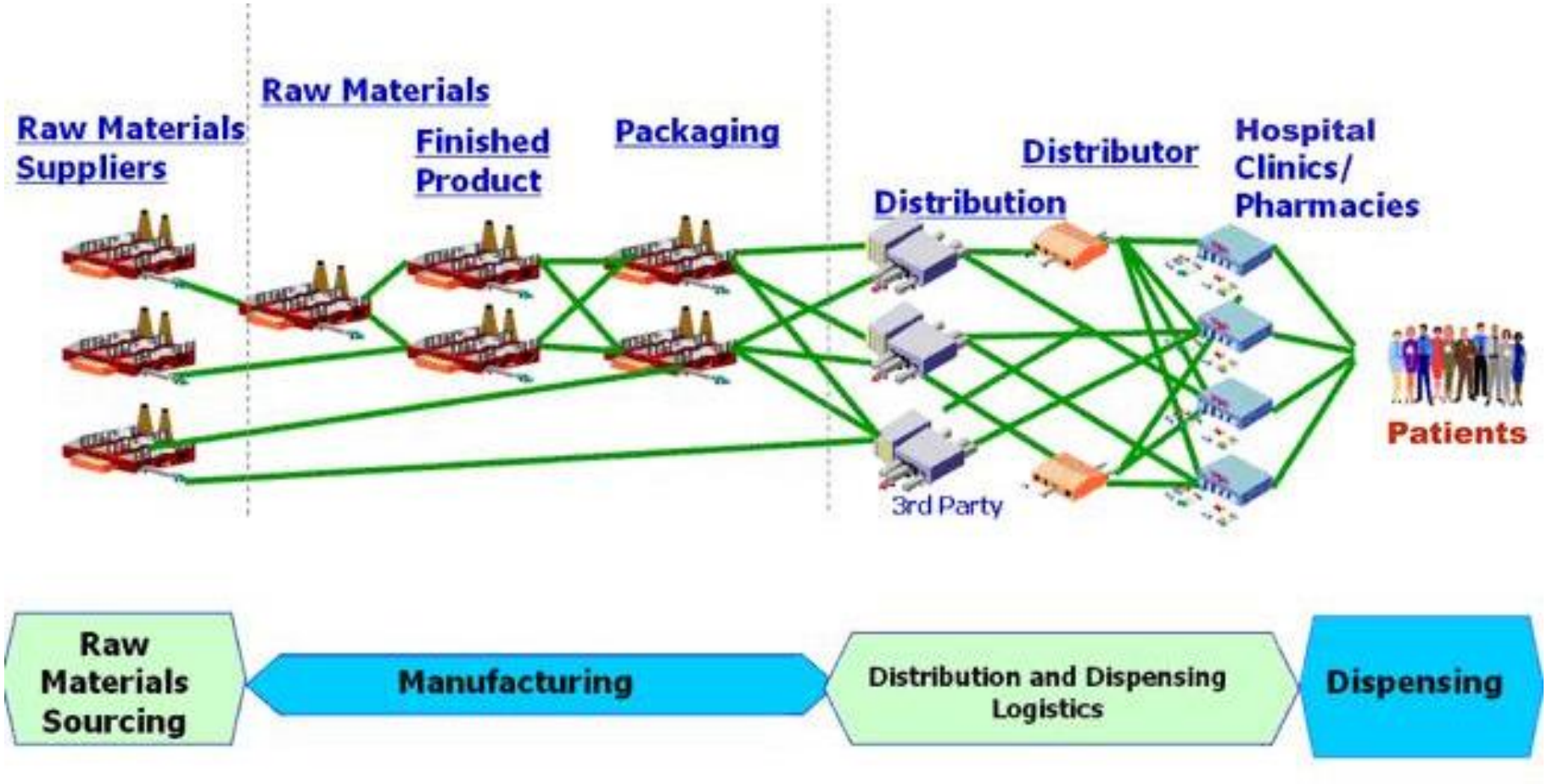
1) Ethical distribution
   - Hospitals
   - Retail Pharmacy



2) OTC distribution
   - Similar but reaches wider network to health shops etc.

