Course notes:

II. Pharmaceutical technology

POSTGRADUATE EUROPEAN RADIOPHARMACY COURSE

Module I: Pharmacy

UNIVERSITY OF LJUBLJANA | FFA Faculty of Pharmacy

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Design of dosage forms

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The lecture has the following learning objectives:

1. Students will be able to describe the factors influencing the selection of dosage form (DF) and its constituents.
2. Students will be able to describe and discuss the main principles of DF and their classification (based on administration route and physical form).
3. Students will be able to describe constituents, preparation and properties of solid DF (solid capsules and tablets).
4. Students will be able to distinguish among liquid DF (solutions, emulsions, suspensions, colloidal dispersions) and discuss their stability issues.
5. Students will be able to describe classification of parenteral preparations, to differentiate among them and interpret their requirements

Summary of the lecture (prepared by Assoc. Prof. Alenka Zvonar Pobirk and Prof. dr. Julijana Kristl):

The formulation of active pharmaceutical substances into the dosage forms requires knowledge from several scientific disciplines. Whilst the physical and chemical properties of active pharmaceutical substances and excipients need to be understood, the factors influencing drug absorption and the requirements of the disease or diagnostic procedure also have to be considered when designing drug delivery system. The design, formulation and evaluation of dosage forms, important for (radio)pharmaceuticals are presented as a text and power point.

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1. PRINCIPLES OF DOSAGE FORM DESIGN

The first lecture in segment of pharmaceutical technology concentrates on dosage forms, which are concerned with the conversion of active ingredients into medicines emphasing the most interesting for radiopharmaceuticals. Dosage form enables delivery of active ingredient into the body in a safe, efficient, reproducible and convenient manner. Which considerations should be taken to design a drug substance into dosage form? Drug substances in their purified state usually exist as white crystalline or amorphous powders or as viscous liquids. Drugs are rarely, if ever, administered to patients in an unformulated state, i.e. solely as pure chemical substances – active substances, but are almost always given in formulated preparations. The vast majority of the available active pharmaceutical compounds, which are potent at the milligram or microgram levels could not be presented in a form providing an accurate and reproducible dosage unless mixed with a variety of excipients and converted into selected dosage forms by controlled technological processes. Indeed, the primary aim of pharmaceutical technology lies in the design, formulation and evaluation of a wide range of dosage forms, each providing an optimized delivery of drug for selected route of administration.

The science of dosage forms and drug delivery may be described as the application of active pharmaceutical substances of either chemical or biological origin to control their *in vivo* temporal and spatial location for clinical benefit. The goal of drug delivery system is to release drug(s) to produce the maximum simultaneous safety and effectiveness. Drug delivery is becoming extremely demanding scientific field. Today's world requires that drug delivery systems be precise in their control of drug delivery and efficiency, and, preferably, respond directly to the local environment stimuli (pH, temperature, enzymes).

Dosage forms can vary from relatively simple solutions to complex drug delivery systems. They provide varied and specialized pharmaceutical functions with the use of appropriate additives or excipients in the formulations. The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a dosage form, which can be manufactured at a large scale with reproducible product quality. In order to ensure product quality numerous features are required – chemical and physical stability with suitable preservation against microbial contamination if appropriate, uniformity of drug dose, acceptability to users including both the prescriber and the patient, as well as suitable packaging and labelling. Ideally, dosage forms should also be independent of a patient, although in practice this feature remains difficult to achieve. Future development in dosage form design may well attempt to accommodate these requirements to a certain extent.
Dosage forms possessing the same amount of an active phaarmaceutical compound (chemically equivalent) do not necessarily elicit the same therapeutic response. The rate at which the drug is released from the dosage form and the subsequent absorption, distribution, metabolism and excretion kinetics determine the bioavailability of the active substance.
There are numerous dosage forms into which a drug substance can be incorporated for a convenient and efficacious treatment of a disease. Dosage forms can be designed for administration by all possible delivery routes to maximize therapeutic response. Preparations can be taken orally or injected, as well as applied to the skin or inhaled. However, it is necessary to relate a drug substance and a disease state beforehand in order to make the correct combination of drug and dosage form as each disease or illness will require a specific type of drug therapy. In addition, factors governing choice of versatile drugs are often formulated into several dosage forms of varying strengths, each having particular pharmaceutical characteristics, which are suitable for a specific application. In order to optimize the bioavailability of drug substance it is often necessary to select carefully the most appropriate chemical derivative of the drug. For example, a derivative, which obtains a specific solubility requirement, as well as its particle size and physical form, which combines with appropriate additives and manufacturing aids that will not significantly alter the properties of the drug molecule. And it is necessary to select the most appropriate administration route(s) and dosage form(s) considering also aspects of manufacturing processes and suitable packaging.

Each dosage form consists of a few very simple principles:

- The right active pharmaceutical ingredient,
- In the right amount,
- distributed to the right place,
- in the right time,
- or the right duration of effect.

It is apparent that before a drug substance can be successfully formulated into a dosage form many factors must be considered. They can be broadly grouped into three categories:

- biopharmaceutical considerations, including factors affecting the absorption, distribution, metabolism and excretion of the drug substance from different administration routes,
- drug factors, such as physical and chemical properties of the drug substance, and
- therapeutic considerations including consideration of the disease to be treated or diagnosed, and patient factors.

The underlying principle of dosage form design considers all these particular parameters and related to each other as well.

1.1. Drug factors in dosage form design

Each type of dosage form requires careful study of the physical and chemical properties of drug substances to achieve a stable and efficacious product. These properties, such as dissolution, crystal size and polymorphic form, solid state stability and drug – additive interaction can have profound effects on the physiological availability as well as physical and chemical stability of the drug. By combining such data with those obtained from pharmacological and biochemical studies the most suitable drug form and excipients can be selected for the formulation of chosen dosage form. Variations in physicochemical properties, occurring for example between batches of the same material or resulting from an alternative technological procedure, can modify formulation requirements as well as processing and dosage form performance. For instance, the fine milling of poorly soluble drug substances can modify their wetting and dissolution characteristics, which are important properties for dosage form. Careful evaluation of these properties and understanding of their effects is therefore important for dosage form design and processing as well as product performance.

1.2. Biopharmaceutical considerations in dosage form design

Biopharmaceutical consideration can be regarded as the study of the relationship between the physical, chemical and biological sciences applied to drugs, dosage forms and drug action. Clearly, understanding of the principles of this subject is important in dosage form design particularly with regard to drug absorption, as well as drug distribution, metabolism and excretion. In general, a drug substance must be dissolved before it can be absorbed via absorbing membranes (in the gastrointestinal tract, lung, and skin) into the body fluids. Active compounds penetrate these membranes in two general ways – by passive diffusion and by specialized transport mechanisms. In passive diffusion that is thought to control the absorption of most drugs, the process is driven by the existing concentration gradient on the membrane with drug molecules passing from regions of high to low concentrations. The lipid solubility and degree of ionization of the drug at the absorbing site influence the rate of diffusion. Several specialized transport mechanisms are postulated, including active and facilitated transport. Once absorbed, the drug can exert a therapeutic effect, yet the site of action is often remote from the site of administration and the drug has to be transported there.

When the drug is administered by dosage forms designed to deliver drugs via the buccal, rectal, intramuscular or subcutaneous routes, it passes directly into the circulation blood from absorbing area, whilst the intravenous route provides the most direct route of all. When delivered by the oral route onset of drug action will be delayed due to required absorption process from GI tract and hepatoenteric blood circulation features. The physical form of the oral dosage form will also influence onset of action with solutions acting faster than suspension, which in turn generally acts faster than capsules, tablets and implants. The choice of administration routes is dependent on a variety of factors, such as local or systemic action is required, or how quick a response to the active substance is needed.

1.3. Therapeutic considerations in design of delivery systems

The nature of the disease or diagnostics for which the medicine is intended is an important factor when selecting the adequate dosage forms to be prepared. Factors, like the need for systemic or local therapy, duration of action required, and whether the drug will be used in emergency situations, need to be considered. In the vast majority of cases a single drug substance is incorporated into various dosage forms to satisfy both the particular preferences of a patient or a physician and the specific needs of a certain situation. For example, many asthmatic patients use inhalation aerosols from which the drug is rapidly absorbed and causes bronhodilatation. Interest has recently been growing in the design of medicines – containing formulations, which deliver drugs to specific “targets” in the body, for example the use of liposomes, microparticles, and nanoparticles, as well as providing drugs over longer periods of time at controlled rates. Undoubtedly more of these sophisticated formulations will be developed and interest is likely to be directed to individual patient requirements such as age, weight, and physiological and metabolic factors, features, which can influence drug absorption and bioavailability.

1.4. Nanotechnology and nanoparticulate drug delivery systems

Nanotechnology and nanoscience are widely seen as having a great potential to bring benefits to many areas of research and application, also at the field of radiopharmaceuticals. Nanosciences is, at its simplest, the study of the fundamental principles of molecules andstructures with at least one dimension roughly between 1 and 100 nanometers. These structures are known as nanostructure. Nanotechnology is application of thesenanostructures into useful nanoscale devices also in medicines (nanoparticles, nanosuspensions, dendrimers, nanofibers, nanodots, etc). Currently, the application of nanoscience is raising new challenges in the safety, regulatory, and ethical domains that require extensive debates on all levels. The size range that holds so much interest is typically from 100 nm down to the atomic level because in this range materials can have different and enhanced properties compared with the same material at a large scale. Nanotechnologies have been used to create tiny features on computer chips for the last few decades. The natural world also contains many examples of nanoscale structures, from milk (a nanoscale colloid) to the sophisticated nanosized and

nanostructured proteins that control a range of biological activities, such as flexing muscules, releasing energy, and repairing cells.

Nanomaterials differ significantly from other materials due to the following two major principal factors: the increased surface area and quantum effects. These factors can enhance properties such as reactivity, strength, electrical characteristics and in vivo behaviour. As the particle size decreases, a greater proportion of atoms are found at the surface compared to inside. Foe example, a particle size 30 nm has 5% of its atoms on the surface, at 10 nm 20%, and at 3 nm 50% of the atoms are on surface. Thus, a nanoparticle has a much greater surface area per unit mass compared with larger particles, leading to greater reactivity. In tandem with surface area effects, quantum effects can begin to dominate the properties of matter as size is reduced to the nanoscale. These can affect the optical, electrical, and magnetic behaviour of materials. Their *in vivo* behaviour can be from increased absorption and therapeutic effect to toxic effect as compared the active ingredient in micro-sized of bigger particles. Additionally, in material science, it is not only the materials but also the way in which they are assembled that really counts. There are interesting possibilities with methods of fabrication of systems from known materials. Techniques such as the laying down of molecular layers to form membranes of precise dimensions and functionality, and three-dimensional printing to design and make individual complex carriers in a range of nano-dimensions allow the novel use of accepted materials.

2. RADIOPHARMACEUTICALS

Radiopharmaceuticals are a radioactive drug intended to humans for diagnosis and therapy. It contains a radioactive moiety (radionuclide) and a biodistribution moiety. Following its administration to a patient (usually by the i.v. route), the radiopharmaceuticals will localise in a specific organ or tissue depending upon the biodistribution moiety. Once the radiopharmaceutical reaches the organ of interest a picture (image) of the organ may then be taken by specialized instruments which can »see« the radiation emitted from the radionuclide. Radiopharmaceuticals are commercially available for imaging (diagnosis) many organs, including the brain, thyroid gland, heart, lungs, liver, spleen, bone, kidneys, pancreas, and others. Therapeutic radiopharmaceuticals are designed to localize in a target organ. However, the type of radiation desired for therapy (i.e., beta particles) is different from that required for diagnosis (i.e., gamma photons). Beta particles are used for therapy because they will deposit virtually all of their energy within the target organ, while gamma photons are very penetrating and are therefore able to leave the body and be detected by the imaging equipment.

In keeping with biopharmaceuticals and nanotechnology development number of new areas of nuclear medicine are emerging/developing, including the use of radiolabelled monoclonal antibodies in the imaging and treatment of targeted cancer cells. Radiolabelled peptides were developed as radiotracers that have the ability to »target« a cell or tissue and deliver a diagnostic signal or a therapeutic agent to the site of the disease. In addition to pharmacokinetic advantage of using smaller molecules for targeting, peptides offer the added

advantage of being able to provide physiologicalevidence of the nature of the disease process or progress of treatment, and may even be able to influence the course of the disease directly. There are many official radioactive pharmaceuticals listed in the Ph. Eur. 11th Ed. A significant majority of them are produced for parenteral administration as injections, much less for peroral as capsules. Pharmacopoeial Monographs dictate specifications for particular radiopharmaceuticals.

3. MEDICAL GASES

A medical gas may be defined as any gas which is inhaled by a patient under the direction of a doctor. In hospitals, pharmacists are often involved with the supply of oxygen, nitrous oxide, nitrous oxide/oxygen mixture, compressed air and vacuum and occasionally more specialized gases. Unless very large quantities are required, medical gases are stored in cylinders made of steel and designed to withstand pressures. There are standards to give details of cylinders, valves, colour codes, pin-index identification and storage. Colour coding and a stencilled chemical symbol are used to identify cylinder contents. Mixture of gases is indicated by alternating colours on the valve end of the cylinder, the body having the colour of the main gas.

Nowadays, in ventilation studies of the lungs radioactive gases are usually replaced by radioactive aerosols of technetium. Concentrated solution of the radiopharmaceutical is usually prepared from a kit and than transferred to nebuliser (equipment for the generation of aerosols). According to definition aerosol is a two-phase system of solid particles or liquid droplets dispersed in air or other gaseous phase. The most fundamentally important physical propert of an aerosol for inhalation is its size that influences aerosol`s ability to penetrate the respiratory tract and thus its clinical efficacy. To penetrate to the peripheral regions, aerosols require a size less than about 5-6 µm, with less than 2µm being preferable for alveolar deposition.

4. CAPSULES

Capsules are solid dosage forms in which active ingredient(s) and/or inert substances are enclosed within shells of various shapes and capacities, usually containing a single dose of active substance. They are intended for oral administration. The capsule shells are made of gelatin or other substances, the consistency of which may be adjusted by addition of other substances such as glycerol or sorbitol. Excipients such as surface-active agents, opaque fillers, antimicrobial preservatives, sweeteners, colouring matter authorised by the competent authority and flavouring substances may be added.

- *Hard capsules* have shells consisting of two prefabricated cylindrical sections one end of which is rounded and closed, the other being open.
- *Soft capsules* have thicker shells than those of hard capsules. The shells consist of one part and are of various shapes. The capsules may bear surface markings.

- *Modified-release capsules* are hard or soft capsules in which the contents or the shell or both contain special excipients or are prepared by a special process designed to modify the rate, the place or the time at which the active substance(s) are released. Modified release capsules include prolonged-release capsules and delayed-release capsules.
- *Gastro-resistant capsules* are delayed-release capsules that are intended to resist the gastric fluid and to release their active substance in the intestinal fluid.

The contents of capsules may be solid, liquid or a paste-like consistency. They consist of one or more active substances with or without excipients such as solvents, diluents, lubricants and disintegrating agents. In hard capsules it is filled in the body of the capsules, which is then closed by the cap of the capsule. The security of the closure may be strengthened by suitable means. In the soft capsules, the production and filling of the capsule is performed in one single step. In both cases it is important that the content do not cause deterioration of the shell. The vast majority of filled capsules, available in different sizes, are intended to be swallowed whole by the patients for the benefit of the medication contained therein. The shell, however, is attacked by the digestive fluids and the contents are released.
Capsules must be tested for Uniformity of contents, Uniformity of mass, Dissolution, Disintegration. They are to be stored in a well-closed container, at a temperature not exceeding 30 °C. The label must state the name of any added antimicrobial preservative.

5. PARENTERAL PREPARATIONS

Parenteral preparations are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body. Parenteral preparations may require the use of excipients to make the preparation isotonic with blood, adjust the pH, increase solubility, prevent the deterioration of active substances and provide adequate antimicrobial properties.
Parenteral preparations are supplied in glass containers, plastic containers or prefilled syringes. Tightness of a container is ensured by suitable means. Closures ensure a good seal, prevent the access of micro-organisms and other contaminants and usually permit the withdrawal of a part or the whole of the contents without removal of the closure. Plastic materials or elastomers of which the closure is made are sufficiently firm and elastic to allow the passage of a needle with the least possible shedding of particles. Closures of multidose containers are sufficiently elastic to ensure that the puncture isresealed when the needle is withdrawn.
Several categories of parenteral preparations may be distinguished: Injections; infusions; concentrates for injections or infusions; powders for injections or infusions; gels for injections; implants; intravitreal preparations.
During the development of a parenteral preparation the effectiveness of the chosen preservative shall be demonstrated. A suitable test method together with criteria for evaluating the preservative properties of the formulation is provided under *Efficacy of antimicrobial preservation* (5.1.3.; Ph. Eur.).

Parenteral preparations are prepared using materials and methods designed to ensure sterility and to avoid microorganisms; recommendations on this aspect are provided in the text on *Methods of preparation of sterile products* (5.1.1; Ph. Eur.). Water used in the manufacture of parenteral preparations complies with the requirements of water for injections in bulk stated in the monograph on Water for injections.
Solutions for infusion or solutions for injections supplied in containers with a nominal content of more than 100 ml that are intended for preparations for human use should comply with a test *Particulate contamination: sub-visible particles* (2.9.19; Ph. Eur.). Products for which the label states that the product is to be used with a final filter are exempt from these requirements.
All Parenteral preparations must comply with the test for *Sterility* (2.6.1.; Ph. Eur.) and are to be stored
in a sterile, airtight, tamper-proof container. The packaging must be labeled with:
- the name and concentration of any added antimicrobial preservative,
- where applicable, that the solution is to be used in conjunction with a final filter,
- where applicable, that the preparation is free from bacterial endotoxins or that it is apyrogenic.

INJECTIONS

Injections are sterile solutions, emulsions or suspensions. They are prepared by dissolving, emulsifying or suspending the active substance(s) and any added excipients in water for injections, in a suitable, sterile non-aqueous liquid or in a mixture of these vehicles. Solutions for injections, examined under suitable conditions of visibility, are clear and practically free from particles. Their formulation involves careful consideration of all the following inter-relating factors: the proposed route of administration; the volume of the injection; the vehicle in which the active compound is to be dissolved or suspended; the osmotic pressure of the solution; the use of a preservative; the stability of the active compound and methods of sterilization; the specific gravity of the injection; the properties of suspensions for injection; the properties of emulsions for injection; containers and closures for injections; particulate contamination of injection.

Emulsions for injection

An emulsion is a dispersion in which the dispersed phase is composed of small droplets of a liquid distributed throughout a vehicle in which it is immiscible. In emulsion terminology, the dispersed phase is referred to as the internal phase and the dispersion medium as theexternal or continuous phase (O/W, W/O). As the external phase of an emulsion is continuous, an oil-in-water (O/W) emulsion may be diluted with water or an aqueous preparation. Emulsions are thermodynamically unstable systems. Generally, in order to prepare a stable emulsion, a third component is necessary, which must be an emulsifying agent for parenteral use. The emulsifiers and stabilizers used should be non-toxic e.g. lecithin, polysorbate 80, gelatin, methylcellulose or serum albumin. Ideally, emulsions should be formulated so that the dispersed droplets are 0.5 – 1.0 µm in diameter. This size corresponds to the size of the

chylomicra, which are the natural transport systems for fat through the blood stream. Unstable emulsions are dangerous since their storage may result in increased droplet size due to coalescence, which could trigger the thrombosis. Emulsions for injection do not show any evidence of phase separation.

Suspensions for injection

Suspensions may be defined as preparations containing finely divided drug particles (generally greater than 1 µm in diameter) distributed uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility. Some suspensions are available in ready-to-use form, i.e. they are already distributed through a liquid vehicle with or without stabilizer and other pharmaceutical additives. Other preparations are available as dry powders for injection and a liquid vehicle is added before administration. This type of product is generally a powder mixture containing the drug and suitable additives which upon dilution and agitation with a specific quantity of vehicle results in the formation of a suspension suitable for administration. Drugs that are unstable if maintained for extended periods of time in the presence of an aqueous vehicle are most frequently supplied as drug powder mixtures for reconstitution at the time of dispensing. Physical stability of a pharmaceutical suspension may be defined as the condition in which the particles do not aggregate and in which they remain uniformly distributed throughout the dispersion. Since this ideal situation is seldom realized the dispersion should be resuspended by a moderate amount of agitation if the particles settle. Sometimes it is necessary to formulate the drug to be injected as a suspension. For example, formulation of a drug of low solubility in an aqueous vehicle requires a suspension; increased stability of a drug can be attained by formulation as suspensions provide an effective depot release. However, the use of suspensions as injections leads to further problems. Suspensions for injection may show a sediment, which is readily dispersed on shaking to give a suspension, which remains sufficiently stable to enable the correct dose to be withdrawn, especially if packed in a multiple – dose container. Therefore, the features as wettability, sedimentation rate, size and shape of particles, thioxotropy etc. must be adressed.

Colloidal dispersions and solubilized products

Colloids can be prepared and used for injections. Albumin, proteins, dextrans and carbohydrate polymers dissolved in water form hydrophilic colloidal solutions. Certain injections are colloidal solutions, e.g. Iron Dextran Injection BP and Iron Sorbitol Injection BP, the latter being a complex of ferric ions, sorbitol and citric acid stabilized with dextran and sorbitol. Solubilized products can also potentially be used as injections. Above their critical micelle concentration surfactants in water form micelles whose center acts as a solvent for lipid–soluble active substance. By selective use of 1 or 2 surfactants and a cosolvent it is possible to solubilize many drugs.

Single-dose preparations: The volume of the injection in a single-dose container is sufficient to permit the withdrawal and administration of the nominal dose using a normal technique.
Multidose preparations: Multidose aqueous injections contain a suitable antimicrobial preservative at an appropriate concentration except when the preparation itself had adequate antimicrobial properties. When it is necessary to present a preparation for parenteral use in a multidose container, the precautions for its administration and more particularly for its storage between successive withdrawals are to be taken.
Antimicrobial preservatives: Aqueous preparations which are prepared using aseptic conditions and which cannot be terminally sterilised may contain a suitable antimicrobial preservative in an appropriate concentration. No antimicrobial preservative is added when:

- The volume to be injected in a single dose exceeds 15 ml, unless otherwise justified,
- The preparation is intended for administration by routes where, for medical reasons, an antimicrobial preservative is not acceptable, such as intracisternally, epidurally, intrathecally or by any other route giving access to the cerebrospinal fluid, or intra-or retro-oculary. Such preparations are presented in single-dose containers.

Injections are tested for *Uniformity of content of single-dose preparations* (2.9.6; Ph. Eur.). Where justified and authorized a tests for *Bacterial endotoxins* (2.6.14; Ph. Eur.) and *Pyrogens* (2.6.8; Ph. Eur.) is carried out.

INFUSIONS

Infusions are sterile, aqueous solutions or emulsions with water as the continuous phase; they are usually made isotonic with blood. They are principally intended for administration in large volume. Infusions do not contain any added antimicrobial preservative. Solutions for infusion, examined under suitable conditions of visibility, are clear and practically free from particles. Emulsions for infusion do not show any evidence of phase separation.
In the manufacture of infusions containing dispersed particles, measures are taken to ensure a suitable and controlled particle size with regard to the intended use. They comply with the requirements prescribed for injections or for infusions, after dilution to suitable volume.

CONCENTRATES FOR INJECTIONS OR INFUSIONS

Concentrates for injections or infusions are sterile solutions intended for injection or infusion after dilution. They are diluted to a prescribed volume with a prescribed liquid before administration. After dilution, they comply with the requirements for injections or for infusions. They comply with the requirements prescribed for injections or for infusions, after dilution to a suitable volume.

POWDERS FOR INJECTIONS OR INFUSIONS

Powders for injections or infusions are solid, sterile substances distributed in their final containers. When they are shaken with the prescribed volume of a prescribed sterile liquid, they rapidly form either clear and practically particle-free solutions or uniform suspensions. They comply with the requirements for injections or for infusions.

Freeze-dried products for parenteral use are considered as powders for injections or infusions; the uniformity of content and uniformity of mass of freeze-dried products for parenteral use are ensured by the in-process control of the amount of the solution prior to freeze-drying. The label states the instructions for the preparation of injections and infusions.

GELS FOR INJECTIONS

Gels for injections are sterile gels with a viscosity suitable to guarantee a modified release of the active substance(s) at the site of injection.

6. SAFE PRODUCTION OF (RADIO)PHARMACEUTICALS

It is important to note that the following is necessary for the safe production of radiopharmaceuticals: the radiopharmacy must be designed to comply with procedures of good manufacturing practice and good radiation protection practice. The majority of radiopharmaceuticals is intended for intravenous administration; therefore, it is of paramount importance that these preparations are sterile. They also contain radionuclides with short half-lives that require their preparation and administration on the same day. Because of constrains of time, it is not possible to use terminal sterilization by autoclaving and hence these injections must be prepared using aseptic techniques. Here highly skilled operators work with sterile ingredients within clean room facilities containing either laminar flow safety cabinets or isolators that provide operator protection as well as product protection. To reduce the radiation dose to the operator three basic principles to radiation protection may be used: shielding, distance and time. Injections are tested for *Uniformity of content of single-dose preparations* (2.9.6; Ph. Eur.).

<u>Take Home Messages:</u>

- DF design: keep in your mind the drug factors together with biopharmaceutical, pharmacokinetic and therapeutic aspects.
- *Formulation aim:* the right API, in the right among, distributed to the right place, at the right time, for the right duration of effect (>>*predictable* therapeutic response).
- DF classification: according to route of administration (official according to Eur. Ph.) or their physical form.
- DF used for radiopharmaceuticals: solid DF (Capsules), gaseous DF, DF for parenteral administration.
- Parenteral DF: sterile, apyrogenic, isotonic (biocompatibility is oblige, not all must be isoosmotic), euhydric etc.
- Be careful when diluting liquid dosage forms (solutions, emulsions, suspensions) in order to preserve appropriate stability!

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DESIGN OF DOSAGE FORMS FOR PHARMACEUTICALS

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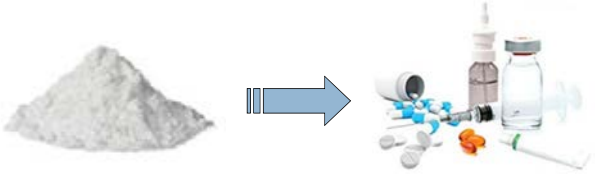
DESIGN OF DOSAGE FORMS FOR (RADIO)PHARMACEUTICALS – **LEARNING OBJECTIVES**

Students will be able:

- to describe the factors influencing the selection of dosage form (DF) and its constituents.
- To describe and discuss the main principles of DF and their classification (based on administration route and physical form).
- To describe constituents, preparation and properties of solid DF (solid capsules and tablets).
- To distinguish among liquid DF (solutions, emulsions, suspensions, colloidal dispersions) and discuss their stability issues.
- To describe classification of parenteral preparations, to differentiate among them and interpret their requirements.

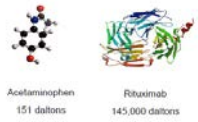
PRINCIPLES OF DOSAGE FORM DESIGN

- Drugs are rarely administered to patients in an unformulated state, i.e. as a pure chemical substance with known pharmacological activity (*active substance),* but are almost always given in formulated preparations.



- Pharmaceutics: the science of dosage form design.

PRINCIPLES OF DOSAGE FORM DESIGN



- Active substance

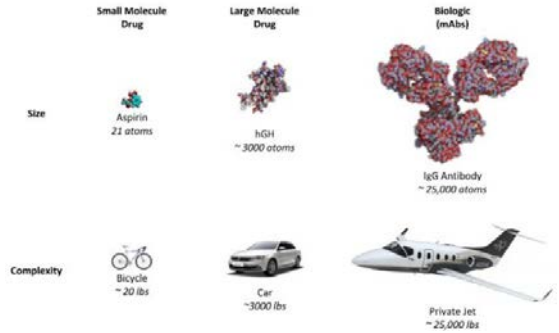
… is any component of medical product intended to furnish *pharmacological activity* or another *direct effect in the diagnosis, treatment or prevention of disease,* or to affect the structure or function of the human or animal body by pharmacological means. A medicinal product may contain more than one active substance.

Equivalent terms: active (pharmaceutical) ingredient - API, drug substance; medicinal substance.

Small molecule vs. *large molecule* (biologics) drugs.

BCS I - IV

ACTIVE SUBSTANCE



PRINCIPLES OF DOSAGE FORM DESIGN: *THE REASONS FOR RARE DIRECT CLINICAL USE OF THE API*

- API handling can be difficult or impossible (e.g. low D).
- Accurate drug dosing can be difficult or impossible.
- API administration can be impractical, unfeasible or not according to the therapeutic aims.
- Some API can benefit from reducing the exposure the the environmental factorst or they need to be chemically stabilised due to the inherent chemical instability.
- APi can be degraded at the site of administration (e.g.: low pH in the stomach).
- API may cause local irritations or injury when they are present at high conc. at the site of administration.
- API can have unpleasant organoleptic qualities (taste, smell - compliance!)
- Administration of API don`t allow modification (improvement) of it`s PK profile.

PRINCIPLES OF DOSAGE FORM DESIGN

- Besides the choice of the API, you need to also make a responsible decision regarding the route of administration and the dosage form (drug delivery system).

http://www.newhealthadvisor.com/Routes-of-Drug-Administration.html

PRINCIPLES OF DOSAGE FORM DESIGN

Disease >> administration route & patient`s age >> DF

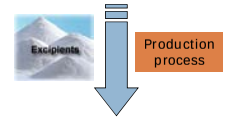
- Excipient

any component, other than the API(s) present in a medicinal product or used in the manufacture of the product.

The intended function of an excipient is to:

1. aid processing of the system during manufacture or
2. protect, support, or enhance stability, bioavailability, or patient acceptability or
3. assist in product identification or
4. enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use.

Usually, more than one excipient is used in the formulation of medicinal product.

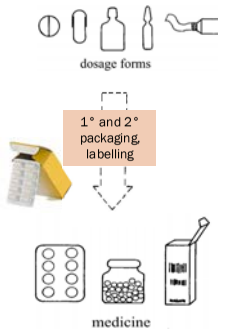


- Diluents/fillers, binders, lubricants, coatings, preservatives, colorants,flavouring agents.

Aid to administer API in **safe**, **efficient**, **reproducible** and **convenient** way.

DOSAGE FORM & MEDICINE

- **Pharmaceutical DF**
  - Determines the **physical form** of the final pharmaceutical preparation.
  - Is a DDS formed by technological processing (drug formulation).
  - Must reflect therapeutic inentions, route of administration, dosing, etc.
- **Pharmaceutical preparation**
  - Particular pharmaceutical product containing API and inactive pharmaceutical ingredients formulated into the particular DF.
  - **Packed and labelled appropriately**
  - According to the origin:
    - **manufactured** in large scales by pharm. industry (**innovative & generic medicines**)
    - **compounded** individually in compounding pharmacies (**extemporaneous preparations, galenic preparations**)



DOSAGE FORM DESIGN CONSIDERATION

Before a drug substance can be successfully formulated into a DF many factors must be considered. They can be divided into three categories:

- **Drug factors**, such as the **physical** and **chemical properties** of the API,
- **Biopharmaceutical & pharmacokinetic considerations**, including factors affecting the rate and extent of drug absorption from different administration routes,
- **Therapeutic considerations** including those of the disease to be treated and patient factors (*age and anticipated conditions*).

DOSAGE FORM DESIGN CONSIDERATION: *PROPERTIES OF DRUG SUBSTANCE*

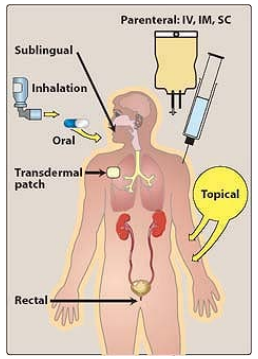
- Properties of API important in DF design (API stability, BA) and potential stresses occuring during production procedures:

PROPERTIES	PROCESSING STRESS	MANUFACTURING PROCEDURES
Particle size, surface area	Temperature	Precipitation, crystalization
Particle surface chemistry	Pressure	Filtration
Solubility	Mechanical stress	Emulsification
Dissolution	Radiation	Sterilization
Partition coefficient	Exposure to liquids	Milling, Mixing
Ionization constant	Exposure to gases	Drying
Crystal properties		Granulation
Polymorphism		Compaction
Stability		Autoclaving
Organoleptic		Crystallization
Molecular weight		Transport
		Storage

Variations in **FI-KE propertis** of API (batch to batch, production process...) can **modify DF performance** and **BA** of API!

DOSAGE FORM DESIGN CONSIDERATION: *BIOPHARMACEUTICAL & PHARMACOKINETIC CONSIDERATION*

- Administration route and distribution
  - *Local or systemic action* required?



http://health-7.com/Lippincotts%20Illustrated%20Reviews%20Pharmacology/1.%20Pharmacokinetics

DOSAGE FORM DESIGN CONSIDERATION:
BIOPHARMACEUTICAL & PHARMACOKINETIC CONSIDERATION

- Administration route and distribution
  - *Local or systemic action* required?
  - *How quickly a response* to drug is needed?

Time of onset of action	Dosage forms
Seconds	i.v. injections
Minutes	i.m. and s.c. injections, buccal tablets, aerosols, gases
Minutes to hours	Short-term depot injections, solutions, suspensions, granules, capsules, tablets, modified-release tablets
Several hours	Enteric-coated formulations
Days to weeks	Depot injections, implants
Varies	Topical preparations

Table: *Variation in time of onset of action for different DF.*

http://health-7.com/Lippincotts%20Illustrated%20Reviews%20Pharmacology/1.%20Pharmacokinetics

DOSAGE FORM DESIGN CONSIDERATION:
THERAPEUTIC CONSIDERATION

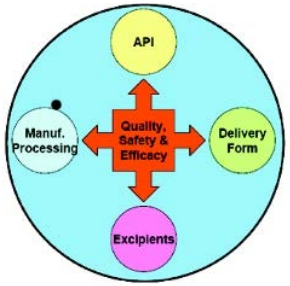
- including consideration of the **disease to be treated** and **patient factors** (age and anticipated conditions)
  - **Ability** of taking medicine is **age dependent!**

Dosing
Choice of DF
Choice and amount of excipients
Need for suitable applicator

  - Properties of API (stability, solubility and especially taste) can represent limiting factors for choice

FORMULATION AIMS

- To produce a dosage form (drug delivery system) with:
  - The right API
  - in the right amount,
  - distributed to the right place,
  - at the right time,
  - for right duration of effect.



OFFICIAL DOSAGE FORMS (1)

European Pharmacopoeia: vol. 1, General chapters

- 5. General Texts
  - *Monographs on dosage forms*

Glossary ... 717
Capsules ... 717
Chewing gums, medicated ... 719
Ear preparations ... 719
Eye preparations ... 721
Foams, medicated ... 723
Granules ... 723
Intramammary preparations for veterinary use ... 725
Intraruminal devices ... 725
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Liquid preparations for cutaneous application ... 728
Liquid preparations for oral use ... 728
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Parenteral preparations ... 735
Patches, transdermal ... 737
Powders for cutaneous application ... 738
Powders, oral ... 738
Premixes for medicated feeding stuffs for veterinary use ... 739
Preparations for inhalation ... 739
Preparations for irrigation ... 743
Pressurised pharmaceutical preparations ... 744
Rectal preparations ... 744
Semi-solid preparations for cutaneous application ... 746
Sticks ... 748
Tablets ... 748
Tampons, medicated ... 751
Vaginal preparations ... 751
Veterinary liquid preparations for cutaneous application ... 752

DOSAGE FORMS

Route of administration (systemic / local)

Physical form

They are classified according to:

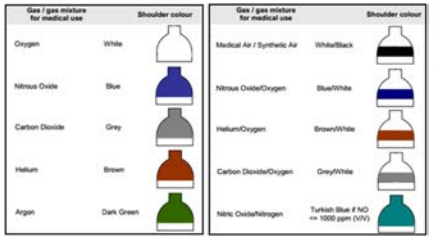
Administration route	Dosage forms
Peroral	Solutions, syrups, suspensions, emulsions, gels, powders, granules, capsules, tablets
Rectal	Suppositories, ointments, creams, powders, solutions
Topical	Ointments, creams, pastes, gels, solutions, topical aerosols, transdermal patches, s.c. injections
Parenteral	Injections (solution, suspension, emulsion forms), implants, irrigation and dialysis solutions
Respiratorial	Pressurised aerosols (solution, suspension, emulsion), powders for inhalation, gases
Nasal	Solutions, gels, liquids for nebulisation
Eye	Solutions, ointments, creams, gels
Ear	Solution, suspension, ointments, creams

Solid
Semisolid
Liquid
Gaseous

GASEOUS DOSAGE FORMS

- MEDICINAL GASES

Def.: Any gas, which is inhaled by a patient under the direction of a doctor.
In hospitals, pharmacists are often involved with the supply of oxygen, nitrous oxide, nitrous oxide/oxygen mixture, compressed air and occasionally more specialized gases.



Cylinders are **color-coded** to reduce accidental use of the wrong gas or vapor;

where the colour coding requires **2 colours** to be applied to cylinders, this may be done either by applying the colours by **banding** or by **quartering**.

GASEOUS DOSAGE FORMS

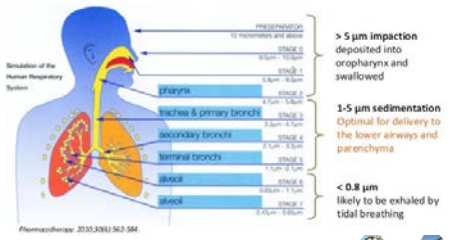
- MEDICINAL GASES

Def.: Any gas, which is inhaled by a patient under the direction of a doctor.
In hospitals, pharmacists are often involved with the supply of oxygen, nitrous oxide, nitrous oxide/oxygen mixture, compressed air and occasionally more specialized gases.

- AEROSOL(S)

A two-phase system of solid particles or liquid droplets dispersed in air or other gaseous phase, displaying considerable stability as a suspension.

Aerosols with a size below 5-6 μm penetrate to the peripheral (respirable) regions;
1-2 μm sized particles are preferable for alveolar deposition.

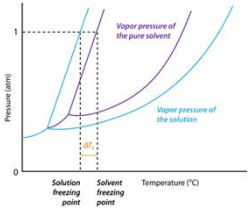


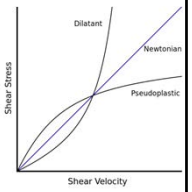
LIQUID DOSAGE FORMS

- SOLUTIONS
  - One homogenous phase, prepared by dissolving one or more **solutes** in a **solvent**.
  - Simple solutions/ colloidal solutions

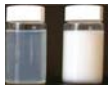
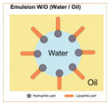
Colligative properties of solutions are properties that depend upon the concentration of solute molecules/ions, but not upon the identity of the solute.

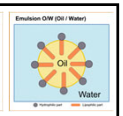
Colligative properties include:
freezing point depression, boiling point elevation, vapor pressure lowering, and **osmotic pressure**.



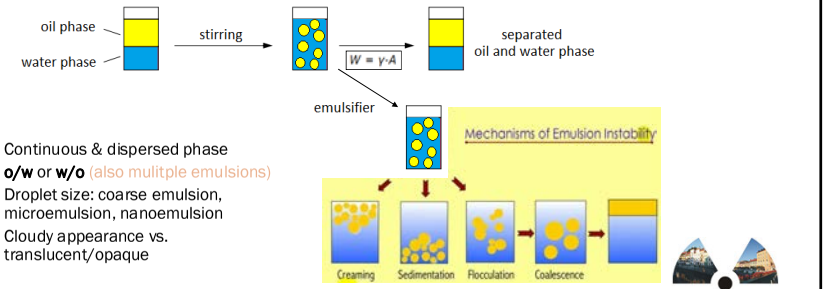


LIQUID DOSAGE FORMS

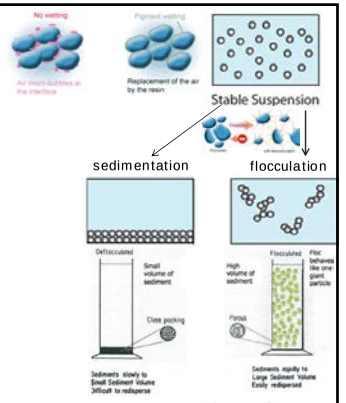


- EMULSIONS
  - A dispersion system consisting of two immiscible liquids (stabilized by emulsifyer(s))



  - Continuous & dispersed phase
  - **o/w** or **w/o** (also mulitple emulsions)
  - Droplet size: coarse emulsion, microemulsion, nanoemulsion
  - Cloudy appearance vs. translucent/opaque

LIQUID DOSAGE FORMS



- SUSPENSIONS
  - Dispersion system where solid particles (**dispersed phase**) are dispersed in a liquid phase (**dispersion medium**).
  - Size of dispersed particles (**up to 0,5mm**); **coarse** and **colloidal** dispersions
  - (May) require shaking before administration.
  - Not intended for systemic administration of higly potent API (highly accurate dosing required)!
  - Excipients: **wetting** agents;
    dispersing/suspending agents
  - Critical parameters of preparations:
    - **Size** of suspending particles and their **distribution**; influencing on:
      - Appearance
      - Sedimentation rate
      - Absorption rate
      - Capability of redispersing.

