UNIT II: CENTRAL STERILE SUPPLY UNIT AND THEIR MANAGEMENT

INTRODUCTION :

Central sterile supply department (CSSD) is a service unit in a hospital that processes, issues, and controls the sterile stores supply to all departments of the hospital. It can be defined as that service, with in the hospital, catering for the sterile supplies to all departments , both to specialized units as well as general wards and OPDs.

The last few years have witnessed an 1 increasing interest in organizing sterilization . The purpose of such a CSSD is to provide all the departments of a hospital with guaranteed sterile equipment ready and available for immediate use in patient care – a step towards the prevention of hospital acquired infections(HAI) . Ideally, CSSD is an independent department with facilities to receive, clean, pack, disinfect, sterilizes, store and distribute instruments as per well-delineated protocols. The essentials of this department are correct design, appropriate equipments, skilful operators and to proper work flow The history of CSSD starts in 1928 when American College Of Surgeons introduced the word CSSD.In1955 the Cambridge Military Hospital established Regular CSSD in United Kingdom. In India, Safdarjang Hospital New Delhi, established the first CSSD in 1965. The planning of a CSSD has to be steered by committee including representatives of departments of administration, infection control, anaesthesia, microbiology, nursing and housekeeping drawing upon their knowledge and experience.

The committee is required to meet monthly even during the running of a fully functional CSSD in order to discuss new procedures or alternations to existing procedures in the light of new knowledge and breakthroughs. The objectives of the department are:

To provide sterilized material from a central department where sterilizing practice is conducted under conditions, which are controlled, thereby contributing to a reduction in the incidence of hospital infection.

To take some of the work of the Nursing staff so that they can devote more time to their patients.

To avoid duplication of costly equipment's, which may be infrequently used.

To maintain record of effectiveness of cleaning, disinfection and sterilization process.

To monitor and enforce controls necessary to prevent cross infection according to infection control policy.

To maintain an inventory of supplies and equipment.

To stay updated regarding developments in the field in the interest of efficiency, economy, accuracy and provision of better patient care.

To provide a safe environment for the patients and staff. Designing of a CSSD: The workload in a CSSD varies from hospital to hospital. The size and location usually depends on the number of the hospitals the CSSD will serve as well as the number of beds and the future expansion of the hospital. However 6 to 10 square feet per bed is recommended as an area of requirement for the CSSD. It should be located as close as possible to the major user areas such as Operation theatres, Accidents and Emergency department and wards. The CSSD layout should be designed for a unidirectional flow.

The CSSD should have four zones for a smooth work flow.

1. The unclean and washing area
2. The assembly and packing area
3. The sterilization area
4. The sterile area The Layout –

1. Entrance lobby
2. Reception and Cleaning room
3. Glove room

4. Work room (Preparation and assembling of packs)
5. Sterilisation room
6. Sterile store room
7. Nurses/Managers room
8. Staff changing room

Workflow in the CSSD Receipt: The material that is to be sterilized coming from various departments arrives in the reception area using stainless steel trolleys via a dedicated elevator. Cleaning: This function means cleaning of the used equipments/materials, rubber and plastic goods either manually or by machines eg. washer-disinfector, ultrasonic cleaner, jet glove washing machines and dryers. This function may also include cleaning of the delivery trolleys..The common items handled by the CSSD stores are syringes and needles; Procedure sets which includes Lumbar puncture, Sternal puncture, venesection, paracentesis. aspiration, catheterization, tracheotomy, suturing, dressing, biopsy, incision & drainage, aortography cardiac resuscitation, gloves, I.V. Fluids, treatment Trays, O.T Instruments, O.T. Linen, infusion Fluids for Renal Dialysis and at times linen from wards etc. Assembly and Packing: It includes checking of glass items for breakages, needles and instruments for sharpness and breakages, assembling of the equipment after washing and drying, making appropriate sets for use by various departments and packaging along with sealing either manually or using a machine before sterilization. Adequate documentation and labeling of each pack should be done and records should be maintained.

Sterilisation: It renders materials sterile for quality patient care. It is achieved by steam sterilizers working at specified cycles of temperature and duration to attain adequate sterility assurance level (SAL). Advantage of steam sterilizers are rapid heating & penetration of loads,destruction of all forms of microbial life and no residual toxicity.Different types of Autolaving machines that can be used are

1. Downward Displacement
2. Vacuum Assisted.
3. Pulsed Steam Dilution . The capacity of the sterilizer is based on the load and the number of cycles per day. The load is calculated by estimating litres to each procedure and converting it into a standard unit i.e st.u(1 st.u = 54L). This value is then divided by the number of cycles that will be run per day to obtain a value of st.u/cycle. The capacity of the sterilizer is then selected based on the value obtained. It is better to have 2 sterilizers in case of breakdowns.

Additionally an ethylene oxide sterilizer can be included in a separate compartment of this area in order to sterilize heat sensitive instruments.

Storage: The function includes storage of sterilized materials where space is also provided for storing distribution trolleys. Sterile store maintains inventory of all types of sterile packs. At the end of the path of the treated material a computer terminal should be provided in order to manage delivery of materials and transport documentation.

Issue and Distribution: The function entails issue of the sterilized packages, dressings, linen, instruments and 3,4 disposables to various departments of the hospitals .