3) Web distribution
   - Web pharmacist
   - Web information sites

Typical pharmaceutical supply chain



Types of Pharmaceutical Firms

The key players include:

(i) Large, research and development-based multinationals with a global presence in branded products, both ethical/prescription and over-the-counter. They tend to have manufacturing sites in many locations. (e.g. prescription medicine marketed in Singapore Cholesterol medication, EZETROL™ and ZOCOR® under registered trademark of Merck & Co.)

(ii) Large generic manufacturers, who produce out-of-patent ethical products and over-the-counter products. E.g. Over- the- Counter / generic drugs - Paracetamol marketed as

a) Panadol by GlaxoSmithKline in Singapore, Australia, Taiwan, etc.

b) Tylenol by Johnson and Johnson's in North America

Types of Pharmaceutical Firms

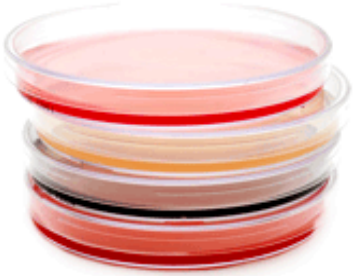
(iii) Local manufacturing companies that operate in their home country, producing both generic products and branded products under licence or contract. (e.g. Paracetamol API local Manufacturers in

a) China - Hebei Jiheng (Group) Pharmaceutical Co., Ltd.

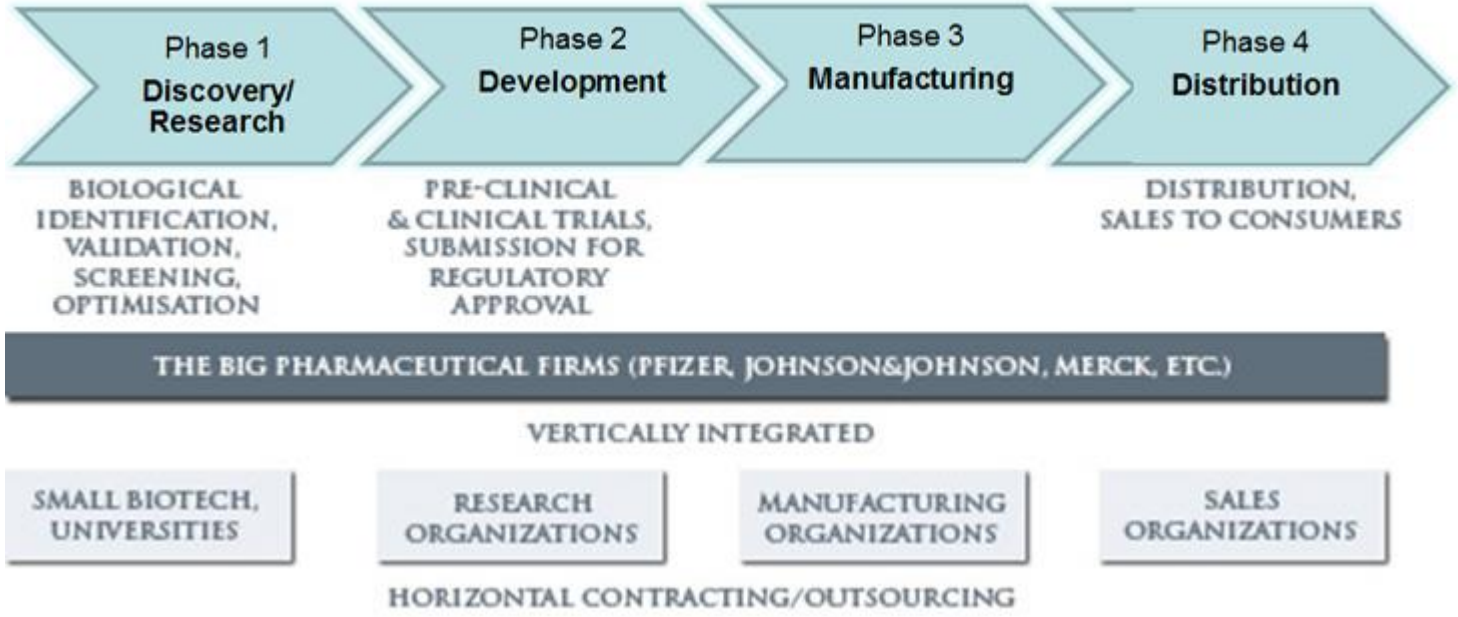
b) Malaysia - Royce Pharma Manufacturing Sdn Bhd.)