Sedimentation and **Stoke`s law**:

$$V = \frac{gd^2(\rho_1 - \rho_2)}{18\eta}$$

SEMISOLID DOSAGE FORMS



1 phase systems

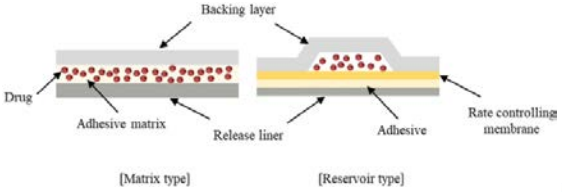
- GELS
  - Consist of either suspensions of small inorganic particles or large organic mol. interpenetrated by a liquid; hydrophilic (**hydrogels**) or hydrophobic (**oleogels**).
- OINTMENTS
  - Semisolids composed of 1 phase; **hydrophilic** (PEG/macrogol), **hydrophobic** (hydrocarbon) or **water-emulsifying** base.
- PASTES
  - Semisolid dispersion system; solid particles (>25%, e.g. ZnO) dispersed in ointments.

2 phase system

- CREAMS
  - Semisolid emulsion systems (o/w, w/o) containing >10% water;
    Hydrophilic (o/w): more comfortable and (cosmetically) acceptable; (less greassy and easily water-washable)
    Hydrophobic (w/o): accomodate and release better lipophilic API; (moisturizing, Cold creams)

FROM SEMISOLID SO SOLID DOSAGE FORMS

- TRANSDERMAL DRUG DELIVERY SYSTEMS (TD PATCHES)
  - Flexible, multilaminated, pharmaceutical preparation of varying size,
  - containing one or more API to be applied to the intact skin,
  - for systemic absorption over prolonged period of time.

https://link.springer.com/article/10.1007/s40005-021-00536-w

FROM SEMISOLID SO SOLID DOSAGE FORMS

- TRANSDERMAL DRUG DELIVERY SYSTEMS (TD PATCHES)
  - Flexible, multilaminated, pharmaceutical preparation of varying size,
  - containing one or more API to be applied to the intact skin,
  - for systemic absorption over prolonged period of time.
- SUPPOSITORIES
  - For rectal administration
  - Different shapes and sizes
  - Melting/dissolving at body T
  - **Excipients: Fatty bases** (hard fat - adeps solidus, cacao butter) or **hydrophilic bases** (PEGs)
- PESSARIES
  - Vagginal administration
  - **Excipients:** PEGs, glycerinated gelatine, adeps solidus...

SOLID DOSAGE FORMS

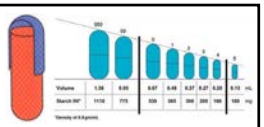
- POWDERS
  - Solid, loose, dry particles of varying degrees of fineness.
  - Powders for external / internal use
  - Simple / complex powders
  - Undevided (bulk) powders / Divided (individually wrapped) powders
  - Containers (single-dose, multidose)
  - Excipients: *fillers, glidants, (taste corrigens)*

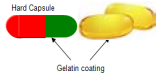
Table 2.9.35.-1.

Classification of powders by fineness		
Descriptive term	x_m (µm)	Cumulative distribution by volume basis, $Q_3(x)$
Coarse	> 355	$Q_3(355) < 0.50$
Moderately fine	180 - 355	$Q_3(180) < 0.50$ and $Q_3(355) \geq 0.50$
Fine	125 - 180	$Q_3(125) < 0.50$ and $Q_3(180) \geq 0.50$
Very fine	≤ 125	$Q_3(125) \geq 0.50$

SOLID DOSAGE FORMS

- CAPSULES
  - For oral administration
  - With hard or soft shells of various shapes and capacities, usually containing a single dose of API.
  - Capsule shells are made of gelatin or other substances (HMPC), its consistency may be adjusted by addition of plasticizers (e.g. glycerol), need for preservatives!
  - The contents of capsules: solid, liquid or of a paste-like consistency; consisting of one or more API with or without excipients (**solvents, diluents, lubricants and disintegrating agents**). The contents do not cause deterioration of the shell!
  - Eur. Ph: **Hard** and **soft capsules**; **gastro-resistant** & **modified release capsules**
  - Limitations of liquid contents:
    - Water < 5%, pH between 2.5 and 7.5
    - Low MW water-soluble and volatile compounds must be excluded
    - Aldehydes, in general, must be excluded (cross-linking!)
    - Contents must flow under gravity at <35°C.





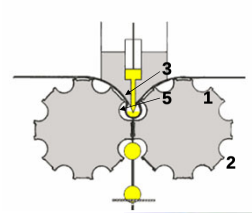
http://faculty.ksu.edu.sa/Diaa/Documents/tablet%20and%20capsules.pdf

SOLID DOSAGE FORMS

- Production/filling of capsules:

Bench scale filling of hard capsules (with powders)

- Filing based on volume (**flow properties**!!!)

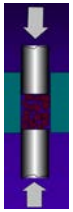


1. Gelatin ribbon
2. Rotary die
3. Filling wedge
4. Filled capsule
5. Pupming mechanism

http://faculty.ksu.edu.sa/Diaa/Documents/tablet%20and%20capsules.pdf

SOLID DOSAGE FORMS

- TABLETS
  - Solid, single-unit dose preparations containing one or more API
  - Obtained by compressing uniform volume of powders/ granules or another suitable manufact. technique (freeze-drying, HME, moulding…)
  - Round, oval or square shape, sometimes with break-marks.
  - Composed of **API** and **excipients** (to aid tableting and DF performance): **diluent, binder, disintegrant, lubricant**, coloring agent, sweetening & flavoring agent.
  - Controlled drug release



https://en.wikipedia.org/wiki/Tablet_press http://www.tofflon.com/en/news-detail.html?news=1570

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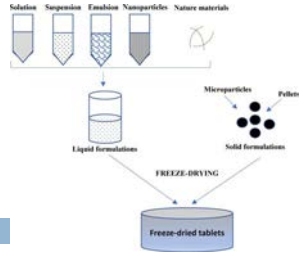

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Eur. Ph.:
- uncoated tablets
- coated tablets
- effervescent tablets
- soluble tablets
- dispersible tablets
- orodispersible tablets
- gastro-resistant tablets
- modified-release tablets
- chewable tablets
- oral lyophilisates

https://spritam.com/

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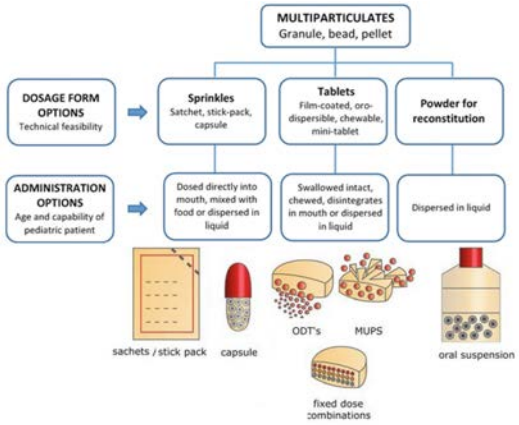
https://spritam.com/

SOLID DOSAGE FORMS

Multiparticulate dosage forms

- granules (0.3 – 1.2 mm)
- pellets (0.5 – 2 mm)
- microcapsules (0.001 – 1 mm)
- mini tablets (1,5 – 3 mm).

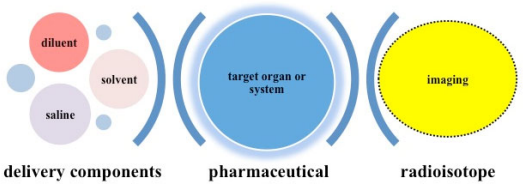
Patient friendly DF



Pediatric drug products with micropellets; from: D.Bar-Shalom,R.Klaus (Eds.). Pediatric Formulations: A Roadmap.

RADIOPHARMACEUTICALS

- Radiopharmaceuticals are a radioactive drug intended to humans for diagnosis and therapy.
- It contains a **radioactive moiety** (radionuclide) and a **biodistribution moiety**. Following its administration to a patient, the radiopharmaceutical will localize in a specific organ or tissue depending upon the biodistribution moiety.



http://maiedge.com/patient-blog/nuclear-medicine-2/what-is-in-a-nuclear-medicine-dose/

Radiopharmaceuticals in *Eur. Ph.*

Examples:

- Ammonia (^{13}N) *injection*
- Carbon monoxide (^{15}O) inhalation gas
- Chromium (^{51}Cr) edetate *injection*
- Cyanocobalamin (^{57}Co) *capsules*
- Cyanocobalamin (57Co) *solution*
- Cyanocobalamin (58Co) capsules
- Cyanocobalamin (^{58}Co) solution
- Fludeoxyglucose (^{18}F) *injection*
- Flumazenil (N-(11C) methyl)injection
- Gallium (67Ga) citrate injection
- Fluorodopa (^{18}F) (prepared by electrophilic substitution) *injection**
- Human albumin injection, iodinated (125I)
- Indium (111In) chloride solution
- Iobenguane (131I) injection for diagnostic use
- Iobenguane (^{131}I) injection for therapeutic use
- Iobenguane (^{131}I) sulfate for radiopharmaceutical preparations*
- Krypton (81Kr) inhalation gas
- Oxygen (15O)
- Sodium iodide (131I) capsules for diagnostic use
- Sodium iodide (131I) capsules for therapeutic use*
- Sodium iodide (131I) solution for radiolabelling etc.

GASEOUS DOSAGE FORMS FOR PULMONARY DRUG DELIVERY

- MEDICINAL GASES and AEROSOLS
  - **Carbon monoxide (15O)**
    Mixture of carbon (15O) monoxide in the gaseous phase and a suitable vehicle such as medicinal air, for diagnostic use.
  - **Krypton-81m inhalation gas** is a mixture of krypton-81m and a suitable vehicle as air.
  - **Ksenon-133 inhalation gas;** normally supplied in a concentration of 5% in 95% CO_2.
  - **Tc-99m pertechnetate (TcO_4) (aerosol)**
  - **Tc-99m DTPA (diethylenetriamine-pentaacetic acid) (aerosol)**

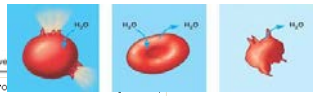
SOLID DOSAGE FORMS (FOR RADIOPHARMACEUTICALS)

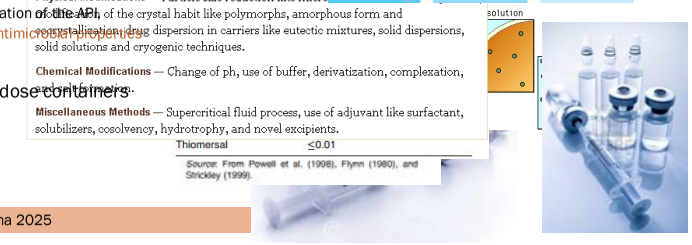
- CAPSULES
  - **Sodium iodide (^{131}I) capsules for diagnostic use**

    contain iodide-131 in the form of sodium iodide on a suitable solid support. The capsules also contain sodium thiosulphate or other reducing agents and may contain a suitable buffer.
  - Capsules (Tc-labelled) are DF of choice for studies of gastric emptying of solids (inofficial).

PARENTERAL PREPARATIONS

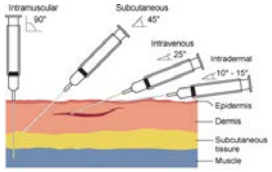
- From Greek words: *Para* (outside) and *Enteron* (intestine).
- Parenteral preparations are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body.
- Parenteral preparations may require the use of excipients
  - to make the preparation isotonic with blood,
  - to adjust the pH,
  - to increase solubility,
  - to prevent the deterioration of the API,
  - to provide adequate antimicrobial preservation.
- Single-dose or multidose containers





PARENTERAL PREPARATIONS

- Dosage forms:
  - Injections (SVP)
  - Infusions (LVP)
  - concentrates for injections or infusions
  - powders for injections or infusions
  - gels for injections
  - Implants
  - Intravitreal preparations



1. Intravenous (IV) - vein
- i. Most rapid onset
- ii. Complete bioavailability
- iii. Bolus dosing or infusion (LVPs)
- iv. Aqueous solutions, fat emulsions
- v. Less irritation

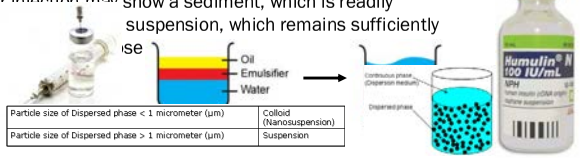
2. Intramuscular (IM) – gluteal (buttocks), deltoid (upper arm), vastus lateralis (thigh)
- i. Easier administration than IV
- ii. Slower onset but prolonged action than IV
- iii. Limited volumes 2-5 mL
- iv. Osmolarity essential, no dilution occurs
- v. Solutions, suspensions & emulsions

3. Subcutaneous (SC) - connective & adipose tissue under the skin
- i. Slower onset than IM
- ii. Technically simpler
- iii. ↓ discomfort & ↓ risk of complications than IM
- iv. < 2 mL
- v. Narrow control of pH and tonicity
- vi. Solutions, suspensions & emulsions
- vii. Drugs ineffective orally - insulin, vaccines

http://www.authorstream.com/Presentation/satishmip-1168599-parenteral-dosage-forms-and-sterilization/

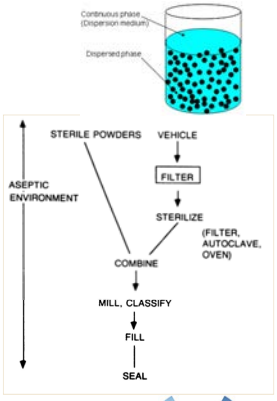
INJECTIONS

- Injections are sterile solutions, emulsions or suspensions. They are prepared by dissolving, emulsifying or suspending the API(s) and any added excipients in water for injections, in a suitable, sterile non-aqueous liquid or in a mixture of these vehicles.
- Solutions for injection, examined under suitable conditions of visibility, are clear and practically free from particles.
  - **Sodium Pertechnetate (^{99m}Tc)**
- Emulsions for injection do not show any evidence of phase separation.
- Suspensions for injection may show a sediment, which is readily dispersed on sl suspension, which remains sufficiently stable to enabl se
-



INJECTIONS

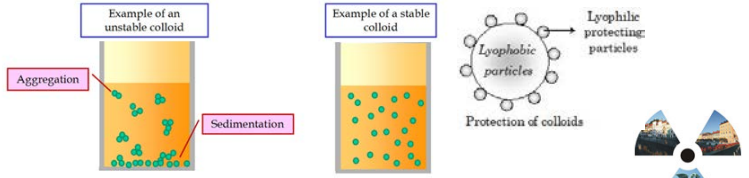
- SUSPENSIONS FOR INJECTIONS:
  - usually contain < 5 % of drug solids with particle diameter < 5 (1!) µm
  - Presence of particles >> more difficult to process and sterilize; *manufacture*: the components are prepared and sterilized separately and then aseptically combined.
  - The final product cannot be filter sterilized (presence of particles in the formulation).
  - Powders can be sterilized by gas, but gas residues must be avoided.
- Tc-99m labeled Macro Aggregated Albumin (MAA)
  - Kits: **lyophilized powders of non-radioactive ingredients sealed under N_2.** A nuclear pharmacist adds 50 - 100 mCi of Na[$^{99m}TcO_4$] to the reaction vial to make the final product.



INJECTIONS

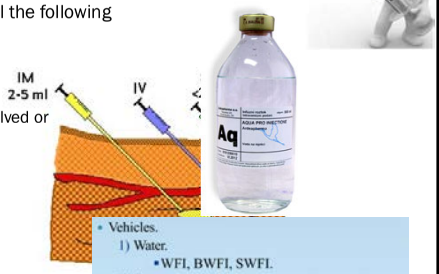
- **Colloidal dispersions**
  - Colloids can be prepared and used for injections. Albumin, proteins, dextrans and carbohydrate polymers dissolve in water for injection to from hydrophilic molecular colloid solution.
  - Technetium (99mTc) colloidal sulphur injection

    Technetium (99mTc) colloidal sulphur injection is a sterile, apyrogenic colloidal dispersion of sulphur, the micelles of which are labelled with technetium-99m. It may be stabilised with a colloid-protecting substance based on gelatin.



INJECTIONS

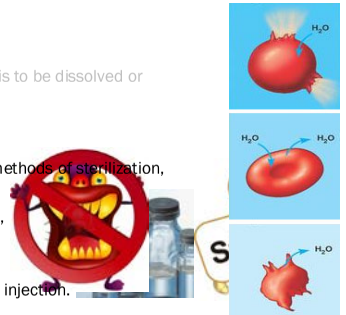
- Their formulation involves careful consideration of all the following inter-relating factors:
  - The proposed route of administration,
  - The volume of the injection,
  - The vehicle in which the active compound is to be dissolved or dispersed,



- Vehicles.
  1) Water.
     - WFI, BWFI, SWFI.
  2) Aqueous vehicles.
     - **E.g.:** Ethyl alcohol, Propylene Glycol.
  3) Non-aqueous vehicles.
     - **E.g:** Fixed oils (corn oil, peanut oil, cotton seed oil.)

INJECTIONS

- Their formulation involves careful consideration of all the following inter-relating factors:
  - The proposed route of administration,
  - The volume of the injection,
  - The vehicle in which the active compound is to be dissolved or dispersed,
  - The osmotic pressure of the solution,
  - The use of preservative,
  - The stability of the active compound and methods of sterilization,
  - The specific gravity of the injection,
  - The properties of suspensions for injection,
  - The properties of emulsions for injection,
  - Containers and closures for injections,
  - Particulate contamination, biopharmacy of injection.



INFUSIONS

- Infusions are sterile, aqueous solutions or emulsions with water as the continuous phase; they are usually made isotonic with blood. They are principally intended for administration in large volume. Infusions do not contain any added antimicrobial preservative.
  - Solutions for infusion, examined under suitable conditions of visibility, are clear and practically free from particles.
  - Emulsions for infusion do not show any evidence of phase separation.
  - *Production:* In the manufacture of infusions containing dispersed particles, measures are taken to ensure a suitable and controlled particle size with regard to the intended use.

POWDERS FOR INJECTIONS OR INFUSIONS

- Powders for injections or infusions are solid, sterile substances distributed in their final containers and which, *when shaken with the prescribed volume of a prescribed sterile liquid*, rapidly form either clear and practically particle-free solutions or uniform suspensions, they comply with the requirements for injections or for infusions.

  Freeze-dried products for parenteral use are considered as powders for injections or infusions.
  - *Production:* the uniformity of content and uniformity of mass of freeze-dried products for parenteral use are ensured by the in-process control of the amount of the solution prior to freeze-drying.

POWDERS FOR INJECTIONS OR INFUSIONS

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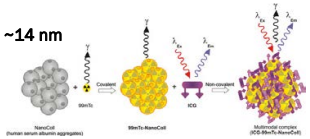
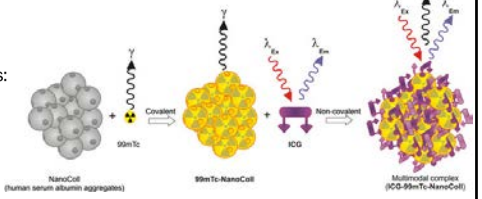
- **NanoColl®;**
  - **^{99m}Tc labeled colloidal human serum albumin; ~14 nm**
- antibody-functionalized NP (not registrated)



POWDERS FOR INJECTIONS OR INFUSIONS

NanoColl®

- Advantages of kits in preparing radiopharmaceuticals:
  - Closed procedures, rapid & easy preparation of products
  - Low radiation hazard to operative
  - Sterile and pyrogen-free product
  - Stable and diagnostically effective product
  - Reproducible and reliable product
  - Long shelf-life of unreconstituted kit
  - Fullly quality-controlled by manufacturer
  - Readily available
  - Economic cost per patient dose in most cases.



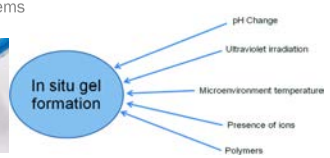
Buckle et al. Nanotechnology (2010); 21(35):355101.

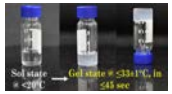
Method of preparation
- Place a vial containing the albumin colloidal particles in a convenient lead shield.
- Aseptically introduce into the vial 1-5 ml Sodium Pertechnetate (^{99m}Tc) Injection Ph. Eur. with a radioactivity ranging from 185 to 5550 MBq (5 to 150 mCi).
- Do not use a breather needle.
- Relieve the excess of pressure in the vial by simply withdrawing an equal volume of gas in the syringe.
- Invert carefully a few times to dissolve the contents of the vial.
- Then allow to stand for 5-10 min at room temperature (15°C -25°C).
- Shake before withdrawing a dose.
- In no case should the preparation be left in contact with air.

CONCENTRATES FOR INJECTIONS OR INFUSIONS, GELS FOR INJECTIONS

- **Concentrates** for injections or infusions are sterile solutions intended for injection or infusion after dilution. They are diluted to a prescribed volume with a prescribed liquid before administration. After dilution, they comply with the requirements for injections or for infusions.

- **Gels** for injections are sterile gels with a viscosity suitable to guarantee a modified release of the active substance(s) at the site of injection.
  - *In situ* gelling systems





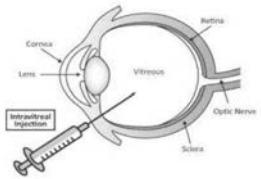
https://link.springer.com/article/10.1007/s13346-020-00800-w

http://www.durect.com/wt/durect/page_name/implants

IMPLANTS & INTRAVITREAL PREPARATIONS

- **Implants** are sterile, solid preparations of a size and shape suitable for parenteral implantation and release the active substance(s) over an extended period of time.
  Each dose is provided in a sterile container.

- **Intravitreal preparations** - sterile preparations for administration or implantation into the vitreous humour. They are solutions, colloidal dispersions, emulsions, suspensions or implants and comply with the requirements for **injections** or **implants**, as appropriate.
  Unless otherwise justified and authorised, they are supplied in single dose containers and do not contain any preservatives.



TAKE HOME MESSAGES

- **DF design**: keep in your mind the drug factors together with biopharmaceutical, pharmacokinetic and therapeutic aspects.
- **Formulation aim**: the right API, in the right among, distributed to the right place, at the right time, for the right duration of effect (>> predictable therapeutic response).
- **DF classification**: according to route of administration (official according to Eur.Ph.) or their physical form.
- **DF used for radiopharmaceuticals**: solid DF (Capsules), gaseous DF, DF for parenteral administration.
- **Parenteral DF**: sterile, apyrogenic, isotonic (biocompatibility is oblige, not all must be isoosmotic), euhydric etc.
- Be careful when diluting liquid DF (solutions, emulsions, suspensions) in order to preserve appropriate stability!

LITERATURE

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- European Pharmacopoeia 11th Ed.
- Florence A.T., Attwood D. (Ed.). Physicochemical Principles of Pharmacy, 5th Ed., Pharmaceutical Press, 2011.
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Sterilization

Assist. prof. dr. Barbara Sterle Zorec enrolled at the Faculty of Pharmacy of the University of Ljubljana (UL FFA) in 2004 as a recipient of the Zois Scholarship. In 2011, she began her doctoral studies in the Biomedicine programme (pharmacy). In cooperation with the Department of Biomedical Engineering at the Faculty of Electrical Engineering (UL FE), where she was also employed, she successfully defended her doctoral thesis entitled "*Study of Physical Methods and Delivery Systems for Increasing Dermal Uptake of Active Ingredients*" in 2017. In recognition of her research, she received the L'Oréal-UNESCO For Women in Science scholarship in 2016. During her academic training, she took part in a research exchange at the University of Canterbury in Christchurch, New Zealand, under the framework of COST funding. In August 2016, she was appointed Head of the Quality Control Department at Wooshin Lapache d.o.o., where she managed departmental operations, set up a physico-chemical analysis laboratory and implemented a comprehensive quality control system, including the preparation of all necessary documentation. As a certified chemical consultant, she was also responsible for the import, storage and safe handling of chemicals. In September 2017, she joined Iskra Medical d.d. as a research specialist with additional responsibilities in quality assurance. Since February 2018, she has been working as a teaching and research assistant at the Department of Pharmaceutical Technology at UL FFA. Her teaching activities are mainly focused on the production and evaluation of solid pharmaceutical dosage forms, including tableting, granulation and coating technologies. Her scientific research is dedicated to the development of dry particle pre-formulations (using electrospraying and spray drying) for 2D printing applications in personalised medicine. She also applies numerical modelling techniques such as Design of Experiments (DoE) and neural networks for the planning, optimisation and evaluation of experimental parameters. Her current research focuses on the production of personalised dosage forms using hot melt extrusion and 3D printing, with an emphasis on sustainability principles to improve drug solubility, permeability and stability.

The lecture aims to achieve the following learning outcomes:

1. Students will comprehend the significance of the sterilization process in pharmaceutical practice.
2. Students will be able to recognize and explain pharmacopeial sterilization methods.
3. Students will develop the ability to critically assess different sterilization techniques.
4. Students will be able to choose the most suitable sterilization method based on the characteristics and properties of the product/material to be sterilized.
5. Students will identify critical control points within specific sterilization methods.
6. Students will be able to outline the procedures for monitoring sterilization, including in-process and final product control.

1. INTRODUCTION

The primary goal of the sterilization process is to eliminate or destroy microorganisms (MOs) present on or within an object or preparation. This process must ensure, with a very high degree of certainty, that the object or preparation poses no risk of infection. The generally accepted benchmark for sterilization performance is achieving a probability of less than one in a million of a nonsterile unit remaining—this corresponds to a sterility assurance level (SAL) of 10^{-6} or better. The likelihood of a microorganism surviving the sterilization process depends on factors such as the quantity, types, and resistance of microorganisms present, as well as the conditions they are exposed to during treatment. The SAL for a specific product and process is determined through rigorous validation studies.

2. STERILIZATION METHODS

The choice of sterilization method for drugs, pharmaceutical preparations, or medical devices largely depends on the specific characteristics of the product. A single sterilization technique cannot be universally applied, as certain materials may be altered or damaged by particular methods. Sterilization approaches are generally classified as either physical or chemical. Physical methods, which involve the application of energy, include moist heat, dry heat, and irradiation. Chemical methods rely on gaseous or liquid sterilizing agents. In contrast, sterile filtration removes microorganisms without inactivating them. Although many sterilization methods exist and are in use, only those capable of achieving a sterility assurance level (SAL) of 10^{-6} are recognized by pharmacopoeias and will be briefly described.

2.1. STEAM STERILIZATION - AUTOCLAVING

Moist heat, delivered as saturated steam under pressure, is considered the most dependable method for eliminating microorganisms. Approximately 80% of its thermal energy exists as latent heat. Upon condensation, saturated steam releases this latent heat instantly. Additionally, the condensation process causes the steam to contract significantly in volume, creating a localized drop in pressure that draws in more steam to restore equilibrium. This mechanism enables rapid and deep penetration, which is especially important for sterilizing porous materials such as surgical dressings.
Key factors in the autoclaving process include the effective removal of residual air, prevention of wet steam formation, avoidance of superheated steam (steam not in equilibrium with its source), and controlled cooling of the autoclave post-sterilization.
Autoclave design must ensure thorough penetration of dry saturated steam throughout the load, minimize the risk of supersaturated steam formation, and guarantee complete air removal from both the chamber and porous materials. Common autoclave types include downward displacement, air-ballasted, spray-cooled, high vacuum, and continuous-flow models.
For terminal sterilization using moist heat, the standard reference condition for aqueous preparations, as specified in the European Pharmacopoeia (Ph. Eur.), is exposure to a minimum of 121°C for 15 minutes. Alternative validated combinations of time and temperature may also be used.

2.2. DRY HEAT STERILIZATION

Dry heat sterilization is typically performed using a hot air oven. These ovens should be electrically heated, thermostatically controlled, and equipped with a fan or turbo blower to ensure continuous forced air circulation. Heat is transferred to the materials primarily through conduction, convection and radiation. Heat transfer by conduction through the shelves plays a minimal role due to the limited contact area between the product and the shelf surface. To maximize radiative heat transfer, heaters are positioned around the chamber walls. However, items placed near the walls may obstruct heat flow to those in the center of the chamber. Therefore, efficient heat transfer via circulating hot air is critical. This is achieved by ensuring optimal air movement through appropriate load sizing and spacing, and

by avoiding overcrowding, which can hinder uniform heat distribution. Prior to sterilization, the chamber is preheated to the target temperature. Heating and sterilization times can be lengthy, depending on the load and required conditions. The standard reference condition for dry heat sterilization, according to the European Pharmacopoeia (Ph. Eur.), is at least 160°C for a minimum duration of 2 hours. However, other validated time-temperature combinations may also be used. For the sterilization and depyrogenation of glassware, higher temperatures—often exceeding 220°C—are commonly employed.

2.3. RADIATION STERILIZATION

Radiation sterilization is a low-temperature process and can serve as a valuable alternative to ethylene oxide sterilization for heat-sensitive (thermolabile) materials. Two main types of radiation are employed: electromagnetic radiation (including ultraviolet and gamma rays) and particulate radiation (high-energy electrons).
Ultraviolet (UV) radiation, particularly at wavelengths between 240 and 280 nm, is bactericidal but has limited penetration depth. It has been used effectively for sterilizing air and thin layers of water; however, it is not considered suitable for sterilizing medical devices or pharmaceutical products.
For such applications, ionizing radiation—typically gamma rays or electron beams—is used. The standard sterilizing dose accepted for achieving a sterility assurance level (SAL) of 10^{-6} is 25 kilograys (kGy).

2.3.1. Gamma Irradiation

The primary source of gamma radiation used for sterilization is the radioactive isotope cobalt-60 (Co^{60}). It is produced by exposing natural cobalt to neutrons in a nuclear reactor and has a half-life of approximately 5.3 years. There is potential for cobalt-60 to be replaced by cesium-137 (Cs^{137}), a byproduct of uranium fission. However, Cs^{137} emits lower-energy radiation (0.66 MeV) compared to Co^{60} (2.81 MeV). The required sterilization dose can be adjusted by varying the exposure time.

2.3.2. High-Energy Electrons

High-energy electron beams are generated by accelerating electrons to energies between 5 and 10 MeV using electron accelerators. At these energy levels, electron penetration is sufficient for effective sterilization, and the risk of inducing radioactivity in the product is negligible. The dose rate of electron beams is significantly higher than that of gamma radiation, allowing for rapid delivery of sterilizing doses.

2.4. GAS STERILIZATION

Although many chemicals possess antimicrobial properties, the need for effective penetration and complete removal limits practical use to chemical vapours. Among these, ethylene oxide (EO) is the most used sterilizing agent. The efficacy of EO depends on several critical parameters: concentration, temperature, relative humidity (minimum of 33%), and exposure time. These factors must be precisely controlled throughout the sterilization process. Proper sterilization also requires ensuring that microorganisms are not shielded or occluded within the load and that EO gas penetrates all materials effectively. Commercial EO sterilizers feature a sealed, heated chamber designed to withstand both high pressure and vacuum. The system is typically connected to a high-efficiency vacuum pump, which removes air before sterilization and evacuates the gas mixture afterward.
Due to EO's toxicity and flammability, these risks are carefully addressed in the design and operation of sterilization units. EO sterilization protocols must be specifically validated for each individual product. EO concentrations between 450 and 1500 mg/L, and temperatures ranging from 25°C to 60°C, are commonly employed depending on the product's characteristics.

2.5. FILTRATION

Thermolabile solutions can be sterilized by filtration using bacteria-retentive filters. Unlike other sterilization methods, filtration does not destroy microorganisms but physically removes them from the solution. Membrane filters with a pore size of 0.2–0.22 µm are typically recommended for this purpose. A wide variety of membrane materials are available, allowing selection based on chemical compatibility with the product. Membrane filters are characterized by high and uniform porosity, which ensures high filtration rates, low fluid retention, and minimal solute absorption—all desirable features for pharmaceutical applications. Filtration may be performed under positive or negative pressure, depending on the system setup. The sterilization process includes filtering the solution through a pre-sterilized filter unit, followed by aseptic transfer of the filtrate into previously sterilized containers, which are then securely sealed to maintain sterility.

3. SELECTION OF STERILIZATION METHODS

The selection of a sterilization method involves balancing the acceptable risk of failing to achieve sterility with the maximum permissible impact on product quality. According to the European Pharmacopoeia (Ph. Eur.), sterilization must be performed using one of the recognized methods. However, modifications or combinations of these methods may be employed, provided that the selected procedure is validated for both sterilization efficacy and product integrity, including that of the container. Wherever feasible, terminal sterilization—sterilizing the product in its final container—is the preferred approach.

- **Moist heat sterilization** is suitable for a wide range of **aqueous preparations**, both parenteral and non-parenteral, as well as for **natural rubbers, many plastics** (e.g., PVC, nylon), **glassware, and surgical dressings**.
- **Dry heat sterilization** is used when moisture-sensitive materials are involved, such as **oils, ointments, waxes, and powders**. It is typically the method of choice for **glassware, syringes, surgical instruments**, and certain equipment.
- For materials that cannot tolerate the high temperatures of heat sterilization, **cold sterilization** techniques must be considered:
    - **Ethylene oxide (EO)** is employed for **thermolabile powders**, specific **plastics and rubbers**, and **surgical instruments**. However, its **reliability is limited** due to the critical control of parameters and challenges in monitoring, making it a secondary option when more robust methods are not applicable.
    - **Radiation sterilization** is highly effective and widely used for **large-scale sterilization** of **plastic disposables**, **Petri dishes**, **surgical instruments**, and **dressings**. Despite its effectiveness, **material degradation** can occur, limiting its applicability. Additionally, **aqueous pharmaceutical solutions are unsuitable** for radiation sterilization due to the **radiolysis of water**.

If none of the terminal sterilization methods are feasible, **sterilization by filtration** followed by **aseptic processing** remains the only viable option.

4. QUALITY ASSURANCE IN STERILIZATION PROCESSES

In the production of sterile pharmaceutical products, it is not sufficient to rely solely on the final sterilization step. Sterility must be integrated into every stage of the manufacturing process. As emphasized by the European Pharmacopoeia (Ph. Eur.): *"The sterility of the product cannot be guaranteed by testing; it must be assured through the use of appropriately validated processes."*

This principle highlights that quality assurance in sterilization is proactive, not reactive. The application of Good Manufacturing Practice (GMP) is essential throughout the design and execution of sterile manufacturing processes. Key requirements include:

- Employment of **qualified personnel** with appropriate training in aseptic techniques and process hygiene.
- Use of **adequate, controlled facilities**, designed to support sterile production.
- Implementation of **suitable production equipment**, engineered for effective cleaning, disinfection, and sterilization.
- **Minimization of bioburden** before sterilization through strict in-process controls and environmental measures.
- **Validation of all critical steps** in the production and sterilization process to ensure consistent efficacy.
- Execution of **environmental monitoring** and **in-process testing**, forming an integral part of ongoing quality assurance.

These measures ensure that sterility is built into the product, rather than tested for after the fact, providing a robust framework for the consistent production of high-quality sterile products.

4.1. STERILIZATION CONTROL

Sterilization control can be categorized into two main types: **in-process control** (which includes physical measurements, chemical indicators, and biological indicators) and **product control** (such as sterility testing).

4.1.1. Physical Measurements

For both moist and dry heat sterilization, it is critical to monitor and record the temperature, particularly in the coldest part of the load or chamber—typically near the drain. Pressure is usually measured using Bourdon-type gauges, though modern sterilizers are increasingly equipped with pressure transducers. Currently, there is no reliable method for measuring relative humidity or assessing steam saturation levels within the chamber or load. Physical measurements are only meaningful if the instruments used are initially calibrated, properly maintained, and regularly verified.

4.1.2. Chemical Indicators

These indicators work by undergoing a chemical or physical change when exposed to sterilization conditions. An effective chemical indicator provides a clear indication that the necessary sterilization parameters have been achieved. Browne's tubes are widely used for heat sterilization due to their affordability and ease of use. Crystal indicators, which melt at sterilization temperatures, also serve this purpose. Heat-sensitive indicators play a role in the Bowie-Dick test, which confirms the complete removal of air from dressing packs. The Royce sachet is a chemical indicator specifically designed for ethylene oxide sterilization. For radiation sterilization, chemical dosimeters provide a precise measure of the absorbed dose and are currently considered the most accurate method available.

4.1.3. Biological Indicators

Biological indicators are composed of selected microorganisms applied to a carrier material, which are strategically placed within the sterilization load. After the sterilization process is complete, the carriers are enclosed and incubated to check for the survival of any microorganisms. These indicators offer a direct evaluation of sterilization effectiveness by reflecting all relevant process parameters. The microorganisms used should be highly resistant to the sterilizing method, consistently reproducible in their response, genetically stable, easy to identify, and non-pathogenic.
All aspects of biological indicator preparation—including cultivation, harvesting, formulation, storage, and the recovery of surviving organisms—must be carefully standardized and tightly controlled.

Indicators may be prepared in forms that mimic the sterilized product, such as liquid suspensions or strips. In some cases, the actual product can act as the medium for the microorganisms. Bacterial spores, due to their high resistance, are the most used organisms in biological indicators.

Key Takeaways:

- The majority of radiopharmaceuticals are administered by injection, so **sterility is essential**.
- **No single sterilization method is universally applicable**—the choice depends on the specific characteristics of the product being sterilized.
- Of the many available sterilization techniques, only five meet **European Pharmacopoeia (Ph.Eur.)** standards for achieving a **Sterility Assurance Level (SAL) of 10^{-6} or better**. These include:
    - Steam sterilization (autoclaving)
    - Dry heat sterilization
    - Ionizing radiation
    - Gas sterilization
    - Filtration and aseptic processing
- **Moist heat sterilization (autoclaving)** is the most reliable and efficient method for microbial destruction in terms of process control, energy use, and time.
- **Dry heat** is suitable not only for sterilization (minimum 160°C for 2 hours) but also for **depyrogenation** when used at temperatures above 220°C.
- **Ionizing radiation** for sterilization employs long-lived radioactive isotopes like **Cobalt-60 (^{60}Co)** and **Cesium-137 (^{137}Cs)**, which have half-lives of 5.3 and 30 years, respectively—unlike the short-lived isotopes used in radiodiagnosis or therapy.
- **Sterility must be designed into the process from the beginning**; it cannot be added at the end. Thus, robust **sterilization control—particularly in-process monitoring—is critical**.

References (further reading):

- Sterilization In: Remington's the science and practice of pharmacy, 20th Ed, 2000
- Encyclopedia of Pharmaceutical Technology, J.Swarbrick, JC Boylan, ed., Vol.1 – Autoclaves and autoclaving, Vol. 4 – Dry heat sterilization and depirogenization, Vol. 5 - Electron beam sterilization, Ethylene oxide sterilization, Vol. 6. Gamma radiation sterilization, Vol. 9 – Microbial control of Pharmaceutics.
- Pharmaceutical microbiology and sterilization. In: Pharmaceutics -the science of dosage form design, M.E. Aulton, ed., Churchill Livingstone Press, 2007
- European Pharmacopoeia, Current Ed, Council of Europe
- Michael E. Aulton, Kevin M. G. Taylor: Aulton's Pharmaceutics
  Chapter 15: Action of physical and chemica agents on mikroorganisms
  Chapter 16: Principles of sterilization
  Chapter 17: Sterilization in practice
- Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 1, Manufacture of Sterile Medicinal Products

STERILIZATION

Assist. prof. dr. Barbara Sterle Zorec

UL FFA

OUTLINE

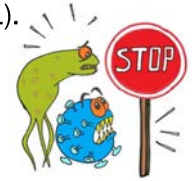
1. Introduction
2. Sterilization methods (Ph.Eur)
   - *Physical methods*
     - Steam sterilization
     - Dry heat sterilization
     - Ionizing radiation sterilization
   - *Chemical methods*
   - *Membrane filtration*
3. Selection of sterilization methods
4. Quality control in sterilization practise

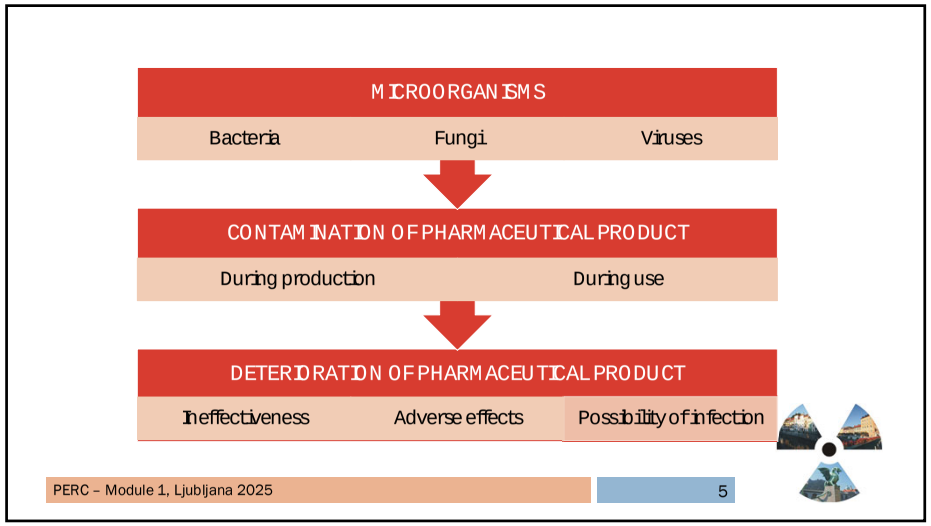
STERILITY?