Process of sterilization: The items to be sterilized at the Central Sterile Supply Department are washed (with detergent or chemical as applicable), sorted in the washing area. linen from wards and OT are to be sent directly to the laundry for cleaning. The laundry washed linen are to be received , packed and forwarded to the CSSD for sterilization. The CSSD technicians or trained nurses shall receive the unsterile packs, inspect them to check the status of the item (torn, punctured, cracked etc) and place them at the unsterile packs storing platform. Entry must be made in CSSD receipts register including date, time, type of instruments in the pack, ward, its source, procedure used for, and case infected or not, name and signature of person handing over, and name and signature of person receiving it.

FLOW PROCESS IN CSSD

The autoclave indicator is pasted in the packs by the CSSD technician and the packs are taken to the main sterilizing area where the sterilizing units are placed .The CSSD technician places the unsterile packs under appropriate temperature and pressure specifications in the sterilizing units. The temperature, pressure specifications and accordingly the temperature period are 0 for Normal Sterilization, temperature of 121 C at 15 lb 0 for 20 minutes, and for Rapid Sterilization , 140 C at 20 lb for 15 minutes.

At the end of the sterilization the packs are removed from the sterilizing units, the autoclave indicators are checked to confirm adequate sterilization of the packs, and incase the sterilization is not adequate the process is to be repeated. A material is pronounced sterile if it achieves 99.99% kill of bacterial spores. Packs which are adequately sterilized are stored in the sterile storage area.

If the sterile packs are torn, if it has been opened, they are wet, etc, and then the whole process is to be repeated again. In case the packs which are sterilized in the CSSD and issued to the departments remains un utilized in the respective user departments for a period of 72 hours , the same are returned to the CSSD department for resterilization.

Registers to be maintained in the CSSD are CSSD receipt register, CSSD issue Register, Equipment Maintenance Record register and Equipment Calibration Register. Maintenance of the equipments are to be done as per the annual maintenance contract (AMC) entered into with the vendor of the respective CSSD equipments. All details in these regard are maintained by the Maintenance Department of the hospital.

All equipments used in the department are to be appropriately calibrated at periodic intervals to ascertain whether they are performing at the expected level and a record of the same is documented in the department as well as with the concerned case workers working in the administration. Indent for setting up an ideal CSSD:

1. Washer disinfector with accessories - The washer should perform pre-rinsing, cleaning, post-rinsing, thermal disinfection, final rinsing and drying phases. Validated programs are secured by access code. Detergents and rinse agents should be automatically dispensed during the cycle.

2. Steam Sterilizers - The sterilizer should meet the relevant standards. The chamber and doors should be made of solid, high quality 316L Stainless steel. The chamber should be jacketed to ensure the temperature uniformity in chamber. The chamber floor is slightly sloped towards an internal drain to facilitate drainage. A stainless steel mesh strainer should be provided to protect the drain port from blockage by debris. The chamber is mounted on a stainless steel framework with height adjustable feet. The internal surface should be electro-chemically treated for high quality smooth finish to facilitate cleaning. The

WARDS/DEPTS BULK STORES DIRTY RECEIPT CLEAN RECEIPT COTTON & GAUZE DISASSEMBLY INSTRUMENT GLOVES RUBBERWARE WASHING AREAS ASSEMBLY INSPECTION PRE - STERILE STORAGE STERILISATION STERILE STORAGE DISTRIBUTION

60 resultant surface should be polished to less than 0.8 μm fineness to protect against corrosion. The internal corners should be rounded off to facilitate efficient cleaning. The sterilizer jacket and door should be completely insulated with mineral rock wool to keep the autoclave cool on the outside. The insulation should be completely encased in a rigid removable sheet housing.

The jacket should be made of 316L quality stainless steel. The chamber should have a warranty for 10 years. The sterilizer should have inbuilt steam generator of adequate capacity. It should be mounted under the sterilizer chamber & should be made of 316 quality

stainless steel. The steam generator should have insulation of thick chloride free mineral rock wool with rigid aluminum sheet housing.

It should have a built in thermostat, pressure safety valve & water level glass gauge inspection device visible from service area. The heating element, not less than 36KW should also be made of stainless steel. It should also have the automatic blow down valve & degassing system for feed water to steam generator. To make the sterilization process faster the capacity of the heating element should not be less than 36 KW.

1.Ultrasonic cleaner (optional) - The units should be a compact free-standing bench model, with a built-in tank manufactured from high-quality (316) stainless steel and a solid-state generator that sends ultrasonic (approx 42,000 cycles per second) impulses through wash water containing detergent and electrical heating; microprocessor controlled display with memory time and temperature functions. The electrical energy should be transformed into sound waves by transducers, fixed to the bottom of the tank. The tank should be made of solid stainless steel (316).

The ultrasonic cleaner should have a display and control which could be easily seen and placed above any liquid for safety and reliability. It should have digital read out timer and temperature setting (up to +69° C (temperature adjustable from 20 to 69 °C) monitoring.-

2. Heat Sealing Machine - Rotary heat sealers should provide validated sealing of sterilization bags and clearview pouches (paper/plastic laminate). These through feed-type sealers should be microprocessor-controlled for highest capacity and ease of operation. The rotary heat sealer should give documentation of process parameters via an integrated printer and could be integrated with documentation system. The ergonomically design should be tilted forward for increased user convenience and space saving installation.

3. Inspection tables, lamps, cleaning equipment, interior water treatment facilities

4. Table top sterilizer with accessories - Table Top Sterilizers should be equipped with B-process as per latest international standards

5. Ethylene Oxide Sterilizer (optional)- Ethylene oxide sterilizer is defined as equipment which uses ethylene oxide as a biocide to destroy bacteria, viruses, fungi and other unwanted organisms. Ethylene oxide is used in sterilization of items that are heat and moisture sensitive. The ETO gas sterilizer should be fully automatic type for sterilization of heat sensitive goods such as anesthetic tubing and endoscopes.