(iv) Contract manufacturers, who do not have their own product portfolio, but produce either key intermediates, active ingredients (AI) or even final products by providing outsourcing services to other companies. (E.g. Sunward Pharmaceutical)

(v) Drug discovery and biotechnology companies, often relatively new start-ups with no significant manufacturing capacity.



Outsourcing in the pharmaceutical chain



- **Big pharmaceutical firms are often able to perform all phases of the chain.**
- **The discovery phase is often contracted out to small biotech companies or universities. More and more, the discovery segment of the value chain is being sent abroad to countries like India and China, where such high-cost procedures can be carried out for relatively low costs. Biopolis in Singapore was built to develop a talent pool for discovery of new drugs.**
- **Specialized clinical research organizations can be contracted to perform the clinical trials.**
- **Some contract manufacturers carry out manufacturing services for intermediates, active ingredients and final products.**

Quality Assurance in Healthcare and Pharmaceutical Supply Chain

- **Global best practices, guidelines and standards in pharmaceutical Supply Chain**
- **Good Manufacturing Practice (by WHO)**
- **Good Distribution Practice (by WHO)**
- **Local guidelines and standards from HSA**

World Health Organization

FDA U.S. Food and Drug Administration

HSA Health Sciences Authority

Good Manufacturing Practice (GMP)

Good Manufacturing Practice **(GMP) is a vital component of Quality Assurance which helps to ensure that medicinal products are consistently produced with the quality standards appropriate for their intended use.**

Under the Medicines Act, all manufacturers and assemblers of medicinal products (both "Western Medicines" and "Chinese Proprietary Medicines" (CPM)) are required to conform to GMP.

HSA's GMP auditors will conduct audits on medicinal product manufacturers and assemblers in accordance with the PIC/S Guide to GMP for Medicinal Products (Part I) and its relevant annexes.

GMP has become a trend to refer to GMP as cGMP. Here, c refers to current rules and regulations that serve the purpose of reminding manufacturers to strictly follow the guidelines and manufacturing procedures that are current and most up to date.

Quick Overview of GMP

Good Manufacturing Practices in Pharmaceuticals
https://youtu.be/07NLWoPwDtg

Scope and Main Principles under GMP

1. **Quality Management – for quality control and assurance**
2. **Personnel – All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs**
3. **Premises and Equipment – Minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build up of dust or dirt and in general, any adverse effect on the quality of products.**
4. **Documentation – Essential part of the quality assurance system**
5. **Production – Operations must follow clearly defined procedures; must comply with GMP**
6. **Quality Control – QC in sampling, specification, testing, as well as the organisation, documentation and release procedures**
7. **Contract Manufacture and Analysis**
8. **Complaints and Product Recall Protocol**
9. **Self Inspection protocol**

