History of Pharmacopoeia

- Pharmacopoeia is an official book in pharmacy which is published by the Government authority.
- Pharmacopoeia consists of various monograph of pharmaceutical substances or drugs.
- Various Pharmacopoeias are published by various Government authority. For examples

  Indian Pharmacopoeia(IP), US Pharmacopoeia(USP), British Pharmacopoeia (BP), European Pharmacopoeia, Japanese Pharmacopoeia etc.
- The history of IP began in the year 1833 when a committee of the East India company's dispensary recommended the publication of Pharmacopoeia and general conspectus of medicinal plants were published in 1844.
- This was followed by IP 1868, which covered both the drugs of BP 1867 and indigenous drugs and plants.
- Then Drugs Enquiry Committee was appointed in 1927 by the government recommended the publication of a National Pharmacopoeia.
- After independence an Indian Pharmacopoeia Committee was constituted in 1948, which prepared the Pharmacopoeia of India (The Indian Pharmacopoeia) **1955**. A Supplement to it was published in **1960**.
- The Indian Pharmacopoeia is published by the Indian Pharmacopoeia Committee (IPC) on behalf of the Government of India, Ministry of Health & Family Welfare.
- The IPC is a Society under the provisions of the Societies Registration Act, 1860 (Act No. 21) for the registration of Literary, Scientific and Charitable Societies.
- The functioning of the Commission is governed by the provisions of the approved Memorandum of Association, Rules and Regulations of the IPC.

- The Commission has set up its headquarters in the campus of the Central Indian Pharmacopoeia Laboratory (CIPL), Ghaziabad, UP. The Director CIPL, also functions as the Secretary-cum-Scientific Director of the IPC.
- The Indian Pharmacopoeia is being produced in fulfillment of the requirement in the Drugs and Cosmetics Rules, 1945 of standards of drugs produced in India and it contributes significantly in the control of the quality of medicinal products.
- The standards of this pharmacopoeia are legally enforceable and are intended to help in the licensing and inspection processes.
- This pharmacopoeia contained western and also traditional drugs, and the same policy continued while preparing the Pharmacopoeia of India **1966** and its **1975** Supplement.
- In the Pharmacopoeia of India **1985** and its Addenda **1989 and 1991**, traditional drugs were not included as publication of a pharmacopoeia of traditional system drugs was taken up separately and only those herbal drugs were included which had supporting definitive quality control standards.
- In the period since the publication of the 1985 Edition there has been a significant increase in the range of drugs produced in India. Keeping this in mind the Committee has deleted or added monographs on a system of priorities based on the medical merit and the extent of use of any given article in the country in its following **1996** Edition and its addenda in **2000, 2002, 2005** and one supplement for Veterinary Products in 2002.
- The Indian Pharmacopoeia **2007** has been prepared in accordance with the principles and designed plan decided by the Scientific Body of the Indian Pharmacopoeia Commission The General Notices, Monographs and new testing methods, etc. based on the introduction of advanced technology and experimental methods widely adopted in India and abroad are being added and updated.

- The contents of Appendices are revised by and large in consonance with those nowadays adopted internationally for monitoring the quality of the drugs.
- The number of monographs in Appendices are expanded further to incorporate the latest technological advances and complies with regulatory requirements.
- IP-2010 – 4 volumes
- IP-2012
- The new seventh edition **IP 2014** includes advanced technology and experimental methods widely adopted in India and abroad.
- The IP 2014 is presented in four volumes which include products of biotechnology, indigenous herbs and herbal products, veterinary vaccines and additional antiretroviral drugs and formulations.
- It incorporates 2548 monographs of drugs out of which 577 are new monographs and 19 New Radiopharmaceutical Monographs and 1 General chapter is first time being included in this edition.

IMPURITIES

- Chemically a compound is impure if it contains undesirable foreign matter i.e. impurities. Thus chemical purity is freedom from foreign matter.

- **Impurities are foreign substances, which are introduced by contamination, adulteration or any other process during the synthesis or preparation of pharmaceutical substances.**

- Impurities may be Foreign Substances (Extraneous Contaminants), Inorganic impurities (can result from the manufacturing process), Process Contaminants (reagents, catalysts, heavy metals, chloride, or sulfate may be introduced during manufacturing or handling procedures), Related Substances (structurally related to a drug substance), Residual Solvents, Specified Degradation Products, Toxic Impurities(significant undesirable biological activity).

Sources of Impurities in pharmacopoeial substances

A list of impurities which may be present in a given pharmaceutical substance can be easily compiled from the knowledge of the raw materials employed, the manufacturing process and stability of the final product. Impurities may also arise from physical contamination and improper storage conditions.

The various sources of impurities in pharmaceutical substances are as follows:

1.**Raw materials employed in the manufacturing of the pharmaceutical substance**:

- Pharmaceutical substances are either isolated from natural sources or synthesized from chemical starting materials.
- The natural sources include mineral sources, plants, animals and microbes. It is essential to verify the source material and to establish its quality otherwise impurities with the raw materials may be carried through the manufacturing process to contaminate the final product.