6. Documentation labeller

7. Process challenge devices

8. Water treatment plant

9. All necessary furniture required for the facility An alarming rate of hospital acquired infections (HAI) in Indian hospitals has highlighted the importance of CSSD. Despite all measures and advancements in technology, hospital acquired infections remain a challenge in healthcare scenario today. The hospitals are required to establish an adequate CSSD set-up and adopt strict quality control processes with the latest technology to mitigate hospital acquired infections. Hence the concept of infection control by FLORENCE NIGHTINGALE who said"No Stronger Condemnation of any hospital or ward could be pronounced than the simple fact that zymotic disease has originated in it or that such disease attack other patients than those brought-in with ". stands true for generations of healthcare to come.

Sterilization:

Sterilization (or **sterilisation**) is a term referring to any process that eliminates (removes) or kills (deactivates) all forms of life and other biological agents (such as viruses which some do not consider to be alive but are biological pathogens nonetheless), excluding prions which

cannot be killed, including transmissible agents (such as fungi, bacteria, viruses, prions, spore forms,unicellular eukaryotic organisms such as Plasmodium, etc.) present in a specified region, such as a surface, a volume of fluid, medication, or in a compound such as biological culture media.[1][2] Sterilization can be achieved with one or more of the following: heat, chemicals, irradiation, high pressure, and filtration. Sterilization is distinct from disinfection, sanitization, and pasteurization in that sterilization kills, deactivates, or eliminates all forms of life and other biological agents.

Applications

Foods

One of the first steps toward sterilization was made by Nicolas Appert who discovered that thorough application of heat over a suitable period slowed the decay of foods and various liquids, preserving them for safe consumption for a longer time than was typical. Canning of foods is an extension of the same principle, and has helped to reduce food borne illness ("food poisoning"). Other methods of sterilizing foods include food irradiation[3] and high pressure (pascalization).[4]

Medicine and surgery

Apparatus to sterilize surgical instruments, Verwaltungsgebäude der Schweiz. Kranken- und Hilfsanstalt, 1914-1918

In general, surgical instruments and medications that enter an already aseptic part of the body (such as the bloodstream, or penetrating the skin) must be sterile. Examples of such instruments include scalpels, hypodermic needles and artificial pacemakers. This is also essential in the manufacture of parenteral pharmaceuticals.

Preparation of injectable medications and intravenous solutions for fluid replacement therapy requires not only sterility but also well-designed containers to prevent entry of adventitious agents after initial product sterilization.

Spacecraft

There are strict international rules to protect the contamination of Solar System bodies from biological material from Earth. Standards vary depending on both the type of mission and its destination; the more likely a planet is considered to bear life, the stricter the requirements are.

Many components of instruments used on spacecraft cannot withstand very high temperatures, so techniques not requiring excessive temperatures are used as tolerated, including heating to at least 120 °C, chemical sterilization, oxidization, ultraviolet, and irradiation.[5]

Quantification

The aim of sterilization is the reduction of initially present microorganisms or other potential pathogens. The degree of sterilization is commonly expressed by multiples of the decimal reduction time, or D-value, denoting the time needed to reduce the initial number N_0 to one tenth (10^{-1}) of its original value.[6] Then the number of microorganisms N after sterilization time t is given by:

$$\frac{N}{N_0} = 10^{\left(-\frac{t}{D}\right)}.$$

The D-value is a function of sterilization conditions and varies with the type of microorganism, temperature, water activity, pH etc.. For steam sterilization (see below) typically the temperature (in °Celsius) is given as index.

Theoretically, the likelihood of survival of an individual microorganism is never zero. To compensate for this, the overkill method is often used. Using the overkill method, sterilization is performed by sterilizing for longer than is required to kill the bioburden present on or in the item being sterilized. This provides a sterility assurance level (SAL) equal to the probability of a non-sterile unit.

For high-risk applications such as medical devices and injections, a sterility assurance level of at least 10^{-6} is required by the United States Food and Drug Administration (FDA)[7]

Heat

Steam

See also: Moist heat sterilization

Front-loading autoclave

A widely used method for heat sterilization is the autoclave, sometimes called a converter or steam sterilizer. Autoclaves use steam heated to 121-134 °C under pressure. To achieve

sterility, the article is heated in a chamber by injected steam until the article reaches a time and temperature setpoint. The article is then held at that setpoint for a period of time which varies depending on the bioburden present on the article being sterilized and its resistance (D-value) to steam sterilization. A general cycle is 20 minutes at 121 °C at 100 kPa, which is sufficient to provide a sterility assurance level of 10^{-4} for a product with a bioburden of 10^6 and a D-value of 2.0 minutes.[8] Following sterilization, liquids in a pressurized autoclave must be cooled slowly to avoid boiling over when the pressure is released. This may be achieved by gradually depressurizing the sterilization chamber and allowing liquids to evaporate under a negative pressure, while cooling the contents.

Proper autoclave treatment will inactivate all resistant bacterial spores in addition to fungi, bacteria, and viruses, but is not expected to eliminate all prions, which vary in their resistance. For prion elimination, various recommendations state 121-132 °C for 60 minutes or 134 °C for at least 18 minutes[*citation needed*]. The 263K scrapie prion is inactivated relatively quickly by such sterilization procedures; however, other strains of scrapie, and strains of CJD and BSE are more resistant. Using mice as test animals, one experiment showed that heating BSE positive brain tissue at 134-138 °C for 18 minutes resulted in only a 2.5 log decrease in prion infectivity.[*citation needed*]

Most autoclaves have meters and charts that record or display information, particularly temperature and pressure as a function of time. The information is checked to ensure that the conditions required for sterilization have been met. Indicator tape is often placed on packages of products prior to autoclaving, and some packaging incorporates indicators. The indicator changes color when exposed to steam, providing a visual confirmation.