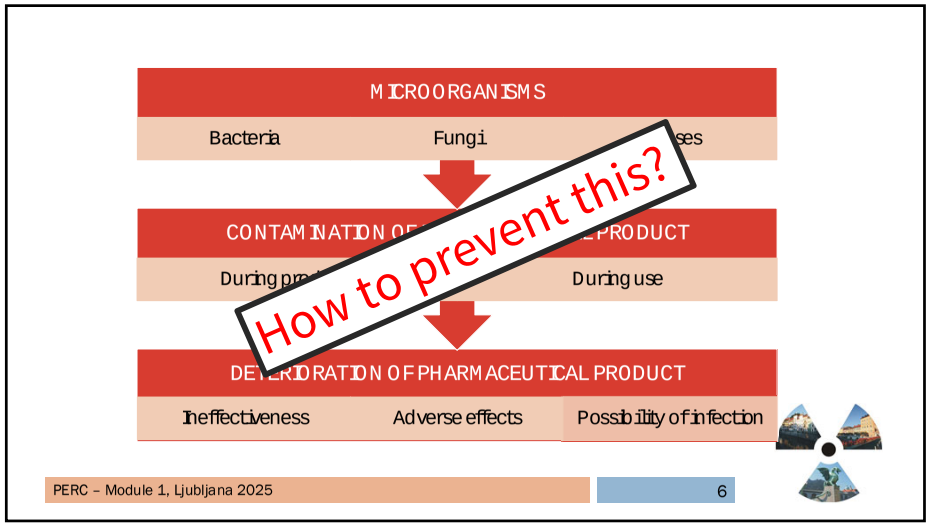
STERILITY

= total absence of viable microorganisms (MO) as it is defined by sterility assurance level (SAL).

= it is neccessary for quality of certain pharmaceutical preparations.







STERILIZATION

STERILIZATION

= **physical/chemical processs** – removes or destroys viable microorganisms (MO) to an acceptable level.

Acceptable level?

SAL ≤ 10^{-6}

STERILITY ASSURANCE LEVEL (SAL)

$$N_t = N_o e^{-kt}$$

Time of exposure to a sterilization procedure

Number of MO per 1 mL after time t

Initial number of MO per 1 mL

Constant coeficient of inactiavtion level of MO

STERILITY ASSURANCE LEVEL (SAL)

$$N_t = N_o e^{-kt} \rightarrow \ln N_t = \ln N_o - kt \rightarrow \log_{10} N_t = \log_{10} N_o \frac{-kt}{2.303}$$

Table 15.1 Death of *Bacillus megaterium* spores in pH 7.0 buffer at 95 °C

Time (min)	Viable cell concentration (mL^{-1})	Percentage of survivors	Log_{10} percentage of survivors
0	2.50×10^6	100	2.000
5	5.20×10^5	20.8	1.318
10	1.23×10^5	4.92	0.692
15	1.95×10^4	0.78	−0.108
20	4.60×10^3	0.18	−0.745
25	1.21×10^3	0.048	−1.319
30	1.68×10^2	0.0067	−2.174

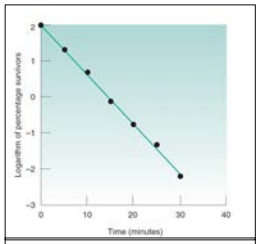


Figure 1: Logarithm of MO concentration versus exposure time to a specific sterilization process.

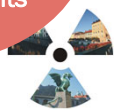
There is **no lower end point** in the ordinate scale – it goes on indefinitely.
Sterility is the complete absence of **MO = 0 MO/mL** → **log0 = -∞.**
Assured sterility would therefore require an infinite exposure time.

STERILITY ASSURANCE LEVEL (SAL)

$$SAL \leq 10^{-6}$$

The probability of survival of MO in a product after it has been exposed to a certain sterilization process.

A maximum of 1 non-sterile unit with 1 single viable microorganism occurs in 106 units of the product.



STERILIZATION METHODS

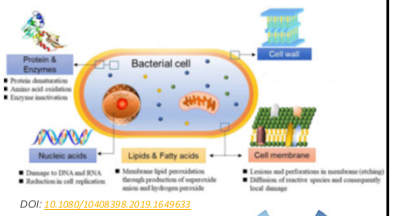
MECHANISMS OF DESTRUCTION OF MO BY STERILIZATION METHODS

Damage of nucleic acid

Damage of cell walls and membranes

Damage of structural, functional proteins

Effect on the ability of MO to reproduce



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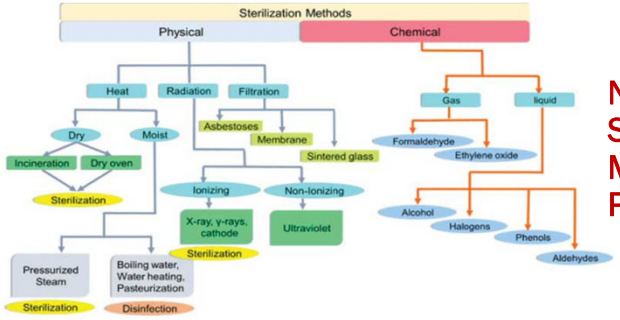
SELECTION OF STERILIZATION METHODS

- Sterilization methods cannot be applied generally!
- Determined by the type of product to be sterilized (radiopharmaceutical preparation, drug, pharmaceutical formulation, medical device...).
- Wherever possible, **terminal sterilization** is chosen!
  Terminal sterilization = process that destroys all viable MO within the final, sealed package.
- If terminal sterilization is not possible, sterilization by filtration and aseptic processing is the only applicable method.

SELECTION OF STERILIZATION METHODS

- **METHODS FOR MO INACTIVATION**
  - **Physical:**
    - Moist heat sterilization (saturated steam under pressure)
    - Dry heat sterilization
    - Ionising radiation sterilization
  - **Chemical:**
    - Gas sterilization
    - Liquid agents
- **METHODS FOR MO REMOVAL**
  - Membrane filtration
- **ASEPTIC PREPARATION**



NOT ALL STERILIZATION METHODS ARE PHARMACOPOEIAL!

PH.EUR. – STERILIZATION METHODS

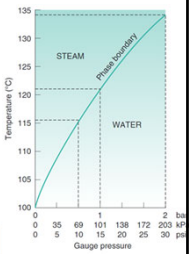
- Steam sterilization (heating in an autoclave)
- Dry heat sterilization
- Ionising radiation sterilization
- Gas sterilization
- Filtration
- Aseptic preparation

„Sterilization may be carried out by one of these methods. Modifications or combinations of these methods may be used, provided that the chosen procedure is validated both with respect to its effectiveness and the integrity of the products including its container or package."

STEAM STERILIZATION - AUTOCLAVING

- The most reliable method for killing MO!
- Sterilizing agent = moist heat in the form of **saturated steam under pressure**
- The effectiveness of **saturated steam:**
  - Large proportion of its heat energy in the form of latent heat ➡ immediate release at condensation by the contact with the cool surface of the load.
  - Rapid penetration of steam (particularly important for porous materials).

Pressure Bar	Temperature °C	Spec. heat KJ/Kg	Latent heat KJ/Kg	Latent heat %
1,7	115	483	2216	82
2,0	121	505	2202	81
2,4	126	530	2185	80
3,0	134	561	2164	79



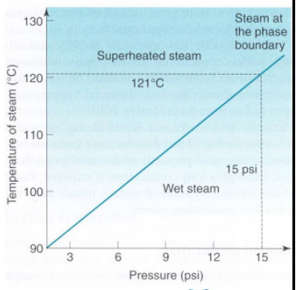
STEAM STERILIZATION - AUTOCLAVING

Superheated steam = steam not in equilibrium with its source

- Steam is heated out of contact with water at constant pressure or if pressure is reduced at constant temperature
- It has the same efficiency at transferring heat, penetrating the load and destroying MO as hot air at the same temperature!

Wet saturated steam = steam containing droplets (water fog) produced by secondary cooling.

- The same lethal properties as dry saturated steam but reduced condensation resulting in less available latent heat.



STEAM STERILIZATION KINETICS - D VALUE

D value = a measure of the thermal resistance of MO.

- It indicates the time in minutes required to destroy 90% of the original number of MO at a given T.

$$\log \frac{N_0}{N} = k \circ (t - t_0)$$

N_0: inital number of MO
N: number of MO after the exposure time t.
k: first order reaction coefficient
T_0: 0

D= -1/k (min)

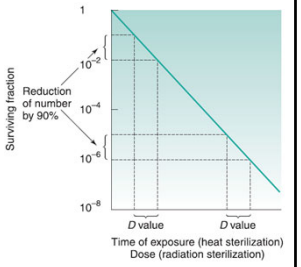


Fig. 16.1 • Calculation of the *D* value. Note that the *D* value remains the same although it is calculated with different surviving fractions.

EFFECT OF DIFFERENT D VALUES ON THE STERILIZATION PROCESS

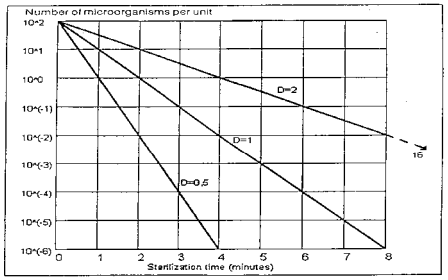


Fig 2. Effect of varying D values on sterilization rate (courtesy, Fedegari Autoclavi).

- Depends on the type and the initial number of MO!

Typical for the species and the conditions of the chosen MO!

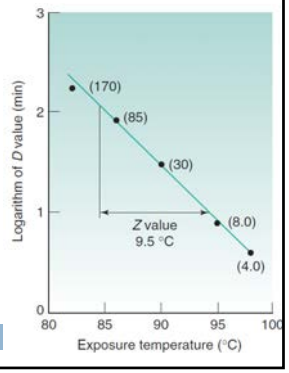
Example: $D_{121} = 5$ ⇨ for a 90% reduction of MO at T=121°C we need 5 minutes.

EFFECT OF TEMPERATURE CHANGES - Z VALUE

- **Z value =** the temperature (°C) that must be increased to reduce the D value by a factor of 10, for a specific MO.
- *(The number of degrees of temperature which causes a 10-fold variation of D).*

- **Evaluation of sterilization process** - relates a change in temperature to a change in the MO mortality rate.
- It is assumed to be equal to 10 in absence of more precise experimental data.

Example: D value for Geobacillus stearothermophilus spores at 110 °C is 20 min and they have a Z value of 9 °C, this means that at 119 °C the D value would be 2.0 min and at 128 °C the D value would be 0.20 min.



AUTOCLAVES

The design of autoclaves must ensure:

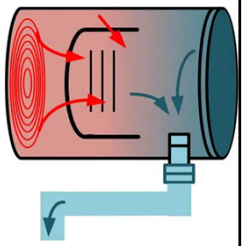
- ❑ permeation of the load with dry saturated steam;
- ❑ minimal formation of superheated steam;
- ❑ elimination of air both from the chamber and from porous material.

AUTOCLAVE TYPES

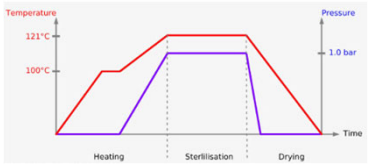
1. **Gravity displacement autoclave**
2. **High vacuum autoclave**
3. **Air ballasted autoclaves**
4. **Spray cooled autoclaves**

GRAVITY DISPLACEMENT AUTOCLAVES

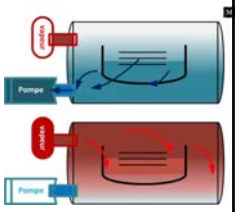
- Steam is generated externally at high pressure and reduced via reducing valves to the autoclave pressure.
- Admit to the top of the chamber via baffle.
- Air is displaced downwards via a drain due to higher density.
- Content is cooled to zero gauge pressure and air is admitted via bacteria proof filter.



Drawback: Due to the lack of a vacuum phase, autoclaves cannot effectively sterilize porous loads or items packed in layers. They also cannot ensure the sterilization of items with hollow sections or lumens.



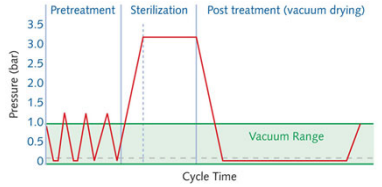
HIGH VACUUM AUTOCLAVES



Operation

- Air is removed by vacuum pressure.
- Prevacuum stage: air is removed by the evacuation of the heated chamber to about 15 mmHg of absolute pressure followed by continuous application of vacuum (**Dynamic**) or by alternate steam injection and evacuation (**Pulsing**).
- Post vacuum stage: steam is quickly removed by evacuation to about 50 mm Hg.
- Sterile air is then admitted until the atmospheric pressure is reached.

ADVANTAGE:
By evacuating the ambient air within the chamber, saturated steam can penetrate and sterilize areas otherwise occupied by air. This mechanism is particularly efficient for sterilizing items with hard-to-reach areas (porous material).



AUTOCLAVES

Air ballasted autoclaves

- ❑Compensation of the pressure drop at the end of the sterilization by introducing warm sterile air.
- ❑Reduction of softening the plastic and distortion of the containers during the pressure drop.

Spray cooled autoclaves

- ❑To reduce the cooling time, specially if there is a large load of bottle fluids, by spraying fine mist of distilled water droplets.
- ❑Breakage of bottles is minimized (if droplets are sufficiently small).

CRITICAL POINTS OF STEAM STERILIZATION

1. Removal of the initial air from the chamber
2. Superheated steam
3. Steam Quality (presence of wet saturated steam)
4. Cooling of the chamber contents after sterilization

STEAM STERILIZATION – PH.EUR.

- Sterilization by saturated steam under pressure is preferred, wherever applicable, especially for aqueous preparations.

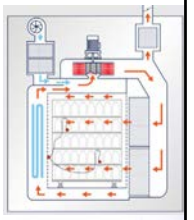
Reference conditions:
- heating at a minimum of **121°C** for **15 min** at **2 bar**
- other combinations of time and T may be used

Process	Minimum temperature (°C)	Minimum holding period (min)
Steam sterilization (autoclaving)	115	30
	121	15
	126	10
	134	3

- The procedures and precautions employed are such as to give SAL of 10^{-6} or better.

Mechanism of MO destruction: Denaturation of critical proteins and nucleic acids by disruption of H-bonding.

DRY HEAT STERILIZATION



Equipment: Hot-air oven, electrically heated, thermostatically controlled and equipped with a fan or turbo blower for continuous forced air circulation.

Mechanism of heat transfer: Conduction, convection, radiation

Sterilization conditions
- ❑ min. 160 °C for at least 120 min (11th Ph.Eur.),
- ❑ min. 170 °C for at least 60 min,
- ❑ min. 180 °C for at least 30 min,
- ❑ in the sterilization tunnel for only a short time at 300 °C.

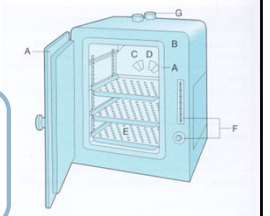
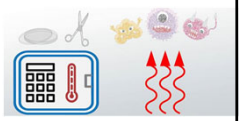


Fig. 18.3 Hot air oven. A. Asbestos gasket; B. outer case containing glass-fibre insulation, and heaters in chamber wall; C. false wall; D. fan; E. perforated shelf; F. regulator; G. vents.

DRY HEAT STERILIZATION



- **T > 220°C** – sterilization and depirogenization
- The procedures and precautions employed are such as to give SAL of 10^{-6} or better.

- Mechanism of MO destruction: non-specific oxidation of the cellular components of MO.
- The process is generally slower and the retention times for dry heat sterilization are much longer than those needed for steam sterilization.

⇩

1g dry air as steam (100°C) ⇨ 1g air (99°C) + 0,995 J/g
1g water as steam (100°C) ⇨ 1g water (liquid) + 2205 J/g

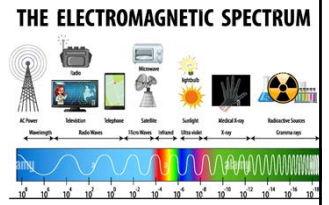
Table 16.1 Time and temperature combinations used for moist and dry heat sterilization

Process	Minimum temperature (°C)	Minimum holding period (min)
Steam sterilization (autoclaving)	115	30
	121	15
	126	10
	134	3
Dry heat	140	180
	150	150
	160	120
	170	60
	180	30

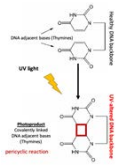
IONISING RADIATION STERILIZATION

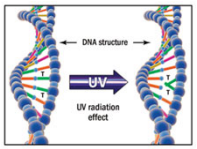
- Non-thermal sterilization method

Types of radiation used for sterilization:
- **Electromagnetic** (UV and gamma)
- **Particulate** (high energy electrons)



UV RADIATION
- 240 - 280nm: bactericidal, but poor penetrating ability
- Use: sterilization of air and water in thin layers





GAMMA IRRADIATION

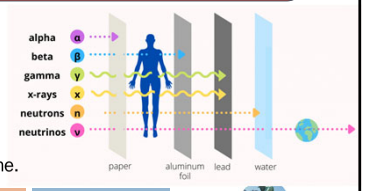
Sources of γ-rays – radioactive isotope of ^{60}Co or ^{137}Cs

^{60}Co – exposing natural Co to neutrons in a reactor

- Radiation consists of two protons and one electron giving a total emission per disintegration of 2,8 MeV
- Half life of 5,3 years
- The intensity of the radiation decreases as it penetrates the material - 10 cm of a product with a density of 1 g/cm^3 reduces the intensity of ^{60}Co by 50%.

^{137}Cs – product of disintegration of uranium

- Half life of 30 years
- Lower energy impute (0.66 MeV)



- High-energy radiation that travels at the speed of light.
- Does not cause radioactivity in the final product.
- Precautions – protection of the environment and the operator.
- Different doses can be administered by varying the exposing time.

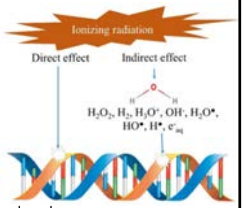
HIGH ELECTRON STERILIZATION

- Acceleration to high energy (5-10 MeV) in electron accelerators.
- At these energy levels electron penetration is satisfactory and problems of induced radiation in the product are minimal.
- The penetration depth of electrons is 1 cm for each MeV of energy when the material density is 1 g/cm^3
- A directional source (controlled by a magnetic field) that can be switched off.
- The dose rate in the electron accelerator is higher than that in the gamma source and sterilizing doses can be achieved very rapidly.

IONISING RADIATION STERILIZATION

Advantages
- Extremely reliable method
- Increase of T is minimal
- Easy to control

Disadvantages
- Degradation in wide variety of materials
- Inappropriate for aqueous solutions



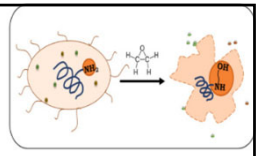
Mechanism of MO destruction:

- **Direct effect:** Destruction of MO due to interactions with the cell nucleus (DNA).
- **Indirect effect:** When the radiation energy is absorbed, electrons and free radicals (hydroxyl, hydrides) are formed in the cytoplasm, which initiate an intensive cascade of chemical reactions that lead to the death of the MO cells.

Protocol for radiation sterilization:

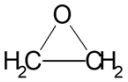
- The accepted sterilization dose is 2.5 Mrad (25 KGy)
  (Gray (Gy) measures the effect of radiation on living tissue (1 Gy = transfer of 1J of energy to 1 kg of living tissue; 1Gy = 100 Rad)
- The effects of radiation are cumulative, the sterilizing dose can be administered in divided doses.

CHEMICAL METHODS GAS STERILIZATION



- **Ethylene oxide**, formaldehyde, hydrogen peroxide, peracetic acid, ozone, chlorine dioxide.
- Ethylene oxide is the only gas successfully used on a large-scale production!
- An alkylating agent, reacts with amino, hydroxyl groups in MO proteins, with purine bases of nucleic acids.
- **Ethylene oxide properties:**
  - Colourless gas at room T with a characteristic ethereal odour;
  - heavier than air;
  - Boiling point: at 11°C

CHEMICAL METHODS
GAS STERILIZATION - Ethylene oxide



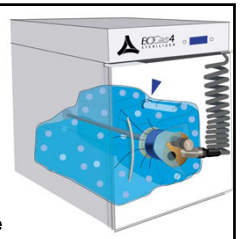
Advantages

- ***Broad application*** - many types of materials can be sterilized (no liquids).
- ***Diffusivity*** (ability of terminal sterilization through packaging material)
- Inactivates a ***wide range of MO*** (including viruses and endospores).

Disadvantages

- ***Toxicity*** – inhalation toxicity (nausea, vomiting), headaches, skin toxicity, carcinogenic, birth defects
- ***Flammability*** – overcome by special mixtures with inert gases such as carbon dioxide (90 % CO_2 in 10 % EtO) or various fluorinated hydrocarbons
- Need for ***correct humidity;***
- ***Explosive;***
- ***Expensive*** (special unit with proper ventilation);
- ***Toxic EtO residues*** and EtO decomposition products (ethylene glycol, ethylene chlorohydrin).

CHEMICAL METHODS
GAS STERILIZATION - Ethylene oxide



Factors affecting sterilization

Relative humidity (RH)

- Water is necessary in alkylation reaction
- It facilitates the transfer of ethylene oxide through polar films
- Range: 33% RH – optimal, **40-60%** - practice

Temperature of sterilization

- **25°- 60°C** - depending on the product with chamber pressure between 14 and 70 Kpa.
- With increasing T exposure time is shorten

Concentration of ethylene oxide

- 450 - 1500 mg/L

Time of exposure

- Slow process (exposure times up to 36 h at lower T)
- Holding times of order of 3h have been used at higher T

Gaseous	Temp.	(°C)	Relative humidity (%)	Holding time	Conc.
Ethylene oxide[5]	40–50	–	40–80	30 min to 10 h	400 mg/L to 1000 mg/L

CHEMICAL METHODS
GAS STERILIZATION - Ethylene oxide

Commercial sterilizers

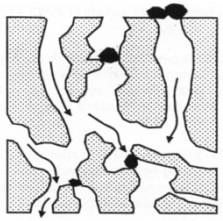
- The toxicity and flammability of EtO must be taken into consideration.
- Heated, gas tight chamber, able to withstand high pressure and vacuum and to provide relative humidity of at least 33%.
- Post sterilization period is required for removal of trace amounts of ethylene oxide.

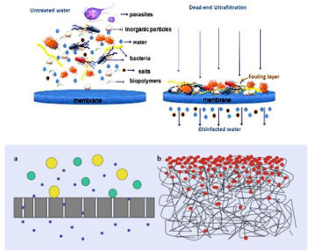
FILTRATION

- Synonyms - microbiological filtration, sterile filtration, membrane filtration
- Use – for thermolabile solutions, heat-sensitive injections and ophthalmic solutions, biological products and air and other gases for supply to aseptic areas.
- Membrane filters - recommended pore size for sterilization: 0.2 - 0.22 µm (not include viruses).
- Always performed under aseptic condition.
- where possible, terminal sterilization processes should be preferred.

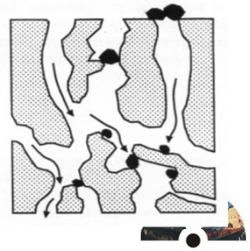
MECHANISMS OF FILTRATION

Sieving





Adsorption and trapping



SELECTION OF STERILIZATION METHODS

It is a balance between

Maximum permissible damage to the product and its packaging!

Maximum acceptable risk of sterility failure!

Where possible, heat sterilisation is the method of choice!

MOIST & DRY HEAT

Use of moist heat sterilization

- Aqueous preparations for parenteral and nonparenteral use
- Natural rubbers
- Many plastics, including PVC and nylon
- Glassware – if unable to withstand dry heat
- Surgical dressing (the high vacuum autoclaves in particular satisfies the essential requirements for total air removal and prevention of excessive condensation)
- Metal instruments – immediate drying required for protection against corrosion

Use of dry heat

- For materials which are damaged by the presence of water (oils, ointments, waxes, powders...)
- Usual method of choice for glassware, syringes, surgical instruments and equipment

NOTE: The mechanisms are different!
Example: The spores of *Bacillus niger* can withstand dry heat 2000 times longer than moist heat at the same T!

RADIATION & ETHYLENE OXIDE

Use of radiation

- For large-scale sterilization of plastic disposable Petri dishes
- Surgical equipment and surgical instruments
- Dressing (particularly adhesive dressings)
- Polyethylene containers
- Packing material using aluminium foil and plastic films.

Use of ethylene oxide

- For thermolabile powders, some plastics and rubbers, surgical instruments, (bronchoscopes, cytoscopes, surgical dressings, woollen blankets, etc.
- Ethylene oxide is highly reactive - care should be taken to ensure that no toxic reaction products are formed during sterilization.
- Reliability is questionable (the critical conditions required and the difficulties in monitoring these conditions).

The method is only recommended where more reliable methods are not practicable!

SELECTION OF STERILIZATION METHODS

If terminal sterilization by one of the methods described above is not possible, sterilization by **filtration and aseptic procedure** are the only applicable methods.

QUALITY ASSURANCE IN STERILIZATION PRACTISE

- ✓ Sterility cannot be instilled into the product at the end of the manufacturing process, but must be planned in at every stage of the process!
- ✓ Ph.Eur.: "The sterility of the product cannot be guaranteed by testing; it has to be assured by the application of suitably validated methods."

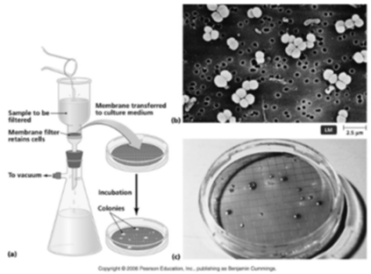
The principles of GMP must be considered:

- Qualified personnel with appropriate training
- Adequate premises
- Suitable production equipment, designed for easy cleaning and sterilization
- Adequate precautions to minimise the bioburden prior to sterilization
- Validated procedure for all critical production steps
- Environmental monitoring and in-process testing procedures

CONTROL OF STERILISATION PROCESS EFFICIENCY

In-process control

Product control (sterility test)



CONTROL OF STERILISATION PROCESS EFFICIENCY

Parametric batch release	Batch release based on sterility test
• Fully validated procedure • monitoring of in-process conditions (T, pressure, relative humidity, radiation dose) • chemical and biological indicators	• Despite the monitoring of the conditions during the process, a sterility test is performed on a suitable sample at the end of each batch of product
Steam sterilization Dry sterilization Ionising radiation sterilization	Gas sterilization

STERILIZATION CONTROL
IN-PROCESS CONTROL

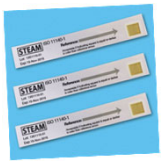
Physical measurements
Recording temperature, pressure and relative humidity.
All instrument must be calibrated, well maintained and regularly checked.

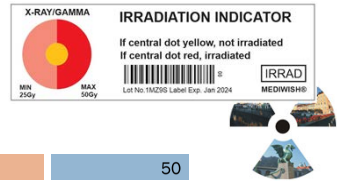
Chemical indicators

Biological indicators

STERILIZATION CONTROL
Chemical indicators

- Chemicals able to change their physical or chemical characteristics if sterilization conditions have been reached.
- We demonstrate that we have achieved sterilization conditions, but they do not confirm the sterility of the product.





STERILIZATION CONTROL
Chemical indicators

- **Browne's tubes** - for heat process; small sealed tubes containing reaction mixture and indicator. Exposure to high T completes reaction producing a change of colour of indicator. Colour change is caused by moist and dry heat – no indication about superheating by autoclaving.
- **Crystal indicators** - crystals that melt at sterilization T. No information about time of exposure and equally affected by moist and dry heat.
- **Heat sensitive tapes** – used in Bowie-Dick test (test to determine the removal of air from porous load).
- **Royse sachet** - for EtO sterilization. Polyethene sachet with reaction mixture ($MgCl_2$, HCl) and indicator. If given conditions are reached formation of ethylene chlorohydrine changes the colour of the indicator.
- **Chemical dosimeters** – accurate measure of the radiation dose absorbed. Polymethyl methacrylate or nylon polyvinyl chloride in the form of slide which are able to spectrophotometrically detected optical density changes induced by radiation.

STERILIZATION CONTROL
Biological indicators

- ✓ Measure sterilization process directly and are able to integrate all sterilization parameters.
- ✓ Standardized preparations of selected MOs for demonstrating sterilization efficacy.
- ✓ The choice of MO type is based on the type of sterilization
- ✓ Must have a sufficiently high D value (resistance) for the given procedure, compared to other MOs.

The selected MO as biological indicator must:
- Posses high & reproducible resistance to the sterilizing agent
- be genetically stable
- be readily characterized
- be easy for cultivation and
- be Non-pathogenic
- be available in form similar to the sterilized item or alternatively, the product itself could be used as suspending medium.

STERILIZATION CONTROL
Biological indicators – Ph.Eur.

STEAM STERILIZATION
- Spores of *Bacillus stearothermophilus*
- D value at 121°C exceeds 1.5 min
- No growth of MO after the exposure to a steam at 121±1°C for 15 min.

DRY HEAT STERILIZATION
- Spores of *Bacilus subtilis*
- D value at 160°C = app. 1 - 3 min

IONISING RADIATION STERILIZATION
- Spores of *Bacilus pumilus*
- D vales exceeds 1.9 kGY
- No growth of MO after the exposure to 25kGy

GAS STERILIZATION
- Spores of *Bacillus subtilis* (EtO sterilization)
- D value exceeds 2,5 min for test cycle involving 600 mg/L EtO, at 54°C and 60 % relative humidity
- No growth of MO after the exposure to test cycle described above for 60 min and to a reduced temperature cycle (600 mg/L EtO, at 30

LITERATURE

1. **Michael E. Aulton, Kevin M. G. Taylor: Aulton's Pharmaceutics**
   Chapter 15: Action of physical and chemica agents on mikroorganisms
   Chapter 16: Principles of sterilization
   Chapter 17: Sterilization in practice
2. **European Pharmacopoeia (Ph. Eur.) 11th edition**
3. **Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use,** Annex 1, Manufacture of Sterile Medicinal Products

Particulate contamination

Prof. Rok Dreu, PhD, M. Pharm., University of Ljubljana, Faculty of Pharmacy, The Chair of Pharmaceutical Technology, has studied pharmacy at Faculty of Pharmacy, University of Ljubljana, where he has graduated in year 2000 and has achieved PhD in pharmaceutical sciences in 2005. His research work is mainly focused on FBD particle coating, mechanics of powder compression, surface free energy of solids and hot-melt technologies. In collaboration with Laboratory of fluid dynamics and thermodynamics at Faculty of Mechanical Engineering he is also involved in study of two-phase flow within Wurster coating chamber and in development of two-phase flow simulation using CFD tools. As professor for field of pharmaceutical technology he is involved in lecturing and practical work at courses of: Industrial pharmacy (Uniform master's study programme Pharmacy), Pharmaceutical technology, Pharmaceutical engineering and Pharmaceutical process equipment (Master's study programme Industrial Pharmacy). He is acting vice-dean for scientific research. He is the current Dean of Faculty of Pharmacy.

The lecture has the following learning objectives:

1. Students are able to identify, describe particle contamination within parenteral dosage forms as defined within Ph.Eur. and USP monographs and interpret used terminology.
2. Students are able to generalise, weather particulate contamination requirements are compulsory for radiopharmaceutical preparations.
3. Students are able to describe, how to perform analysis of sample for presence of sub-visible particles and interpret the results according to harmonized Ph. Eur. monograph 2.9.19. Particulate contamination: sub-visible particles.
4. Students are able to describe, how to perform analysis of sample for presence of visible particles and interpret the results according to Ph. Eur. monograph 2.9.20. Particulate contamination: visible particles.
5. Students are able to predict potential sources of particulate contamination and explain the hazardous nature of particulate contaminants.

Summary of the lecture:

Abstract

Particulate contamination presents additional, unnecessary hazard to the patient and should be excluded from parenteral preparations at all costs. Absence of particulate matter within parenteral preparations is also mandatory from regulatory point of view. Although methodology for determining the potential presence of visible and sub-visible particulate matter is clearly set forward by the monographs in Pharmacopoeias (Ph.Eur., USP), it must

be stressed that no other quality control test, parenteral or non-parenteral, presents more difficulties for quality control specialists than inspection and analysis of injectable solutions for the presence of particulate matter. While quality control will define the state of product, it will however not assure its quality. In order to fulfil the quality requirements in repeatable manner one has to know potential sources of particulate burden and should select materials, plan production procedure and control environment conditions accordingly. This course chapter is oriented towards identification of particulate contamination, use of specific terminology, clear presentation of officinal tests for visible and sub-visible particles with interpretation of results and should inform the student with regard to the nature and sources of particulate contamination, with additional comment to particulate behaviour in human body and specifics, related to radiopharmaceutical preparations.

Introduction

Particulate contamination of parenteral dosage forms (injections and infusions) is consisted of randomly-sourced, extraneous, mobile particulate matter which is unintentionally present in the solutions of parenteral product. Due to its heterogeneous composition and small amount of material it cannot be quantitated analytically. Despite the general definition, particulate burden can also stem from dosage form intrinsic sources, such as rubber, glass, metal and plastic particles coming from product contact surfaces with primary packaging or administration sets and devices, as well as a consequence of precipitation reactions that occur in the product over time. However, in the latter cases this causes a more uniform source of particles and leads to the true contamination of product. Such contamination can be controlled by appropriate control of production process, careful selection and quality control of packaging material and rational development of robust dosage forms and as such should be diminished by manufacturer and health personnel at any cost. The only acceptable particle burden from the quality control point of view is that, composed of species present in random numbers, i.e. no sharp particle size distribution peak is present when analysed for particle size distribution, polydispersity is the key. Particulate burden is introduced to the product during the stages of product manufacturing, during extemporaneous compounding and during drug administration. Common sources of particulate matter during parenteral product manufacturing are: air, room surfaces, processing equipment with moving parts and high attrition spots, people, protection clothing and product filters. Particulate contamination is, although unwanted, unavoidable to a certain degree. Natural state of particle size distribution within air is such that we can expect linear direct inverse relationship between the logarithm of the particle size and the logarithm of the cumulative number of particles per unit volume. This means that number of particles increases exponentially with decrease in particle size and furthermore that we can extrapolate the number of particulate burden in air at any size by knowing the concentration of particles at certain size level. Ph.Eur. and USP monographs demand low parenteral product particle burdens and are oriented towards number of particles in a certain product volume (number concentration) equal and above the sizes of 10 and 25 microns as well as above 50 microns

range. Such demands can only be met with use of aseptic manufacturing and clean room design of production site. Manufacturing steps, where parenteral product is directly exposed to surrounding are therefore conducted in clean room of class A in order to meet regulatory quality specifications. The laminar air flow regime of class A is a key as already turbulently ventilated room of class B is not sufficient to meet the requirements. The main reason for that is that diminished number of personnel together with protective clothing poses particle generation source of such frequency that generated particles cannot be diluted and effectively rinsed by the otherwise directional flow of air in the class B clean room design. Alternative to laminar air flow cabinets is technology of isolators and restricted access barrier systems (RABS). Although pharmacopoeia defines the way of quality control testing with regard to acceptable parenteral product (injections, infusions) particulate burden, it is of utter importance to understand that only rigorous quality control testing will not assure the needed product quality. The only way to achieve expected results from particle contamination point of view and to just confirm reasonable expectations by quality testing is careful design of manufacturing process together with personnel clothing and behaviour, altogether having maximal reduction of possible contamination sources in mind.

Particulate burden – does it matter

Without doubt a lot of effort and careful planning is needed in order to limit parenteral product contamination to acceptable limits, but what are the practical implications of particle contamination quality specifications with regard to particulate matter health hazard? Physiological effects and particulate hazard to the patient can be divided into occlusion effect in which parenterally introduced particles may block blood vessels and cause tissue ischemia or can potentially provoke foreign body reaction, as particles interact with cells of the reticuloendothelial system (RES). The RES removes particles between 1 and 10 µm in diameter. Most injected particles between 5 and 15 µm tend to be trapped in the capillary beds of the lung, and less in the spleen and liver. Once trapped in the lung, there appears to be a mechanism for the particles to pass through the capillary walls to be ultimately excreted in the sputum. Interestingly, it was demonstrated that the larger particles are being removed more rapidly. Some particles will cause an inflammatory response and can even be potentially carcinogenic. Certain types of particulate matter such as talc, cellulose or asbestos particles, and cotton fibres are highly undesirable. These should be minimized or avoided altogether by careful control of the manufacturing procedures. It is known that acute over dosage of particulate has resulted in death, but chronic effects of intravenous particulate matter are poorly documented. The size, number, rate of introduction and type of particle entering the bloodstream will all contribute to what harm if any particles are actually produced. Regulatory bodies are focused on particle burden above 10 microns in size. The blood vessel occlusion problem occurs, if many large particles are introduced in a short period of time. This diminishes the tissue capability to compensate particulate burden, as all of the collateral perfusion pathways may be blocked in such case. The health condition of the person receiving solutions containing particulate matter matters

greatly with respect to potential harm of introduced particles. It was demonstrated that clinical effects of the particulate burden were significantly different for intact tissue when compared to ischemic muscle tissue. These findings suggest that particle contaminants may not pose a major threat in intact tissue, but may severely endanger tissue perfusion in patients with prior microvascular compromise of vital organs (i.e., after trauma, major surgery, or sepsis) and thus predispose to complications such as acute respiratory distress syndrome or multiple organ failure. In case of patients that received large volumes of intravenous fluid, postoperative pulmonary infarction could be due to particulate thrombosis.

Regulatory requirements, testing methodology and interpretation of results

Ph. Eur. and USP have harmonized the definition of particulate contamination and procedures of particulate contamination analysis. Ph. Eur. monograph on Parenteral preparations: Solutions for injection and infusion (also solutions suspended from Powders for injections or infusions) states that all parenteral units are examined under suitable conditions of visibility (visual inspection) and should be clear and practically free from particles. Inspection process is supported by another monograph requirement that product container must be transparent. The interpretation of the requirement “practically free from particles” refers to the lot (batch) of the product. The visual inspection process is designed and qualified to ensure that every lot of parenteral preparations is practically free from visible particles. Inspection procedure for visible particles is defined in Ph. Eur. Monograph **2.9.20 Particulate contamination: visible particles**. Every container whose contents show evidence of visible particulates is rejected. Acceptable quality levels - AQL (highest percentage of rejected product) are from 0.25 % to 1.0 % of rejection rate within the batch, otherwise rejection or resorting of the whole batch follows. The percentage of AQL is upon the subjective judgement of inspector. High product rejection rate leads to conclusion that manufacturing process is poorly designed and must be answered by process inspection and redesign. Monograph on parenteral preparations also states that solutions for infusions or injections should comply with the test **2.9.19 Particulate contamination: sub-visible particles**. Additionally it defines, that preparations for which the label states that the product is to be used with a final filter are exempt from sub-visible particle test requirements, provided that it has been demonstrated that the filter delivers a solution that complies with the test. Radiopharmaceutical preparations are exempt from sub-visible particle test requirement.

