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 **Questions.**

1. Sterilization is an essential stage in the processing of any product destined for parenteral administration or for contact with broken skin.  Discuss?
2. Discuss the importance of sterilization in the production of Pharmaceutical products.
3. Explain Gaseous Sterilization, its Sterilizer design, and operation.
4. What is Radiation Sterilization?

1) Sterilization is an essential stage in the processing of any product destined for parenteral administration, or for contact with broken skin, mucosal surfaces, or internal organs, where the threat of infection exists. In addition, the sterilization of microbiological materials, soiled dressings and other contaminated items is necessary to minimize the health hazard associated with these articles.

Sterilization processes involve the application of a biocidal agent or physical microbial removal process to a product or preparation with the object of killing or removing all microorganisms. These processes may involve elevated temperature,reactive gas, irradiation or filtration through a microorganism-proof filter. The success of the process depends on a suitable choice of treatment conditions, e.g. temperature and duration of exposure. It must be remembered, however, that with all articles to be sterilized there is a potential risk of product damage, which for a pharmaceutical preparation may result in reduced therapeutic efficacy, stability or patient acceptability. Thus, there is a need to achieve a balance between the maximum acceptable risk of failing to achieve sterility and the maximum level of product damage that is acceptable. This is best determined from a knowledge of the properties of the sterilizing agent, the properties of the product to be sterilized and the nature of the likely contaminants. A suitable sterilization process may then be selected to ensure maximum microbial kill/removal with minimum product deterioration.

2) It is an **important** process as it ensures the **product** remains **sterile**. All medical, ophthalmic and parenteral equipment are **sterilized** in batches, and usually **sterilized** using heat. The **products** themselves however are not thermally **sterilized** as the heat may damage it.

 **Importance of Sterile Pharmaceutical Supplies**

PharmTechhas reported that an estimate of one out of every 100,000 drug containers contains a contaminant, which results in approximately 30,000 accidents in the US due to contaminated drugs. They further state that there are two distinct categories of contamination related to injectable drugs, and these statistics are solely related to single events that occur throughout the US and not representative of other infections seen in outbreak episodes affecting several patients.

Injectable drugs are administered directly into the bloodstream, bypassing the immune defences associated with the gastrointestinal system. Therefore, it is essential that pharmaceutical companies comply with strict government regulations to guide quality control programs to ensure regulatory requirements are met.

The question is, "If there are strict regulations for production of sterile pharmaceutical supplies, then why are we seeing such statistics related to infectious outbreaks from contaminated drugs?" This article will explore the difference between pharmaceutical manufacturing companies and compounding pharmacies and the regulations specific to each.

3) Gaseous sterilization, as it is presently used and understood, is a fortuitous outgrowth of the field of agricultural and industrial fumigation. During the period between World Wars I and II, gaseous compounds were developed to combat insect infestation in grain and grain products. Among the gaseous chemicals so developed were ethylene oxide and methyl bromide.

Later, it was found that ethylene oxide reduced the microbial contamination of the treated foods, and this discovery led to the application and issue of patents concerning its formulation and use as a gaseous decontaminant and sterilant. By 1942, the use of gaseous ethylene oxide to reduce the microbial population of spices and gums had been described in several journals of food technology and manufacture. Early in World War II, the U. S. Government deemed it necessary to establish a biological warfare laboratory under the jurisdiction of the Chemical Corps of the U. S. Army. The use of gaseous fumigants as sterilants was reinvestigated by this group, and the results of their investigations with ethylene oxide were published by Phillips & Kaye in 1949. Since their first paper gave a thorough review of the work on ethylene oxide prior to 1949, no attempt will be made to discuss these early reports. This review will cover much of the work of the past decade, particularly the past four years, and will overlap an extensive review published by Phillip four years ago and a recent brief review by Phillips & Warshowsky. Common gases used in sterilisation are:

* **Ethylene oxide:** A powerful alkylating agent that destroys microorganisms by chemical reaction, primarily with cell DNA.  The destructive mechanism largely follows first-order kinetics and depends on concentration, humidity, and temperature.”
* **Ozone:** A potent oxidizing agent produced by passing a stream of oxygen or air through a high-voltage electrical field.  Ozone is an effective biocidal agent for treatment of water supplies and has demonstrated lethality at concentrations from 2%-10% in air.”
* **Chlorine dioxide:**  An effective sterilizing gas.  Pure chlorine dioxide is metastable and therefore is generated as needed.  Chlorine dioxide in noncarcinogenic, nonflammable, and effective at ambient temperatures.”
* **Nitrogen dioxide:**   A sterilizing gas effective at ambient temperature.  Liquid nitrogen dioxide is converted to a gas on introduction to the target chamber.  Nitrogen dioxide is nonexplosive and its residues are noncarcinogenic, noncytotoxic, and nonteratogenic.”