Biological indicators can also be used to independently confirm autoclave performance. Simple bioindicator devices are commercially available based on microbial spores. Most contain spores of the heat resistant microbe *Geobacillus stearothermophilus* (formerly *Bacillus stearothermophilus*), which is extremely resistant to steam sterilization. Biological indicators may take the form of glass vials of spores and liquid media, or as spores on strips of paper inside glassine envelopes. These indicators are placed in locations where it is difficult for steam to reach to verify that steam is penetrating there.

For autoclaving, cleaning is critical. Extraneous biological matter or grime may shield organisms from steam penetration. Proper cleaning can be achieved through physical scrubbing, sonication, ultrasound or pulsed air. [9] Pressure cooking and canning are analogous to autoclaving, and when performed correctly renders food sterile.

Moist heat causes destruction of micro-organisms by denaturation of macromolecules, primarily proteins. This method is a faster process than dry heat sterilization.

Dry Heat


Dry heat sterilizer

Dry heat was the first method of sterilization, and is a longer process than moist heat sterilization. The destruction of microorganisms through the use of dry heat is a gradual phenomenon. With longer exposure to lethal temperatures, the number of killed microorganisms increases. Forced ventilation of hot air can be used to increase the rate at which heat is transferred to an organism and reduce the temperature and amount of time needed to achieve sterility. At higher temperatures, shorter exposure times are required to kill organisms. This can reduce heat-induced damage to food products.[10]

The standard setting for a hot air oven is at least two hours at 160 °C. A rapid method heats air to 190 °C for 6 minutes for unwrapped objects and 12 minutes for wrapped objects.[11][12] Dry heat has the advantage that it can be used on powders and other heat-stable items that are adversely affected by steam (e.g. it does not cause rusting of steel objects).

Flaming

Flaming is done to loops and straight-wires in microbiology labs. Leaving the loop in the flame of a Bunsen burner or alcohol lamp until it glows red ensures that any infectious agent gets inactivated. This is commonly used for small metal or glass objects, but not for large objects (see Incineration below). However, during the initial heating infectious material may be "sprayed" from the wire surface before it is killed, contaminating nearby surfaces and objects. Therefore, special heaters have been developed that surround the inoculating loop with a heated cage, ensuring that such sprayed material does not further contaminate the area. Another problem is that gas flames may leave carbon or other residues on the object if the object is not heated enough. A variation on flaming is to dip the object in 70% or higher ethanol, then briefly touch the object to a Bunsen burner flame. The ethanol will ignite and burn off rapidly, leaving less residue than a gas flame.

Incineration

Incineration is a waste treatment process that involves the combustion of organic substances contained in waste materials. This method also burns any organism to ash. It is used to sterilize medical and other biohazardous waste before it is discarded with non-hazardous waste. Bacteria incinerators are mini furnaces used to incinerate and kill off any micro organisms that may be on an inoculating loop or wire.[13]

Tyndallization

Named after John Tyndall, Tyndallization[14] is an obsolete and lengthy process designed to reduce the level of activity of sporulating bacteria that are left by a simple boiling water method. The process involves boiling for a period (typically 20 minutes) at atmospheric pressure, cooling, incubating for a day, then repeating the process a total of three to four times. The incubation periods are to allow heat-resistant spores surviving the previous boiling period to germinate to form the heat-sensitive vegetative (growing) stage, which can be killed by the next boiling step. This is effective because many spores are stimulated to grow by the heat shock. The procedure only works for media that can support bacterial growth, and will not sterilize non-nutritive substrates like water. Tyndallization is also ineffective against prions.

Glass bead sterilizers

Glass bead sterilizers work by heating glass beads to 250 °C. Instruments are then quickly doused in these glass beads, which heat the object while physically scraping contaminants off their surface. Glass bead sterilizers were once a common sterilization method employed in dental offices as well as biologic laboratories,[15] but are not approved by the U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) to be used as a sterilizers since 1997.[16] They are still popular in European as well as Israeli dental practices although there are no current evidence-based guidelines for using this sterilizer.[15]

Chemical sterilization

Chemiclav

Chemicals are also used for sterilization. Heating provides a reliable way to rid objects of all transmissible agents, but it is not always appropriate if it will damage heat-sensitive materials such as biological materials, fiber optics, electronics, and many plastics. In these situations chemicals, either as gases or in liquid form, can be used as sterilants. While the use of gas and liquid chemical sterilants avoids the problem of heat damage, users must ensure that article to be sterilized is chemically compatible with the sterilant being used. In addition, the use of chemical sterilants poses new challenges for workplace safety, as the properties that make chemicals effective sterilants usually make them harmful to humans.

Ethylene oxide

Ethylene oxide (EO or EtO) gas is commonly used to sterilize objects that are sensitive to temperatures greater than 60 °C and / or radiation such as plastics, optics and electrics. Besides moist heat and irradiation, ethylene oxide is the most common sterilization method, used for over 70% of total sterilizations, and for 50% of all disposable medical devices[*citation needed*].