For e.g., aluminum is usually accompanied by alkali and alkaline earth compounds, barium and magnesium impurities are found in calcium minerals, lead and heavy metals are found as impurities in many sulphide.

- Rock salt used for the preparation of sodium chloride is contaminated with small amounts of calcium and magnesium chlorides, so that sodium chloride prepared from rock salt will definitely contain traces of calcium and magnesium compounds impurities.

2. Method of Manufacture:

- The Process or method of manufacture may introduce new impurities into the final product due to contamination by reagents, catalysts and solvents.employed at various stages of the manufacturing process.
- The new impurities may also arise from the reaction vessels and reaction intermediates.

(A)Reagents employed in the manufacturing process:

- Calcium carbonate is prepared by the interaction of a soluble calcium salt with a soluble sodium carbonate. Therefore, the final product ($CaCO_3$) contains small amount of soluble alkali as impurities which were not removed by the washing process.

$$CaCl_2 + Na_2CO_3 \rightarrow CaCO_3\downarrow + 2\,NaCl$$

Soluble Soluble Precipitate Soluble

- Anions like Cl^- and SO_4^{-2} are common impurities in many substances because of the use of hydrochloric acid and sulphuric acid respectively in processing.

(B) Regents used to eliminate other impurities:

- Barium is used in the preparation of potassium bromide to remove sulphate which arise form the bromine used in the process. It is likely that potassium bromide will now be contaminated by traces of barium.

(C) Solvents:

- Most of the pharmaceutical substances are prepared in solvated crystalline form.
- Small amounts of solvents employed in preparation and purification of reaction intermediates or the final product may also result in the contamination of the pharmaceutical substances.
- Water is the cheapest solvent available and is used quite frequently in the preparation of inorganic pharmaceuticals.
- Water can be the major source of impurities as different types of water containing different types and amount of impurities are available.

(i) Tap water: Containing impurities of Ca^{2+}, Mg^{2+}, Na^{+}, Cl^{-}, CO_3^{-2} and SO_4^{-2} in trace amounts. The use of tap water on large scale will lead to the contamination of the final product with these impurities because the impurities will remain in the product even after washings.

(ii) Softened water: It is almost free from divalent cations (Ca^{2+}, Mg^{2+}) but contains more of Na^{+} and Cl^{-} ions as impurities because of the usual chemical water softening process. Therefore, the final products obtained using softened water as solvent will not have Ca^{2+} and Mg^{2+} impurities but still contain Na^{+} and Cl^{-} impurities.

(iii) Demineralized water: It is prepared by means of ion-exchange and is free from Na^{+}, Ca^{2+}, Mg^{2+}, Cl^{-}, SO_4^{-2} and CO^{-2} etc. It may have pyrogens, bacterias and organic impurities. So, it is a better solvent than tap water or softened water but the economic factors discourage its use on large scale.

(iv) Distilled water: It is free from all organic and inorganic impurities and is therefore the best as a solvent but it is quite expensive. As it is free from all impurities, it does not pass on any impurities to the final products.

(D) Reaction vessels:

- The reaction vessels employed in the manufacturing process may be metallic such as copper, iron, cast iron, galvanized iron, silver, aluminium, nickel, zinc and lead.
- Glass and silica are also used in the construction of the chemical plants but now many of these are replaced by stainless steel and variety of other alloys.
- Some solvents and reagents employed in the process may react with the metals of reaction vessels, leading to their corrosion and passing traces of metal impurities into the solution, contaminating the final product. Similarly, glass vessels may give traces of alkali to the solvent.
- **For Ex** - Lead (Pb) may be found as impurity in commercial sulphuric acid which has been manufactured by lead chamber process. Also, substances prepared by

electrolytic process, may contain electrode material as an impurity e.g. antimony, bismuth etc.

(E) Intermediates:

- Sometimes, an intermediate substance produced during the manufacturing process may contaminate the final product
- **For Ex -** Sodium bromide is prepared by reaction of sodium hydroxide and bromine in slight excess.

$$6\ NaOH + 3\ Br_2 \rightarrow NaBrO_3 + 5\ NaBr + 3\ H_2O$$

The sodium bromate an intermediate product is reduced to sodium bromide by heating the residue (obtained by evaporating the solution to dryness) with charcoal.

$$NaBrO_3 + 3\ C \rightarrow NaBr + 3\ CO$$

Sodium bromate Sodium bromide

If sodium bromate is not completely converted to the sodium bromide then it is likely to be present as an impurity.