Particulate contamination: visible particles test can be summarized in a way that every parenteral unit is manually inspected in front of black and white background, while gently swirling or inverting the container. Every unit is observed in time span of 5 s for presence of any particle. If particles are detected, presence is recorded and the contaminated unit is discarded. Every unit in a batch is inspected. Effectiveness of the method relies on the capability of the viewer, the size of the target and the contrast of the target against the

viewing background. Particles of 50 microns or larger diameter can be detected by visual inspection. Human factors that influence the inspection process include: actual visual acuity, aptitude, fatigue, environment, intensity of illumination and inspection speed. Manual inspection method can be improved by the use of a semi-automatic procedure (machine). Such inspection is four to five times faster than the manual inspection procedure. At the point of the inspection, equipped with a magnifying glass, the sample is automatically stopped and the inertia is causing the particles to move within the liquid. The decision with regard to the unit adequateness is still operator dependant and relies on operator skills. Manual inspection procedures can also be replaced by completely automated visual procedures. By use of different sources of illumination inspection machines can detect particles with different optical properties. The confirmation of particle presence can base on the light obscuration principle. Additionally, image analysis can provide information with the regard to container defects and filling volume. The probability of removing inadequate unit by automated process must be comparable to the classical method by human vision.

Particulate contamination: sub-visible particles test can be carried by application of two interchangeable methods. Regardless of the used method, the test is always carried out under conditions limiting particulate contamination, preferably in a laminar-flow cabinet. Appropriate examining conditions are demonstrated by simulating the testing procedure and replacing the sample with the particle-free water R. Number of tested product samples depends on the product batch size and selected AQL.

Method 1 is an automated light obscuration test, which is applied preferably, unless a product possess reduced clarity, increased viscosity or is prone to production of gas bubbles. Light obscuration method relies on the particle casting shadow on a photodetector while moving along the measurement cell together with fluid flow. The change in the base-line signal from the light-obscuration counter is a function of the cross-sectional area of the particle in the beam. The size of the particle is calculated out of AUC (area under the curve), assuming that we are facing a spherical particle. The method is recording the number of particles according to size. Inspected sample complies with the requirement if sample V > 100 mL and resulting concentration is $\leq$ 25 particles/mL $\geq$ 10 μm and also $\leq$ 3 particles/mL $\geq$ 25 μm, or if sample V $\leq$ 100 mL and resulting concentration is $\leq$ 6000particles /container $\geq$10 μm and also $\leq$ 600 particles/container $\geq$ 25 μm.

Method 2 is a microscopic particle count test. The sample is filtered with an application of vacuum and a membrane filter and then left on air to dry. Particles of certain size classes are counted under the microscope with the calibrated ocular micrometer and a mechanical stage for holding and transversing the entire examination area of the filter. Counting procedure is traditionally conducted manually but can be also replaced by automated microscopic analytical systems consisted of an automated microscope and image analysis system. Inspected sample complies with the requirement if sample V > 100 mL and resulting concentration is $\leq$ 12 particles/mL $\geq$ 10 μm and also $\leq$ 2 particles/mL $\geq$ 25 μm, or if sample V

≤ 100 mL and resulting concentration is ≤ 3000 particles /container ≥10 μm and also ≤ 300 particles/container ≥ 25 μm.

Specifics of radiopharmaceuticals

Parenteral radiopharmaceuticals must comply with the Particulate contamination: visible particles test. Although radiopharmaceuticals are exempt from Particulate contamination: sub-visible particles test requirements in Ph. Eur., USP is not quoting such exemption. Sub-visible particles concentration in radiopharmaceuticals can be after extemporaneous compounding decreased by final filtration, using a membrane filter with a pore size of 0.22 μm. Such filter is otherwise used for preparation of particle-free water R from purified water. Additionally, the whole procedure of radiopharmaceuticals preparation could be simulated and validated for presence of sub-visible particles with use of nonradioactive aqueous test solution or particle-free water.

Take home messages:

- Absence of visible and sub-visible particles is mandatory for parenteral preparations and can be tested by use of harmonized analytical procedures.
- Testing of individual units for particulate contaminants represents only quality control and cannot replace quality assurance activities.
- Particulate contamination (visible or invisible) of parenteral preparations should be avoided by careful selection of materials, planning of production procedure and by controlling environment conditions.
- Sub-visible particle testing of radiopharmaceutical preparations is not viable on small scale production, while presence of visible particles can be assessed. Membrane filtration techniques prior to administration can be practical solution of the problem.
- Presence of particulate contaminants in parenteral preparations presents serious health hazard for the patient.

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PARTICULATE CONTAMINATION

PHARMACEUTICAL TECHNOLOGY
PARENTERAL DOSAGE FORMS AND TESTING

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Ljubljana, 2021

INTRODUCTION

INTRODUCTION

No quality control test, parenteral or nonparenteral, presents more difficulties for quality control specialists than inspection and analysis of injectable solutions for the presence of foreign particulate matter. The oldest, yet most commonly used, test for particulate matter evaluation involves human visual examination. Such examination is subjective, time consuming, and limited in the types of parenteral products and containers that can be inspected. This has stimulated many studies regarding ways of not only improving efficiency of human inspection, but also developing and improving methods of detecting particulate matter electronically.

The U.S. Pharmacopeia (USP) requirement for injectable products specifies that "each final container of injection be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents show evidence of contamination with visible foreign material be rejected" (1). Additional specifications are required for subvisible particulate matter content and analysis in large-volume injections (LVIs) for single-dose infusion and in small-volume parenterals (2).

The European Pharmacopeia (EP) contains sections on subvisible particulate contamination and visible particulate contamination (3).

Why are injectable solution products to be free of visible evidence of particulate matter? Primarily, lack of particulate matter conveys a clean, quality product, indicative of the high-quality standards employed by the product manufacturer. Moreover, in recent years, particulate matter has become known as a potential hazard to the safety of the patient undergoing parenteral therapy. While there still seems to be a lack of sufficient clinical data to incriminate particles as producers of significant clinical complications during parenteral therapy, it is a universal belief in the health care field that particulate matter does present a clinical hazard and must be absent from the injectable solution.

Akers, Larrimore, Guazzo. Parenteral quality control – sterility,pyrogen, particulate, and package integrity testing 3th Ed., Marcel Dekker, 2003.

INTRODUCTION

- **Ph. Eur. 9th Ed.: Particulate contamination of injections and infusions consists of extraneous, mobile undissolved particles, other than gas bubbles, *unintentionally present* in the solutions.**
- **USP30**: Particulate matter consists of mobile, randomly-sourced, extraneous substances, other than gas bubbles, that cannot be quantitated by chemical analysis due to the small amount of material that it represents and to its heterogenous composition.
  (definition was harmonized in 2007)
- Particulate is insoluble material *inadvertently* left in an injectable product during manufacture (*enviroment, equipment, personel, packaging components = container-closure system),* during extemporaneous coumpounding and drug administration *(sets and devices for administration).*

UNDESIRABLE, UNWANTED MOBILE INSOLUBLE MATTER OF VARIABLE COMPOSITION.

PARTICULATE CONTAMINATION IN PARENTERAL SOLUTIONS

Ph. Eur. 9th Ed.:

- **Monograph on Parenteral preparations:** Solutions for injection and infusion (solutions suspended from Powders for injections or infusions), examined under suitable conditions of visibility, are clear and practically free from particles.
- Injectable solutions are required to be clear and practically free from particles that can be observed on visual inspection (visible particles).
  Particulate contamination: Visible particles test is not clearly quoted in the **Parenteral preparations** monograph but the **requirement** for container transparency due to visual inspection also exist.
- Solutions for infusion or injection should comply with the test **Particulate contamination: sub-visible particles.** Radiopharmaceutical preparations are exempt from these requirements.
  Preparations for which the label states that the product is to be used with a final filter are exempt from these requirements, providing it has been demonstrated that the filter delivers a solution that complies with the test.

REMARK: Sub-visible particles concentration in radiopharmaceuticals after extemporaneous coumponding could be decreased by final filtration.

PARTICULATE CONTAMINATION IN PARENTERAL SOLUTIONS

USP 39:

- **Monograph on INJECTIONS:** All articles intended for parenteral administration shall be prepared in a manner designed to exclude particulate matter as defined in **Particulate Matter in Injections** and other foreign matter.

  Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter ("visible particulates") in its contents. Every container whose contents shows evidence of visible particulates shall be rejected.

  All LVI and SVI are subject to the light obscuration or microscopic procedures and limits for subvisible particulate matter set forth in **Particulate Matter in Injections,** unless otherwise specified in the individual monograph. Radiopharmaceutical preparations are not specifically exempt from requirements in **Particulate Matter in Injections**.

  Constituted solutions: Particulate Matter - Constitute the solution as directed in the labeling supplied by the manufacturer of the sterile dry dosage form: the solution is essentially free from particles of foreign matter that can be observed on visual inspection.

PARTICULATE CONTAMINATION IN PARENTERAL SOLUTIONS

Encyclopedia of Pharmaceutical Technology (3rd ed.):

- **Monograph on Drug Delivery: Parenteral Route:**
  Most radioactive agents are produced to be used within hours of preparation because of the very short half-lives of the radioactive element. As with other sterile dosage forms, diagnostic agent products are to be sterile, pyrogen-free, and particulate free.

REMARK: Particulate free requirement can be (due to practical reasons) tested for presence of visible particles. Subvisible particles could be tested via light obscuration method but there is problem in the volume of injection (sample) as Pharmacopeia assumes mass production of the parenteral preparations.

Methods, equipment, containers, enviroment and personal protection should therefore be chosen in such a way that particulate contamination risk is minimized. The whole procedure of radiopharmaceutics preparation could be simulated and validated for presence of subvisible particles with use of nonradioactive aqueous test solution or particle-free water.

NATURE AND ORIGINS OF PARTICULATE MATTER

- INTRINSIC CONTAMINATION
  - Materials originally present in the solution, not removed by filtration stages of manufacture prior to filling.
  - Materials left on the final container and its seal, not removed by the washing process.

Cellulose, cotton fibers, rubber, glass, plastic fragments, metal particles, rust, dandruff, sand, undissolved chemicals, asbestos, starch, talc, clay, lubricating and machine oil, plasticizer and silicon oil droplets, insect parts, fungi, bacteria and bacterial fragments, viruses, human skin flakes.

- EXTRINSIC CONTAMINATION
  - Materials from environment falling into the product and its container during preparation (the filling operation).
    - Rubber, metal and plastic particles coming from product contact surfaces.
    - Administration sets and devices.
    - Aging of the glass surface.
    - Elastomeric stoppers.
    - Precipitation reactions that occur in the product over the time.

COMMON SOURCES OF PARTICULATE MATTER

1. Chemicals: a. Undissolved substances,
b. Trace contaminants

2. Solvent impurities

3. Packaging components: a. Glass, b. Plastic, c. Rubber, d. Intravenous applicators

4. Environmental contaminants: a. Air, b. Surfaces, c. Insect parts

5. Processing equipment: a. Glass, b. Stainless steel, c. Rubber, d. Rust

6. Filter fibers

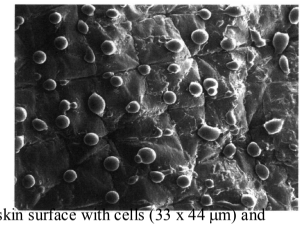
7. People: a. Skin, b. Hair, c. Gowning

ASSURING PARTICLE FREE CONDITIONS

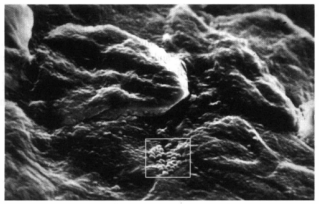
Personnel:

Behavior of the staff is very important for aseptic preparation procedures as people represent the largest source of contamination in aseptic manufacturing. Adequately dressed person is still generating 10^6 particles/min $\geq$ 0,5 µm, 150.000 particles/min $\geq$ 5 µm and 16 particles/min, which are carrying microorganisms.

Therefore clean rooms should be occupied by minimum number of people at all times. People should be trained and should comply to strict rules of hygiene and cleanliness, wear prescribed clothing and act according to prescribed rules of conduct.



- skin surface with cells (33 x 44 µm) and droplets of sweat; 10^9 cells are released per a day

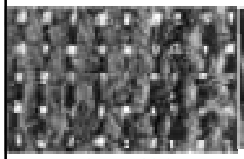


- microcolony of bacteria on skin surface

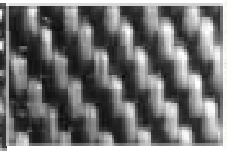
ASSURING PARTICLE FREE CONDITIONS

Prescribed clothing for personnel working in clean rooms:

- class D: one should wear basic protecting clothing and suitable shoes. Hair and beard are covered.
- class C: one should wear special protecting clothing that are not generating fibers and other particles. Hair and beard are covered.
- class A and B: one should wear special sterilized protecting clothing that are no not generating fibers and other particles. Hair and beard are covered completely. One should wear face mask and goggles, sterilized gloves without talc and sterilized shoe overcoats.



- structure of cotton fabric; large voids (100 µm) can be seen, fabric is generating fibers



- structure of fabric suitable for protective clothing in clean rooms; small voids and ordered structure of fibers

a) clothing for classes C or D
b) clothing for classes A or B
c) clothing for class A

COMMON SOURCES OF PARTICULATE MATTER

- Potential source of particulate contamination is extemporaneous compounding in a pharmacy – pharmacist, doctor or nurse can inadvertently put particulate back into the product by poor practice and manipulation.

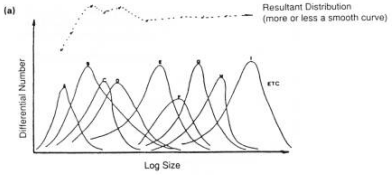
Due to many sources and routes of contamination, particle contamination is by its nature:

inadvertent and almost inevitable.

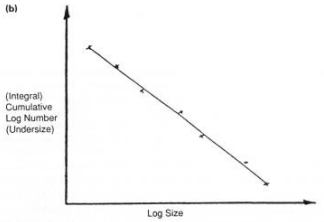
→Testing = **QC**!

SIZE, NUMBER AND SIZE DISTRIBUTION OF CONTAMINATING PARTICLES

- ✓ Ideally, from a QC point of view, each species should be present in random numbers.
- ✓ **If one dominating species is present, then the product is truly contaminated.**



- Cumulative numbers of particles per unit volume (Y)
- Particle diameter (X)
- Log-log
- Direct inverse relationship



METHODS FOR DETECTING AND COUNTING PARTICULATE MATTER

Ph. Eur. 9th Ed.: General chapters: Methods of analysis

- **2.9.19.** Particulate contamination: sub-visible particles
  1. Light obscuration particle count test
  2. Microscopic particle count test
- **2.9.20.** Particulate contamination: visible particles

PARTICULATE CONTAMINATION: SUB-VISIBLE PARTICLES

Ph. Eur. 9th Ed.: 2.9.19. Particulate contamination: sub-visible particles

- Method 1 is preferably applied
- When: reduced clarity, increased viscosity → Method 2
- Products that produce gas bubbles → Method 2

1. Light obscuration particle count test
2. Microscopic particle count test

The tests are carried out under conditions limiting particulate contamination, preferably in a laminar-flow cabinet.

Use the *particle-free water R*!

PARTICULATE CONTAMINATION: SUB-VISIBLE PARTICLES → method 1

Ph. Eur. 9th Ed.:Light obscuration particle count test

Automatic determination of the size of particles and number of particles according to size!

Method

•LVP and SVP > 25 mL → single units are tested

•SVP < 25 mL → more units: V not less than 25 mL

•Appropriate sampling plan

•Remove 4 portions: V not less than 5 mL (1st portion disregard) → calculate the mean number of particles

Evaluation

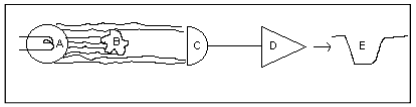
•Test 1A (V > 100 mL) → (≤ 25/mL ≥10 µm) ∧ (≤ 3/mL ≥ 25 µm)

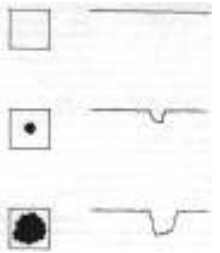
•Test 1B (V ≤ 100 mL) → (≤ 6000/container ≥10 µm) ∧ (≤ 600/container ≥ 25 µm)

LIGHT-OBSCURATION INSTRUMENTS

- Principle

A) Light source
B) Particle – casting a shadow on
C) Photodetector
D) Amplifier
E) Shadow reduced signal produced by photodetector





The change in base-line signal from light-obscuration counter as a function of the cross-sectional area of the particle in the beam.

LIGHT-OBSCURATION INSTRUMENTS

Light obscuration particle counter
KL-04
Rion Co., Ltd.

■Specifications

Detection principle	Light-obscuration method
Light source	Laser diode (wavelength: 780 nm, max. rated output: 3 mW)
Laser product classification	Class 1, IEC 60825-1: 2001
Light detector	PIN type photodiodes
Materials of component parts exposed to sample fluid	
Sampling tube	PFA (SUS304 available as option)
Sensor area	Synthetic quartz, PFA, perfluoro
Syringe pump	Borosilicate glass, Kel-F (PCTFE), PTFE, PFA
Tube/packing/connector	PTFE, PCTFE
Sample container plate	Polyacetal
Calibration	Using polystyrene latex (PSL) particles (refractive index 1.6) in pure water
Measurable particle size range	1.3 to 100 μm (when using PSL particles in pure water)
Particle size division	1 to 20channels (freely selectable)
Sample flow rate	25 mL/min (10 mL/min available as factory option)
Maximum particle concentration	10 000 particles/mL (with 10 μm PSL particles, counting loss loss 10 %)
Counting efficiency	100 ± 5 % (when measuring PSL particles of 10 μm and comparing the count of more than 5 μm with a reference unit)
Sensor resolution	Less than or equal to 10 % (in the vicinity of 10 μm PSL particles)
Threshold accuracy	Within 5 % (when particle concentration is less than 6 000 particles/mL in the vicinity of 10 μm and 15 μm PSL particles.)
Flow rate accuracy	Within 2 % (when measuring 10 mL volume)
Sample volume accuracy	Within 2 % (when measuring 10 mL volume)
Syringe volume	25 mL
Sample fluid temperature range	+15 to +30 ℃ (no condensation on flow cell walls)
Sample fluid connectors	
Inlet	Supplied sampling tube to be connected to INLET on sensor
Outlet	2 × 3 dia. flanged tube to be connected to OUTLET on syringe pump
Power requirements	100 to 240 V AC, 50/60 Hz, approx. 100 V (Supplied power cord only for use in Japan, with 100 V AC)
Dimensions, weight	Approx. 363 (H) × 360 (W) × 230 (D) mm (excluding protruding parts), Approx. 14 kg
Optional Accessories	Printer (recommended for use with KL-04) Oki Electric Microline 22NR High speed (148 ppm) and high resolution (1200×600 dpi)
	PFA sampling tube (2 × 4 dia., length 100 mm) set (includes nut)
	SUS sampling tube (2 × 3 dia., length 100 mm) set (includes nut and 2 pieces of packing)
	SUS sampling tube (1 × 2 dia., length 100 mm) set (includes nut and 2 pieces of packing)

PARTICULATE CONTAMINATION: SUB-VISIBLE PARTICLES

Ph. Eur. 9th Ed.: 2.9.19. Particulate <u>contamination</u>: sub-visible particles

- Method 1 is preferably applied
- When: reduced clarity, increased viscosity → Method 2
- Products that produce gas bubbles → Method 2

<u>1. Light obscuration particle count test</u>

<u>2. Microscopic particle count test</u>

The tests are carried out under conditions limiting particulate contamination, preferably in a laminar-flow cabinet.

Use the *particle-free water R*! To check the test conditions: determine the particulate contamination with *particle-free water R!*

PARTICULATE CONTAMINATION: SUB-VISIBLE PARTICLES ➔ method 2

Ph. Eur. 9th Ed.: Microscopic particle count test

Binoculare microscope with the calibrated ocular micrometer and a mechanical stage for holding and transversing the entire examination area, 2 illuminators. Filter assembly (vacuum), membrane filter (1 μm or finer in nominal pore size).

<u>Method</u>

•LVP and SVP > 25 ml → single units are tested; SVP < 25 ml → more units are combined in a cleaned container (!diluting to 25 ml with *particle-free water R* or appr. solvent without cont. of particles – powders for parenteral use)

•Filtration with application of vacuum, drying the membrane filter, counting the number of particles under the microscope (total filter count or partial filter count)!

<u>Evaluation</u>

•Test 2A (V > 100 ml) → (≤ 12/ml ≥10 μm) ∧ (≤ 2/ml ≥ 25 μm)

•Test 2B (V ≤ 100 ml) → (≤ 3000/container ≥10 μm) ∧ (≤ 300/container ≥ 25 μm)

PARTICULATE CONTAMINATION: SUB-VISIBLE PARTICLES ➔ method 2

- The particle sizing process with the use of the <u>CIRCULAR DIAMETER GRATICULE</u> is carried out by transforming mentally the image of each particle into a circle and then comparing it to the 10 μm and 25 μm graticule reference circles.

<u>Disadvantages:</u>

•The filter absorbs oily materials – are not seen as particles.

•Amorphous, gelatinous materials are difficult to measure and should not be measured.

•There is built-in error at the lower-size treshold at 10,0 μm of around 10 %.

•Time for analysis and the careful training of dedicated technicians!

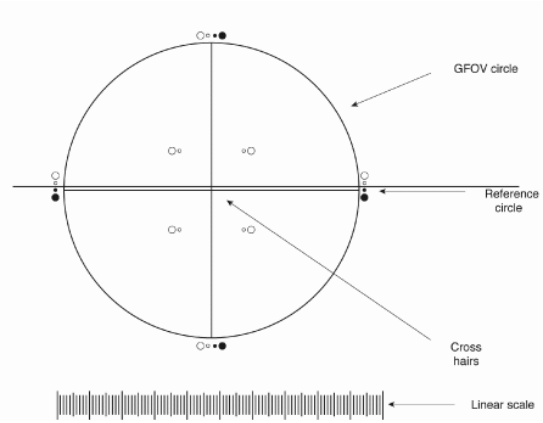
<u>Advantages:</u>

•Particles are - measured directly by the analyst and can be characterized morphologically. Agglomerated particles are recognized and can be sized individually.

•Results are unaffected by bubbles.

•The membrane can be retained for subsequent evaluation (batch record).

CIRCULAR DIAMETER GRATICULE



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METHODS FOR DETECTING AND COUNTING PARTICULATE MATTER

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PARTICULATE CONTAMINATION: VISIBLE PARTICLES

Ph. Eur. 9th Ed.: 2.9.20. Particulate contamination: visible particles

- A matt black panel in a vertical position
- A non-glare white panel next to the black panel
- An adjustable lampholder with a suitable, shaded, white-light source and light diffuser (illumination: 2000 – 3750 lx)

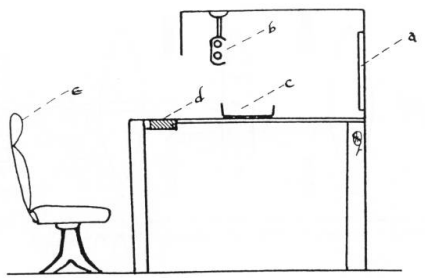
Effectiveness of the method relies on:

- ***the capability of the viewer,***
- ***the size of the target,***
- ***the total background illumination,***
- ***the contrast of the target against the viewing background.***

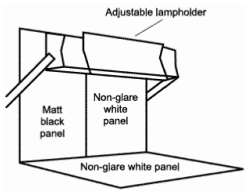
- Gently swirl or invert the container, ensuring that fine air bubbles are not formed.
- Observe for about 5 s in front of white panel.
- Repeat the procedure in front of black panel.

RECORD THE PRESENCE OF ANY PARTICLE!

PARTICULATE CONTAMINATION: VISIBLE PARTICLES



Cross-section of inspection booth:
a – black an white backboard; b – two-tube strip light; c – collection baskets for rejects; d – conveyor belt; e – laboratory chair.



Apparatus for visible particles
Ph. Eur. 8th Ed.

Other validated methods may be used.

PARTICULATE CONTAMINATION CONTROL – USE OF SEMI AUTOMATIC APPROACH

CLASSICAL OPTICAL CONTROL

- ampoules are visually inspected against contrast background under controlled lightning.

USE OF SEMI AUTOMATIC MACHINE

- inspection is 4 to 5 times faster than manual inspection procedure,
- At the point of inspection the sample is stopped and the inertia is causing the particles to move within the liquid. After the visual inspection the inadequate unit is removed manually by operator or by machine instructed by operator.
- The inspection point is equipped with magnifying glass.
- The decision with regard to the unit adequateness is still operator dependant and relies on operator skills.

PARTICULATE CONTAMINATION CONTROL – USE OF AUTOMATIC APPROACH

- With use of automatic control machines the manufacturers can replace human inspection, while still retaining comparable accuracy and limit of detection,
- the larger throughput of inspection machines is being exploited,
- by use of different source of illumination inspection machines can detect particles with different optical properties,
- the confirmation of particle presence can base also on the light obscuration principle,
- image analysis can provide information with regard to container defects and filling volume.

STATISTICS OF UNIT REJECTION – AUTOMATIC INSPECTION CONTROL

- 100 % of the lot is inspected for the presence of visible particles; Acceptable quality level (AQL) for the lot is from 0,25% to 1% rejection rate. This independent of the inspection method.
- Probability of removing inadequate unit relies primarily on particle size and less on its number concentration.
- Statistics of detecting the presence of particles and subsequent unit removal in case of machine inspection is defined in the table. The probability of removing inadequate unit is comparable to the classical method by human vision.

Particle concentration	Particle size [µm] 50% rejection probability	Particle size [µm] 100% rejection probability
50 particles per mL	18.82	51.45
5 particles per mL	19.96	54.88
1 mL ampoule, 1 particle	20.07	55.21
2 mL ampoule, 1 particle	20.08	55.25
5 mL ampoule, 1 particle	20.09	55.28
10 mL ampoule, 1 particle	20.10	55.29
20 mL ampoule, 1 particle	20.10	55.29
50 mL vial, 1 particle	20.10	55.29
1 L infusion, 1 particle	20.10	55.29

PHYSIOLOGICAL EFFECTS AND PARTICULATE HAZARD TO THE PATIENT

- **OCCLUSION** – in which a particle may block a blood vessel.
  - ➢ RES – remove particles between 1 and 10 µm in diameter.
  - ➢ LUNG, spleen, liver ...
  - ✓ Problem: so many large particles that all of the collateral pathways are blocked.
- **HOST RESPONSE** – depending on the chemical identitiy of the particle, and size and shape.
  - ➢ Interaction with cells of the reticuloendothelial system (RES) → foreign body reaction!
  - ✓ Problem: chronic reaction → can be potentially carcenogenic.

HIGHLY UNDESIRABLE PARTICULATE: Asbestos, talc, cellulose particles, cotton fibres!

Fortunatly the glass is generally inert (in the case of all-glass ampoules it is almost inevitably injected)!

Particulate contamination from siliconized rubber stoppers, *International Journal of Pharmaceutics, Volume 74, Issues 2-3, 16 August 1991, Pages 175-181*
F. Pavanetto, B. Conti, I. Genta and T. Modena

Abstract

Elastomeric closures are an essential packaging for parenteral drug products and they represent a possible **source of particulate matter**. The purpose of this study was to analyze the particulate contamination of siliconized rubber closures and to evaluate how different **siliconization processes** influence stopper quality. Sixteen types of rubber stoppers from the same manufacturer, differing in rubber formulation, shape, size, method and degree of siliconization were analyzed. Particulate analyses were performed on aqueous stopper eluates and on stoppers in the conditions of use, using two methods: **light blockage and optical microscopy**. The amount of silicone extractable from the closures was quantified by IR-spectrophotometry. **Results show that the siliconization method and the degree of siliconization can affect the particulate burden of pharmaceutical rubber closures**.

Author Keywords: Rubber closure; Silicone; Elastomeric material; Particulate matter; Parenteral product; Pharmaceutical packaging; Sterilization

Particulate matter contamination of small volume parenterals, *International Journal of Pharmaceutics, Volume 51, Issue 1, 1 April 1989, Pages 55-61*
F. Pavanetto, B. Conti, I. Genta, R. Ponci, L. Montanari and S. Vianello

Abstract

Particulate contamination in 34 types of liquid and 16 types of dry **small volume parenterals** (SVPs) manufactured in Italy have been studied. Particle counting was performed by a **light blockage method**. All the examined products met the SVP-USP XXI standard; the powders in general were more contaminated than liquids, overall for the largest particle sizes. The current **USP particulate matter limits for SVPs** can be regarded as suitable for the sterile powders, but appear to be too broad for the liquids. The LVP-USP contamination standard is adequate to the presently available quality of liquid SVPs and could be adopted for this dosage form.

Author Keywords: Particulate matter; Small volume parenteral; Compendial standard; Quality control; Contamination

Photoinduced particulate matter in a parenteral formulation for bisnafide, an experimental antitumor agent, *Pharmaceutical Development and Technology, Volume 4, Issue 3, August 1999, Pages 439-447.*
Rubino JT, Chan LL, Walker JT, Segretario J, Everlof JG, Hussain MA

Abstract

This paper assesses the cause of particulate formation in vials of the experimental antitumor agent bisnafide and investigates pharmaceutical techniques to reduce the number of particulates in the product. Solution preparation and particulate isolation were performed under Class 100 laminar air flow. Reversed-phase HPLC and infrared microscopy were used to characterize, drug and isolated particulate matter, whereas a Hiac particle counter was used to quantify the particulate matter. Particulate matter was observed following agitation of the drug solutions and war; found to be associated with specific lots of drug substance. HPLC of the isolated particulate matter indicated that the particulates consisted largely of bisnafide and impurities that were identified as the products of photodegradation, confirmed to be the result of the photolytic cleavage of bisnafide to form a poorly soluble aldehyde. The aldehyde may, in turn, interact with bisnafide molecules to form the particulate matter as suggested by the observed pH-dependent reversibility of the particulate phenomenon. **The particulate matter could be reduced by protecting solutions of bisnafide from light during chemical synthesis and production of the dosage form and, alternatively, by reducing the solution pH to 3.0 or less, addition of surfactants below their critical micelle concentration, and removal of impurities by froth flotation of the bisnafide solutions.**

Author Keywords: agitation, froth flotation, particulate matter, photodegradants, surfactants

Glass vials for small volume parenterals: Influence of drug and manufacturing processes on glass delamination, *Pharmaceutical Development and Technology, Volume 6, Issue 3, 2001, Pages 393 – 405.*
Ennis RD, Pritchard R, Nakamura C, Coulon M, Yang TY, Visor GC, Lee WA

Abstract

Purpose: Studies were initiated to examine the effect of formulation and process variables on the delamination process and also the influence of the glass manufacturing process, supplier, and glass surface treatment. Methods: Stress testing was performed by exposing filled vials to multiple sterilization cycles followed by accelerated stability testing. Delamination incidence was determined by visual examination, light obscuration (HIAC), and microscopical methods. The inner surface of vials front each supplier and lot were also examined by scanning electron microscopy. Results: Vials sourced from Supplier A had smooth surfaces as demonstrated by SEM examination, whereas vials sourced from Suppliers B and C displayed extensive surface imperfections such as pitting and/or deposits. These imperfections were localized to the vial wall, adjacent to the vial bottom, and increased with sulfate treatment. **Delamination incidence increased in those vial lots with increased surface imperfections.** Thus, vials sourced from Supplier A had the lowest frequency of delamination. Sulfate treatment and high pH increased delamination incidence to as high as 100%. Conclusion: These results demonstrate the importance of the surface morphology created during the vial forming process. **Given the differences observed, filial vial selection should include extensive microscopical and product stress testing studies on multiple vial lots.**

Author Keywords: containers, delamination, glass, parenterals, particulate matter, scanning electron microscopy, small volume parenteral

Particulate matter contamination of intravenous antibiotics aggravates loss of functional capillary density in postischemic striated muscle, *American Journal of Respiratory and Critical Care Medicine, Volume 165, Issue 4, February 2002, Pages 514 -520.* Lehr HA, Brunner J, Rangoonwala R, Kirkpatrick CJ

Abstract

Through the increased use of less expensive and counterfeit medicines, the contamination of parenteral fluids and drugs by particulate matter poses an increasing health hazard worldwide. However, the mechanism of action of such contamination has never been conclusively demonstrated. We have systemically injected the particles contained in three different 1-g preparations of the antibiotic cefotaxime into hamsters and visualized the functional capillary density in striated skin muscle, using intravital fluorescence microscopy. Injection of particles from either of the three preparations did not affect capillary perfusion in normal muscle (n = 3 hamsters, each). However, injection of particles from two generic drug preparations, but not the original preparation or the saline control, significantly reduced capillary perfusion in muscle tissue that had previously been exposed to 4 h of pressure-induced ischemia and 2 In of reperfusion (n = 9 hamsters per group). Histological sections demonstrated birefringent particles mechanically obliterating the microcirculation of the striated muscle. The loss of capillary perfusion due to particle injection or injection of standardized microspheres was dependent on the extent of ischemia/reperfusion-induced muscle injury, with more capillaries lost in the more severely compromised muscle areas. **These findings suggest that particle contaminants may not pose a major threat in intact tissue, but may severely compromise tissue perfusion in patients with prior microvascular compromise of vital organs (i.e., after trauma, major surgery, or sepsis)** and thus predispose to complications such as acute respiratory distress syndrome or multiple organ failure.

Author Keywords: capillary perfusion, intensive care, microsphere, reperfusion injury, side effect

Physical compatibility of neonatal total parenteral nutrient admixtures containing organic calcium and inorganic phosphate salts, *American Journal of Health-system Pharmacy, Volume 62, Issue 11, June 2005, Pages 1177 – 1183.*
Parikh MJ, Dumas G, Silvestri A, Bistrian BR, Driscoll DF

Abstract

Purpose. The compatibility of calcium and phosphate salts in total parenteral nutrient (TPN) admixtures at the highest concentrations recommended for preterm and term infants was studied.

Methods. Particulate matter from eight different macronutrient combinations was measured and counted (range, 1.8-50 mu m) by a laser-based, single-particle optical sensing technique. Measurements were performed at four intervals after compounding the formulations under aseptic conditions (within 1 hour of preparation and at 6, 24, and 30 hours) at 23-27 degrees C. The number of particles measuring >= 5, >= 10, and >= 25 mu m per milliliter of TPN admixture was recorded. Detailed visual inspections were also performed at these intervals, and pH was measured at the beginning (time 0) and end of the study (30 hours). Precipitated material was characterized by polarized microscopy and infrared spectroscopy.

Results. **The TPN admixture with the lowest concentration of amino acids (0.5%), as well as the highest pH, resulted in significant growth of particulate matter over time.** At 30 hours, the particle growth was accompanied by visible evidence of precipitation, which was confirmed to be dibasic calcium phosphate. Neither significant particle growth nor precipitation was noted in the remaining seven formulations, which had amino acid concentrations of 1-4%.

Conclusion. **Commonly used organic calcium and inorganic phosphate salts in cysteine-added, lipid-free TPN formulations at the highest recommended amounts for neonates were compatible when the amino acid concentration was between 1% and 4% and the dextrose concentration was 5% or 10%.** The salts remained compatible for up to 30 hours at a room temperature of up to 27 degrees C. **Precipitation of dibasic calcium phosphate occurred with lower amino acid concentrations and higher pH values.**

Author Keywords: nutrition, precipitation, trophamine, solubility, crystals

A new stressed test to predict the foreign matter formation of minodronic acid in solution, *International Journal of Pharmaceutics, Volume 251, Issues 1-2, 30 January 2003, Pages 99-106*
Katsutoshi Nakamura, Shigeharu Yokohama, Masataka Katsuma, Toyohiro Sawada and Takashi Sonobe

Abstract

A formulation containing 0.5 mg/ml minodronic acid, 40 mM citrate, pH 4.5, and sodium chloride, stored in regular flint glass ampoules, was stable without particulate increase under high temperature conditions, such as 40 °C for 6 months, or 50 or 60 °C for 3 months. However, when stored at 25 °C, there was an increase in greater than or equal to 2 μm particles at the 5-month timepoint. This demonstrated that **long-term stability** cannot simply be predicted by the evaluation of samples just stored at higher temperatures. Therefore, a new stressed test was designed which is useful in the rapid selection of formulations that are stable and without **particulate increase**. Since the particulate matter is apparently a complex of minodronic acid and aluminum ions leaching from ampoules, samples were placed at 80 °C for up to 4 weeks to accelerate aluminum leaching. **Although no particulate increase was observed directly after storage at 80 °C, 4 freeze–thaw cycles following the storage caused a drastic particulate increase.** The evaluation of samples subjected to the freeze–thaw cycles indicated that the following formulation modifications have inhibitory effects on particulate generation: (1) addition of meglumine, diethanolamine, mannitol, or glycerol to the formulation; (2) increase of citric acid concentration; (3) decrease of minodronic acid concentration. These modifications also worked well for samples stored at 25 °C for 6 months, and particulate increase did not occur. This method is a powerful tool for predicting the stability of minodronic acid in solution.

Author Keywords: Minodronic acid ; Parenteral formulation; New stressed test; Particle; Complex; Aluminum ion

back

The role of excipients in parenteral radiopharmaceutical preparations

Assist. Prof. Biljana Janković is a senior scientist in pharmaceutical company Lek and assistant professor of pharmaceutical technology at the Faculty of Pharmacy (University of Ljubljana). She received her Ph.D. from the University of Ljubljana in 2011 in area of mechanical properties of pharmaceutical materials. Her area of interest were nanomechanical attributes of active and inactive pharmaceutical ingredients, material characteristics of polymers essential for control release systems as well as applications of atomic force microscopy and nanoindenter in pharmaceutical technology.

The lecture has the following learning objectives:

1. Students are able to assess the factors that affect radiopharmaceuticals before or during formulation.
2. Students are able to predict factors that impact radiopharmaceuticals after formulation.
3. Students are able to discriminate formulation factors that are in manufacturer's practice and those that can be controlled by radiopharmacist.

Summary of the lecture:

General application of radiopharmaceuticals is by parenteral route, therefore quality requirements for this type of products should be the same as for other parenterals: sterile, pyrogen free, particular matter-free in solution state and preferably isotonic, especially for large volumes. Radiopharmaceutical composition includes target materials, optionally carriers, inactive ingredients and solvent. The actual quantity of radioactive material compared with quantities of excipients is usually very small; therefore excipients can greatly influence the quality of the radiopharmaceutical preparations. The requirement for sterility demands that the excipients must be able to withstand terminal sterilization or aseptic processing; therefore factors can limit the choice of excipients. Radiopharmaceuticals commonly contain categories of excipients that are also used in conventional drugs. They may contain the following inactiveingredients:

- solvent and co-solvents
- polymeric and surface active compounds
- diluents
- tonicity agents
- pH modifiers
- antimicrobial preservatives
- chelating and/or complexing agents

- antioxidants

Water for injection (Ph. Eur) is the most frequently used solvent in parenteral preparations, which can be mixed or substituted with a co-solvent for improvement of solubility or stability of drugs. Moreover, in 50% of parenteral solutions, ethanol and propylenglycol are used as non-aqueous solvents. Polyethylenglycol (PEG) is utilized in less extent for preparation of parenteral products due to presence of residual peroxides which may results in the degradation of the drug in co-solvent systems.

To increase drug solubility or wetting property, *surfactants* can be added to the parenteral products. Particular valuable as solubilizing agents are those possessing hydrophilic-lipophilic balance (HLB) more than 15 and belong to class of hydrophilic surfactants.

Among all, Polysorbate80 (Tween 80) and Polysorbate 20 (Tween 20) are the most commonly applied. The main difference between them is stability issue related to the presence of unsaturated fatty acid (e.g.Tween80), which can lead to excessive oxidation when present in parenteral solutions. For enhancement of radiopharmaceutical parenteral products the following agent can be added: chelating substances, antioxidants and in certain cases preservatives. *Chelating agents* serve to complex heavy metals and consequently to ameliorate the function of antioxidants and preservatives. Citric, tartaric and amino acids as well as calcium salt of EDTA are categorized in this group of inactive ingredients.

Antioxidants are primarily utilized for prevention of drug oxidation as well as excipients in the final dosage form. They can be classified as true antioxidants (e.g. butylated hydroxytoluene), reducing agents (e.g. ascorbic acid) and antioxidant synergists (e.g. EDTA) based on the mechanism of action. On the other hand compatibility of antioxidants with the drug, packaging system and the body should be studied carefully (interactions, adsorption on plastic materials…).

For ensuring adequate microbiological quality of multidose injections it is recommended to use the following *preservatives*: benzylalcohol, parabens (methyl, propyl), chlorocresol and in certain cases thiomersal. British and European pharmacopeia prohibits antimicrobials for single-dose injections where the dose volume is greater than 15mL.