Ethylene oxide treatment is generally carried out between 30 °C and 60 °C with relative humidity above 30% and a gas concentration between 200 and 800 mg/l, and typically lasts for at least three hours. Ethylene oxide penetrates well, moving through paper, cloth, and some plastic films and is highly effective. Ethylene oxide can kill all known viruses, bacteria (including spores) and fungi, and is compatible with most materials even when repeatedly applied. However, it is highly flammable, toxic and carcinogenic with a potential to cause adverse reproductive effects. Ethylene oxide sterilizers require biological validation after sterilization installation, repairs or process failure.

A typical process consists of a preconditioning phase, an exposure phase, and a period of post-sterilization aeration to remove ethylene oxide residues and by-products such as ethylene glycol and ethylene chlorohydrine.

The two most important ethylene oxide sterilization methods are: (1) the gas chamber method and (2) the micro-dose method. To benefit from economies of scale, ethylene oxide has traditionally been delivered by flooding a large chamber with a combination of ethylene oxide and other gases used as diluents (usually CFCs or carbon dioxide). Drawbacks of this method include air contamination produced by CFC's and ethylene oxide residuals, operator exposure risks, training costs and flammability issues requiring special handling and storage.

Ethylene oxide is still widely used by medical device manufacturers for larger scale sterilization, but ethylene oxide is becoming less popular in hospitals[*citation needed*] . Since ethylene oxide is explosive at concentrations from 3% to 100%[*citation needed*] , ethylene oxide was traditionally supplied with an inert carrier gas such as a CFC or halogenated hydrocarbon. The use of CFCs as the carrier gas was banned because of concerns of ozone depletion[17] and halogenated hydrocarbons are being replaced by systems using 100% ethylene oxide because of the much greater cost of the blends. In hospitals, most ethylene oxide sterilizers use single use cartridges (e.g. 3M's Steri-Vac line,[18] or STERIS Corporation's Stericert sterilizers[19]) because of the convenience and ease of use compared to the former plumbed gas cylinders of ethylene oxide blends. Another method using 100% ethylene oxide is the micro-dose sterilization method, developed in the late 1950s, using a specially designed bag to eliminate the need to flood a larger chamber with ethylene oxide. This method is also known as gas diffusion sterilization, or bag sterilization. This method minimizes the use of gas.[20]

Other reasons for the decrease in use of ethylene oxide are the well-known health effects. In addition to being a primary irritant, ethylene oxide is now classified by the IARC as a known human carcinogen.[21] The US OSHA has set the permissible exposure limit (PEL) at 1 ppm calculated as an eight-hour time weighted average (TWA) [29 CFR 1910.1047] and 5 ppm as a 15-minute TWA. The NIOSH Immediately dangerous to life and health limit for ethylene oxide is 800 ppm.[22] The odor threshold is around 500 ppm[23] and so ethylene oxide is imperceptible until concentrations well above the OSHA PEL. Therefore, OSHA

recommends that continuous gas monitoring systems be used to protect workers using ethylene oxide for sterilization.[24] Employees health records must be maintained during employment and after termination of employment for 30 years.

Nitrogen dioxide

Nitrogen dioxide (NO_2) gas is a rapid and effective sterilant for use against a wide range of microorganisms, including common bacteria, viruses, and spores. The unique physical properties of NO_2 gas allow for sterilant dispersion in an enclosed environment at room temperature and ambient pressure. The mechanism for lethality is the degradation of DNA in the spore core through nitration of the phosphate backbone, which kills the exposed organism as it absorbs NO_2. This degradation occurs at even very low concentrations of the gas.[25] NO_2 has a boiling point of 21 °C at sea level, which results in a relatively high saturated vapor pressure at ambient temperature. Because of this, liquid NO_2 may be used as a convenient source for the sterilant gas. Liquid NO_2 is often referred to by the name of its dimer, dinitrogen tetroxide (N_2O_4). Additionally, the low levels of concentration required, coupled with the high vapor pressure, assures that no condensation occurs on the devices being sterilized. This means that no aeration of the devices is required immediately following the sterilization cycle.[26] NO_2 is also less corrosive than other sterilant gases, and is compatible with most medical materials and adhesives.[26]

The most-resistant organism (MRO) to sterilization with NO_2 gas is the spore of Geobacillus stearothermophilus, which is the same MRO for both steam and hydrogen peroxide sterilization processes. The spore form of G. stearothermophilus has been well characterized over the years as a biological indicator in sterilization applications. Microbial inactivation of G. stearothermophilus with NO_2 gas proceeds rapidly in a log-linear fashion, as is typical of other sterilization processes. Noxilizer, Inc. has commercialized this technology to offer contract sterilization services for medical devices at its Baltimore, MD facility.[27] This has been demonstrated in Noxilizer's lab in multiple studies and is supported by published reports from other labs. These same properties also allow for quicker removal of the sterilant and residuals through aeration of the enclosed environment. The combination of rapid lethality and easy removal of the gas allows for shorter overall cycle times during the sterilization (or decontamination) process and a lower level of sterilant residuals than are found with other sterilization methods.[26]

Ozone

Ozone is used in industrial settings to sterilize water and air, as well as a disinfectant for surfaces. It has the benefit of being able to oxidize most organic matter. On the other hand, it is a toxic and unstable gas that must be produced on-site, so it is not practical to use in many settings.