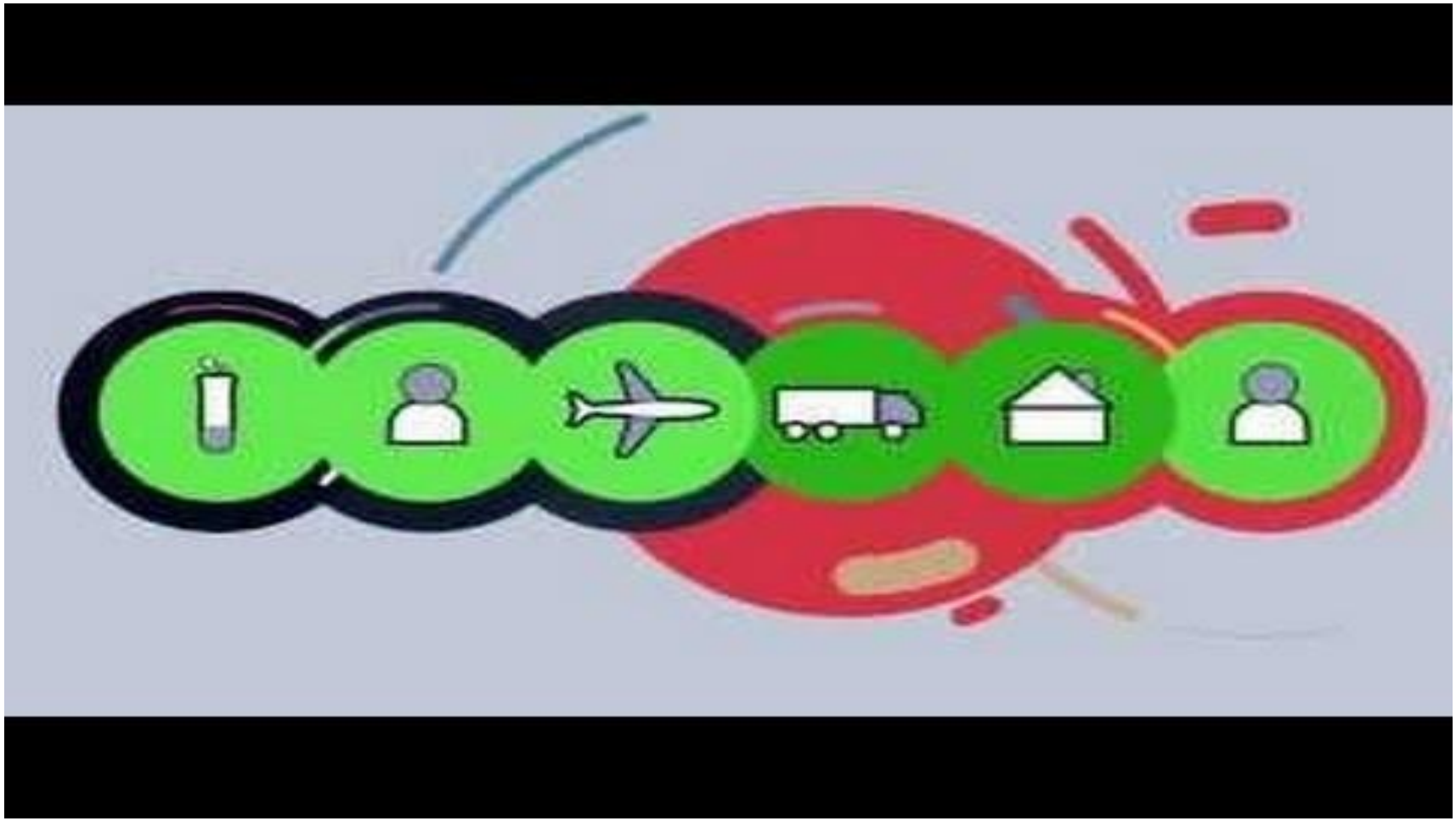
Good Distribution Practice (GDP)

Good Distribution Practice (GDP) **is a vital component of Quality Assurance. The guide is intended for those involved in the storage, transportation and distribution of starting materials and medicinal products. It aims to describe the critical and important controls for the storage, trade and distribution of these materials.**

It requires the company to establish a quality system to ensure that products are consistently stored and handled as required by the marketing authorization or product specification, thereby maintaining the quality of the products being distributed.

HSA's auditors will conduct audits on the company in accordance to the GDP- HSA (Ref. No.: GUIDE-MQA-013-005)

Quick Overview of GDP



GOOD DISTRIBUTION PRACTICE - The Idea Behind
https://youtu.be/_APQLPHIffg

Scope and Main Principles under GDP

GDP has a scope that is similar to GMP, but is more focused in addressing areas in a typical storage and distribution facility.

The followings are the sub-sections listed under the guidance notes from HSA which are common areas of audit/ assessment.