Buffers maintain the pH of the formulation with the aim to optimize solubility and stability. For parenteral products, the pH should be as much as close to physiological pH. Phosphate, citrate and acetate are the most common buffers used in parenteral forms. Their concentrations should be adjusted in order to avoid formation of any pain during subcutaneous application. The selection of the buffers is also related to their stability during final sterilization or lyophilization. When large volume is required to be administered intravenously, the solution should be physiologically acceptable (compatible), in particular with the erythrocytes. For such function, parenteral solutions should be isotonic. Definition of isotonic solution is related to net gain or loss of water by cell, or other change in the cell when it is in contact with that solution. Iso-osmotic solution is associated with the equilibrium in net transfer of material between the semipermeable membrane.

Dextrose and sodium chloride are used to adjust tonicity in the majority of formulations. To adjust

the tonicity of some solutions, namely to prepare isotonic/isoosmotic systems, physiological values of osmolarity should be known. There are several methods for adjusting the tonicity of an aqueous solution provided. The most prominent of these are the freezing point depression method, the NaCl equivalent method and isotonic solution V-value method.

Many radiopharmaceuticals differ from conventional drugs, however, because their preparation (reconstitution) involves one or more chemical reactions that require unusual excipients. Furthermore, the self-absorption of emitted radiation may result in the radiolytic decomposition of many radiopharmaceuticals. Hence, several excipients are used predominately in radiopharmaceutical formulations, although they occasionally may be used for other drugs. These includes: reducing agents, transfer ligands, colloid stabilizing agents and free radical scavengers.

Reducing agents are required for technetium Tc-99m radiopharmaceuticals. Technetium Tc-99m, in the chemical form of sodium pertechnetate (+7 oxidation state), must be reduced to a lower oxidation state so that it can be chelated or otherwise complexed by the intended ligand to form the final Tc-99m radiopharmaceutical. *Reducing agents* must be readily soluble in water and stable at the indented pH of the formulated product. *Transfer ligands* are agents that typically undergo rapid reactions with reduced technetium to form weak chelates thus keeping the reduced technetium in a soluble form until it is transferred to the principal ligand. Examples of such transfer ligands are citrate, gluconate and tartrate. Such approach is practical in case when kinetics of complexation with the principal ligand is slow or when a heating step is essential to expose chelating groups on the major ligand. Transfer ligands should be readily soluble in water. *Colloid stabilizing agents* are relatively large lyophilic molecules that coat the lypophobic surface of individual colloid particles and prevent or inhibit clumping. Examples of such excipients consider gelatin and dextran (readily soluble in water). Moreover, the colloid stabilizing agent may be charged, thus causing the repulsion between coated colloid particles. For enhancement of radiochemical purity of radiopharmaceuticals, free scavengers can be utilized. *Free radical scavengers* preferentially interact with oxidative or reductive free radicals that otherwise would result in degradation of formulation components. Examples of free radical scavengers include methylene blue and aminobenzoic acid. According to physicochemical characteristics, free scavengers are readily soluble in water.

During the development of parenteral dosage forms or radiopharmaceutical product, the formulator selects excipients that will provide a stable, efficacious and safe product. Criteria for the selection of excipient and its supplier are therefore very important and selection is based on following key points:

- influence of excipient on the overall quality, stability, and effectiveness of drug product
- compatibility of excipient with drug, packaging system and sterilization process
- the amount or percentage of excipients that can be added to the drug product
- dose volume, single or multiple dose use
- solubility issues with radiopharmaceutical solution
- oxidation and/or radiolytic decomposition

- modification of pH solution
- presence of aluminum and stannous ions
- What is the cost of the excipient and is it readily available?
- Is the excipient production under GMP standards?
- Will the excipient supplier certify the material to meet USP, BP, EP, JP, and other pharmacopoeias?

Take home messages:

The special concern of the lecture will be related to differentiations between the factors affect radiopharmaceuticals before or during formulation and those that impact radiopharmaceuticals after formulation. Additionally, the focus will be associated to formulation factors that are in manufacturer' practice and those that can be controlled by the radiopharmacists.

References (further reading):

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Role of excipients in parenteral radiopharmaceutics

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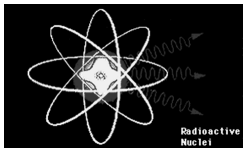
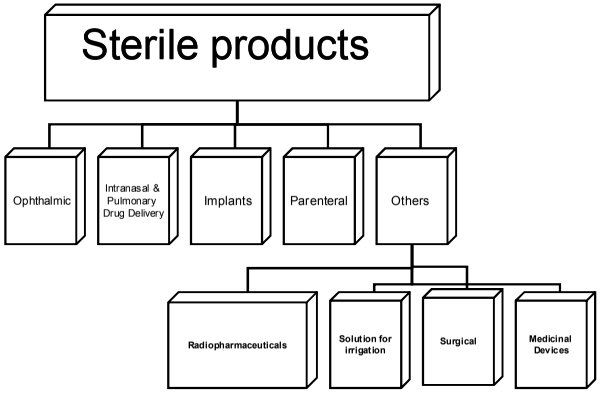


AGENDA

- Introduction
- Types of excipients
- Function and selection of excipients
- Solvents and cosolvents
- Surface active substances
- Antioxidants, Chelating agents, Preservatives
- Tonicity adjusters
- Isotonicity iso-osmoticity, basic definitions
- Tonicity calculation and its adjusting
- Conclusion
- References

INTRODUCTION



PARENTERAL RADIOPHARMACEUTICS

Examples of parenteral radiopharmaceutics

1) $Na_2H^{32}PO_4$ sodium orthophosphate, 37 - 370 MBq/ml

- **Indications**: It is a radiopharmaceutical intended for the treatment of primary polycythemia and primary polythrombocythemia when all alternative forms of treatment fail to produce results.
- **Dosage form**: Solution for injection
- **Excipients:** sodium chloride, disodium hydrophosphate dodecahydrate, water for injections

2) Meta-iodo[^{131}I]benzylguanidine sulphate, 370 - 740 MBq/ml

- **Indications:** Meta-iodobenzylguanidine-^{131}I (MIBG-^{131}I) is a radiopharmaceutical used in cancer therapy. It is used in treating disseminated, malignant, metastatic lesions, such as pheochromocytoma, paraganglioma, neuroblastoma, neuroendocrine tumors of gestroenteropancreatic tract, and sometimes medullary thyroid carcinoma.
- **Dosage form**: Solution for injection
- **Excipients:** sodium metabisulphite, copper (II) sulfate pentahydrate, sodium acetate trihydrate, acetic acid, benzyl alcohol, sodium chloride, water for injection.

PARENTERAL RADIOPHARMACEUTICS

Examples of parenteral radiopharmaceutics

3. Sodium 2-[^{131}I] iodohippurate [3.7 - 74 MBq/ml]

- **Indication:** In diagnostics of kidney failure and urine outflow disorders (dynamic kidney scintigraphy, renoscintigraphy).
- **Dosage form:** solution for injection
- **Excipients:** benzyl alcohol, sodium chloride, water for injections.

4. Strontium chloride $^{89}SrCl_2$ with radioactive concentration of 37.5 MBq/ml

- **Indications:** Strontium chloride $^{89}SrCl_2$ is indicated for the palliation of pain from bone metastases. The best documented use of strontium chloride-^{89} is in case of osteoblastic or mixed metastases from prostate cancer and breast cancer
- **Dosage form:** solution for injection, clear, colorless solution
- **Excipients:** Strontium chloride, Sodium chloride, Water for injections

PARENTERAL RADIOPHARMACEUTICS

Examples of parenteral radiopharmaceutics

5. FluGlucoScan™ Injection - 18F Fluorodeoxyglucose (18F-FDG) – Product monograph

- **Indication:** Injection is an intravenous diagnostic radiopharmaceutical for Positron Emission Tomography (PET). FluGlucoScan Injection is indicated in PET for diagnostic use in patients for:
  (1) the evaluation of pulmonary nodules to distinguish benign from malignant and the evaluation of non-small cell and small cell lung cancers for staging and restaging and;
  (2) the evaluation of colorectal cancer for recurrence, restaging, and distant metastases.
- **Dosage form:** parenteral solution
- **Excipients:** FluGlucoScan Injection is supplied as a multi-dose (20 mL), sterile, non-pyrogenic injection vial containing a calibrated amount of ^{18}F - FDG in approximately 16 mL of citrate buffer and / or saline without preservatives. The pH of the solution is between 4.5 and 7.5. **Sodium citrate, saline and Sterile Water for Injection** are used as formulation excipients. Product is prepared on a daily basis with expiry time of 12 hours from the calibration time noted on the label.

6. AdreView - Iodine I-123 iobenguane

- **Indications:** Indicated for use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests
- **Dosage form:** solution for injection
- **Excipients:** sodium dihydrogen phosphate dehydrate, disodium hydrogen phosphate dehydrate, benzyl alcohol at pH = 5.0 – 6.5

Radiopharmaceutical composition

Radiopharmaceutical composition includes:

- ❑ Target material
- ❑ Carrier (optionally)
- ❑ Inactive ingredients
- ❑ Solvents

The actual quantity of radioactive material compared with quantities of excipients is usually very small; therefore excipients can greatly influence the quality of the radiopharmaceutical preparations.

INNACTIVE INGREDIENTS

Radiopharmaceuticals commonly contain categories of excipients that are also used in conventional drugs (parenterals). They may contain the following inactive ingredients:

- ❑ Solvent and co-solvents
- ❑ Polymeric and surface active compounds
- ❑ Diluents
- ❑ Tonicity agents
- ❑ pH modifiers
- ❑ Antimicrobial preservatives
- ❑ Chelating and/or complexing agents
- ❑ Antioxidants

SOLVENTS AND COSOLVENTS

Solvents for parenteral use should have definite requirements:

- Pharmacologically inert
- Miscible with body fluids
- Nontoxic
- Non-sensitizing
- Non-irritating
- Effective at maintaining the solubility
- Physically and chemically stable
- Fluid or rendered fluid at body T
- Unaffected by changes of pH
- Capable of being sterilized

SOLVENTS AND COSOLVENTS

Water for injections (Ph. Eur)

- The most commonly used solvent for parenterals
- Can be combined or substituted with a co-solvent to improve the solubility and stability o drugs
- It is non-pyrogenic, sterile distilled water

Quality requirements for water for injections:

1. Clarity & color
2. Acidity/alkalinity
3. Oxidisable substance
4. Bacterial Endotoxin Test (BET)
5. Sterility test
6. Residue on evaporation

- Water for injections free from carbon-dioxide
- Water for injections free from dissolved air in water

SOLVENTS AND COSOLVENTS

Water miscible solvents

- Poor solubility of drug in water can be improved by addition of water miscible co-solvent(s).

Example:

- Drug , soluble in water (30°C) at 4µg/ml, but up to 160 mg /ml in anhydrous PEG 400.
- Any concentration between these limits can be achieved by using a suitable mixture of water and PEG.

Water miscible solvents include: butylene glycol, poly- ethylene glycol (PEG 400; 600), glycerol, ethanol, propylene glycol.

SOLVENTS AND COSOLVENTS

Ethanol

- dilute aqueous ethanol good solvent for many poorly water soluble drugs
- physiologically effective; caution!
- producing pain and tissue damage on injection
- EtOH must be diluted with dextrose or saline solution

Glycerol

- Little solubilizing capacity
- Used to adjust tonicity

Propylene glycol

- Cause pain on injection
- with benzyl alcohol increases solvent capacity (as local anesthetic)

Polyethylene glycols PEG

- low osmotic activity
- may not be stable in water after long period of time,
- autoxidation, capable of affecting easily oxidizing material

SOLVENTS AND COSOLVENTS

- Ethanol and propylene glycol are used alone or in combination with other solvents in more than 50 % of parenterals.
- Propylene glycol – higher myotoxicity and hemolyzing effects in comparison to PEG.
- Presence of residual peroxide in PEG may result in the degradation of the drug in co-solvent system. It is important to use unbleached/or peroxide free PEGs in formulation.

POLYMERIC AND SURFACE ACTIVE AGENTS

Function:

- To impart viscosity or act as suspending agents
- To act as solubilizing, wetting, or emulsifying agents (HLB<15)
- Polysorbat 80 is the most commonly used surfactant in parenterals
- Polysorbat 80 – polyoxyethylene sorbitan ester of oleic acid (unsaturated fatty acid)
- Polysorbate 20 – sorbitan ester of lauric acid (saturated fatty acid).
- Level of residual peroxides – stability issue

Solubilisers, wetting agents/emulsifiers	Concentration [%]
Dimethyl acetamide	0.01
Ethanol	0.61 – 49.0
Glycerol	14.6-25.0
PEG 400, 600	0.01-50.0

CHELATING AGENTS

Function:

- To complex heavy metals and improve efficacy of antioxidants and preservatives

Common chelating agents:

- Citric acid, tartaric acid, EDTA (calcium, sodium salts)

Note:

A complexing agents should not be used in metalloprotein formulations, where the protein subunits are held by the metal.

Excipient	Frequency	Range	Example
Calcium disodium EDTA[a]	9	0.01–0.1%	Wydase® (Wyeth-Ayerst) 0.1% w/v
Disodium EDTA	38	0.01–0.11%	Calcijex® (Abbott) 0.11% w/v
Sodium EDTA	1	0.20%	Folvite® (Lederle) 0.20%
DTPA[b]	1	0.04%	Magnevist® (Berlex) 0.04%

[a]EDTA = Ethylenediaminetetraacetic acid.
[b]DTPA = Diethylenetriaminepentaacetic acid; pentetic acid.

ANTIOXIDANTS

Function:

- Prevention of the oxidation of active substances and excipients in the finished products.

Categorization of antioxidants:

- True antioxidants: chain-termination by reacting with free radicals, e.g. butylated hydroxytoluene.
- Reducing agents: they have a lower redox potential than the drug and get preferentially oxidized, e.g. ascorbic acid.
- Antioxidant synergists: enhance the effect of antioxidants, e.g. EDTA

Antioxidants	Concentration [%]
Ascorbic acid	0.02-0.1
Thiourea	0.005
BHT	0.005-0.002

ANTIOXIDANTS

Excipient	Frequency	Range	Example
Acetone sodium bisulfite	4	0.2–0.4% w/v	Novocaine® (Sanofi-Winthrop) 0.4% w/v
Ascorbate (sodium/acid)	8	0.1–4.8% w/v	Vibramycin® (Pfizer) 4.8% w/v
Bisulfite sodium	31	0.02–0.66% w/v	Amikin® (Bristol Myers) 0.66% w/v
Butylated hydroxy anisole (BHA)	3	0.00028–0.03% w/v	Aquasol A® (Astra) 0.03% w/v
Butylated hydroxy toluene (BHT)	3	0.00116–0.03% w/v	Aquasol A® (Astra) 0.03% w/v
Cystein/Cysteinate HCl	3	0.07–1.3% w/v	Acthrel® (Ferring) 1.3% w/v
Dithionite sodium (Na hydrosulfite, Na sulfoxylate)	1	0.10%	Numorphan® (Endo Lab) 0.10%
Gentisic acid	1	0.02% w/v	OctreoScan® (Mallinckrodt) 0.02% w/v
Gentisic acid ethanolamine	1	2%	M.V.I. 12® (Astra) 2%
Glutamate monosodium	2	0.1% w/v	Varivax® (Merck) 0.1% w/v
Formaldehyde sulfoxylate sodium	9	0.02–0.5% w/v	Terramycin solution (Pfizer) 0.5% w/v
Metabisulfite potassium	1	0.10%	Vasoxyl® (Glaxo-Wellcome) 0.10%
Metabisulfite sodium	32	0.02–1% w/v	Intropin® (DuPont) 1% w/v
Monothioglycerol (Thioglycerol)	6	0.1–1%	Terramycin solution (Pfizer) 1%
Propyl gallate	2	0.02%	Navane® (Pfizer) 0.02%
Sulfite sodium	7	0.05–0.2% w/v	Enlon® (Ohmeda) 0.2% w/v
Tocopherol alpha	1	0.005% w/v	AmBisome® (Fujisawa) 0.005%
Thioglycolate sodium	1	0.66% w/v	Sus-Phrine® (Forest) 0.66% w/v

ANTIOXIDANTS

- Inhibition of oxidation and/or radiolytic decomposition of radiopharmaceuticals can be diminished by:
  - minimizing the exposure of radiopharmaceuticals to atmosphere
  - purging of solution with nitrogen,
  - limiting introduction of air into the vial
  - avoiding vigorous shaking,
  - minimizing addition of standard sodium chlorine for dilution.

PRESERVATIVES

Function:

- Assurance of microbiological quality of multidose parenterals
- Cannot be substitute for inadequate GMP
- They are discouraged from being used in single-dose injections where the dose volume is greater than 15 mL.

- most common preservatives in parenteral formulations: benzyl alcohol and parabens (methyl, propyl).
- allergic reactions can be severe
- compatibility studies
- take care of their solubility (may go in oily phase),
- electrostatic bonding on glass surfaces of bottles
- Benzyl alcohol is volatile, therefore it cannot be used for lyophilized dosage form.

PRESERVATIVES

Excipient	Frequency	Range	Example
Benzalkonium chloride	1	0.02% w/v	Celestone Soluspan® (Schering) 0.02% w/v
Benzethonium chloride	4	0.01%	Benadryl® (Parke-Davis) 0.01% w/v
Benzyl alcohol	85	0.75–10%	Progesterone (United Res) 10%
Chlorbutanol	18	0.25–0.5%	Codine phosphate (Wyeth-Ayerst) 0.5%
m-Cresol	5	0.1–0.35%	Humalog® (Lilly) 0.35%
Myristyl gamma–picolinium chloride	2	0.0195–0.169% w/v	Depo-Provera® (Pharmacia-Upjohn) 0.169% w/v
Paraben methyl	52	0.05–0.18%	Inapsine® (Janssen) 0.18% w/v
Paraben propyl	44	0.01–0.1%	Xylocaine w/ Epinephrine (Astra) 0.1% w/v
Phenol	50	0.2–0.5%	Calcimar® (Rhone-Poulanc) 0.5% w/v
2-Phenoxyethanol	4	0.50%	Havrix® (SmithKline Beecham) 0.50% w/v
Phenyl mercuric nitrate	3	0.001%	Antivenin® (Wyeth-Ayerst) 0.001%
Thimerosal	48	0.003–0.012%	Atgam® (Pharmacia-Upjohn) 0.01%

PRESERVATIVES

- **Benzyl alcohol** is of limited applicability for radiopharmaceuticals since it is vasodilator and cannot be used with a radiotracers such as ^{133}Xe in saline solution intended for regional blood flow measurements.
- It is not recommended to be used for parenteral preparation in pediatric population less than 2 years.

BUFFERS

Function:

Added to formulation to adjust the pH with the aim to optimize solubility and stability.

Requirement:

- pH of the product should be close to physiological pH (7.4)
- Buffer capacity (function of type and conc. Of buffer; maximal capacity when pH = pKa)
- The pKa change with T should be very low (lyophilized products, sterility conditions may affect pH dramatically)
- Compatibility of drug with buffer

The most commonly used buffers for adjustment of formulations are phosphate, citrate (dual function as chelating agent), and acetate

Amino acids such as lysine and glycine serves as buffers and stabilizing agents for protein and peptide formulations.

TONICITY ADJUSTERS

Function:

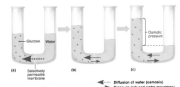
- are used to modify osmolality of product – to adjust tonicity;
- Dextrose and NaCl are used as tonicity adjusters in majority of formulations;
- When large volume is required to be administered intravenously, the solution should be physiologically acceptable - compatible with tissues and, in particular, the erythrocytes.
- **A compatible solution is said to be isotonic.**

TONICITY ADJUSTERS

Basic expressions and definitions in tonicity

- Osmosis (diffusion of a solvent from a solution of low solute concentration into more concentrated one through a semi-permeabile membrane).
- Osmotic pressure (external pressure that must be applied to solution in order to prevent it being diluted by the entry of solvent via process known as osmosis).
- isoosmotic (physical term)
- **isotonic** (should be used *only* with reference to *in-vivo* fluids)
- ISOTONICITY = physiological compatibility

Osmosis, osmotic pressure

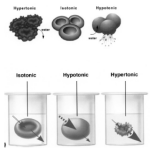


TONICITY ADJUSTERS

Isotonicity – physiological compatibility?

- 0.9 % NaCl solution is isoosmotic and isotonic with physiological fluids
- solutions of urea, boric acid, soluble ammonium salts can be isoosmotic with body fluids, but cause hemolysis of red blood cells, NOT isotonic
- in practice: isotonic = isoosmotic

Iso-, hyper-, hypo- tonicity



REDUCING AGENTS

- Reducing agents are required for technetium Tc 99m radiopharmaceuticals.
- Technetium Tc 99m, in the chemical form of sodium pertechnetate (+ 7 oxidation state), must be reduced to a lower oxidation state so that it can be chelated or otherwise complexed by the intended ligand to form the final Tc 99m radiopharmaceutical.
- The reducing agent, **typically a stannous salt**, generally is formulated in the kit for the preparation of the technetium Tc 99m radiopharmaceutical.
- ***Functional Mechanism****:* The reducing agent (e.g., stannous ion) must be present in sufficient quantity to reduce all of the technetium atoms to the intended oxidation state but must not produce undesired reduction products or other impurities (e.g., stannous hydroxide precipitates).
- ***Physical Properties:*** Reducing agents (e.g., stannous salts) must be readily soluble in water

TRANSFER LIGAND

- In the preparation of certain radiopharmaceuticals, the radiometal (e.g., stannous-reduced technetium Tc 99m) is first chelated by a relatively weak chelating ligand and then is transferred to the principal chelating ligand or complexing moiety.
- Examples of such transfer ligands include **citrate, gluconate,** and **tartrate.**
- ***Functional Mechanism****:* Transfer ligands typically undergo rapid reactions with reduced technetium to form weak chelates, thus keeping the reduced technetium in a soluble form until it is transferred to the principal ligand. This procedure is especially useful when the kinetics of complexation with the principal ligand is slow or when a heating step is necessary to expose chelating groups on the principal ligand.
- ***Physical Properties:*** Transfer ligands must be readily soluble in water

COLLOID STABILIZING AGENTS

- Lyophobic colloids tend to clump together and form large aggregates in order to minimize their surface-area to-volume ratio.
- Colloid stabilizing agents are relatively large lyophilic molecules that coat the surface of each individual colloid particle and prevent or inhibit clumping.
- Examples of colloid stabilizing agents include **gelatin** and **dextran**.
- ***Functional Mechanism:*** The colloid stabilizing agent coats the surface of the lyophobic colloid particles, making them appear lyophilic. Additionally, the colloid stabilizing agent may be charged, thus causing the coated colloid particles to repel one another.
- ***Physical Properties****:* Colloid stabilizing agents must be readily soluble in water

CONCLUSION

- Radiopharmaceuticals commonly contain categories of excipients that are also used in conventional drugs (parenterals).
- Choice of inactive ingredients should be carefully perform in order to assure adequate stability of radiopharmaceuticals (low impurity level).
- Beside excipients, mixing order of excipients, heating, incubation can have significant impact on radiopharmaceutical physical and chemical stability.

Pharmaceutical packaging

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The lecture has the following learning objectives:

1. Students are able to recognize and reduce possible weak points, connected with pharmaceutical packaging in their radiopharmacies, production sites,...
2. Students are familiar with materials used in field of Pharmaceuticals, their use, advantages/ disadvantages and have the knowledge what kind of material could be used for their desired product to be in accordance with legislation and user friendly..
3. Students are able to pack radiopharmaceutical to be shipped from their facility in accordance with legislation and equip it with needed documentation.

Summary of the lecture (prepared by Aljaž Sočan, MPharm and Prof. dr. Stane Srčič):

1. Function of drug package

During its life a pack has a number of functions to perform, including storage, carriage, display, sale, use, etc. All of this requires in depth consideration, when designing the packaging. A pack, by a simple definition, is an economical means for a product that provides its:

- presentation
- protection
- identification / information
- convenience / containment / compliance

A pack provides these properties until the product is used or administered, paying due attention to any relevant environmental issues.

The term “pack” covers all the components involved. The *primary* or immediate pack consists of materials in direct contact with the product. The *secondary* pack and sometimes-*tertiary* components enable the product to be stored, transported and displayed

(secondary), and possibly assist use (tertiary). Tertiary components may include ancillary components, e.g. leaflets or inserts, dispensing spoons and measures.

Presentation

Presentation is important in providing confidence and enhancement of the product image. This may be achieved by the aesthetics and/or functional aspect of the pack.

Identification / information

The printed pack or its ancillary printed components (e.g. package inserts) serve to provide identity as well as information. Much of this information has to meet the legal requirements of the country of sale.

Convenience

Convenience is normally associated with product use or administration. It may be a feature related to the pack (e.g. a metered dose aerosol) or to the product-pack (e.g. a unit dose eye drop which both eliminates the need for a preservative and reduces risk associated with cross-infection by administering only a single dose). A unit dose pack also offers a number of other convenience factors, such as no risk associated with opening and reclosing, size of pack, and others.

Containment

Containment is probably the most basic aspect of any pack. Powders, gases and liquids can only be purchased if they are contained in a pack.

Compliance

A pack, in terms of achieving compliance, requires strong consideration, since it can detract or encourage the user adherence to the recommended use.

Protection

It is almost the most important factor and frequently the most complex in a design of a pack. Broadly, the pack must afford protection against several below stated primary hazard (climate, physical or mechanical). However, before proceeding to how the product-pack may have to stand up to certain hazards, the drug entity, the ingredients and the final formulation have been exposed to a range of conditions prior the packaging investigations being started: susceptibility to T, pressure, oxygen, CO2, moisture, heavy metals, bacteria, mould, pH, etc. Those informations provide a broad indication of what protection is required.

Climate hazards (T, RH)

Physical or mechanical hazards

A product pack system can either be static (during storage) or in a state of motion (during carriage, handling or use). Physical hazards arising from both can occur at any time to the packaging material, the product/and or packed product. In terms of the physical/mechanical hazards, we distinguish between:

- Shock – impact (drops form tops of pallets, back of trucks,…)
- Compression (is usually associated with stacking, for instance, a pallet of glass containers may be significantly heavier than plastic)
- Vibration (associated with the vehicle travels along a rutted or bumpy road. Under certain circumstances vibration may cause direct problems with the product, i.e. segregation of powder, separation of emulsions, surface dulling of tablets, settling down the product, abrasion of surfaces).

Contamination

Drug package has to protect product from different types of contamination.

Contamination may be chemical, biological and/or with particulate matter. It can arise from several sources:

- Airborne environmental source :
  Dirt, dust, grit and hairs are constantly present in a non-filtered atmosphere. They vary from invisible sub-micrometre particles to clearly visible and definable units. Contamination from the environment depends also on the atmospheric conditions (dry, low RH) and any electrical changes carried by the particles and the material, which may become contaminated
- Not airborne environmental source:
  this involves placing the product or its components onto a pre-contaminated surface.
- Contamination arising from physical actions:
  these can emerge from fracturing or breaking (e.g. glass fragments arising when opening a glass ampule), abrasions or vibrations between same or different surfaces (e.g.rubber can suffer a form of abrasion when a needle passes through it)
- Contamination arising from the production process:
  mostly referring to chemical and biological contaminations. The latter can derive from insect, animals, humans, moulds, bacteria and yeast

Minimising particulate contamination is related to the product-pack form, the type and source of contamination, and the environment. Adequate control of these will produce relatively particle-free situation.

Pack- product compatibility

Compatibility basically covers any exchange, which will occur between the product and the pack. Incompatibility may be associated with interaction, migration, leaching, adsorption, and absorption, extraction, whereby ingredients may be lost, gained, or chemically/physically altered. Such exchanges may be identified as organoleptic changes, increase in toxicity/irritancy, loss or gain of microbial effectiveness, precipitation; turbidly, colour change, pH shift, degradation, etc.

External influences may catalyse, induce or even nullify chemical changes.

Chemical interactions and product contamination can also arise from impurities in the ingredients, accidental ingredients arising from the production process, or abrasion between contact surfaces. Some examples of these are:

- Adsorption of chemical entities onto component surface (preservatives, EDTA)
- Adsorption and surface evaporation (volatile preservatives, e.g. chlorbutanol, phenol, show rapid loss through low-density polyethylene)
- Other surface-active ingredients, which may be found in plastic material loss into product by solution, surface abrasion, etc., including anti-static additives, slip additives etc.
- Detachment of glass spicules may occur when alkaline solution of citrate, tartrate or salycilates are stored in soda glass containers
- Organoleptic changes (permeation of volatile or odorous substances through plastic material, e.g. loss of perfume)

Environmental considerations

After all, we have to consider certain environmental issues too. These are receiving increasing attention and include:

- Conservation of earth's nature resources (renewable and non-renewable)
- Conservation of energy and minimum use of energy
- Minimising pollution, from row material production to pack disposal
- Disposal of packaging materials
- Models of material disposal and recovery, including recycling, reuse, and chemical recovery

It is speaking about the "four R", i.e. recovery, recycling, reuse and reduce.

In EU the packaging disposal is covered by "The Packaging and packaging Waste directive 94/62/EC".

2. Drug Packaging Material

In primary drug packaging five main classes of material are used: glass, metals, plastics, elastomeric materials and paper.

Glass

Glass, originally the most widely used drug packaging material, is still favoured for many drug packages due to its advantages. These include its transparency, excellent resistance to the effects of most liquids and complete absence of permeability for gases. Glass is

produced by melting a mixture of inorganic oxides (mainly SiO_2), alkali and earth oxides. An alternative to these oxides is B_2O_3, which is used to reduce the melt's viscosity. Boron containing glass has a higher melting point and a lover coefficient of thermal expansion, which makes the glass more durable and heat resistant. It is also more inert, since it does not contain the leachable oxides of alkali and alkaline earth metals. When cooled, the molten glass solidifies without crystallizing, forming an amorphous structure that is clear. Stabilizer of PbO_2 and Al_2O_3 prevent devitrification, which is a slow crystallization process at room temperature that gradually reduces the clarity of glass. Glass is coloured by adding Iron oxide, Manganese dioxide and Sulfur to produce amber tint, which excludes all light at wavelengths below 450 nm. Glass is used where inertness and perfect barrier are important. Nowadays plastic containers displaced most of the glass, since they have lower weight, reduced production costs and the fact that they are shatterproof.

Metals

Metals are nowadays used only for the packaging of aerosols, as a foil in laminates for blisters and strips and in other composite structure. In all other drug-packaging applications plastics are preferably used, primarily because of lower production costs. In primary drug packaging only tinplate and aluminium are used, while the poor corrosion resistance of uncoated steel limits its use for containers of bulk products.

Tinplate

Tinplate of thickness about 0.1 mm (1/1000 inch) is usually coated with various polymers. The primary use of tinplate in drug packaging is for the production of aerosol cans.

Aluminium

This material is produced by hot and cold rolling to strips and is in different thicknesses used for the formation of different containers (e.g. strips of 25 microns thickness are is used for the formation of rigid containers, 3 – 5 mm thick for semi grid foil container, 1 mm thick for blister construction and 0.3 mm thick for foil used in laminate to provide a gas barrier).

Plastics

Plastics are the fastest growing packaging material for food, drugs and countless other products. In most drug package categories, plastics now dominate. The exceptions are aerosol cans and parenteral vials, where metal and glass dominate, respectively.

Advantages of plastics over glass and metal are:

- low density (plastics: 1 – 1.5 g/cm^3 , glass: 2 –2.5 g/cm^3, aluminum: 2.7 g/cm^3, tinplate 8.5 g/cm^3)
- plastics are lightweight and thus easier to handle (e.g. lifting, carrying and dispensing),
- easy manufacturing of plastics packages,
- like metal and unlike glass, plastic containers are shatterproof,
- like glass and unlike metal, plastic can be crystal clear or totally opaque,
- enabled heat sealing (e.g plastic films),

- plastics can be easily handled (e.g. printing, metallised,..)

There are some disadvantages too:

- plastic packing material cannot match the gas inpermeability and chemical inertness of Type I glass,
- some plastics are susceptible to stress cracking in the presence of alcohols, organic acids, ethers and many oils,
- plastic cannot match glass for resistance to heat, sunlight, and oxygen. Plastics producers use additives to improve the resistance of their products, but additions can leach from plastics when in contact with certain solvents that are used in drug formulation,
- plastic is an extremely poor conductor of electricity and retains electrostatic charges which attract undesirable dust particles. This can be compensated by incorporating antistatic additives,
- traces of low molecular weight polymer fragments that are more soluble in solvents can be present. In “pharmaceutical grade” plastics this problem must be minimized.
-

Elastomeric materials

They are complex materials composed from two to ten different raw materials. They are classified as saturated or unsaturated. Highly unsaturated elastomers have “rubbery” mechanical properties but poor resistance to water, solvents, and oils.

In drug packaging, elastomers are used mainly for parenteral container closures. Their use arises from two unique physical properties of elastomers; (a) compressable: allows to seal small irregularities inside of the neck of a parenteral vial; (b) resealable: allows to completely close after a hypodermic needle has been withdrawn.

Paper

In the packaging world broadly, paper is used more than any other material, but except for label, paper plays an insignificant role in primary packaging of drugs. Paper, of course, is still the best for secondary and tertiary drug packaging: the carton that contains the primary package and the corrugated shipping container that contain both.

3. Packaging and transport of radiopharmaceuticals

Radiopharmacies, whether they are operated by hospitals or commercial organisations, commonly supply radiopharmaceuticals to several hospitals. Transport of these radioactive materials is normally by road. In Europe, an Agreement Concerning the International Carriage of Dangerous Goods by Road (ECE 2008), known as ADR, specifies the requirements for the transport of radioactive materials. ADR refers to IAEA document: Regulations for the Safe Transport of Radioactive Material - 2012 Edition Specific Safety Requirements, which represents global guidelines for packaging and transport of Radioactive Material. As ADR has no provision for enforcement, individual countries have incorporated its requirements into

their own legislation (UK for example: The Carriage of Dangerous Goods and Use of Transportable Pressure Equipment Regulations 2009 (SI2009)). The regulations cover all radioactive materials with few exceptions such as nuclear weapons and smoke detectors for domestic use. Parts of the regulations that apply to the transport of radiopharmaceuticals and summary how a radiopharmacy might comply with regulations will be summarized in this chapter.

As with any activity that is regulated by law, there is no substitute for reference to the original legislation. In summary, the regulations specify:

- The types of packaging used for radioactive materials
- The Maximum activity in a package
- The maximum level of radioactive contamination on a package
- The labels to be displayed on packages
- The documentation that must accompany a consignment of radioactive material
- The placards to be displayed on a vehicle
- The duties of the driver in the event of an accident
- That a fire extinguisher is carried unless only up to ten Expected Packages are being transported
- That a quality assurance programme exists to demonstrate compliance with the regulations
- That a safety adviser is appointed

Packages

Although ADR describes eight types of packages for the transport of radioactive material, only two (The Expected Package and the Type A Package) are relevant to the transport of radiopharmaceuticals. A summary of the condition relevant to each is shown in Table 1 bellow.

Table 1 : Conditions for package types used to transport radiopharmaceuticals

Category	**Package Type**	**Maximum activity**	**Maximum radiation level at any point on external surface**	**Transport Index (TI)**
Not applicable	Excepted	Yes (isotope specific)	Not more than 5 uSv/h	Not applicable
I-White	Type A	None	Not more than 5 uSv/h	Not applicable
II-Yellow	Type A	None	More than 5 uSv/h but not more than 500uSv/h	More than 0 but not more than 1
III-Yellow	Type A	None	More than 500 uSv/h but not more than 2mSv/h	More than 1 but not more than 10

An Excepted Package:

Contains a limited activity of radionuclide. The principal requirements for an Excepted package are as follows:

- The Package is designed to retain its contents under routine transport conditions
- The package bears the marking RADIOACTIVE on an internal surface in such manner that warning of the presence of radioactive material is visible on opening the package
- The activity of the radionuclide in the package does not exceed a specified value. The activity limits for radionuclides that are used in nuclear medicine and might be transported in Excepted Packages are shown in table
- The dose rate at any point of the surface does not exceed 5uSv/h.
- The contamination level at any point of the external surface does not exceed 4Bq/cm2 for beta emitters, gamma emitters and low toxicity alpha emitters, and 0,4Bq/cm2 for all other alpha emitters.

The advantage of using Excepted Package is that the requirements for transport are minimal. In practice, an Excepted Package is often inappropriate as the activity required for a patient is greater than the package limit.

If the radiopharmaceutical does not meet the requirements of an Excepted Package, it must be transported in a *Type A Package*. The regulations specify many requirements for Type A Package, and are as follows:

- The package is designed to withstand normal conditions of transport. To demonstrate this, the package design satisfies a series of specified tests that include tests for ingress of water spray, free drop, stacking and penetration.
- The smallest external dimension is not less than 100mm.
- Sufficient absorbent material is included to absorb twice the volume of the liquid contents or the package has primary inner and secondary outer containment such that liquid contents are retained if the inner container leaks.
- The package is closed with a tamper evident seal.
- The contamination level at any point of external surface does not exceed 4Bq/cm2 for beta emitters, gamma emitters and low-toxicity alpha emitters, and 0,4Bq/cm2 for all other alpha emitters.

A radiopharmacy can use a package of their own, however they must perform the complete process of testing the package and demonstrate that it complies with the requirements of a Type A package. Numerous of tests must be performed and the data must be archived, facts that make this option unattractive. A more efficient alternative is to use commercially available Type A Packages, which are supplied with certificate of compliance.

Labelling the packages

Packages must be labelled with the name and address of either the consignor or consignee, or both. The only other labelling requirement on the outside of an ***Excepted Package*** is the

UN number (i.e. ***UN 2910***). The warning of the presence of radioactive material must be visible inside the package when it is opened.

Type A Packages

must be marked on the outside of the packaging with TYPE A, the UN number (UN 2915) and the proper shipping name »Radioactive Material, Type A Package«. Type A Packages are classified into three categories depending on the maximum radiation level at the surface and at 1 metre from the external surfaces, the latter being used to calculate the Transport Index (TI). To determine the TI, the radiation level in mSV/h is measured at a distance of 1 metre and multiplied by 100. The three categories, which have different identification labels to simplify recognition and to facilitate control during handling, are described in Table. An example of each is shown in Figure 1. The label displays the name and the activity of the radionuclide in the package. Those for Category II-Yellow and III-Yellow also display the TI. A Type A Package must bear the appropriate identification label on two opposite sides.

Figure 1: (a) Category I – White, (b) Category II – Yellow and (c) Category III – Yellow labels for Type A Packages

Each consignment of packages containing radioactive material must be accompanied by a **transport document** that contains the following information for each package:

- The name and address of the consignor
- The name and address of consignee
- The UN number : UN2910 – Excepted Package, UN2915 – Type A Package
- The proper shipping name – this is »Radioactive Material, Excepted Package - limited quantity of material« for Excepted Package and »Radioactive Material, Type A Package« for Category I-White, II-Yellow, III-Yellow package
- The United Nations Class Number "7"
- The name or symbol of the radionuclide
- A description of the physical form of the material (i.e. Liquid, Solid, Gas, Powder)
- A description of the chemical form of the material (i.e. organic compound, Inorganic Compound)
- The maximum activity of the package contents
- The category of a package (i.e. I-White, II-Yellow or III-Yellow)
- The Transport Index (for Categories II-Yellow and III-Yellow only)

- A declaration signed and dated by the consignor that the materials are described, packed, marked and labelled in accordance with the relevant regulations. A facsimile signature is acceptable.

For a consignment that consists solely of Excepted Packages, the transport document need to show only the UN Number. However, to avoid the complication of preparing two types of document depending on the content of the consignment, it may be more practical to issue a full transport document for each consignment.
Vehicles used for the Carriage of radioactive materials must be equipped with two portable fire extinguishers with a minimum capacity of 2 kg dry powder. If only Excepted Packages are being carried, the vehicle is exempt from requirement to carry fire extinguishers. The vehicle is also required to be equipped with an eye rinsing liquid and for each crew member a warning vest, portable lighting equipment, a pair of protective gloves and eye protection.
No placards are required on a vehicle in which only Excepted Packages are being carried. When category I, II, or III Packages are being carried, placards must be displayed on both sides and the rear of the vehicle. The placard design is shown in Figure 2 below.

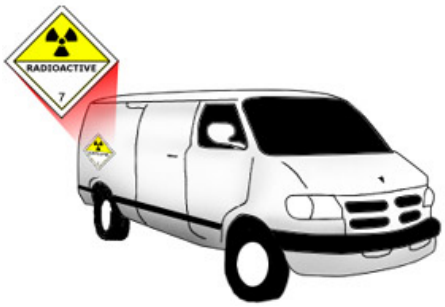

Figure 2: Vehicle placard (minimum dimensions 250 mm*250 mm)
Vehicles carrying dangerous goods are required to display an orange plate on the front and rear. Only fireproof notice (Figure 3) is necessary if TI is less than 3, number of packages contained is less than 10 and weight is less than 3.5 tonnes.