(F) Atmospheric contamination during the manufacturing process:

- Atmosphere may contain dust (aluminium oxide, sulphur, silica, etc.) and some gases like carbon dioxide, sulphur dioxide, arsine and hydrogen sulphide. These may contaminate the final product during the manufacturing process.
- Some substances with atmospheric carbon dioxide and water may get contaminated during their preparation
- e.g. sodium hydroxide readily absorbs atmospheric carbon dioxide when exposed to atmosphere.

$$2\ NaOH + CO_2 \rightarrow Na_2CO_3 + H_2O$$

Calcium hydroxide solutions can absorb carbon dioxide from the atmosphere to form calcium carbonate.

$$Ca\ (OH)_2 + CO_2 \rightarrow CaCO_3 + H_2O$$

(G) Manufacturing hazards:

- If the manufacturer is able to control and check impurities from the all above mentioned sources there exists certain manufacturing hazards which can lead to product contamination. The various manufacturing hazards can lead to:

i) Particulate contamination

- The unwanted particulate matter can arise by a number of ways, such as accidental inclusion of dirt or glass, porcelain, plastic or metallic fragments from sieves, granulating, tabletting and filling machines and the product container.
- It may also arise from the bulk materials used in the formulation or from dirty or improperly maintained equipments
- **e.g.** metal particles found in eye ointments packed in metal tubes made up of tin and aluminum.

(ii) Cross-contamination of the product:

- This manufacturing hazard has to be considered in the preparation of solid dosage forms. Cross-contamination of product can occur by air-born dust arising out of handling of powders, granules and tablets in bulk.
- Cross-contamination is dangerous particularly in case of steroidal and other synthetic hormones and therefore, it should be carefully controlled.
- Precautions, such as use of face mask and special extraction equipment can minimize these undesirable contaminations.

(iii) Contamination by microbes:

- Many products, like liquid preparations and creams intended for topical applications are contamination by microbes from the atmosphere during manufacturing.
- For all products intended for parenteral administration and ophthalmic preparations, sterility testing is done and it provides an adequate control for microbial contaminations in such preparations.
- Microbial contamination can be controlled by adding suitable antimicrobial and antifungal agents.

iv) Errors in the manufacturing process:

- Sometimes in a liquid preparation, there is incomplete solution of the solute. This is to be detected by the normal analytical methods as it can lead to major error.
- A proper check on the efficiency of mixing, filling, tabletting, sterilization etc. should be exercised in order to obtain a product of maximum purity and desired quality.
- Special precautions are required to be observed to avoid mixing and filling errors in the preparation of low dosage forms (≥5mg) such as tablets and capsules containing highly potent medicaments.

(v) Errors in the packaging:

- Similar looking products, such as tablets of the same size, shape and colour, packed in similar containers can result in mislabeling of either or both of the products.
- Adequate care should be taken to avoid the handling of such products in the close proximity.

3. Instability of the product:

(A) Chemical instability:

- Impurities can also arise during storage because of chemical instability of the pharmaceutical substance.
- Many pharmaceutically important substances undergo chemical decomposition when storage conditions are inadequate.
- This chemical decomposition is often catalyzed by light, traces of acid or alkali, traces of metallic impurities, air oxidation, carbon dioxide and water vapours.

- The nature of the decomposition can easily be predicted from the knowledge of chemical properties of the substance.
- All such decompositions can be minimized or avoided by using proper storage procedures and conditions.
- The photosensitive substances should be protected from light by storing them in darkened glass or metal containers thereby inhibiting photochemical decomposition.
- Materials susceptible to oxidation by air or attack by moisture should be stored in sealed containers and also be prevented by adding suitable antioxidants. Materials susceptible to oxidation by air or attack by moisture should be stored in sealed containers and also be prevented by adding suitable antioxidants.

(B) Changes in physical properties:

- Pharmaceuticals may undergo changes in physical properties during storage. There can be changes in crystal size and shape, sedimentation and caking of the suspended particles.
- These physical changes are not always avoidable and may result in significant changes in the physical appearance, pharmaceutical and therapeutic effects of the product.
- Particle size and consequently surface area is a critical factor in determining the bioavailability of the low solubility drug such as griseofulvin.
- Physical changes such as sedimentation and claying in case of multidose suspension may constitute a safety hazard leading to the possibility of under dosage and later to over dosage of the drugs.

(C) Reaction with container material:

- The possibility of reaction between the container material and the contents can not be ruled out as it constituents a safety hazard.
- Preparations susceptible to reaction with metal surfaces e.g. salicylic acid ointment must not be packed in metal tubes.
- Solutions of substances which are alkali-sensitive e.g. atropine sulphate injection must be packed in glass ampoules which comply with the test of hydrolytic resistance therefore such preparations must not be packed in containers made from soda glass.
- Plastic containers and closures must be carefully evaluated because of their tendency to give undesirable additives, such as plasticizers, particularly in the presence of non-aqueous solvents.
- Rubber closures are more susceptible to absorb medicaments, antioxidants and bactericides from solution, unless they are appropriately pretreated by immersion in solutions of the concerned compounds.

(D) Temperature:

- The rate of chemical decomposition and physical changes of stored products depends upon the temperature.

- The susceptible substances may have temperature storage requirements assigned to them in order to protect them against undesirable decomposition.