Ozone offers many advantages as a sterilant gas; ozone is a very efficient sterilant because of its strong oxidizing properties (E = 2.076 vs SHE[28]) capable of destroying a wide range of pathogens, including prions without the need for handling hazardous chemicals since the ozone is generated within the sterilizer from medical grade oxygen. The high reactivity of ozone means that waste ozone can be destroyed by passing over a simple catalyst that reverts it to oxygen and ensures that the cycle time is relatively short. The disadvantage of using ozone is that the gas is very reactive and very hazardous. The NIOSH immediately dangerous to life and health limit for ozone is 5 ppm, 160 times smaller than the 800 ppm IDLH for

ethylene oxide. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLH): NIOSH Chemical Listing and Documentation of Revised IDLH Values (as of 3/1/95)[29] and OSHA has set the PEL for ozone at 0.1 ppm calculated as an 8 hour time weighted average (29 CFR 1910.1000, Table Z-1). The Canadian Center for Occupation Health and Safety provides an excellent summary of the health effects of exposure to ozone. The sterilant gas manufacturers include many safety features in their products but prudent practice is to provide continuous monitoring to below the OSHA PEL to provide a rapid warning in the event of a leak. Monitors for determining workplace exposure to ozone are commercially available.

Glutaraldehyde and formaldehyde

Glutaraldehyde and formaldehyde solutions (also used as fixatives) are accepted liquid sterilizing agents, provided that the immersion time is sufficiently long. To kill all spores in a clear liquid can take up to 22 hours with glutaraldehyde and even longer with formaldehyde. The presence of solid particles may lengthen the required period or render the treatment ineffective. Sterilization of blocks of tissue can take much longer, due to the time required for the fixative to penetrate. Glutaraldehyde and formaldehyde are volatile, and toxic by both skin contact and inhalation. Glutaraldehyde has a short shelf life (<2 weeks), and is expensive. Formaldehyde is less expensive and has a much longer shelf life if some methanol is added to inhibit polymerization to paraformaldehyde, but is much more volatile. Formaldehyde is also used as a gaseous sterilizing agent; in this case, it is prepared on-site by depolymerization of solid paraformaldehyde. Many vaccines, such as the original Salk polio vaccine, are sterilized with formaldehyde.

Hydrogen peroxide

Hydrogen peroxide, in both liquid and as vaporized hydrogen peroxide (VHP), is another chemical sterilizing agent. Hydrogen peroxide is strong oxidant, which allows it to destroy a wide range of pathogens. Hydrogen peroxide is used to sterilize heat or temperature sensitive articles such as rigid endoscopes. In medical sterilization hydrogen peroxide is used at higher concentrations, ranging from around 35% up to 90%. The biggest advantage of hydrogen peroxide as a sterilant is the short cycle time. Whereas the cycle time for ethylene oxide may be 10 to 15 hours, some modern hydrogen peroxide sterilizers have a cycle time as short as 28 minutes.[30]

Drawbacks of hydrogen peroxide include material compatibility, a lower capability for penetration and operator health risks. Products containing cellulose, such as paper, cannot be sterilized using VHP and products containing nylon may become brittle.[31] The penetrating ability of hydrogen peroxide is not as good as ethylene oxide[*citation needed*] and so there are limitations on the length and diameter of lumens that can be effectively sterilized and guidance is available from the sterilizer manufacturers. Hydrogen peroxide is primary irritant and the contact of the liquid solution with skin will cause bleaching or ulceration depending on the concentration and contact time. It is relatively non-toxic when diluted to low concentrations, but is a dangerous oxidizer at high concentrations (> 10% w/w). The vapor is also hazardous, primarily affecting the eyes and respiratory system. Even short term exposures can be hazardous and NIOSH has set the Immediately Dangerous to Life and Health Level (IDLH) at 75 ppm,[22] less than one tenth the IDLH for ethylene oxide (800 ppm). Prolonged exposure to lower concentrations can cause permanent lung damage and consequently OSHA has set the permissible exposure limit to 1.0 ppm, calculated as an 8-

hour time weighted average.[32] Sterilizer manufacturers go to great lengths to make their products safe through careful design and incorporation of many safety features, though there are still workplace exposures of hydrogen peroxide from gas sterilizers are documented in the FDA MAUDE database.[33] When using any type of gas sterilizer, prudent work practices will include good ventilation, a continuous gas monitor for hydrogen peroxide and good work practices and training.[34][35]

Vaporized hydrogen peroxide (VHP) is used to sterilize large enclosed and sealed areas such as entire rooms and aircraft interiors.

Peracetic acid

Peracetic acid (0.2%) is a recognized sterilant by the FDA[36] for use in sterilizing medical devices such as endoscopes.

Potential for chemical sterilization of prions

Prions are highly resistant to chemical sterilization. Treatment with aldehydes such as formaldehyde have actually been shown to increase prion resistance. Hydrogen peroxide (3%) for one hour was shown to be ineffective, providing less than 3 logs (10^{-3}) reduction in contamination. Iodine, formaldehyde, glutaraldehyde and peracetic acid also fail this test (one hour treatment). Only chlorine, phenolic compounds, guanidinium thiocyanate, and sodium hydroxide (NaOH) reduce prion levels by more than 4 logs; chlorine (too corrosive to use on certain objects) and NaOH are the most consistent. Many studies have shown the effectiveness of sodium hydroxide.[37]

Radiation sterilization

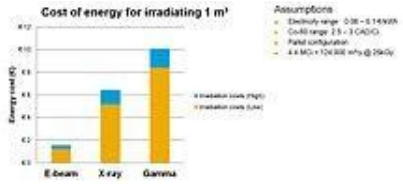
Sterilization can be achieved using electromagnetic radiation such as electron beams, X-rays, gamma rays, or irradiation by subatomic particles.[38] Electromagnetic or particulate radiation can be energetic enough to ionize atoms or molecules (ionizing radiation), or less energetic (non-ionizing radiation).