This vehicle is carrying **RADIOACTIVE MATERIAL** In case of accident get in touch at once with **THE POLICE** and Hospital Name City, Postcode Telephone number

Figure 3: Fireproof notice

Drivers of vehicles in which radioactive materials are transported must receive training. If the total number of packages carried does not exceed 10 and the sum of the TI does not exceed 3, attendance at a specialised training course is not required. However, drivers must receive training relevant to their duties. For drivers involved in the transport of radiopharmaceuticals, this includes knowledge of:

- The need to exercise reasonable care
- How to stow the packages securely in the vehicle
- The restriction on carrying passengers
- The need to carry the transport document and to produce it for inspection when requested
- The need to remain with the vehicle except when delivering packages
- When to display placards on the vehicle and the fireproof notice in the cab and the need to remove them from display once the radioactive materials have been delivered
- The action to be taken in the event of the loss of a package, an accident or a breakdown

The provision of this training should be documented. A regular reminder of the main requirements can be provided by including them on the transport document.

QA programme

To demonstrate compliance with the regulations, the radiopharmacy is required to maintain a quality assurance (QA) programme that includes:

- Audit to demonstrate compliance with the regulations
- Maintaining records of all consignments
- Testing of Type A packaging
- Measurements of surface contamination on packages

The ADR requires the appointment of a **safety adviser** who is responsible for helping to prevent the risks inherent in the transport of radioactive materials with regard to persons, property and the environment. The principal duties of the adviser are to:

- Monitor compliance with regulations
- Advise on the carriage of radioactive materials
- Prepare an annual report on the radiopharmacy's activities in the carriage of radioactive materials

The adviser may be a member of staff in the radiopharmacy's organisation or may be contracted externally. The adviser is required to undergo training, pass an examination and hold a vocational training certificate.

Take home messages:

- Packaging technology is a clearly defined discipline, but it must have the basis in the understanding of pharmaceutical products generally, the characteristics of formulations and dosage forms, and the general physical and chemical properties of drug substances. The packaging operation must be considered as an essential part of any drug discovery and development programe.
- The excellent developed drug product without an optimal pack is waste of time, human effort and money.

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PHARMACEUTICAL PACKAGING

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PRESENTATION OVERVIEW

- Types of pharmaceutical packaging, its role, factors influencing pharmaceutical packaging.
- Materials used in pharmaceutical packaging.
- Packaging, labelling of radiopharmaceuticals.

IS PACK A HUMAN INVENTION?

Not at all !!

Natural products:

Nutshell : mechanical, protection from animals
Pumpkin: drying, protection from animals
Apple: drying, protection from animals
Grape: same

PACK IN EVERYDAY LIFE?

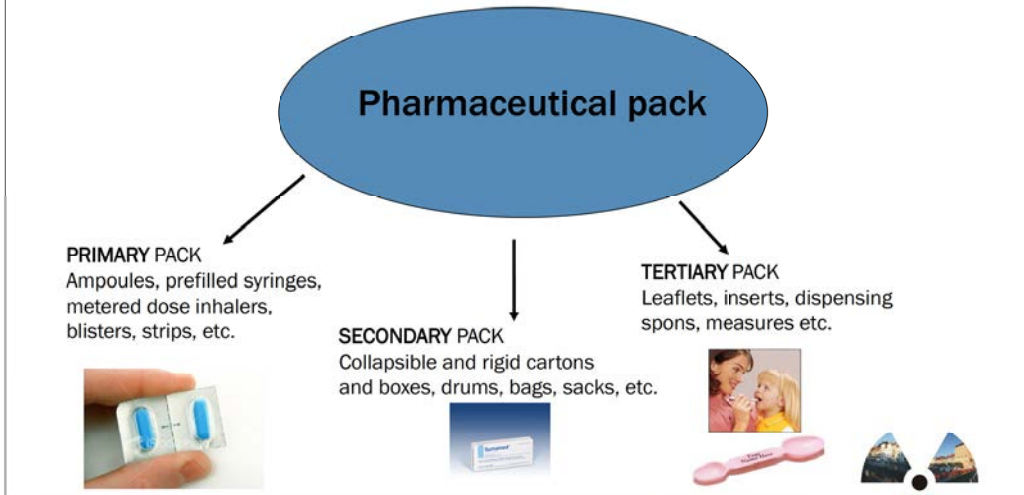
- Almost every human activity is connected with a pack.

Food
Technical materials
.
.
Cosmetics
Health accessories
Drugs

THE FUNCTION OF PACKS

1. "Life"
2. Storage
3. Carriage-distribution
4. Display
5. Sale
6. Use
7. Etc.

Anyway, we have primary, secondary and even tertiary pack:
- skin
- clothes
- cars, trains etc.



PACKS ARE DIVIDED...

According to basic **material employed**:
- Glass
- Plastic
- Metal
- Paper

According to **type**:
- Bottle
- Tube
- Blister
- Sachet etc.

According to **use**:
- single use (non-recloseable)
- multi use (recloseable)

FACTORS THAT INFLUENCE THE PHARMACEUTICAL PACK

1. The **type of dosage form** (physical state, sterile/non-sterile, unit/multi-dose)
2. The route or **mode of administration** (oral, local, parenteral, orifice introduction, inhalation)
3. The type of pack/material (style / type)
4. The **mode of sale** and marketing area (ethical, OTC-over the counter)
5. Administration (mode of dispensing, use of pack wich act as a device)
6. Administration by a device separate to pack

WHAT ARE THE FUNCTIONS OF PHARMACEUTICAL PACK ?

1. PRESENTATION
2. PROTECTION
3. IDENTIFICATION / INFORMATION
4. CONVENIENCE / CONTAINMENT / COMPLIANCE

Including:

- primary
- secondary and
- tertiary pack

PRESENTATION (IMAGE OF THE PRODUCT, PACK CONFIDENCE)

- Ethical or semiethical products are relatively simple, elegant and not over-dressed

- OTC (selling also through advertising) are designed more to eye appeal

IDENTIFICATION / INFORMATION

THE PRINTED PACK OR INSERTS SERVE TO PROVIDE BOTH IDENTITY AND INFORMATION (LEGAL REQUIREMENTS)

- Type of product
- Product formulation
- Product trade name
- Strenght / quantity
- Mode of usage / administration
- Expirity date or date of manufacture
- Batch No
- Shelf life declaration
- Storage instruction
- Product category (OTC, ethical)
- Precautions
- Manufacturer's name and adress
- Bar code or similar
- Warnings, e.g. Keep out of reach of children

Directive 2001/83/EC
Commission Delegated Regulation (EU) 2016/161

CONVENIENCE IS ASSOCIATED WITH:

Product use or administration;

- related to the pack (metered dose aerosol)
- related to the product-pack (unit dose eye drops)

CONTAINMENT

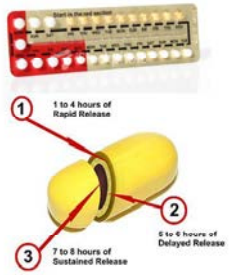
Powders, liquids and gases can be only distributed, purchased and used if they are contained in a pack.

It is probably the **most basic aspect** of any pack.

COMPLIANCE

Willingness to follow a prescribed course of treatment.

Pack can either detract or encorouge compliance.



PROTECTION

The most important factor and frequently the most complex. Pack must afford protection against the following **primary hazards:**

- MECHANICAL : handling (storage, carriage)
- CLIMATIC: temperature, light, humidity (surrounding atm.)
- BIOLOGICAL: microbiological (bacteria, moulds, yeasts) and biological (insects, rodents)
- CHEMICAL: interaction and exchange between the product and pack, pack and surrounding
- USE: patient, professional, misuse, abuse, adulteration

SCRAP CART MIST MARD

S – shock
C – compression
R – rattle (vibration)
A – abrasion
P – puncture

C – contemination/compatibility betwen pack/product
A – ageing
R – rodents, similar animal sources of contamination
T – theft

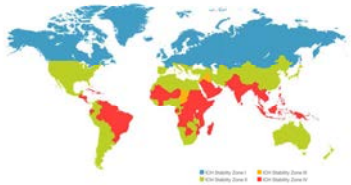
M – moisture (RH, rain, sea water)
I – insects
S – sunlight or any any light sources
T – temperature (extremes)

M – microbiological
A – atmospheric (gasses, pressure differentials, dirt, dust, oxygen, carbon dioxide,...
R – reuse/recycling/recovery/reduce ("four Rs")
D – disposal (indirect hazards associated with ultimate dosposal of pack-product (polution risks)

PHYSICAL (MECHANICAL) HAZARDS

- Shock-impact (G factor/impact load factor, fragility factor): drops from... impact from...
- Compression (during stacking): design of primary pack, position in final pack (blisters horizontaly/on-edge), failure in function of closuring systems
- Vibration (direct problems with the product independent of the pack; segregation of powders, separation of emulsions,surface dulling of tablets,... abrasion-printed surfaces) distortion of flexible packs, loosening or leakage from closures
- Puncture (external object, within the pack)

CLIMATIC HAZARDS



- Temperature
- Humidity / Moisture
- Atmospheric gases

TEMPERATURE ⟶ Stability – physical - chemical

Four zones(ICH):

Zone I (21º C, RH 45%)	lower temperate Europe
Zone II (26 º C, RH 60%)	upper temperate Europe
Zone III (31 º C, RH 40%)	tropical dry
Zone IV_a (31 º C, RH 70%)	tropical humid
Zone Iv_b (31 º C, RH 75%)	tropical very humid

VARIABLE TEMPERATURE CONDITIONS MAY CAUSE CHANGES...

...changes other than arise from storage at controlled temperature

- The pack "breathes"(in/out exchange).
- The closure loosens or tightens.
- Laminates separate or delaminate, usually starting at edges
- Materials "age" faster

Climatic Zone	Temperature	Humidity	Minimum Duration
Accelerated Ambient	40°C ± 2 °C	75% RH ± 5% RH	6 Months
Accelerated Refrigerated	25°C ± 2 °C	60% RH ± 5% RH	6 Months
Accelerated Frozen	5°C ± 3 °C	No Humidity	6 Months
Intermediate	30°C ± 2 °C	65% RH ± 5% RH	6 Months

Accelerated and Intermediate stability testing conditions

STORE IN A COOL AND DRY PLACE ! (*DECLARED CONDITIONS*) STATEMENTS BELOW 30ºC :

- up to 25 ºC
- 2-8 ºC : refrigerate, do not freeze
- below 8 ºC : refrigerate
- below -5 ºC : freeze
- below -18 ºC : deep freeze

Controlled room T is between 15 and 25 ºC (Ph. Eur.)

with excursions which allow a total range of 15-30 ºC (USP)

MOISTURE (HUMIDITY)

Moisture can exist as either a vapour or a liquid (rain, flooding, condensation), changes because of water can be extremely diverse:

- Hydrolysis
- Weight gain (stickiness), weight loss (increased concentration)
- Chemical interaction (effervescence)
- Drying out, caking, hardening, softening
- Changes in microbial growth or microbial effectiveness
- Dimensions changes, swelling, contraction (product and/or pack)
- Changes in appearance (dulling, loss of gloss)
- Organoleptic changes (flavour, odour)
- Changes in electrostatic effects ⟶ it collects dust and dirt (dry conditions charge plastics)

EXCHANGE OF MOISTURE (PRODUCT-PACK-SURROUNDINGS)

- The closuring system is not fully effective (RH differential gradient)
- The materials used are permeable (to some degree all plastic material)
- The pack may "breathe" (changes in external T and pressure lead to increased loss, gain (capillary chanels))
- Increasing/reducing the pressure within a pack (hot fill, compression of flexible containers during capping), absorbtion (dessicant), emission of moisture; T dependent
- Capillaries and capillary attraction (folds in areas where seals are made)
- Wicking (moisture transport via exposed end)

Packs which are basically impermeable, i.e. metal, glass and foils, largely rely on the effectiveness of the seal or closure.

ATMOSPHERIC GASES: O_2, CO_2, N_2

- oxydation type of interactions (rancidity of oils and fats)
- resinification of volatile oils
- absorption (reaction), reduced pressure, collapse of pack (gas flushing with inert gas)
- acceleration by light, T and catalytic substances (degradation of vit B1, catalysed by Cu)

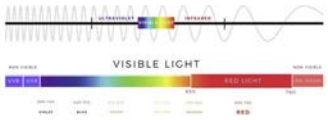
pH shift to acid range (possible chemical reaction)

As a flushing gas, e.g.ampoule filling, blisters, strips etc.

INTERNAL / EXTERNAL ATMOSPHERE

- Hot filling (product airspace contraction/condensation, partial vacuum).
- Terminal autoclaving (closure efficiency, dimensional changes, pressure in pack).
- External changes in atmospheric pressure (sea level, high altitude).
- Capping flexible container.
- Inadequate ullage in the container (high vapour pressure, high thermal coefficients of expansion (alchohol)).
- Vacuum packaging (retention of vacuum).
- Product change leading to pressure change (acid/alkali interaction, metal acid/alkali reaction leading to release of hydrogen or absorbtion of oxygen or CO_2 container headspace,...).
- Efficiency of nitrogen flushing.
- Extremes of temperature.
- Filling to incorrect weight, volume, number (product/ullage ratio).

SUNLIGHT / LIGHT
IR—VIS—UV

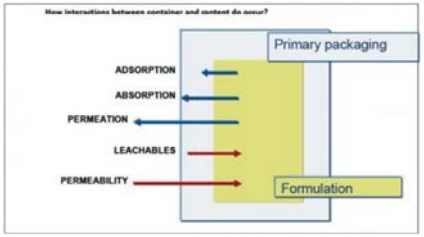


- Metals, foils: reflect IR, VIS, UV
- Glass (colours): absorbs IR, VIS, UV
- UV : the most serious risk – photochemical changes to both product and pack

CONTAMINATION

- Chemical interactions (pack-product)
- Organoleptic effects
- Exchange of ingredients (pack-product)

- Particulates
- Biological - microbiological causes



Atmospheric contamination:
- Microbiological
- Particulate airborne

Particualte contamination:
- Airborne (dirt, dust, fibres, grit, hairs,...)
- Direct (cut, rubbed, torn, punctured,...)

Contamination can arise from:
- Physical actions
- Fabrication processes
- in-house production and processing
- Chemical contamination

AVOIDANCE or ELIMINATION? Stick to GMP!

BIOLOGICAL CONTAMINATION

- Insects, including termites
- Animals, including rodents
- Moulds, bacteria, yeasts, pyrogens (microbial aspects/bioburden)
- Human pilferage, adulteration,... (tamper-resistent closures)

Requirements of sterile products and aseptic packaging.

Need to minimise microbiological contamination (involvement of QA: GMP, GLP,...).

How these organisms can survive, can be controlled.

Special pack characteristics.

BIOLOGICAL CONTAMINATION

Control:

- Cleanliness
- Good hygiene
- Removal of factors necessary to survival of viable organisms (moisture, oxygen (anaerobic !), nutrients (product itself?))

Pack must be an effective barrier to moisture and gases so that entry does not support growth or, if the product is made sterile, re-entry of bioburden is prevented.

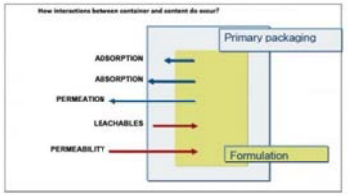
Control can be exerted by use of preservative systems (desinfectants,bactericides, bacteriostatics, fungicides), STERILISATION.

CHEMICAL HAZARDS AND COMPATIBILITY

compatibility: any exchange wich will occur between:

product / pack, pack / product

(impurities, ingredients,..)



incompatibilitiy:

interaction, migration, leaching, adsorption, absorption, extraction - ingredients may be lost, gained, chemically, physically altered (organoleptic changes, increase in toxicity / irritancy, loss / gain of microbial effectiveness, precipitation, haze, turbidity, colour change, pH shift, degradation,...)

ENVIRONMENTAL ISSUE

This issue is receiving a great publicity and includes:

- Conservation of natural resources (non-renewable)
- Conservation of energy and minumum use of it
- Minimising pollution
- Disposal of packaging materials
- Models of packaging materials disposal
- Recovery- four R : recovery, recycling, reuse and reduce (materials involved)

THE PACKAGING AND PACKAGING WASTE DIRECTIVE 94/62 EC

- Open dumping, material is left to break down naturally
- Sanitary landfill (use of large holes in the ground, after filling covering with soil, generation of undesireable gases)
- Incineration (process of controlled combustion)
- Composting (relatively energy intensive)
- Reuse (containers are returned, cleaned and use for the same or similar products, e.g. milk, beer).

The future packaging technologist will have to consider disposal as a part of the brief and even design the pack from materials with the most effective disposal or recovery in mind.

EUROPEAN PHARMACOPOEIA 11.8

- 1.3 GENERAL CHAPTERS
- 1.3.1 Materials for containers and containers
- **3.1. *Materials used for the manufacture of containers***
- 3.2. *Containers*
- 3.3. *Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes*

3. MATERIALS FOR CONTAINERS AND CONTAINERS

Dear Aljaž,

Bring from the store...

½ kg of bread

2 beers

5 l of milk....

Ah, forget about it...

Just bring the beer.

Your big momma ☺

MATERIALS FOR CONTAINERS

1. GLASS
2. METALS
3. PLASTICS
4. ELASTOMERS
5. COMBINATION MATERIALS (films,foils and laminations)
6. PAPER

GLASS

- The oldest and originally the most widely used drug packaging material.
- Mixture of inorganic oxydes (SiO_2, Na_2O, CaO, B_2O_3,PbO_2, Al_2O_3)
- ***Type I***: borosilicate glass inert (high hydrolitic resistance), suitable for most preparations wheather or not for parenteral use
- ***Type II***: soda-lime-silica glass wich surface was treated/de-alkalized (sulphuring, sulphating), suitable for most acidic,neutral, aqueous preparations wheather or not for parenteral use
- ***Type III***: untreated soda-lime-silica glass, average or somewhat above average chemical resistance, sutable for non-aqueous preparations for parenteral use, powders for parenteral use (except freeze-dried preparation), preparations not for parenteral use
- Type IV

GLASS ADVANTAGES

- Totally impermeable to all gases
- Excellent clarity
- Easy to clean and sterilize with heat
- Easy farbrication
- It is filling friendly
- Good compressional strenght
- Glass is easy hot filled

GLASS DISADVANTAGES

- High density, heavier containers, brittle character
- Thick containers, heavier, more expensive
- If it breaks, glass shatters into numerous fragments (e.g. ampoule opening)

METALS

Tinplate, Aluminum (Steel)
Lead, Tungsten

ADVANTAGES

- Strong, shatterproof (aerosol containers)
- Totally impermeable to all gases
- Good heat conduction (100 times better than glass and 400 times better than plastics). It can also be a disadvantage!

Aerosols, foils and laminates (blister, strip)

PLASTICS

Packaging material for: food,... ,countless products, drugs

ADVANTAGES

- Low density
- A light weight (lifting, carrying, dispensing, manufacturing)
- Shatterproof
- Can be clear or totally opaque
- Heat sealing possibility
- Can be treated: printing, labeling, etc.

DISADVANTAGES

- Gas permeability, chemical non-inertness
- Stress cracking in the presence of alcohols, organic acids, ethers, oils
- Susceptible to heat, sunlight, oxygen (ageing !)
- Poor conductor of electricity (it retains electrostatic charges and attracts dust and dirt)
- Traces of low molecular polymers fragments (pharmaceutical grade plastics)

POLYETHYLENE (PE)

- High density PE (HDPE):
  the most widely used plastic material in drug packaging
- Low density PE (LDPE)

OTHERS:

- Linear low density polyethylene (LLDP)
- Polyvinyl chloride (PVC)

Polypropylene (PP), compared to PE:
- Better resistance to greases and oils
- Better odour barrier
- Less tendency to adsorb actives
- Lower additives content

- Polyvinilidene chloride (PVDC):
  improved gas and water vapours resistance , e.g. blister, strip
- Polystyrene (PS)
- Polyesters (e.g. polyethylene terephtalate, soft drinks)
- Polyamides (nylon)
- Fluorine containig polymers (teflon, Aclar :
  good barrier to water vapours, comparable to PVDC)
- Polyurethane (foam as bottle stuffing)

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PLASTIC MATERIALS PERMITED FOR USE IN PHARMACEUTICAL CONTAINERS BY PH. EUR.

- PVC (human blood, blood components, aqueous sol. for i.v. infusion)
- PVC (components used in blood transfusion)
- LDPE (parenteral, ophthalmic prep.)
- HDPE (parenteral)
- PP (parenteral)
- Ethylene-vinyl acetate copolymer (total parenteral nutrition)
- Slicone oils (lubricant)
- Silicone elastomer (closures, tubing)

COMPOSITE FILMS (FOILS, LAMINATES)

include plastics, metal and paper; strenght, stiffness, heat stability, gas barrier, controlled light transmission, low cost

ELASTOMERS

Complex materials containing different raw material, mainly as containers closers for parenterals.

PAPER

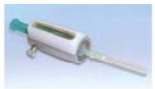
As secondary and tertiary packaging material in drug packaging

RADIOPHARMACEUTICALS

- Majority: parenterally applied solutions, lyophilised (freeze dryied)
- Efficacy, stability, safety of entity on storage and administration largely depends on the nature and preformance of packaging components
- Safety, personal radiation protection

Materials:

- Glass (type I)
- Plastics (PE, PP, PS, PVC)
- Aluminium, lead, tungsten (seal, shield)
- Rubber, elastomers (natural rubber, synthetic polyisoprene, butil, chlorobutyl, bromobutyl rubber) “half stop position”

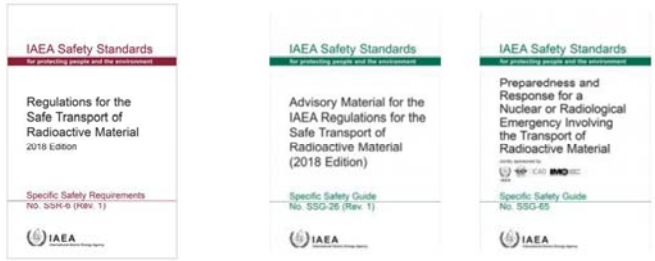


THE PACKAGING AND TRANSPORTATION OF RADIOACTIVE MATERIAL ARE RULED BY LOCAL LAW IN ACCORDANCE BY:

ADR (European Agreement concerning the International Carriage of Dangerous Goods by Road)

THE PACKAGING AND TRANSPORTATION OF RADIOACTIVE MATERIAL ARE RULED BY LOCAL LAW IN ACCORDANCE BY:

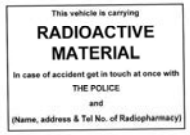
- IAEA: Regulations for the Safe Transport of Radioactive Material - 2012 Edition; Specific Safety Requirements; **IAEA Safety Standards Series SSR-6**



IAEA (INTERNATIONAL ATOMIC ENERGY AGENCY): REGULATIONS FOR THE SAFE TRANSPORT OF RADIOACTIVE MATERIAL - 2018 EDITION

1. The type of packaging that can be used for radioactive materials.
2. The maximum activity that can be in the package.
3. The maximum level of radioactive contamination that is allowed on a package.
4. The QA programme to demonstrate a compliance with the regulations.
5. The documentation that must accompany radioactive material.

6. The placards that are to be displayed on a package.
7. The vehicle must carry a fire extinguisher unless only a small number of packages are being carried.
8. The labels that are to be displayed on a vehicle.
9. The duties of the driver in the event of an accident.



PACKAGE OF RADIOPHARMACEUTICALS

1. Excepted Package
2. Type A Package

GENERAL REQUIREMENTS (SECTION VI,PARA.607-618)

- The package shall be so ***designed*** in relation to its mass, volume and shape that it can be ***easily and safely transported***. In addition, the package shall be so designed that it can be ***properly secured*** in or on the conveyance during transport.
- The ***design*** shall be such that any lifting attachments on the package will not fail when used in the intended manner and that if failure of the attachments should occur, the ability of the package to meet other requirements of these Regulations would not be impaired. The design shall take account of appropriate safety factors to cover snatch lifting.
- ***Attachments*** and any other features on the outer surface of the package which could be used to lift it shall be designed either to support its mass in accordance with the requirements, or shall be removable or otherwise rendered incapable of being used during transport.
- As far as practicable, the packaging shall be so designed and finished that the ***external surfaces are free from protruding features*** and can be ***easily decontaminated.***
- As far as practicable, the ***outer layer of the package*** shall be so designed as to ***prevent the collection and the retention of water.***

- Any ***features added*** to the package at the time of transport which are not part of the package shall ***not reduce its safety***.
- The package shall be ***capable of withstanding the effects of any acceleration, vibration or vibration resonance which may arise under routine conditions of transport*** without any deterioration in the effectiveness of the closing devices on the various receptacles or in the integrity of the package as a whole. In particular, nuts, bolts and other securing devices shall be so designed as to prevent them from becoming loose or being released unintentionally, even after repeated use.
- The ***materials*** of the packaging and any components or structures shall be physically and chemically compatible with each other and with the radioactive contents. Account shall be taken of their ***behavior under irradiation***.
- All ***valves*** through which the radioactive contents could escape shall be ***protected against unauthorized operation***.
- The ***design*** of the package shall take into account ***ambient temperatures and pressures*** that are likely to be encountered in routine conditions of transport.
- For radioactive material having other dangerous properties, the package design shall take into account those properties.

EXCEPTED PACKAGE (PROPER SHIPPING NAMES)

UN 2908	**RADIOACTIVE MATERIAL, EXCEPTED PACKAGE – EMPTY PACKAGING**
UN 2909	RADIOACTIVE MATERIAL, EXCEPTED PACKAGE – ARTICLES MANUFACTURED FROM NATURAL URANIUM OR DEPLETED URANIUM OR NATURAL THORIUM
UN 2910	**RADIOACTIVE MATERIAL, EXCEPTED PACKAGE – LIMITED QUANTITY OF MATERIAL**
UN 2911	RADIOACTIVE MATERIAL, EXCEPTED PACKAGE – INSTRUMENTS OR ARTICLES

EXCEPTED PACKAGE
LIMITED ACTIVITY OF RADIOACTIVE MATERIALS

- The ***quantity*** of radioactive material (radionuclide) in the package shall ***not exceed relevant limits*** for the package (transport ***by post 1/10*** of relevant limits)
- ***Empty packages*** having contained radioactive material
- Contain instruments or articles in limited quantities
- Contain articles manufactured of natural uranium,depleted uranium or natural thorium
- The package is designed to ***retain its contents under normal transport conditions***
- Radiation level at any point on the ***external surface*** shall not exceed ***5μSv/h***
- ***No special labels are required on the outside***, warning (RADIOACTIVE) must be visible inside of the package when it is opened.

CAUTION
This package contains excepted quantities of **RADIOACTIVE MATERIALS**

MAXIMUM ACTIVITIES THAT CAN BE TRANSPORTED IN EXCEPTED PACKAGES

Table 1. Activity Limits for Common Radionuclides in Excepted Packages

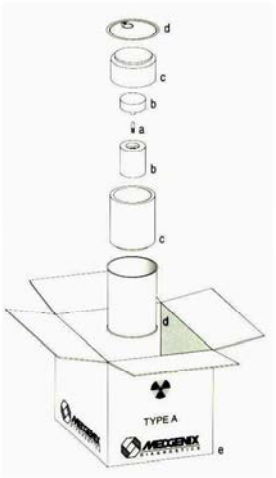
Radionuclide	Activity limit (MBq)
Bromine-77	300
Carbon-11	50
Carbon-14	200
Chromium-51	3,000
Cobalt-57	800
Cobalt-58	100
Fluorine-18	50
Gallium-67	600
Gold-198	50
Indium-111	200
Iodine-123	600
Iodine-125	200
Iodine-131	50
Iridium-192	50
Iron-59	80
Molybdenum-99	50
Phosphorus-32	30
Rubidium-81	90
Selenium-75	300
Strontium-89	50
Technetium-99m	800
Thallium-201	1000
Xenon-133	2000
Yttrium-90	20

IF RADIOPHARMACEUTICAL DOES NOT MEET THE REQUIREMENTS OF AN ***EXCEPTED PACKAGE***, IT MUST BE TRANSPORTED IN A ***PACKAGE TYPE A.***

THE REQUIREMENTS OF THIS PACKAGE ARE THE FOLLOWING:

- The smallest ***external dimension*** is not less than ***10 cm***.
- The package is closed with a ***tamper-evident seal***
- The package retains its contents under ***reduced pressure***
- Sufficient absorbent material is included to absorb twice the volume of the liquid contents
- The package is designed to ***withstand normal conditions of transport*** (free drop, penetration etc.)
- ***Maximum radiation level*** at any point on the ***external surface*** of package or overpack shall not exceed ***2mSv/h*** (exclusive use 10mSv/h)

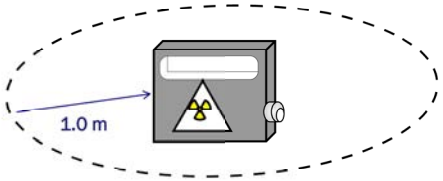
Requirements for Type A package: Section VI (Para.635 – 651)



TYPE A PACKAGE: PROPER SHIPPING NAMES

UN 2915	RADIOACTIVE MATERIAL, TYPE A PACKAGE, non-special form, non-fissile or fissile-excepted
UN 3327	RADIOACTIVE MATERIAL, TYPE A PACKAGE, FISSILE, non-special form
UN 3332	RADIOACTIVE MATERIAL, TYPE A PACKAGE, SPECIAL FORM, non-fissile or fissile-excepted
UN 3333	RADIOACTIVE MATERIAL, TYPE A PACKAGE, SPECIAL FORM, FISSILE

TRANSPORT INDEX (TI)



The ***Transport Index*** is the maximum radiation level, in mSv/h, at a distance of 1 m from the external surface of the package, multiplied by 100.

The categories of packages, are determined by the Transport Index and the maximum radiation level at any point on the surface of the package.

CATEGORIES OF PACKAGES

Transport Index	Max dose rate on the surface	Category
0 (ie < 0.05)	to 5 µSv/h	I-WHITE
> 0 to 1	>5 µSv/h to 0.5 mSv/h	II-YELLOW
> 1 to 10	>0.5 mSv/h to 2 mSv/h	III-YELLOW
> 10	>2 mSv/h to 10 mSv/h	III-YELLOW (exclusive use)

White-I Label

surface < 5.0 µSv/h

1.0 m < 0.05 µSv/h

TI = 0

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Yellow-II Label

surface < 500 µSv/h, > 5 µSv/h

1.0 m < 10 µSv/h

0 < TI < 1.0

Yellow-III Label

surface > 500 μSv/h, < 2000μSv/h

1.0m > 10μSv/h, < 100μSv/h

1.0 < TI < 10

PACKAGE LABELS

- Package type
- Isotope, activity
- Transport index (surface dose)
- Identification (consignor, consignee)
- OVERPACK

TRANSPORT DOCUMENTATION

Each consignment of packages containing radioactive material must be accompanied by a transport document that contains the following information for each package:

- The ***name and address of the consignor***
- The ***name and address of consignee***
- The ***UN number*** : UN2910 – Excepted Package, UN2915 – Type A Package
- The ***proper shipping name*** – this is »Radioactive Material, Excepted Package - limited quantity of material« for Excepted Package and »Radioactive Material, Type A Package« for Category I-White, II-Yellow, III-Yellow package
- The ***United Nations Class Number*** »7«
- The ***name or symbol of the radionuclide***

TRANSPORT DOCUMENTATION

- A ***description of the physical form*** of the material (i.e. Liquid, Solid, Gas, Powder).
- A ***description of the chemical form*** of the material (i.e. organic compound, Inorganic Compound).
- The ***maximum activity*** of the package contents.
- The ***category of a package*** (i.e. I-White, II-Yellow or III-Yellow).
- The ***Transport Index*** (for Categories II-Yellow and III-Yellow only).
- A ***declaration signed and dated by the consignor*** that the materials are described, packed, marked and labelled in accordance with the relevant regulations. A facsimile signature is acceptable.

CONCLUSION

Packaging technology is a **clearly defined discipline**, but it must have the basis in the **understanding** of pharmaceutical products generally, the **characteristics** of formulations and **dosage forms**, and the general physical and chemical **properties** of drug substances. The packaging operation must be considered as an **essential part of any drug discovery** and development programe.

The excellent developed drug product without an optimal pack is waste of time, human effort and money.

ENJOY YOUR STAY IN SLOVENIA

Quick recommendations …



Aseptic preparation

Assist. Prof. Petra Kolenc, MPharm, PhD, Division of Nuclear Medicine, University Medical Centre Ljubljana

Petra Kolenc is radiopharmacist at the Division of Nuclear Medicine for last 25 years. In 2009 she received EANM, European Postgraduate Specialization Certificate in Radiopharmacy and in 2012 Specialization in Radiopharmacy at University of Ljubljana, Slovenian Chamber of Pharmacy and Ministry of Health. In 2011 she got PhD degree at University of Ljubljana, Faculty of Pharmacy. Next to the involvement in routine preparation and QC of radiopharmaceuticals she is involved in research work, being responsible person - coordinator for the research at the Division. She is involved in different national and international research projects. Her main research area is in the peptide-based radiopharmaceuticals, from development stage to the translation into clinical setting. She is involved in a teaching at under- and postgraduate level (Faculty of Pharmacy, Faculty of Medicine, Faculty of Health Sciences, Faculty of Mathematics and Physics, ESMIT/EANM). She is former member of Radiopharmacy Committee of the EANM, former member of ESMIT project group, member of the Extended Expert Council for the field of nuclear medicine in Slovenia and member of the Research Council at University Medical Centre Ljubljana.

In June 2021 Petra Kolenc become an assist. prof. at Faculty of Pharmacy, University of Ljubljana.

The lecture has the following learning objectives:

1. Students are able to understand the role of aseptic preparation in the process of preparation of sterile medicinal products
2. Students are able to explain key elements of the aseptic process
3. Students are able to perceive basic principles of maintaining the integrity of the aseptic processing area
4. Students are able to understand the role of regular monitoring of clean areas
5. Students are able to discriminate between EU GMP regulating manufacturing sites and different rules and guidelines dedicated to healthcare establishment

Summary of the lecture:

By definition a radiopharmaceutical is any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose. The majority of radiopharmaceuticals are produced as sterile preparations intended for parenteral administration. The manufacture of sterile products is subject to special

requirements in order to minimize risks of microbiological, particulate and pyrogen contamination. Similarly, in healthcare establishments it is of utmost importance to organize operations in the radiopharmacy in a way to maintain the sterility of the product throughout the dispensing process. In Europe manufacture of medicinal product in comercial sites is subjected to pharmaceutical production standards lay down in Guidelines of Good Manufacturing Practice of Pharmaceuticals – EU GMP. Anex 1 of the EU GMP covers "Manufacture of Sterile Medicinal Products" specifically.

Since GMP of pharmaceuticals is covered already within other lecture(s) the lecture of aseptic preparation will mainly focus on good practices for preparation of medicinal products in healthcare establishments as presented in documents such as PIC/S guide PE 010–4, chapter 5.19 Extemporaneous preparation of radiopharmaceuticals in European Pharmacopoeia and Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals (EANM Radiopharmacy Committee)**.**

Whereas PIC/S Guide PE 009 applies to industrial manufacture of distributed medicinal products, the basic requirements presented in PIC/S gu ide PE 010–4 apply to the preparation of medicinal products normally performed by healthcare establishments for direct supply to patients. Clear distinction is made between industrial and small-scale extemporaneous preparation of radiopharmaceuticals, providing guidance on GPs distinct from industrial standards.

A small-scale radiopharmaceutical is any in-house radiopharmaceutical prepared on a small scale at non-commercial sites for PET, SPECT or therapeutic applications. A small-scale radiopharmacy is a facility where the small-scale preparation of radiopharmaceuticals is carried out under a license that is in accordance with national regulations. The term small-scale radiopharmacy is not related to the size of the facility, which may vary in a broad range, but only to the kind of radiopharmaceutical preparation performed.

Regardless of the scale any aseptic activitiy is performed in a grade A environment i.e. in a laminar flow cabinet.

Table 1: Maximum permitted total particle concentration for cleanroom classification - EU GMP, Annex 1

Grade	**Maximum limits for total particle ≥ 0.5 µm/m^3**		**Maximum limits for total particle ≥ 5 µm/m^3**	
	at rest	**in operation**	**at rest**	**in operation**
A	3 520	3 520	Not specified (a)	Not specified (a)
B	3 520	352 000	Not specified (a)	2 930

C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined (b)	29 300	Not predetermined (b)

(a) Classification including 5µm particles may be considered where indicated by the CCS or historical trends.
(b) For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

Clean room is an area in which the number of airborne particles of a particular size is controlled. Historically, in 1961 Whitfield and his colleagues developed the world's first cleanroom and clean benches. They discovered that the air emerging from HEPA (high-efficiency particulate air) filters had a uniform and predictable speed, and that the flow could carry away particles in its path. That phenomenon became known as „laminar flow". Their unic idea was: "Why try to "control" contamination? Why not just eliminate it?"

The first HEPA filters were developed for Atomic Energy Commission during World War two for use in facilities manufacturing components for the atomic bomb project. These HEPA filters were originally designed to capture microscopic radioactive particles too small for effective removal by existing types of filters. HEPA filters used today are much more efficient as the one in 1940s.

HEPA filter is a type of mechanical air filter it works by forcing air through a fine mesh that traps particles. In the pharmaceutical industry, HEPA filters are used as terminal filters for the processing or filtration of air in production spaces. They are mandatory in sterile production. To qualify as a type A HEPA filter the filter must capture at least 99,97% of particles 0.3 microns in size.

Grade A is the local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. As described above, such conditions are normally provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated.

As there is no terminal sterilization of aseptic products the microbiological environment in which they are prepared is of the utmost importance. Therefore, the environment should be controlled and only authorized people should be allowed to have access. Unless there is a proper justification available, the background environment for laminar airflow cabinets should meet grade B requirements, with grade D required for pharmaceutical isolators. Based on risk assessment, considering time between preparation, use of closed system and nature and composition of the closed system, Annex 3 of PIC/S PE 010-4 suggests grade C background

environment for LFCs to be sufficient. In case of immediate administration in some cases, subjected to risk assessment, C grade area may be sufficient even in case of open aseptic procedure.

There are several sources of particulates, humans being the major one. We're constantly shedding skin cells and hair cells. Proper gowning and controlled movements with sedentary position minimize the shedding of the particles within a clean room.

Personnel involved in aseptic processing, should have specific competency and skills in aseptic technique. They should be periodically assessed by performing media fill simulations, using broth or a similar nutrient media to simulate the aseptic procedure.

Similarly, process validation of aseptic procedures should be performed by using media fills to simulate the aseptic procedure and should be performed initially as well as subsequently on a regular basis, according to the risk, and whenever significant modifications have been made to the equipment or to the process. The process simulation test should imitate as closely as possible routine aseptic procedures (i.e. manipulations that are normally conducted) and include all the critical production steps. Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.

In addition to media fill simulations monitoring is performed to obtain evidence that the process, operators and facility are operating under control. Monitoring consists of qualification activities (classification “at rest”) and environmental monitoring of units in use (environmental monitoring “in operation”). For pharmaceutical applications the major criteria upon which the sterile facilities are assessed should be the risk of microbiological contamination of the product. However, because of the imprecision and variability associated with microbiological test methods it is recommended to complement microbiological environmental control with more practical physical monitoring.

Cleaning is also an important factor in the process of maintaining the requirements of designated clean room(s)/area(s). Cleaning and disinfecting agents should be free from viable microorganisms and those used in grade A and B areas should be sterile and spore free. The effectiveness of cleaning should be routinely demonstrated, by microbiological surface sampling e.g. contact plates or swabs. Periodic use of sporicidal cleaning agents should be considered to reduce contamination from spore forming microorganisms.

Aseptic handling practices of radiopharmaceuticals must be balanced with radiation safety considerations. Radiation exposure to personnel is directly proportional to the quantity of radiation handled and the time handling the radioactivity; minimizing handling time will minimize radiation exposure. Personnel handling radiopharmaceuticals may work quickly in a controlled and safe manner, including multiple hand movements in and out of the grade A laminar air flow cabinet during aseptic processes. Radiation exposure follows the inverse square law; increasing the distance between the operator and the radioactivity source will

decrease radiation exposure to personnel by the square of the distance. To increase the distance tweezers and grippers may be used, including in a garade A environment. Radiation exposure to personnel decreases with the use of shielding materials, therefore various shielding materials (e.g., lead, tungsten) is tipically udes. The use of shielding, such as vial, and syringe shields, is usually required throughout the radiopharmaceutical handling process, including within an grade A environment.