1. Personnel
2. Premises And Facilities
3. Stock Handling And Stock Control
4. Disposal Of Products
5. Documentation
6. Product Complaints
7. Product Recall
8. Returned Materials
9. Counterfeit Products
10. Self-Inspection
11. Contract Activities
12. Handling Of Active Pharmaceutical Ingredient or Intermediates

Personnel

- **Key personnel in charge of warehousing functions should possess appropriate knowledge and experience, and where applicable, the relevant professional and technical qualifications for the tasks assigned to them.**
- **Products or substances regulated under the Misuse of Drugs Regulations (i.e. Controlled Drugs) shall be placed under the direct supervision of a pharmacist registered with the Singapore Pharmacy Board.**
- **Provide relevant Training programme**
- **Training records documentation**

Premise & Equipment / Facilities

- **Floor Area - Permanent address**
- **Lay out plan**
- **Store approval by relevant regulatory authority**
- **Adequate storage areas with segregations of products, including protection from excessive heat or undue exposure to direct sunlight**
- **Appropriate for the products – built for/ adapted to the purpose**
- **Sufficient security to prevent unauthorized access and misappropriation of the goods.**
- **Separate receiving bay/area should be available.**
- **Receiving and dispatch area should be appropriately designed.**
- **Adequate lighting and ventilation.**

Premise & Equipment / Facilities

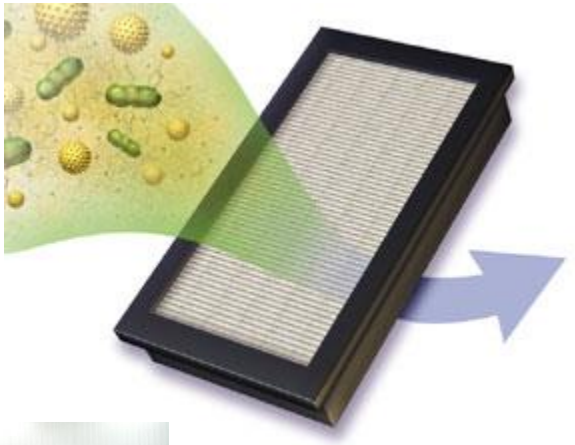
Many pharmaceutical products require some form of special storage requirements:

1. Temperature / Humidity control
   – Use of cold room with backup generator, proper temperature and humidity monitoring.
2. Controlled exposure to UV rays
   – Storage away from sunlight

Premise & Equipment / Facilities

3. Clean environment

- Use of HEPA (High Efficiency Particulate Air) filter which can remove at least 99.97% of airborne particles 0.3 micrometers (µm) in diameter.
- Epoxy painted flooring for easy cleaning
- Above floor racking for easy of cleaning and prevent dust accumulation



Premise & Equipment / Facilities

Cleanliness

- **The storage areas should be dry, clean and free of accumulated waste and dust.**
- **Cleaning SOP(s) and programme should be available**
- **Cleaning Records must be kept**

Pest Control

- **The storage area should be designed and equipped to prevent the entry of insects, rodents and other pests/animals.**
- **There should be a pest control programme to identify and prevent pest infestation. Appropriate records should be kept.**

Premise & Equipment / Facilities

Storage/ Warehousing

- **Storage off the ground**
- **Segregation (i.e. designated areas for quarantine, saleable stock, expired, rejected/damaged, recalled and returned products)**
- **Precaution against deterioration**
- **Identify materials that require special handling; e.g. Storage precaution against Sunlight**
- **Controlled environmental storage conditions requirements - e.g. Cold Room with thermometer/ hygrometer recording**
- **Security**
- **Material Labelled**
- **Written Procedure on Storage and distribution**

Stock Handling & Control

Receiving and Handling

- **Written Procedure; Distribution records and duration of storage to be kept**
- **Appropriate types of checks to be conducted against relevant documentation/ label description, type and quantity**

Stock Rotation and Control

- **EEFO (Earliest-Expiry-First-Out)/ FIFO**
- **Stock Reconciliation**

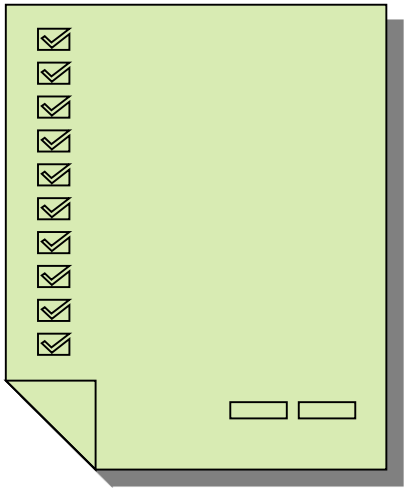
Deliveries to Customer

- **Written Procedure**
- **Security; Storage condition; Protection of the quality of materials during transportation to customers**
- **Specialized means for special products e.g. use of dry ice; use of temperature monitoring devices**