4)

Commercial radiation sterilization has existed since the late 1950s and has grown tremendously in popularity over the last 60 years. Radiation sterilization relies on ionizing radiation, primarily gamma, X-ray or electron radiation, to deactivate microorganisms such as bacteria, fungi, viruses and spores. Due to numerous advantages over heat or chemical based sterilization techniques, this method is particularly attractive in medicine and healthcare-related fields. For example, radiation sterilization is readily applied during tissue allograft preparation, pharmaceutical packaging and medical device manufacturing.

Radiation can be lethal to biological organisms by inducing genetic damage and chemical changes in key biological macromolecules. During sterilization treatment, the sample of interest is bombarded with high energy electrons or high energy electromagnetic radiation, which leads to the formation of extremely unstable free radicals, molecular ions and secondary electrons. These radiation products then react with nearby molecules to fracture and alter chemical bonds. DNA in particular is highly sensitive to the damaging effects of radiation and will break, depolymerize, mutate and alter structure upon exposure to ionizing radiation. Incomplete repair of DNA damage ultimately leads to loss of genetic information and cell death. Thus, radiation can kill harmful microorganisms and be used as a sterilization technique.

**Sources of Radiation**

Three forms of radiation commonly used for commercial radiation sterilization include gamma radiation, electron beam (e-beam) radiation and X-ray radiation

**Gamma Radiation**

Gamma radiation sterilization is the most popular form of radiation sterilization. Co-60 and, to a lesser extent, Cs-137 serve as radiation sources and undergo decomposition to release high energy gamma rays. The produced electromagnetic radiation is highly penetrating and can kill contaminating microorganisms. Both radioisotopes are viable sources of radiation due to their highly stability (with half-lives >5 years) and gamma emission properties. However, Co-60 tends to be favored because it can be easily manufactured from natural metal, is not fissile or flammable and is less soluble in water.

**Electron Beam Radiation (E-Beam Radiation)**

Sterilization can alternatively be accomplished using electron beam irradiation. [2] High energy electrons capable of inducing biological damage are generated by electron beam accelerators. In most cases, electron energies of ~10 MeV are used, but the exact energies can be tuned to optimize penetration depth and limit breakdown of the irradiated material.

Gamma irradiation and e-beam irradiation differ in sample penetration depth, exposure time required for effective sterilization and product compatibility. Because the penetration ability of electrons is lower than that of gamma rays, e-beam sterilization is limited in application to lower density or smaller products. However, e-beam sterilization can use higher dosages and shorter treatment times (seconds vs. min/hours) as compared to gamma radiation sterilization, allowing for higher throughput and reducing negative effects on treated products. In terms of cost, e-beam sterilization is equivalent to or less expensive than gamma sterilization.

**X-Ray Radiation**

Electron beam accelerators will also generate X-rays for sterilization. X-rays are produced when high energy electrons from the accelerator interact with high atomic number nuclei, such as atoms of tungsten or tantalum. In a process known as Bremsstrahlung, the deceleration of the electron when passing the nucleus results in the release of X-rays. Electron energies of 5-7 MeV are commercially used; the energies of the resultant X-rays lie along a spectrum ranging from zero to the energy of the electron beam.

In practice, X-rays used for sterilization can be more penetrating than either gamma-rays or electron beams. They are largely directional since generated X-rays propagate in the same direction as the incident electron. Thus, a concerted stream of X-rays is sent towards the product of interest and multiple rows of products can be sterilized simultaneously. Of radiation sterilization techniques, X-ray sterilization can achieve the highest dose uniformity ratio (DUR), the ratio between maximum and minimum dose required for sterilization. DUR measures the range of doses delivered to the product and is important to optimize for irradiation sensitive materials in order to minimize degradation