For safety reasons, LAF Cabinets with a vertical downward air flow exhausting vertically from the cabinet and not towards the operator or isolators should be used when working with radioactive drugs.

Take home messages:

- Aseptic preparation maintains the sterility of previously sterilized medicinal products, but it is not the sterilization method
- Risk assessment is an important tool that complements the guidelines and guidance documents and allows defined deviations from the basic recommendation
- Most probable source of contamination in clean areas is personnel. Proper gowning, disinfecting, aseptic techniques, monitoring and cleaning are essential to maintain sterility
- Proper education and knowledge of all personnel working in clean areas is a one of the key elements to the success

References (further reading):

- EU GMP, Volume 4 Good manufacturing practice (GMP) Guidelines. https://ec.europa.eu/health/documents/eudralex/vol-4_en.
- PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments. Version PE 010–4, March 2014. https://www.picscheme.org/en/publications.
- European Pharmacopoeia, current version, 5.19 Extemporaneous preparation of radiopharmaceuticals.
- Gillings et al. Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals. EJNMMI Radiopharmacy and Chemistry (2021) 6:8
- Aerts J, Ballinger JR, Behe M, Decristoforo C, Elsinga PH, Faivre-Chauvet A, Mindt TL, Kolenc Peitl P, Todde S, Koziorowski J. Guidance on current good radiopharmacy practice for the small-scale preparation of radiopharmaceuticals using automated modules: a European perspective. J Labelled Compd Radiopharm. 2014;57:615–20.
- USP General Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging. Reprinted from USP 42–NF 37. https://www.usp.org/chemical-medicines/general-chapter-825.

ASEPTIC PREPARATION

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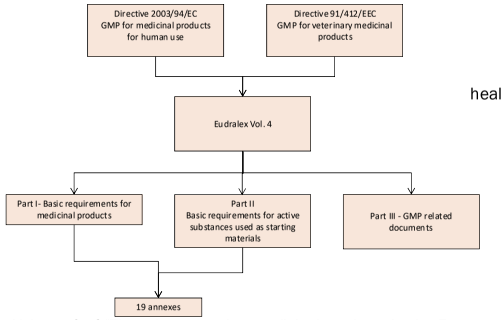
univerzitetni klinični center ljubljana

CONTENT

- Aseptic preparation – maintaining sterility
- Requrements
  - Preparation of radiopharmaceuticals in healthcare establishments (GMP vs. cGRPP/PICs requirements)
- Aseptic processing
- Monitoring
- Other guidance documents

EUDRALEX - VOLUME 4 - GOOD MANUFACTURING PRACTICE (GMP) GUIDELINES



European Commission

health.ec.europa.eu/medicinal-products/eudralex_en

Annex 1 Manufacture of Sterile Medicinal Products (New!, 25.8.2023)

Annex 3 Manufacture of Radiopharmaceuticals

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.

PIC/S - PHARMACEUTICAL INSPECTION CONVENTION SCHEME

PIC/S PHARMACEUTICAL INSPECTION CONVENTION PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 010-4
1 March 2014

PIC/S GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS

- **PIC/S GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS**
  - **Annex 1: GUIDELINES ON THE STANDARDS REQUIRED FOR THE STERILE PREPARATION OF MEDICINAL PRODUCTS**
  - **Annex 3: GOOD PRACTICES FOR THE PREPARATION OF RADIOPHARMACEUTICALS IN HEALTHCARE ESTABLISHMENTS**

Scope

Whereas PIC/S Guide PE 009 applies to industrial manufacture of distributed medicinal products, the basic requirements presented in this Guide apply to the preparation of medicinal products normally performed by healthcare establishments for direct supply to patients.
Clear distinction is made between industrial and small scale extemporaneous preparation of radiopharmaceuticals, providing guidance on GPs distinct from industrial standards.

GLOSSARY

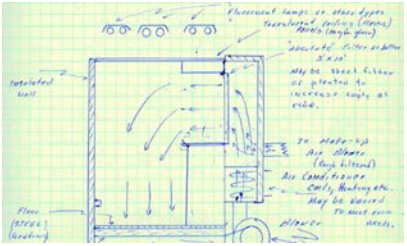
Radiopharmaceutical	A radiopharmaceutical is any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.
Small-scale radiopharmaceutical	A small-scale radiopharmaceutical is any in-house radiopharmaceutical prepared on a small scale for PET, SPECT or therapeutic applications.
Small-scale radiopharmacy	A small-scale radiopharmacy is a facility where the small-scale preparation of radiopharmaceuticals is carried out under a license that is in accordance with national regulations. The term small-scale radiopharmacy is not related to the size of the facility, which may vary in a broad range, but only to the kind of radiopharmaceutical preparation performed.

(SMALL) HOSPITAL SETTING

ANNEX 1 (PIC/S PE 010-4) - GUIDELINES ON THE STANDARDS REQUIRED FOR THE STERILE PREPARATION OF MEDICINAL PRODUCTS

- Sterile preparations are considered to be high risk category products.
- The sterile preparation of medicinal products includes:
  - The preparation of terminally sterilized products
  - The aseptic preparation of products
- Handling and filling of **aseptically prepared products** (open and closed procedures) should be performed in a **grade A environment in a laminar flow cabinet** (LFC) or a positive pressure pharmaceutical isolator. The room should have a positive pressure (ideally 10 – 15 Pascals) and air flow relative to the surrounding areas of a lower grade in order to protect the product from contamination.

HISTORY



Whitfield's notebook page showing "Cross section of clean room"

In 1961 Whitfield and his colleagues developed the world's first cleanroom and clean benches. They discovered that the air emerging from HEPA (high-efficiency particulate air) filters had a uniform and predictable speed, and that the flow could carry away particles in its path. That phenomenon became known as „laminar flow".

Basic idea: Why try to "control" contamination? Why not just eliminate it?

GMP, ANNEX 1, COMTAMINATION CONTROL STRATEGY

Topic	Main Change Highlight
Contamination Control Strategy (CCS)	Now a **mandatory, site-wide strategy** for preventing contamination. Must be a **living document** continuously reviewed and integrated into operations.
Quality Risk Management / Pharmaceutical Quality System (QRM / PQS)	**QRM and PQS fully embedded** throughout the document. All decisions and controls must follow a **risk-based approach**
Environmental Monitoring (EM)	**Stricter requirements** for viable and non-viable particle monitoring, with enhanced expectations for **trending and responses**.
Cleanroom Design	Emphasis on **airflow visualization**, **airlock integrity**, and **minimizing contamination risks** through better design and control of personnel/material flow.

ASEPTIC PREPARATION
CLEAN ROOM - EU GMP CLASSIFICATION (Annex 1 – new, 25.8.2023))

Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified (a)	Not specified (a)
B	3 520	352 000	Not specified (a)	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined (b)	29 300	Not predetermined (b)

(a) - Classification including 5 um particles may be considered where indicated by the Contamination Control Strategy (CCS) or historical trends.

Aseptic activities must be carried out in a grade A area.

Grade A:

The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated.

ASEPTIC PREPARATION
CLEAN ROOM - EU GMP CLASSIFICATION (Annex 1 – new, 25.8.2023))

Maximum permitted microbial contamination level during qualification

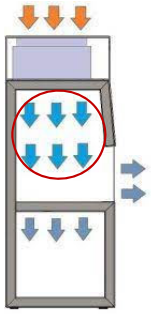
Grade	Air sample CFU/m³	Settle plates (diameter 90 mm) CFU/4 hours (a)	Contact plates (diameter 55 mm) CFU/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

HEPA FILTERS

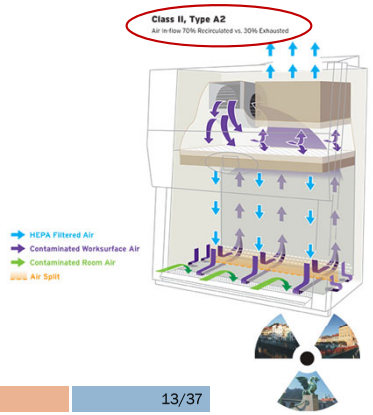
A closer look at a HEPA filter

- HEPA (high-efficiency particulate air) filter is a type of mechanical air filter; it works by forcing air through a fine mesh that traps particles.
- In the pharmaceutical industry, HEPA filters are used as terminal filters for the processing or filtration of air in production spaces. They are mandatory in sterile production.
- To qualify as a type A HEPA filter the filter must capture at least 99,97% of particles 0.3 microns in size.

Laminar Airflow (LAF) unit, Unidirectional Airflow (UDAF, EuGMP, Anex 1)) unit



Laminar Flow (LAF) Cabinets with a vertical downward air flow exhausting vertically from the cabinet and not towards the operator or isolators should be used when working with radioactive drugs.



WORKING ENVIRONMENT/BACKGROUND ENVIRONMENT

As there is no terminal sterilization of aseptic products the microbiological environment in which they are prepared is of the utmost importance. Therefore the environment should be controlled and only authorized people should be allowed to have access. Unless there is a proper justification available, the background environment for LFCs and BSCs should meet grade B requirements, with grade D required for pharmaceutical isolators.

	Working environment	Background environment
LFC/BSC	Grade A	Grade B
Isolators	Grade A	Grade D

BUT...

RADIOPHARMACEUTICALS (ANNEX 3) WORKING ENVIRONMENT/BACKGROUND ENVIRONMENT

Any justification for **background environments** of a lesser grade should be based on a documented risk assessment which should be performed with great care. Possible factors which could be considered in such a risk assessment include:

- Time between preparation and use
- Use of a closed system
- Nature and composition of product

	Open workstation	Closed (isolator)
Preparation method		
Open aseptic	B *Note	D
Closed aseptic	C	D
Open terminally sterilised	D	D
Closed terminally sterilised	D	D

* Note: Immediate administration may allow a C grade area to be used, subject to a risk assessment.

MONITORING (PARTICLE COUNTING, MICROBIAL CONTAMINATION)

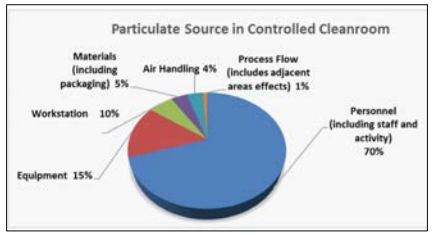
Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [a]	29 300	Not predetermined [a]

Grade	Air sample CFU /m³	Settle plates (diam. 90 mm) CFU /4 hours[a]	Contact plates (diam. 55mm), CFU / plate[b]	Glove print, Including 5 fingers on both hands CFU / glove
A	No growth[c]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

EU GMP: For grade A, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.

PARTICULATES

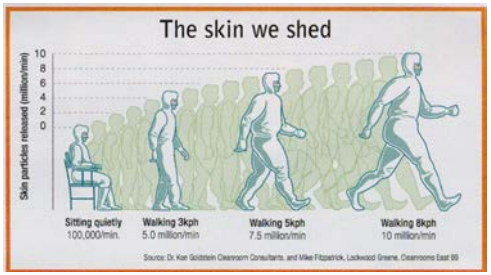
Particles can carry different microbes, this is the main reason why we perform particle monitoring (particle counting).



Particle sizes:

- Human Hair: 50-150 microns
- Household dust and lint: 0.01-100 microns
- Pollen: 10-110 microns
- Mold: 1-50 microns
- Pet dander: 0.1-10 microns
- Tobacco Smoke or Soot: 0.01-1 micron
- Viruses and Bacteria: 0.001-10 microns

PARTICULATES



- Humans are a source of particulates. We're constantly shedding skin cells and hair cells
- A sedentary person in a standing or sitting position generates approximately 100,000 particles per cubic foot. Moving from a sitting to a standing position generates 2.5 million particles per cubic foot.
- Moderate activity generates 30 million particles per cubic foot. Industrial processes in manufacturing or machine shops generate billions of particles per cubic foot.

ASEPTIC PROCESSING

The key elements of the aseptic process include:

a) Maintaining the integrity of the aseptic processing area, and care of the workstation and its environment.

b) Handling and preparation of starting materials, especially any disinfection processes.

c) Entry of materials into the processing area.

d) Standard aseptic processing techniques, including not-touching critical surfaces, correct positioning of materials within the laminar air flow, and use of specific pieces of equipment and regular sanitisation of gloves.

e) Segregation and flow of materials to ensure no accidental cross contamination or mix up of prescriptions or products.

f) Removal of product and waste materials from the processing area.

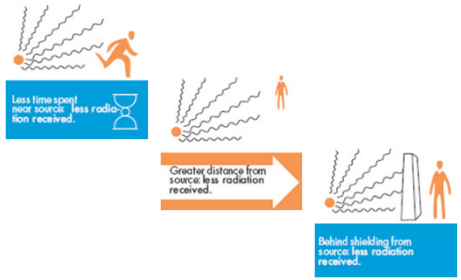
g) All aseptic processing should be carried out by competent staff who are authorized to perform their work by the Responsible Person.

h) The number of people present in the room should be kept to a minimum (however, during media fills the maximum permitted number of people should be present so as to present a worst case challenge).

i) Only sterile materials should be taken into grade A or B areas e.g. settle plates, swabs, and cleaning materials. Product solutions that are nonsterile should be filtered through a sterile filter of nominal pore size of 0.22 micron (or less) before being taken into Grade A or B areas. When this is not possible, adequate decontamination measures should betaken.

RADIATION SAFETY CONSIDERATIONS

- minimizing handling time
- increasing the distance
- use of shielding materials



PERSONNEL

Training - sufficient appropriate personnel, suitably qualified, trained and experienced in the aseptic technique

Eu GMP, Annex 1:

7.12 Clothing should be chosen to limit shedding due to operators' movement.

7.13 A description of typical clothing required for each cleanliness grade is given below:

Grade B (including access / interventions into grade A): appropriate garments that are dedicated for use under a sterilised suit should be worn before gowning (see paragraph 7.14). Appropriately sterilised, non-powdered, rubber or plastic gloves should be worn while donning the sterilised garments. Sterile headgear should enclose all hair (including facial hair) and where separate from the rest of the gown, it should be tucked into the neck of the sterile suit. A sterile facemask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles. Appropriate sterilised footwear (e.g. over-boots) should be worn. Trouser legs should be tucked inside the footwear. Garment sleeves should be tucked into a second pair of sterile gloves worn over the pair worn while donning the gown. The protective clothing should minimize shedding of fibres or particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification. Garments should be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.

GOWNING PROTOCOL (EXAMPLE: USP GENERAL CHAPTER <825> RADIOPHARMACEUTICALS – PREPARATION, COMPOUNDING, DISPENSING, AND REPACKAGING)

- Before entering the changing room, remove all make up such as lipstick, blush, eye shadow, eye liner, mascara, powder, and/or any other cosmetic that is applied on the face or neck area.
- Before entering the clean area, personnel must remove outer garments (e.g., bandanas, coats, hats, jackets, sweaters, vests); all cosmetics; all hand, wrist, and other exposed jewelry including piercings that could interfere withthe effectiveness of the garbing (e.g., the fit of gloves, cuffs of sleeves, and eye protection). Nail products (e.g., artificial nails, polish, extenders) are prohibited. Natural nails must be kept neat and trimmed. Remove ear buds and headphones.
- Do not bring electronic devices that are not necessary for compounding or other required tasks.

GOWNING PROTOCOL (EXAMPLE: USP GENERAL CHAPTER <825> RADIOPHARMACEUTICALS – PREPARATION, COMPOUNDING, DISPENSING, AND REPACKAGING)

- Immediately before entering clean area personnel must wash hands and arms up the elbows with soap and water for at least 30 s and then dry hands using low-lint towels. Alternatively, hand washing may be performed after donning shoe covers, head/hair covers, and face mask, as described below.
- Personnel must don the following garb–shoe covers, head/hair/facial hair covers, face mask–in an order that eliminates the greatest risk of contamination, as defined in facility SOPs.
- If not already performed personnel must then wash hands and arms up to the elbows with soap and water for at least 30 s and then dry hands using low-lint towels. Electronic hand dryers are not permitted.
- Personnel must then perform hand antisepsis cleansing using a suitable alcohol-based hand rub.
- Personnel must then don a low-lint gown with sleeves that fit snugly around the wrists and enclosed at the neck. Disposable gowns are preferred. If reusable gowns are used, a clean gown must be donned daily. Garment should produce little or no particulate emission. This requires the fabric or material to be stable, possessing a high ability to resist breakdown.

GOWNING PROTOCOL (EXAMPLE: USP GENERAL CHAPTER <825> RADIOPHARMACEUTICALS – PREPARATION, COMPOUNDING, DISPENSING, AND REPACKAGING)

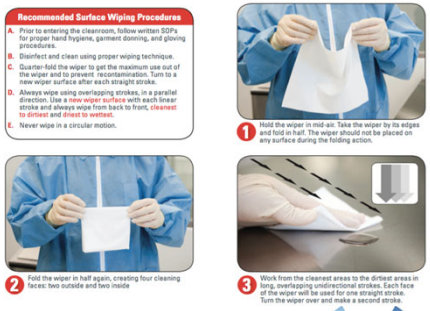
- Personnel must then aseptically don sterile, powder-free gloves. Gloves must completely and snugly cover the ends of the gown cuffs so that skin on the wrists and upper hands is completely enveloped.
- Because gloves may not remain sterile due to touching or handling potentially nonsterile materials, personnel must periodically apply sterile 70% IPA to gloves while balancing the risk of radioactivity contamination.
- Personnel must also routinely inspect the gloves that they are wearing for holes, punctures, radioactivity contamination, or tears. If a defect, radioactivity contamination, or malfunction is detected, personnel must immediately remove the gloves, repeat antiseptic hand cleansing using an alcohol-based hand rub, and don new sterile gloves.
- Direct personnel touch contamination is the most common source of microorganisms, so personnel must avoid touch contamination of container septa, needles, syringe and needle hubs, and other critical sites.

CLEANROOM ATTIRE

PREMISES - SURFACE CLEANING

Cleaning

- Cleaning and disinfecting agents should be free from viable micro organisms and those used in Grade A and B areas should be sterile and spore free.
- The effectiveness of cleaning should be routinely demonstrated, by microbiological surface sampling e.g. contact plates or swabs.
- Periodic use of sporicidal cleaning agents should be considered to reduce contamination from spore forming microorganisms.
- Virucidal cleaning agents should be used to decontaminate areas where blood products or viruses are handled.
- For sterile alcohol sprays and other materials brought into clean areas an in use expiry date should be defined.



CLASSIFICATION/MONITORING FREQUENCIES (PIC/S PE 010-4)

Classification tests

Laminar flow cabinets (LFCs) / Biohazard Safety Cabinets (BSCs):	
Particle counts	Yearly
Room air changes per hour	Yearly
Air velocities on workstations	Yearly
HEPA filter integrity checks	Yearly
Isolators:	
Isolator alarm functional tests	Yearly
Isolator leak test	Yearly
HEPA filter integrity checks	Yearly

"At rest" conditions (complete installation with production equipment but without personnel, i.e. unmanned) should be specified. Appropriate air filtration (terminal HEPA filters for grades A, B and C) and a sufficient number of air changes should be defined in order to reach the specified conditions. In order to meet "in operation" conditions, these areas should be designed to reach the "at rest" conditions after a short "clean up" period of 15-20 minutes after completion of operations.

MONITORING – RECOMENDED FREQUENCES (PIC/S)

Physical monitoring

Laminar flow cabinets (LFCs) / Biohazard Safety Cabinets (BSCs):	
Pressure differentials between rooms	Before beginning of work, usually daily
Pressure differentials across HEPA filters (workstation)	Before beginning of work, usually daily
Particle counts	Quarterly in the operational state
Isolators:	
Pressure differentials across HEPA filters	Before beginning of work, usually daily
Isolator glove integrity	Visual checks every session
Isolator pressure hold test (with gloves attached)	Weekly

Microbiological monitoring

	Direct working environment (Grade A zone)	Background environment
Settle plates	Every working session	Weekly
Glove finger dabs	At the end of each working session	At the end of each working session
Surface samples (swabs or contact plates)	Weekly	Monthly
Active air samples	Quarterly	Quarterly

"In operation" monitoring may be performed during normal operations, simulated operations or during media fills as worst-case simulation is required for this.

EANM GUIDANCE ON VALIDATION AND QUALIFICATION – STRUCTURE OF THE DOCUMENT

Todde et al. EJNMMI Radiopharmacy and Chemistry (2017) 2:8
DOI 10.1186/s41181-017-0025-9

EJNMMI Radiopharmacy and Chemistry

GUIDELINE ARTICLE Open Access

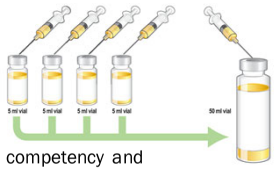
Guidance on validation and qualification of processes and operations involving radiopharmaceuticals

S. Todde[1*], P. Kolenc Peitl[2], P. Elsinga[3], J. Koziorowski[4], V. Ferrari[5], E. M. Ocak[6], O. Hjelstuen[7], M. Patt[8], T. L. Mindt[9,10] and M. Behe[11]

- Documentation
- Validation Master Plan
- User requirement specifications
- Qualification of equipment
- Computerised systems
- Validation of classified rooms
- Cleaning Validation
- Process validation
- Validation of aseptic operations via Media fill

EANM GUIDANCE ON VALIDATION AND QUALIFICATION – STRUCTURE OF THE DOCUMENT

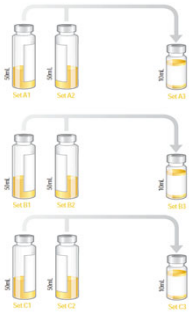
- **Additional Information – Practical Examples**
  - **Example 1**: Qualification of a production instrument: automated system for the preparation of F-18 labelled radiopharmaceuticals
  - **Example 2:** Process Validation
  - **Example 3**: Validation of operating personnel with Media fill test



Personnel involved in aseptic processing, should have specific competency and skills in aseptic technique. Their aseptic technique should be periodically assessed by performing media fill simulations. The justification for the frequency of these periodic assessments should be documented. This should be complemented by regular observation of aseptic technique to ensure that the operator can prepare dosage units precisely and safely.

MEDIA FILL

- Process validation of aseptic procedures should be performed by using broth or a similar nutrient media to simulate the aseptic procedure (media fills) and should be performed initially as well as subsequently on a regular basis, according to the risk, and whenever significant modifications have been made to the equipment or to the process.
- The process simulation test should imitate as closely as possible routine aseptic procedures (i.e. manipulations that are normally conducted) and include all the critical production steps.
- Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.



EANM GUIDELINES ON CURRENT GOOD RADIOPHARMACY PRACTICE (CGRPP) FOR THE SMALL-SCALE PREPARATION OF RADIOPHARMACEUTICALS

Gillings et al. EJNMMI Radiopharmacy and Chemistry (2021) 6:8
https://doi.org/10.1186/s41181-021-00123-2

EJNMMI Radiopharmacy and Chemistry

GUIDELINE ARTICLE Open Access

Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals

Nic Gillings[1*], Olaug Hjelstuen[2], Jim Ballinger[3], Martin Behe[4], Clemens Decristoforo[5], Philip Elsinga[6], Valentina Ferrari[7], Petra Kolenc Peitl[8], Jacek Koziorowski[9], Peter Laverman[10], Thomas L. Mindt[11], Oliver Neels[12], Meltem Ocak[13], Marianne Patt[14] and Sergio Todde[15]

- the recommendations of the Radiopharmacy Committee of the EANM for the small-scale preparation of radiopharmaceuticals
- They are intended for non-industrial sites such as hospital radiopharmacies, nuclear medicine departments, and academic PET centres

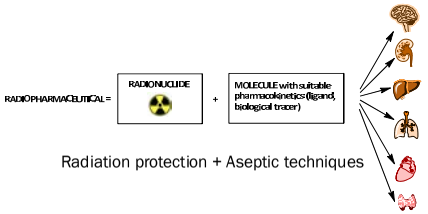
cGRPP, STRUCTURE OF REVISED GUIDELINE

- Part 1: Common section, general guidelines
- Part 2: Guidelines for preparation of radiopharmaceuticals from licensed components (generators, radionuclide precursors, and kits)
- Part 3: guidelines for preparation of radiopharmaceuticals from non-licensed components

  Laid out in the format of European Union Good Manufacturing Practice as defined in Eudralex

cGRPP CHAPTERS

- **Chapter 1: Pharmaceutical quality system**
- **Chapter 2: Personnel**
- **Chapter 3: Premises and equipment**
- **Chapter 4: Documentation**
- **Chapter 5: Production**
- **Chapter 6: Quality control**
- **Chapter 7: Outsourced activities**
- **Chapter 8: Complaints and recall**
- **Chapter 9: Self-inspection**



OTHER GUIDANCE DOCUMENTS


Protocols and Methods

Guidance on current good radiopharmacy practice for the small-scale preparation of radiopharmaceuticals using automated modules: a European perspective

Joel Aerts,[a,b] James R. Ballinger,[c] Martin Behe,[d] Clemens Decristoforo,[e] Philip H. Elsinga,[f] Alain Faivre-Chauvet,[g] Thomas L. Mindt,[h] Petra Kolenc Peitl,[i] Sergio C. Todde,[j] and Jacek Koziorowski[k,*]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edqm

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE

EUROPEAN PHARMACOPOEIA 8.7

5.19. Extemporaneous preparation of radiopharmaceuticals

04/2016:51900

5.19. EXTEMPORANEOUS PREPARATION OF RADIOPHARMACEUTICALS

This general chapter is published for information.

1. SCOPE AND DEFINITION

2. PREMISES AND EQUIPMENT

5. General texts

QUALITY RISK MANAGEMENT (QRM)

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-022-05738-4

GUIDELINES

Check for updates

EANM guideline on quality risk management for radiopharmaceuticals

Nic Gillings[1] · Olaug Hjelstuen[2] · Martin Behe[3] · Clemens Decristoforo[4] · Philip H. Elsinga[5] · Valentina Ferrari[6] · Oliver C. Kiss[7] · Petra Kolenc[8] · Jacek Koziorowski[9] · Peter Laverman[10] · Thomas L. Mindt[11] · Meltem Ocak[12] · Marianne Patt[13] · Sergio Todde[14] · Almut Walte[15]

Received: 18 January 2022 / Accepted: 17 February 2022

Eu GMP, Annex 1: This Annex provides general guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products **applying the principles of Quality Risk Management (QRM)**, to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.

FURTHER DISCUSSION

- Facility, Personnel, Monitoring
- GMP vs, cGRPP guidelines, PICs; different national and institutional protocols
- Radiation protection, parenteral medicinal products legislation

Water for pharmaceutical use

Assist. prof. dr. Špela Zupančič works at the Faculty of Pharmacy of the University of Ljubljana. She obtained her Master's degree in pharmacy in 2013, and completed a PhD in pharmaceutical nanotechnology at the Faculty of Pharmacy of the University of Ljubljana, in 2017. In 2013, she attended Erasmus exchange program at the School of Pharmacy, University College London, UK, where she performed research work for 4.5 months and in 2015, she visited Department of Mechanical and Industrial Engineering University of Illinois at Chicago, USA, where she worked under Distinguish. Prof. Dr. Alexander L. Yarin for 6.5 months. In scope of the European project ORBIS, she was on secondment at Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, USA for 6 months in 2023 in the laboratory of distinguished prof. Tamara Minko.

She participates in teaching in the Uniform master's study programme Pharmacy, the University study programme Cosmetology, and in the master's programme Industrial pharmacy. Her research expertise includes formulation and characterization of nanofibers, liposomes, polymeric, and solid lipid nanoparticles, design of nanodelivery systems for controlled drug release, incorporation of bacteria into delivery systems, mathematical modelling of drug release, and development of characterization methods for new dosage forms.

Awards: 2021 – Certificate of recognition for young university teachers for excellent teaching and research results (University of Ljubljana); 2021 – Jožef Stefan Golden Emblem awards for outstanding contributions made to science in Doctoral theses; 2017 – the national award For Women in Science from L'Oréal and Slovenian National Commission for UNESCO;·2016 – 3rd place at Slovenian Science Slam; ·2014 – Dean award for outstanding research achievements at UL-Faculty of Pharmacy and Krka Prize for Special Achievements in Research; 2013 – Faculty award for average grade above 8.75; Membership: Controlled Release Society, Slovenian Pharmaceutical Society.

<u>The lecture has the following learning objectives:</u>

1. Students are able to understand chemical characteristics of water.
2. Students are able to list all possible water contaminants.
3. Students are able to understand the underlying basics of methods of water purification.
4. Students are able to select the methods of water purification based on the impurities.
5. Students are able to recommend contamination control approaches in pharmaceutical water systems.
6. Students are able to define the characteristics of water in Ph. Eur.
7. Students are able to decide which water quality to use in a given situation.

Summary of the lecture (prepared by assist. prof. dr. Špela Zupančič and assist. prof. dr. Izidor Sosič):

Water is the most widely used substance and the third most common molecule in the Universe. It is also the life-necessary compound and the most important raw material or starting material in the production, processing, and formulation of pharmaceutical products. In pharmaceutical use, it is also used as a cleaning agent for rinsing vessels, equipment, and primary packaging material. It has unique chemical properties due to its polarity and the ability to form an infinite hydrogen-bonded network with localized and structured clustering. As a result, water has 74 anomalous properties in physico-chemical characteristics, i.e. many of the properties of water are quite different from those expected of other liquids. For example, as a liquid, water is much denser than expected and as a solid, it is much lighter than expected when compared with its liquid form.

Potable water is the raw material ('feed water') that is used to produce water for pharmaceutical use. The quality of potable water is determined by the WHO and ISO drinking water guidelines. In addition, many developed countries specify additional standards for drinking water and in the EU these standards are stated in the European Drinking Water Directive. In the US, on the other hand, the directives are defined by The National Primary Drinking Water Regulations. Drinking water specifications establish a reasonable set of maximum allowable levels of chemical and microbiological contaminants. Of note, in modern pharmacopoeias there are no monographs for potable water.

Water is capable of dissolving, absorbing, adsorbing or suspending a wide variety of compounds. Therefore, water from natural sources contains different contaminants, ranging from inorganic compounds (salts), organic impurities, gases, particles/colloids/solids, microorganisms, and microplastics. The type and concentration of contaminants depend on geological, meteorological, and biospherical influences. Within inorganic compounds, the most common impurities are magnesium and calcium salts (in the form of bicarbonate or carbonate), as well as iron salts. In the group of naturally occurring organic impurities, tannins, phenols, and humic acids are prevalent, whereas artificial organic compounds are mostly found in the form of chlorinated solvents (by-products of chlorination), detergent residues, phthalates, herbicides, insecticides, and some other hydrocarbon pollutants, such as polyaromatic hydrocarbons. Oxygen (O_2), nitrogen (N_2), and carbon dioxide (CO_2) are the gaseous impurities found in water, whereas silt, clay, and soil are the particles that are also deemed as water impurities. Microorganisms represent the greatest obstacle towards the required water quality and are particularly troublesome because of fast growth, even in nutrient-depleted conditions. Moreover, the microbial by-products and cellular fragments, such as lipopolysaccharides and nucleases, are also problematic and need to be removed under proper conditions. Microplastics are plastic particles with a dimeter smaller than 5 mm. It is estimated that there is 51 trillion

microplastic particles in the seas, which are accumulated in the marine animals. Its negative effect on animals is already detected (e.g. infertility), whereas there is lack of studies about the toxic effect to human.

Contaminants may represent hazards either themselves or by interacting with intended product substances. To tackle this problem and to obtain water of desired purity and characteristics that is fit for a specific purpose, different water purification methods can be utilized. After the general pre-treatment of raw water, one can use several methods, such as:

- distillation
- deionization
- electrodeionization
- filtration methods
    - reverse osmosis
    - ultrafiltration
    - microfiltration
- adsorption on activated carbon
- UV-based technologies

These methods are based on different mechanisms by which the contaminants are removed. There is no method that is able to remove all impurities, so to produce the level of water purity required, a careful selection of different and complementary techniques is required. It is thus of essence that each method's advantages and disadvantages are understood, as this knowledge represents the basis for selecting a proper water purification technique when faced with contaminated raw water.

Pharmaceutical water systems can be roughly divided into water purification, storage, and distribution systems. Each of these three systems should follow defined general principles and requirements with the goal to produce, distribute and store water of desired purity and specifications. The most important aspect of these systems is microbiological contamination control, representing the greatest risk during the production, storage, and distribution of water for pharmaceutical use. Also, careful system performance monitoring is imperative and needs to be properly documented. Besides general principles, each system must comply with specific requirements that will be overviewed during the lecture.

The general water quality specifications and standards are defined in several documents and in Europe, the most important document for waters for pharmaceutical use is the European pharmacopoeia (current version, Ph. Eur. 11.3). In Ph. Eur. 11.3, waters for pharmaceutical use are defined, and the procedures for their production, storage, and distribution are recommended. Ph. Eur. 11.3 defines these types of water: **purified water** (purified water in bulk, purified water in containers), **water for injections** (water for injections in bulk,

sterilized water for injections), **water for preparations of extracts** (see Figure 1); **Highly purified water** was suppressed from the Ph. Eur on April 1, 2019. In the lecture, we will focus on purified water, and water for injections. More importantly, the limits for various impurities or classes of impurities are either specified or recommended (will be overviewed during the lecture). The grade of water used should also take account of the nature and the intended uses of the finished product and the stage at which the water is used. Companies wishing to supply markets with waters for pharmaceutical use must meet the strict requirements from the relevant pharmacopoeia.

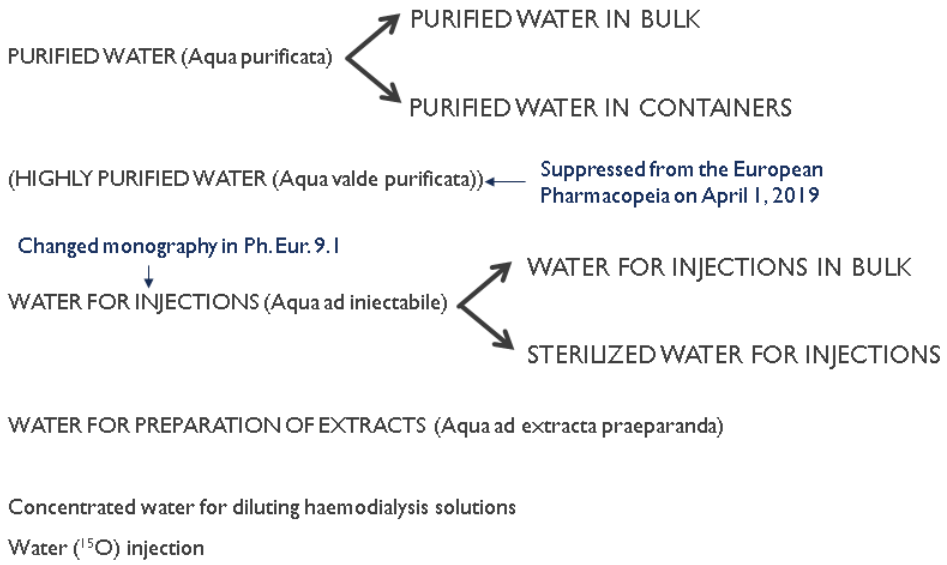

Figure 1. Waters for pharmaceutical use, as defined in the Ph. Eur. 11.3

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<u>Take-home messages:</u>

- water has unique chemical properties and many physico-chemical anomalies
- potable water is feed water for all waters for pharmaceutical use
- water purification techniques depend on the type of contaminants in feed water
- distillation and reverse osmosis target the whole range of contaminants with good efficiency
- pharmaceutical water systems should be configured to prevent microbial proliferation and recontamination
- standards for waters for pharmaceutical use are provided in pharmacopoeias
- water for injections is the highest quality of pharmacopeia waters
- water for injection needs to be used to prepare radiopharmaceuticals for parenteral administration, whereas purified water is used for preparation of oral delivery systems

References (further reading):

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- *United States Pharmacopoeia and National Formulary* (USP 42-NF 37). General Chapter 1231: Water for pharmaceutical purposes; https://hmc.usp.org/sites/default/files/documents/HMC/GCs-Pdfs/c1231.pdf (please note: this is a link to the USP 37 version)
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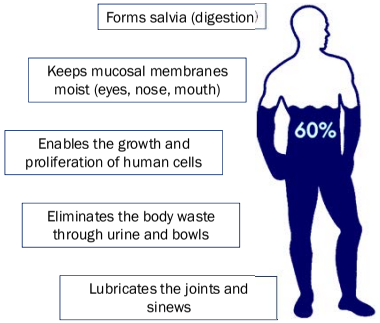
WATER FOR PHARMACEUTICAL USE

assoc. prof. dr. Špela Zupančič, M. Pharm.

WATER – THE NECESSITY OF LIFE



- Forms salvia (digestion)
- Keeps mucosal membranes moist (eyes, nose, mouth)
- Enables the growth and proliferation of human cells
- Eliminates the body waste through urine and bowls
- Lubricates the joints and sinews
- The needed component to produce hormones and neurotransmitters
- Regulates temperature sweating and respiration
- It acts as a shock absorber for the brain and spinal cord
- Participate in conversion of food into available components through digestion
- Participate in the delivery of oxygen and nutrients all over the body

WATER

demineralised water
tap water
distilled water
water for injections
dionised water
drinking water
purified water
feed water
source water
mineral water
potable water
water for the production of extracts

WATER FOR PHARMACEUTICAL USE

Water can be used:

- for cleaning agent for rinsing vessels, equipment, primary packaging material
- during synthesis of active ingredient
- during production of final product
- as an excipient
- for reconstitution of the product

We can choose between:

- Potable water
- Water for preparation of extracts
- Purified water
- Water for injections

AIM

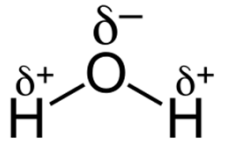
Why is water so special?
How to prepare water with defined quality?
What is the difference between these waters?
Which water to use for specific pharmaceutical use?

CONTENT

1 Physiochemical properties of water
2 Potable water
3 Water contaminants
4 Water purification methods
5 Pharmaceutical water systems
6 Waters in the pharmacopoeias
7 Which water to use for preparation of (radio)pharmaceuticals?

WATER PHYSICO-CHEMICAL CHARACTERISTICS

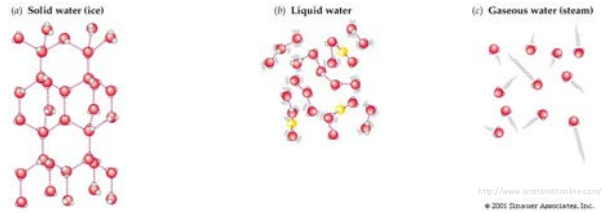
- one of the smallest by volume (0.03 nm^3) and the lightest molecules
- water has over 70 anomalies in physico-chemical characteristics
- **polarity** and **H-bonds** - unique chemical properties



WATER PHYSICO-CHEMICAL CHARACTERISTICS

WATER PHYSICO-CHEMICAL CHARACTERISTICS

- water molecules form an infinite **hydrogen-bonded** network with localized and structured clustering
- formation and breaking of H-bonds is a dynamic process that takes about 0.1 ps (10^{-13} s)

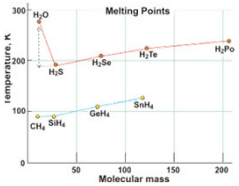


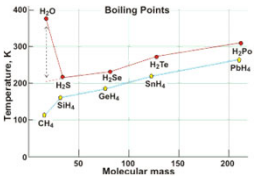
In solid form, each water molecule forms 4 H bonds (tetrahedrally arranged), average lifetime: (10^{-5} s)

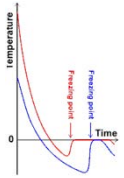
In liquid water (near 0 °C), each water molecule form on average 3.4 H-bonds, average lifetime: (1 – 20×10^{-12} s)

WATER PHYSICO-CHEMICAL CHARACTERISTICS

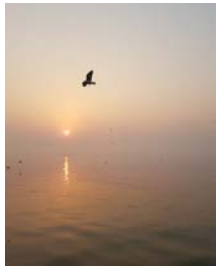
- the anomalous properties are those where the behavior of liquid water is quite different from what is found with other liquids
  - unusually high melting point and boiling point
  - the Mpemba effect – hot water may freeze faster than cold water!