Documentation and Self Inspection

Documentation

- **Documentation system**
- **SOP signed and formalized**
- **Computerized record**
- **Poison labels**
- Legal record (e.g. Sales Records, Signed order and invoices)
- **Records and procedures are needed for the followings:**
  - Training
  - Cleaning / Sanitisation
  - Pest Control
  - Receiving, handling, delivery and disposal
  - Complaints
  - Recalls
  - Returns
  - Self Inspection



Self Inspection

- **SOP and records**

Product Complaints, Recalls, Returned Goods & Disposal

Product Complaints

- **Establish SOP and keep records**
- **System for investigation and review**

Recalls

- **Establish SOP and keep records**
- **Designated person to be in charge**
- **Establish level of recall**

Returned Goods

- **Establish SOP and keep records**
- **Establish assessment criteria**
- **Authorization for re-sale**

Disposal

- **Written procedure and evidence of disposal**

Segregation of goods

- Quarantined goods - Stocks which have been withheld for sale due to various reasons e.g. damaged, received with broken seals, leaking.
- Returned goods – Stocks returned by customer, these stocks need to be reassessed for quality assurance.
- Recalled goods – Stocks brought back to warehouse from customers due to recall.
- Rejected goods – Stocks rejected by customers due to various reasons e.g. damaged, defective.

Serialization and track and trace

A serialization/track and trace capability helps support GDP (medicinal products) /GMP/GDP (medical devices) in terms of

- Tracking from raw to intermediate to bulk products/active pharmaceutical ingredients and distribution of final products
- Meeting product security requirements during receiving and deliveries
- Providing products specification when required
- Keeping Legal records (Form E/Sales records)
- The basis for register for controlled drugs (e.g. morphine)
- Drug complaints recall and return traceability to raw material
- Information records for clinical trials
- Keeping distribution records of medical devices
- Stock rotation
- Calibration requirements

Pharmaceutical Logistics – Sample Audit Checklist

Audit checklist specific to areas based on the requirements:

- Production areas/ Redressing areas
  - √ Is there evidence of a security management system?
  - √ Is there adequate working space at the production area?
  - √ Are thermometers present to monitor room/ ambient temperature?
  - √ Are there written procedures on each production process?
- Storage areas of products
  - √ Is there adequate storage area?
  - √ Is sufficient lights and ventilation present?
  - √ Is there evidence of product zoning and segregations?
  - √ Are the storage locations/ shelves appropriately labeled?
  - √ Are off ground shelves used for storage?
  - √ Are the product stored at required temperature and away from sunlight?

Pharmaceutical Logistics – Sample Audit Checklist

- Stock handling and control systems - Inbound
  - √ Checks conducted against documents during receiving to ensure correct item, quantity batch number etc.
  - √ Procedure to ensure that products near expiry are not accepted.
  - √ Inbound and outbound zones are clearly marked.
  - √ Damaged and tampered products are moved to respective location.
- Stock handling and control systems – outbound & delivery
  - √ Written procedures in place for stock handling and stock control
  - √ Checks to ensure procedures are followed
  - √ Ensure EEFO (Earliest-Expiry-First-Out)/ FIFO
  - √ Stock reconciliation in place
  - √ Keep distribution records kept for required duration
- Internal and external communications, including orders management, customers' enquiries and product complaints
  - √ Are there SOPs for proper handling of complaints, recalls and disposals?
  - √ Is there a reliable system for investigation and review?

Learning Outcomes

- Describe a typical pharmaceutical supply chain and identify the key players in the supply chain of pharmaceuticals.
- Describe the stages and activities in primary and secondary manufacturing of medicine.
- Describe the different distribution channels commonly used for the pharmaceutical industry.
- Recognize the importance for a quality assurance system including safety, health and environmental regulation for specific requirements peculiar to the manufacturing, distribution, transportation and handling of pharmaceutical products along the supply chain
- Identify the best industrial practices and the local authorities who ensure the implementation of quality assurance system for pharmaceutical logistics activities.