Non-ionizing radiation sterilization

Ultraviolet light irradiation (UV, from a germicidal lamp) is useful for sterilization of surfaces and some transparent objects. Many objects that are transparent to visible light absorb UV. UV irradiation is routinely used to sterilize the interiors of biological safety cabinets between uses, but is ineffective in shaded areas, including areas under dirt (which may become polymerized after prolonged irradiation, so that it is very difficult to remove). It also damages some plastics, such as polystyrene foam if exposed for prolonged periods of time.

Further information: Ultraviolet germicidal irradiation

Ionizing radiation sterilization



Efficiency illustration of the different radiation technologies (electron beam, X-ray, gamma rays)

The safety of irradiation facilities is regulated by the United Nations International Atomic Energy Agency and monitored by the different national Nuclear Regulatory Commissions. The incidents that have occurred in the past are documented by the agency and thoroughly analyzed to determine root cause and improvement potential. Such improvements are then mandated to retrofit existing facilities and future design.

Gamma radiation is very penetrating, and is commonly used for sterilization of disposable medical equipment, such as syringes, needles, cannulas and IV sets, and food. It is emitted by a radioisotope, usually Cobalt-60(^{60}Co) or caesium-137 (^{137}Cs).

Use of a radioisotope requires shielding for the safety of the operators while in use and in storage. With most designs the radioisotope is lowered into a water-filled source storage pool, which absorbs radiation and allows maintenance personnel to enter the radiation shield. One variant keeps the radioisotope under water at all times and lowers the product to be irradiated into the water towards the source in hermetic bells; no further shielding is required for such designs. Other uncommonly used designs use dry storage, providing movable shields that reduce radiation levels in areas of the irradiation chamber. An incident in Decatur Georgia, US, where water-soluble caesium-137 leaked into the source storage pool, requiring NRC intervention[39] has led to use of this radioisotope being almost entirely discontinued in favour of the more costly, non-water-soluble cobalt-60. Cobalt-60 gamma photons have about twice the energy, and hence greater penetrating range, of Caesium-137 radiation.

Electron beam processing is also commonly used for sterilization. Electron beams use an on-off technology and provide a much higher dosing rate than gamma or x-rays. Due to the higher dose rate, less exposure time is needed and thereby any potential degradation to polymers is reduced. A limitation is that electron beams are less penetrating than either gamma or x-rays. Facilities rely on substantial concrete shields to protect workers and the environment from radiation exposure.

X-rays: high-energy X-rays (produced by bremsstrahlung) allow irradiation of large packages and pallet loads of medical devices. They are sufficiently penetrating to treat multiple pallet loads of low-density packages with very good dose uniformity ratios. X-ray sterilization does not require chemical or radioactive material: high-energy X-rays are generated at high intensity by an X-ray generator that does not require shielding when not in use. X-rays are generated by bombarding a dense material (target) such as tantalum or tungsten with high-energy electrons in a process known as bremsstrahlung conversion. These systems are energy-inefficient, requiring much more electrical energy than other systems for the same result.

Irradiation with X-rays or gamma rays, electromagnetic radiation rather than particles, does not make materials radioactive. Irradiation with particles may make materials radioactive, depending upon the type of particles and their energy, and the type of target material: neutrons and very high-energy particles can make materials radioactive, but have good penetration, whereas lower energy particles (other than neutrons) cannot make materials radioactive, but have poorer penetration.

Sterilization by irradiation with gamma rays may however in some cases affect material properties.[40]

Irradiation is used by the United States Postal Service to sterilize mail in the Washington, D.C. area. Some foods (e.g. spices, ground meats) are sterilized by irradiation.

Subatomic particles may be more or less penetrating, and may be generated by a radioisotope or a device, depending upon the type of particle.

Sterile filtration

Fluids that would be damaged by heat, irradiation or chemical sterilization, such as drug products, can be sterilized by microfiltration using membrane filters. This method is commonly used for heat labile pharmaceuticals and protein solutions in medicinal drug processing. A microfilter with pore size 0.2 μm will usually effectively remove microorganisms.[41] In the processing of biologics, viruses must be removed or inactivated, requiring the use of nanofilters with a smaller pore size (20 -50 nm) are used. Smaller pore sizes lower the flow rate, so in order to achieve higher total throughput or to avoid premature blockage, pre-filters might be used to protect small pore membrane filters.

Membrane filters used in production processes are commonly made from materials such as mixed cellulose ester or polyethersulfone (PES). The filtration equipment and the filters themselves may be purchased as pre-sterilized disposable units in sealed packaging, or must be sterilized by the user, generally by autoclaving at a temperature that does not damage the fragile filter membranes. To ensure proper functioning of the filter, the membrane filters are integrity tested post-use and sometimes before use. The non-destructive integrity test assures the filter is undamaged, and is a regulatory requirement.[42] Typically, terminal pharmaceutical sterile filtration is performed inside of a cleanroom to prevent contamination.

Preservation of sterility

A curette in sterile packaging.

Instruments that have undergone sterilization can be maintained in such condition by containment in sealed packaging until use.

Aseptic technique is the act of maintaining sterility during procedures

MANUFACTURING OF STERILE AND NON STERILE PRODUCTS

Hospitals are slowly moving from buying all their medical requirements from outside by making and manufacturing a part of their medicinal requirements within their premises.