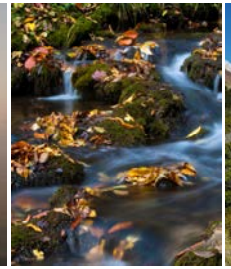






http://www1.lsbu.ac.uk/water/water_anomalies.html





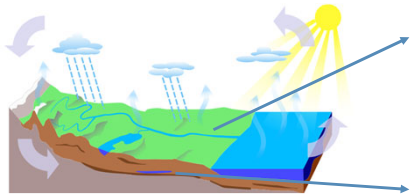
WATER SOURCES FOR POTABLE WATER

- Natural surface waters (e.g. rivers and reservoars)
- Deep bed well waters
- Sea waters

„Our planet consists mostly of oceans and seas but only small percent of water -0,007% is drinkable."
3x Environment

WATER SOURCES

- there is no pure water in nature due to water's unique chemical properties
- the type and concentration depend on geological, meteorological, and biospherical influences



SURFACE WATER
higher in biological material
higher in particulates
lower in dissolved ions

GROUND WATER
higher in dissolved ions
lower in particulates
lower in biological material

Surface waters: sea water (aqua marina), river water (aqua fluvialis)
Ground waters: mineral waters, spring waters (aqua mineralae), groundwater (aqua fontis, aqua fontana)

WATER CONTAMINANTS

- gases
- inorganic compounds
- organic compounds
- particles / colloids
- microorganisms
- nano and microplastics

GASES

oxygen (O_2) nitrogen (N_2) carbon dioxide

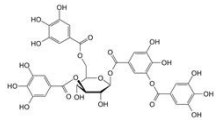
- gases are usually removed by degasification:
  - heating,
  - membrane degasification,
  - pressure reduction, ...

INORGANIC COMPOUNDS

- the exact types of compounds depend on the **chemical composition of surrounding rocks**
- the most common are **Mg^2**, **Ca^2** and **Fe^2** salts
- as counterions, the **bicarbonate** and **carbonate** are prevalent
- cations: Na^+, Ca^{2+}, Fe^{2+}, Mg^{2+}, Al^{3+}
- anions: Cl^-, HCO_3^-, SO_4^{2-}, CO_3^{2-}, ClO^-, PO_4^{3-}
- **more problematic ions**: Pb^+, Cu^{2+}, Mn^{2+}, NO_3^-, SiO_4^{4-}, $Si_2O_7^{6-}$, hydrogen sulfide (in areas of thermal activity)

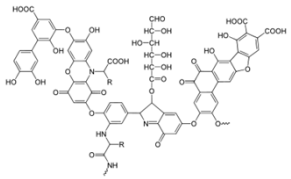
ORGANIC IMPURITIES - naturally occurring

tannins



phenols

humic acids



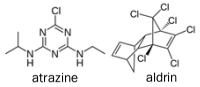
lignin

folic acid pyrogens

ORGANIC IMPURITIES - artificial

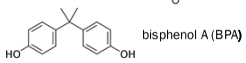
chlorinated solvents (CH_2Cl_2, $CHCl_3$, CCl_4) - byproducts of chlorination

herbicides, insecticides



atrazine aldrin

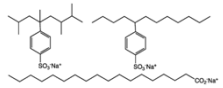
phthalates



bisphenol A (BPA)

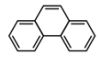
endocrine disrupting compounds (EDCs)

detergent residues



antibiotics

other hydrocarbon trace pollutants, e.g. PAH



phenantrene

COLLOIDS AND PARTICLES

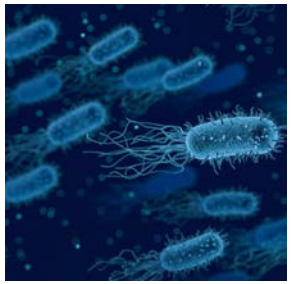
COLLOIDS

- Size: < 1 µm
- inorganic or organic particles
- form a stable nanosuspension that does not precipitate
- removed in the pretreatment phase by **sand filtration** or by **coagulation** (addition of $FeSO_4$)

PARTICLES

- Size: > 1 µm
- e.g. silt, clay, soil
- removed in the pretreatment phase by **sedimentation**

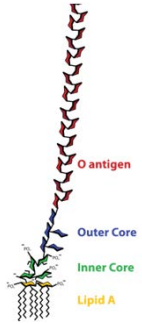
MICROORGANISMS



- one of the major obstacles to successful treatment of water
- particularly troublesome because of fast growth (even in nutrient-depleted conditions)
- **protozoa**
  - *Giardia lamblia*
  - *Cryptosporidium*
- **bacteria**
  - Gram negative (*Escherichia coli, Pseudomonas, Shigella, Campylobacter,…*)

➡ microbial byproducts and cellular fragments (such as LPS and nucleases) are more problematic

PYROGENS



Lipopolysaccharides (LPS)

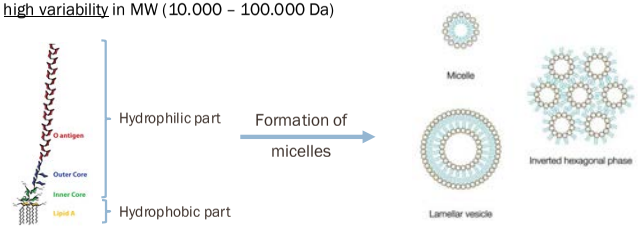
- an integral part of the outer membrane of Gram negative bacteria
- are released upon bacterial cell lysis
- categorized as endotoxins and have pyrogenic activity

→ **can cause fewer when released into the bloodstream**

PYROGENS

Lipopolysaccharides (LPS)

- thermally stable and insensitive to pH changes
- high variability in MW (10.000 – 100.000 Da)



- endotoxin levels measured in ‚endotoxin units' (EU) or IU
- **difficult to remove**

MICROPLASTICS


Photo by Naja Bertolt Jensen

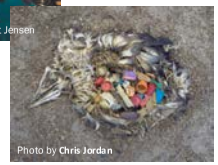


Photo by Chris Jordan

- 51 trillion microplastic particles in the seas
- plastic fragments < 5 mm
- **Primary** microplastics – directly released in the environment as small particles.
- **Secondary** microplastics – originate from degradation of larger plastic objects.
- found in food and drinks, including beer, honey and tap water
- accumulated in the bodies and tissues of many organisms
- lead to infertility of some animals
- animal death by malnutrition

Water sources for potable water

Water purification methods

Potable water

Water purification methods

- Water for preparation of extracts
- Purified water
- Water for injections

POTABLE WATER

DRINKING WATER, TAP WATER (*Aqua potabile*)

* the quality of potable water is determined by:
  * the **WHO** (*Guidelines for drinking-water quality, 4th edition, incorporating the 1st addendum, 2017*),
  * **ISO** (*ISO 24510, ISO 24511 and ISO 24512, Activities relating to drinking water and wastewater services*) drinking-water guidelines, and
* other relevant directives include:
  - **in EU, the European Drinking Water Directive (2020/2184)**
  - in US, The National Primary Drinking Water Regulations (NPDWR)
* in modern **pharmacopoeias there are no monographs for potable water**
* potable water is the raw material that is used to produce water for pharmaceutical use → regular testing needed to confirm the quality

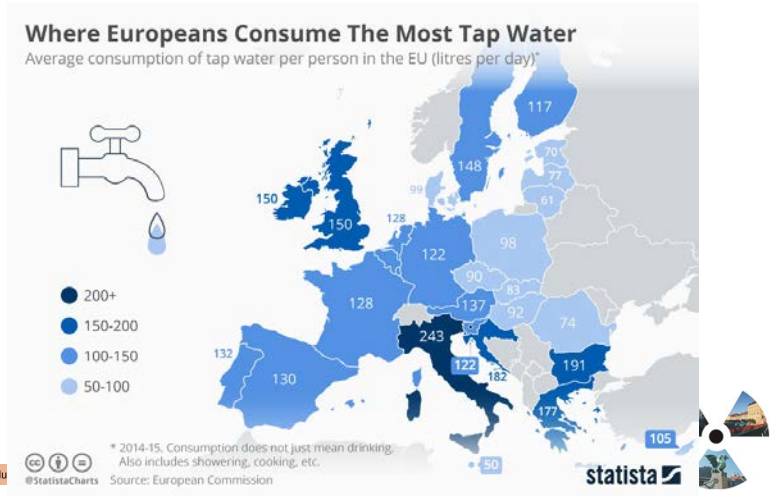
POTABLE WATER

European Drinking Water Directive (2020/2184)

- *1. This Directive concerns the quality of water intended for human consumption for all in the Union.*
- *2. The objectives of this Directive are to protect human health from the adverse effects of any contamination of water intended for human consumption by ensuring that it is wholesome and clean, and to improve access to water intended for human consumption.*

Need to monitor and regularly test:

- **microbiological** parameters
- **chemical** parameters
- **indicator** parameters



Water sources for potable water

Water purification methods

Potable water

Water purification methods

- Water for preparation of extracts
- Purified water
- Water for injections

WATER PURIFICATION METHODS

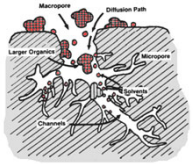
- the nature, type, and concentration of impurities define the selection of a water purification technique!
- there is no single process that can remove all contaminants in water
- to produce the level required a combination of processes is needed
- the method of choice is not defined in the Ph. Eur.

METHODS:

- distillation
- deionization
- electrodeionization
- reverse osmosis
- ultrafiltration
- microfiltration
- adsorption (activated carbon)
- UV technology

ADSORPTION (ACTIVATED CARBON)

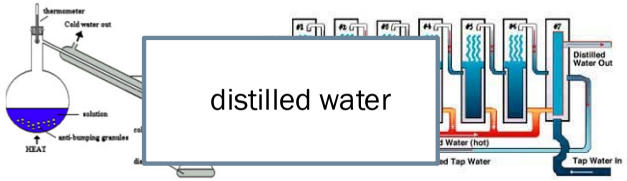
- high surface area of particles: 500 – 1500 m^2/g
- adsorbs many organic compounds, mostly used for excess chlorine removal
- the efficiency is based on flow regulation



ADVANTAGES	DISADVANTAGES
• effective removal of a large range of organic substances • large capacity	• very little effect on other contaminants • possibility of bacterial contamination • sanitization of carbon bed should be performed often • equilibrium after all active sites are occupied

DISTILLATION

- a process of separating the components by selective evaporation and condensation



single-effect

multiple-effect – re-using the heat energy

ADVANTAGES	DISADVANTAGES
• removes a large percentage of all types of contaminants • average investment • perceived as easy to operate	• contaminants can be generated during process • high operating costs – heating and cooling • regular maintenance (acid) • pretreatment (DI) required

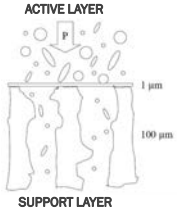
MICROFILTRATION

- a filtration method used to separate microorganisms and suspended particles from process water
- used in conjunction with other separation processes
- typical particle size used for microfiltration ranges from about 0.05 to 10 µm

ADVANTAGES	DISADVANTAGES
• 100% removal of bacteria and particles larger than pore size • **sterilizing filtration (0.22 µm membranes)** • minimum maintenance – replace when required • high flow rates	• minimum effect on other contaminants • surface of the membrane may be subject to fouling or plugging

ULTRAFILTRATION

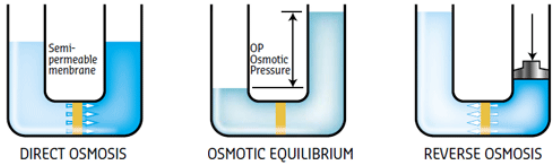
- a filtration method relies on similar principles as reverse osmosis but uses lower pressures and more permeable membranes
- ultrafilters are asymmetric membranes
- small size molecules go through the membrane, whereas larger molecules (above NMWL) are retained



ADVANTAGES	DISADVANTAGES
• effective removal (> 99%) of organics above NMWL • very efficient at removing pyrogens • low risk of scaling • low use of energy	• almost no removal of ions, gases and low MW organics • regular back flushing is necessary to remove retained particles • high quality feed water is desirable

REVERSE OSMOSIS

- a membrane filtration method that removes many types of large molecules (bacteria, pyrogens, organics) and ions from water solutions



Reverse Osmosis operating principle

Ions: rejection > 97%

Organics (MW > 100 Da): rejection > 99%

Particles, bacteria: rejection > 99%

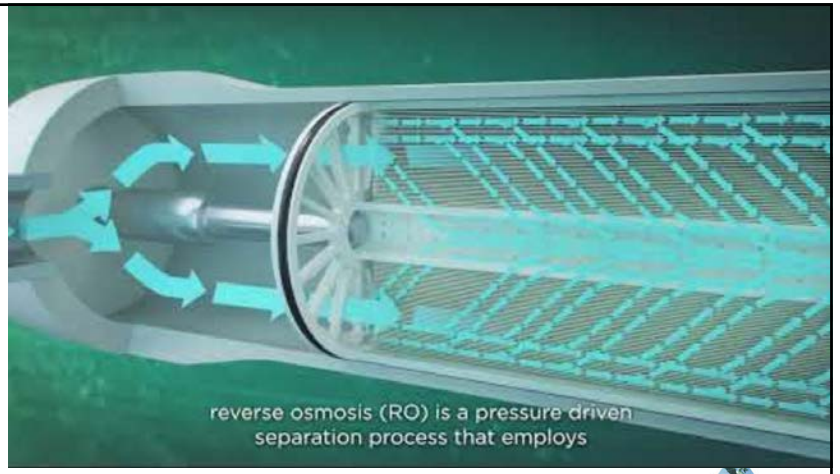
https://www.youtube.com/watch?v=aVdWobbv_Y&t=1s

REVERSE OSMOSIS

- the purity of the feed water and the effectiveness of the filter membrane define the quality of the product water
- a selection of reverse osmosis membranes are available to address varying water conditions and requirements

ADVANTAGES	DISADVANTAGES
• removes a fair percentage of all contaminants • low operating costs (low energy needs) • no need for strong acid and bases cleaning • good control of operating parameters (flow, pressure, conductivity)	• RO membranes are subject to plugging, fouling, piercing (particles, chemical attack) and scaling • high water consumption • danger of microbial growth on membrane • gases are not effectively removed

REVERSE OSMOSIS



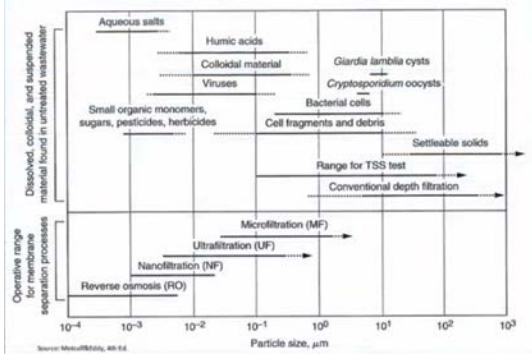
https://www.youtube.com/watch?v=6TFXO9cagIU

FILTRATION

- Membrane pore sizes can vary depending on filter type.

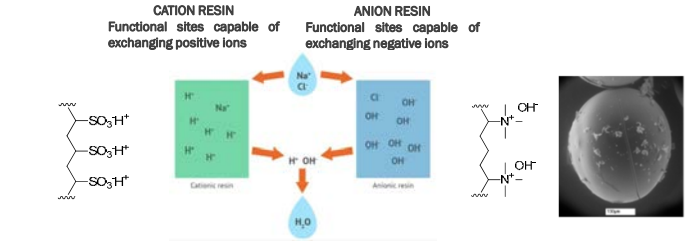
- **Particle filtration** removes particles of **> 1 µm**
- **Microfiltration** removes particles of **> 50 nm**
- **Ultrafiltration** removes particles of **> ~3 nm**
- **Nanofiltration** removes particles of **> 1 nm**
- **Reverse osmosis** removes particles **> 0.1 nm**

WATER PURIFICATION METHODS



DEIONIZATION (or demineralization or ion exchange)

- a process by which both positive and negative ions are removed and replaced by H^+ and OH^-
- predominantly used for water softening as a pretreatment method for reverse osmosis
- ion exchange resin consist of spherical beads (d = 0.3 – 1.2 mm)



DEIONIZATION (or demineralization or ion exchange)

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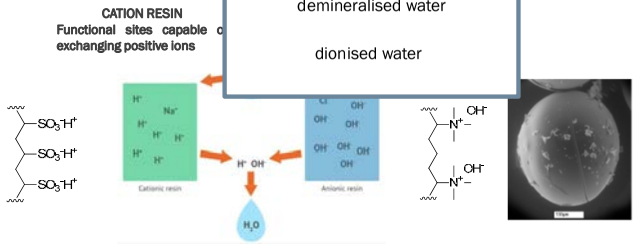
- predominantly used for water softening as a pretreatment method for reverse osmosis
- ion exchange resin consist of sp

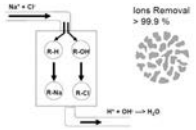
demineralised water

dionised water



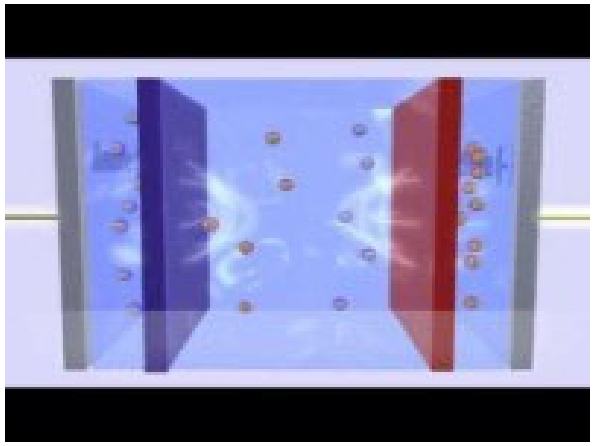
DEIONIZATION (or demineralization or ion exchange)

- mixed-bed deionization – a 50/50 mixture of cation and anion resin combined in a single ion exchange column



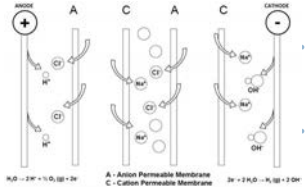
ADVANTAGES	DISADVANTAGES
• very effective method at removing ions (final conductivity: 0.1 – 1.0 µS/cm)	• does not eliminate other contaminants • limited capacity depending on binding sites density (good feed water necessary) • resin is a haven for microbial growth • possibility of particles release

ELECTRODEIONIZATION



https://www.youtube.com/watch?v=wNCcpx9IeG4

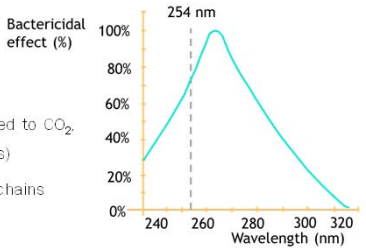
ELECTRODEIONIZATION



- a continuous deionization, where ion selective permeable membranes, mixed-bed ion exchange resin and electric current are used
- the resin is permanently regenerated by a weak electric current

ADVANTAGES	DISADVANTAGES
• very efficient removal of ions (< 0.2 µS/cm) • low energy consumption • high water recovery • low maintenance • less prone to microbial contamination	• does not eliminate other contaminants • good feed water is a must to prevent plugging or fouling of resins and scaling at electrodes

UV TECHNOLOGY



- photochemical oxidation
- eliminates trace organics at 185 nm → typically converted to CO_2, which equilibriates to HCO_3^- (removed by ion exchange resins)
- eliminates microorganisms at 254 nm by breaking the DNA chains
- the device must be propery sized for the water flow

ADVANTAGES	DISADVANTAGES
• traces of organics converted to HCO_3^- • can be used to continously ‚sanitize' circulating water • easy to operate • limited energy use	• polishing technique only – may be overwhelmed if organics conc. is high • organics converted, not removed • limited effect on other contaminants • good design required for optimum work

WATER PURIFICATION METHODS

CONTAMINANT	STILL	DI	RO	UF	MF	AC
IONS						
ORGANICS						
PARTICLES COLLOIDS						
BACTERIA VIRUSES						
GASES						

PHARMACEUTICAL WATER SYSTEMS

prevent unacceptable microbial and chemical contamination

water production/ purification | **water storage** | **water distribution**

- QA involved in approval of use after installation and maintenance work
- **regular monitoring** of water sources and treated water
  - **chemical and microbiological**
  - **endotoxin** level where relevant
- monitoring **documentantion** of system performance
- validated **sanitization** procedure followed on a routine basis

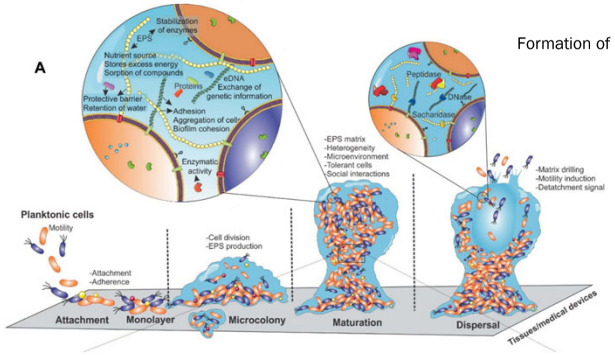
WATER STORAGE AND DISTRIBUTION SYSTEMS

Once purified, water can be used directly or is fed into a storage vessel (more frequently!) for subsequent distribution.

GENERAL:

- water storage and distribution should work in conjunction with the purification plant → delivery of water of **consistent** quality
- this system should be configured to prevent microbial proliferation and recontamination
- **on-line and off-line monitoring** is necessary to ensure that the specifications are maintained (**flow, pressure, temperature, conductivity, pH and total organic carbon**)

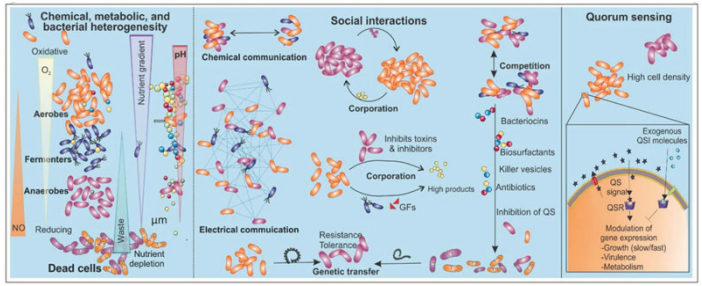
MICROBIAL CONTAMINATION



Formation of **BIOFILM**

Infection and Drug Resistance 2020:13

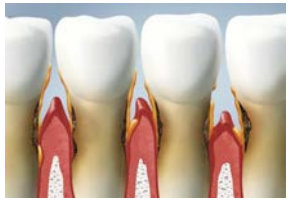
BIOFILM



Infection and Drug Resistance 2020:13

WHY BIOFILM PRESENTS A BIG PROBLEM?

https://www.membraworld.com/biofilm/?lang=en



https://www.dentist-lieberman.com/palm-harbor-dentist/2014/12/22/myths-about-gum-disease-palm-harbor-dentist/

HOW TO PREVENT THE GROWTH OF BIOFILM?

Water treatment equipment, storage and distribution systems should have:

- features to control the proliferation of microorganisms
- techniques for sanitizing the system

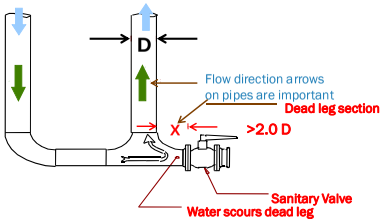
CONTAMINATION CONTROL TECHNIQUES (1):

- continuous **turbulent flow** circulation
- **avoid dead legs**
- **hygienic pattern diaphragm valves**
- **shortest possible length** of pipe work
- pipe work of ambient temperatures system should be isolated from hot pipes
- pipework systems should be **sloped and fully drainable**

HOW TO PREVENT THE GROWTH OF BIOFILM?

- **dead legs** are stagnant areas where there is no flow → this allows microbial contamination
- a consensus in the industry that a dead leg should not be greater than twice the diameter of the pipe

If **D = 25mm** and **X > 50mm**, we have a dead leg that is too long.



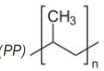
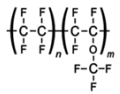
HOW TO PREVENT THE GROWTH OF BIOFILM?

MATERIALS:

- compatibility
- prevention of leaching
- corrosion resistance

} in the full range of the working and sanitization temperature of the water system

Appropriate WPU system contact materials include:

- *stainless steel Grade 315 L (low carbon)*
- *polypropylenes (PP)* 
- *polyvinylidene-difluorides (PVDF)* 
- *perfluoroalkoxyl alkanes (PF)* 

HOW TO PREVENT THE GROWTH OF BIOFILM?

CONTAMINATION CONTROL TECHNIQUES:

- the growth of microorganisms can be inhibited by:
  - **ultraviolet** radiation sources in pipework
  - maintaining the system heated (65-80 °C)
  - sanitizing the system periodically using hot water (guidance temperature > 70 °C)
  - sterilizing or sanitizing the system periodically using superheated hot water or clean steam
  - routine chemical sanitization using **ozone** or other suitable chemical agents

HOW TO PREVENT THE GROWTH OF BIOFILM?

- on-line and off-line monitoring is necessary to ensure that the specifications are maintained (flow, pressure, temperature, conductivity, pH and total organic carbon)

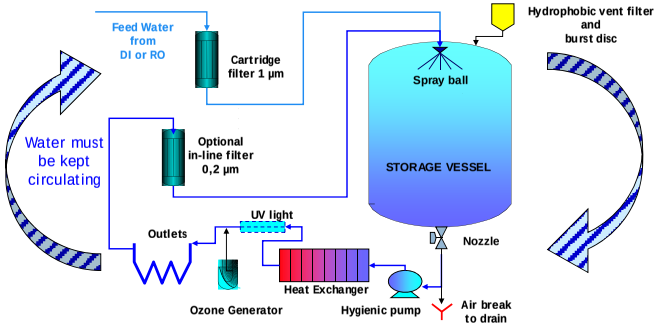
Planktonic bacteria
G⁻ microorganisms
- need < 1 mg/L organic carbon
- sensitive to ↑ T

← Prevention: **↑ T**

G⁺ microorganisms
- need more organic molecules
- thermophiles – some can survive over 100 °C

← Prevention: **↓ TOC**

WATER STORAGE AND DISTRIBUTION SYSTEMS



WATER QUALITY SPECIFICATIONS

- the standards (for bulk and dosage form types) are provided in the pharmacopoeias
- the **limits for various impurities** or classes of impurities are either specified or recommended
- companies should meet the **strict requirements** from the relevant pharmacopoeia
- potable water
  - not covered by a monograph
  - must comply with the regulations laid down by the competent authority
  - testing at the manufacturing site
  - in the production care should be taken to control microbiological contamination
  - source feed water for pharmacopoeial waters

WATERS IN EUROPEAN PHARMACOPOEIA

PURIFIED WATER (Aqua purificata)
- PURIFIED WATER IN BULK
- PURIFIED WATER IN CONTAINERS

WATER FOR INJECTIONS (Aqua ad iniectabile)
- WATER FOR INJECTIONS IN BULK
- STERILIZED WATER FOR INJECTIONS

WATER FOR PREPARATION OF EXTRACTS (Aqua ad extracta praeparanda)

Concentrated water for diluting haemodialysis solutions

Water (^{15}O) injection

WATERS IN US PHARMACOPOEIA

Water used in the pharmaceutical industry and related disciplines is classified by the US Pharmacopoeia (USP) as follows:

- USP Purified Water
- USP Water for Injection
- USP Water for Hemodialysis
- USP Pure stream

BULK MONOGRAPHED WATERS

- USP Sterile Purified Water
- USP Sterile Water for Injection
- USP Bacteriostatic Water for Injection
- USP Sterile Water for Irrigation
- USP Sterile Water for Inhalation

STERILE MONOGRAPHED WATERS

WATERS IN EUROPEAN PHARMACOPOEIA 11

Water, purified (Ph. Eur. 0008) PW	Water for preparation of extracts (Ph. Eur. 2249)	Water for injections (Ph. Eur. 0169) WFI
Water for the preparation of **medicines other than those** that are required to be both **sterile and apyrogenic**, unless otherwise justified or authorised.	Water intended for the preparation of ***Herbal drug extracts (0765)*** complies with the section **PW in bulk or PW in containers** in the monograph PW (0008), or is water intended for human consumption of a quality equivalent to that defined in **Directive 98/83/EC.**	Water for the preparation of medicines for **parenteral administration** when water is used as **vehicle** (WFI in bulk) and for **dissolving or diluting substances or preparations for parenteral administration** (sterilized water for injections).

DEFINITION

WATERS IN EUROPEAN PHARMACOPOEIA 11

Water, purified (Ph. Eur. 0008) PW	Water for preparation of extracts (Ph. Eur. 2249)	Water for Injections (Ph. Eur. 0169) WFI
prepared by **distillation**, by **ion exchange**, by **reverse osmosis OR** by any other suitable method ...	When water intended for human consumption is used as water for preparation of extracts it is **clear, colourless liquid**.	**Water for injections in bulk** Obtained from water that complies with the regulations on water intended for human consumption or from purified water: - **by distillation** - **by a purification process that is eqivalent to distillation.** Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electrodionisation, ultrafiltration or nanofiltration. **Sterilized water for injection** WFI in bulk has been distributed into suitable containers, closed and **sterilized by heat** in conditions that the product still complies with the test for bacterial endotoxins

PRODUCTION

	Water for extracts	PW in bulk	PW in containers	WFI in bulk	Sterilized WFI
Microbiological monitoring (2.6.12)	< 100 CFU/mL	< 100 CFU/mL	< 100 CFU/mL	< 10 CFU/ 100 mL	complies with the test for sterility
Bacterial endotoxins (2.6.14)	-	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL
TOC (2.2.44)	-	< 0.5 mg/L	< 0.5 mg/L	< 0.5 mg/L	-
Conductivity (2.2.38)	2500 µS/cm (20 °C)	5.1 µS/cm (25 °C)	5.1 µS/cm (25 °C)	1.3 µS/cm (25 °C)	< 25 µS/cm (less than 10 mL) < 5 µS/cm (more than 10 mL) (25 °C)
Nitrates	< 50 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm
Aluminium (2.4.17)	-	< 10 ppb	< 10 ppb	< 10 ppb	< 10 ppb
Chlorides (2.4.4)	-	-	pass test	-	< 0.5 ppm
Sulfates	-	-	pass test	-	pass test
Ammonium	-	-	< 0.2 ppm	-	< 0.6 ppm (less than 50 mL) < 0.2 ppm (more than 50 mL)
Heavy metals (2.4.8)	-	< 0.1 ppm	< 0.1 ppm	-	-
Calcium and magnesium	-	-	pass test	-	pass test
Acidity or alkalinity	-	-	pass test	-	pass test
Oxidizable substances	-	pass test	pass test	-	pass test
Residue on evaporation	-	-	< 0.001 %	-	< 0.004 % (less than 10 mL) < 0.003 % (more than 10 mL)

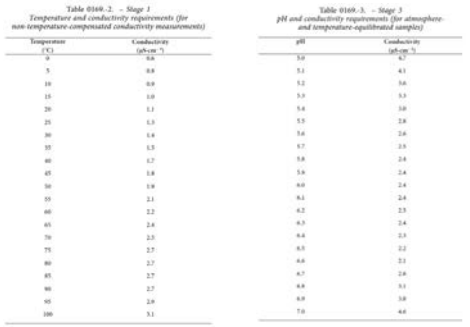
	Water for extracts	PW in bulk	PW in containers	WFI in bulk	Sterilized WFI
Microbiological monitoring (2.6.12)	< 100 CFU/mL	< 100 CFU/mL	< 100 CFU/mL	< 10 CFU/ 100 mL	complies with the test for sterility
Bacterial endotoxins (2.6.14)	-	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL
TOC (2.2.44)	-	< 0.5 mg/L	< 0.5 mg/L	< 0.5 mg/L	-
Conductivity (2.2.38)	2500 µS/cm (20 °C)	5.1 µS/cm (25 °C)	5.1 µS/cm (25 °C)	1.3 µS/cm (25 °C)	< 25 µS/cm (less than 10 mL) < 5 µS/cm (more than 10 mL) (25 °C)
Nitrates	< 50 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm
Aluminium (2.4.17)	-	< 10 ppb	< 10 ppb	< 10 ppb	< 10 ppb
Chlorides (2.4.4)	-	-	pass test	-	< 0.5 ppm
Sulfates	-	-	pass test	-	pass test
Ammonium	-	-	< 0.2 ppm	-	< 0.6 ppm (less than 50 mL) < 0.2 ppm (more than 50 mL)
Heavy metals (2.4.8)	-	< 0.1 ppm	< 0.1 ppm	-	-
Calcium and magnesium	-	-	pass test	-	pass test
Acidity or alkalinity	-	-	pass test	-	pass test
Oxidizable substances	-	pass test	pass test	-	pass test
Residue on evaporation	-	-	< 0.001 %	-	< 0.004 % (less than 10 mL) < 0.003 % (more than 10 mL)

2.2.44. TOTAL ORGANIC CARBON IN WATER FOR PHARMACEUTICAL USE

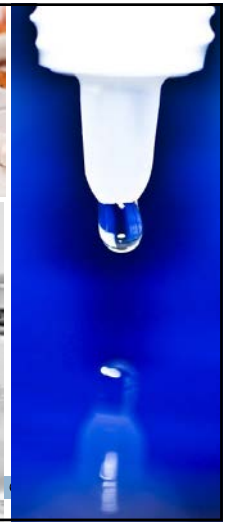
- TOC – determination is an indirect measure of organic substances in water
- General method: complete oxidation of the organic molecules in the samples water to produce CO_2 followed by measurement of the amount of CO_2 produced.
- Need to discriminate between organic and inorganic carbon (present as carbonate)
- Limit of detection: 0.05 mg/L

	Water for extracts	PW in bulk	PW in containers	WFI in bulk	Sterilized WFI
Microbiological monitoring (2.6.12)	< 100 CFU/mL	< 100 CFU/mL	< 100 CFU/mL	< 10 CFU/ 100 mL	complies with the test for sterility
Bacterial endotoxins (2.6.14)	-	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL
TOC (2.2.44)	-	< 0.5 mg/L	< 0.5 mg/L	< 0.5 mg/L	-
Conductivity (2.2.38)	2500 µS/cm (20 °C)	5.1 µS/cm (25 °C)	5.1 µS/cm (25 °C)	1.3 µS/cm (25 °C)	< 25 µS/cm (less than 10 mL) < 5 µS/cm (more than 10 mL) (25 °C)
Nitrates	< 50 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm
Aluminium (2.4.17)	-	< 10 ppb	< 10 ppb	< 10 ppb	< 10 ppb
Chlorides (2.4.4)	-	-	pass test	-	< 0.5 ppm
Sulfates	-	-	pass test	-	pass test
Ammonium	-	-	< 0.2 ppm	-	< 0.6 ppm (less than 50 mL) < 0.2 ppm (more than 50 mL)
Heavy metals (2.4.8)	-	< 0.1 ppm	< 0.1 ppm	-	-
Calcium and magnesium	-	-	pass test	-	pass test
Acidity or alkalinity	-	-	pass test	-	pass test
Oxidizable substances	-	pass test	pass test	-	pass test
Residue on evaporation	-	-	< 0.001 %	-	< 0.004 % (less than 10 mL) < 0.003 % (more than 10 mL)

CONDUCTIVITY



	Water for extracts	PW in bulk	PW in containers	WFI in bulk	Sterilized WFI
Microbiological monitoring (2.6.12)	< 100 CFU/mL	< 100 CFU/mL	< 100 CFU/mL	< 10 CFU/ 100 mL	complies with the test for sterility
Bacterial endotoxins (2.6.14)	-	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL	< 0.25 IU/mL
TOC (2.2.44)	-	< 0.5 mg/L	< 0.5 mg/L	< 0.5 mg/L	-
Conductivity (2.2.38)	2500 µS/cm (20 °C)	5.1 µS/cm (25 °C)	5.1 µS/cm (25 °C)	1.3 µS/cm (25 °C)	< 25 µS/cm (less than 10 mL) < 5 µS/cm (more than 10 mL) (25 °C)
Nitrates	< 30 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm	< 0.2 ppm
Aluminium (2.4.17)	-	< 10 ppb	< 10 ppb	< 10 ppb	< 10 ppb
Chlorides (2.4.4)	-	-	pass test	-	< 0.5 ppm
Sulfates	-	-	pass test	-	pass test
Ammonium	-	-	< 0.2 ppm	-	< 0.6 ppm (less than 50 mL) < 0.2 ppm (more than 50 mL)
Heavy metals (2.4.8)	-	< 0.1 ppm	< 0.1 ppm	-	-
Calcium and magnesium	-	-	pass test	-	pass test
Acidity or alkalinity	-	-	pass test	-	pass test
Oxidizable substances	-	pass test	pass test	-	pass test
Residue on evaporation	-	-	< 0.001 %	-	< 0.004 % (less than 10 mL) < 0.003 % (more than 10 mL)



DRUG DELIVERY SYSTEMS

- Important excipient
- Different roles of water

RADIOPHARMACEUTICALS

WATER FOR PHARMACEUTICAL USE

Water can be used:

- for cleaning agent for rinsing vessels, equipment, primary packaging material
- during synthesis of active ingredient
- during production of final product
- as an excipient
- for reconstitution of the product

We can choose between:

- Potable water
- Water for preparation of extracts
- Purified water
- Water for injections

WHERE TO FIND INFORMATION

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2020
EMA/CHMP/CVMP/QWP/496873/2018

Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on the quality of water for pharmaceutical use

WHICH WATER TO USE?

Water present as an excipient in the final formulation

STERILE MEDICINAL PRODUCTS

Sterile medicinal products	Minimum acceptable quality of water
Parenteral	WFI
Biologics (including vaccines and ATMP)	WFI
Ophthalmic (excluding ATMP)	Purified
Haemofiltration solutions **Haemodiafiltration solutions**	WFI
Peritoneal dialysis solutions	WFI
Irrigation solutions	WFI
Nasal/Ear preparations	Purified
Cutaneous preparations	Purified

WHICH WATER TO USE?

NON-STERILE MEDICINAL PRODUCTS

Non-sterile medicinal products	Minimun acceptable quality of water
Vaccines for non-parenteral use	Purified*
Oral preparations	Purified
Nebuliser solutions	Purified**
Cutaneous preparations	Purified***
Nasal/ear preparations	Purified
Rectal/vaginal preparations	Purified

* **WFI** is recommended in order to ensure the vaccines' safety and product quality

** **In certain disease states (eg. cystic fibrosis),** medicinal products administered by nebulisation are required to be sterile and non-pyrogenic. In such cases, **WFI** should be used.

*** For some products such as v**eterinary teat dips**, it may be **acceptable to use potable water** where justified and authorised taking account of the variability in chemical composition and microbiological quality.

WHICH WATER TO USE?

Water used during manufacture of medicinal products but not present in the final formulation.

Manufacture	Minimun acceptable quality of water
Granulation	Purified*
Tablet coating	Purified
Used in formulation prior to non-sterile lyophilisation	Purified
Used in formulation prior to sterile lyophilisation	WFI

* For some veterinary premix products eg. granulated concentrates it may be acceptable to use potable water where justified and authorised taking account of the variability in chemical composition and microbiological quality.

WHICH WATER TO USE?

Water used for cleaning/rinsing.

Cleaning/Rinsing of Equipment, Containers, Closures	Minimun acceptable quality of water
Initial rinse for non-sterile products	Potable
Initial rinse for sterile products	Purified
Final rinse	Purified Water or use same quality of water as used in manufacture of medicinal product, if higher quality than Purified Water

More details in EMA Guidline on the quality of water for pharmaceutical use

WHICH WATER TO USE?

Water used during the manufacture of Active Substances (AS)

Type of manufacture	Product requirements	Minimun acceptable quality of water
Synthesis of all intermediates of AS prior to final isolation and purification steps	No requirement for sterility or apyrogenicity in AS or the pharmaceutical product in which it will be used.	Potable*
Final isolation and purification	No requirement for sterility or apyrogenicity in AS or the pharmaceutical product in which it will be used.	Potable
Final isolation and purification	AS is not sterile, but is intended for use in a sterile, non-parenteral product	Purified

More details in EMA Guidline on the quality of water for pharmaceutical use

* Purified Water should be used where there are technical requirements for greater chemical purity.

CONCLUSIONS – ‚TAKE-HOME' MESSAGES

- water has unique chemical properties
- **potable water** is feed water for all waters for pharmaceutical use
- water purification techniques depend on the **type of contaminants in feed water**
- **distillation and reverse osmosis** target the whole range of contaminants with good efficiency
- pharmaceutical water systems should be configured to **prevent microbial proliferation and recontamination**
- standards for waters for pharmaceutical use are provided in pharmacopoeias
- WFI is the highest quality of pharmacopoeial waters

- Radiopharmaceuticals
  - parenteral administration – sterile water for injection
  - oral delivery – purified water

https://forms.cloud.microsoft/e/5HpWkXx9xS