Factors which determine the economy of a hospital:

In order to develop the adequate control over budget for manufacturing, hospital pharmacist is required to consider the following factors:

1. Material requirement
2. Manufacturing requirement
3. Manufacturing staff
4. Manufacturing capacity
5. Manufacturing equipment
6. Operating cost

1. Material requirement: the raw material, packaging material and other materials required for manufacturing can be determined by various formulae.
2. Manufacturing requirement: for manufacturing requirement the consumption rate for each item is calculated by reviewing the previous record and comparing this figures with the present requirements.
3. Manufacturing staff: too many or too less personnel disturb the manufacturing programmed.

4. Manufacturing capacity: it depends on the availability of equipment and economy of hospital to fulfill the requirements.
5. Manufacturing equipments: the type and size of manufacturing equipment required in a hospital depends upon manufacturing programme, like the quantities to be produced, duration of production time, availability of physical facilities and the availability of persons.
6. Operating cost: operating cost include both direct cost, i.e. labour, cost of material etc. and direct cost like maintenance of building, insurance policies, space maintenance etc.

Factors effecting make or buy decision are

1. Quality
2. Quantity
3. Cost
4. Assurance of supply

DEMAND AND COSTING :

The production of sterile and non sterile pharmaceuticals preparation in a hospital depends upon the requirements of the hospital and is directly related to the future demand. Forecasting is always done to estimate current and future demand of the product. There are three methods of demand estimation:

1. Judgemental
2. Past history
3. Casual model

Costing: whenever any item is required in large quantity daily then it is economical. Hence cost benefit analysis is always done because it is very beneficial before you start manufacturing a products. Cost per unit can be calculated and includes following parameters:

Direct cost:

Cost of raw materials
Container and closures expenses
Wages
Labels and carton expenses
Testing charges

Indirect cost:

Water and electricity charges
Furniture and house keeping
Office cost
Printing and stationary charges
Security and licensing fee
Depreciation of machine and building
Repairs of machines
Cost of laboratory animals

Now the total cost includes the sum of the direct cost and pro-rata indirect cost and cost per unit can be calculated using formula

Cost per unit=total cost/number of units

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF STERILE PRODUCTS, PARENTERAL PREPARATIONS (SMALL VOLUME INJECTABLES AND LARGE VOLUME PARENTERALS) AND STERILE OPHTHALMIC PREPARATIONS

Note*: The General Requirements as given in Part I of this Schedule relating to Requirements of Good Manufacturing Practices for Premises and Materials for pharmaceutical products shall be complied with, mutatis mutandis, for the manufacture of Sterile products, Parenteral preparations (Small Volume Injectables and Large Volume Parenterals) and Sterile Ophthalmic Preparations. In addition to these requirements, the following Specific Requirements shall also be followed, namely: -*

1. General –
Sterile products, being very critical and sensitive in nature, a very high degree of precautions, prevention and preparations are needed. Dampness, dirt and darkness are to be avoided to ensure aseptic conditions in all areas. There shall be strict compliance in the prescribed standards especially in the matter of supply of water, air, active materials and in the maintenance of hygienic environment.

2. Buildings And Civil Works –
2. 1. The building shall be built on proper foundation with standardised materials to avoid cracks in critical areas like aseptic solution preparation, filling and sealing rooms.

2. 2. Location of services like water, steam, gases etc. shall be such that their servicing or repair shall not pose any threat to the integrity of the facility.

Water lines shall not pose any threat of leakage to aseptic area.
2. 3. The manufacturing areas shall be clearly separated into support areas (e.g. washing and component preparation areas, storage areas etc.), preparation areas (e.g. bulk manufacturing area, non-aseptic blending areas etc.) change areas and aseptic areas. Operations like removal of outer cardboard wrappings of primary packaging materials shall be done in the de-cartoning areas which are segregated from the washing areas. Wooden pallets, fiber board drums, cardboard and other particle shedding materials shall not be taken inside the preparation areas.

2. 4. In aseptic areas –
(a) walls, floors and ceiling should be impervious, non-shedding, nonflaking and non-cracking. Flooring should be unbroken and provided with a cove both at the junction between the wall and the floor as well as the wall and the celing;

(b) walls shall be flat, and ledges and recesses shall be avoided. Wherever other surfaces join the wall (e.g. sterilisers, electric sockets, gas points etc.) these shall be flush with the walls. Walls shall be provided with a cove at the joint between the ceiling and floor;

(c) ceiling shall be solid and joints shall be sealed. Light-fittings and airgrills shall be flush with the walls and not hanging from the ceiling, so as to prevent contamination;

(d) there shall be no sinks and drains in Grade A and Grade B areas;

(e) doors shall be made of non-shedding material. These may be made preferably of Aluminium or Steel material. Wooden doors shall not be used. Doors shall open towards the higher-pressure area so that they close automatically due to air pressure. ;

(f) Windows shall be made of similar material as the doors, preferably with double panel and shall be flush with the walls. If fire escapes are to be provided, these shall be suitably fastened to the walls without any gaps;

(g) the furniture used shall be smooth, washable and made of stainless steel or any other appropriate material other than wood.

2. 5. The manufacturing and the support areas shall have the same quality of civil structure described above for aseptic areas, except the environmental standards which may vary in the critical areas.

2. 6. Change rooms with entrance in the form of air-locks shall be provided before entry into the sterile product manufacturing areas and then to the aseptic area. Separate exit space from the aseptic areas is advisable. Change rooms to the aseptic areas shall be clearly demarcated into 'black', 'gray' and 'white rooms' with different levels of activity and air cleanliness. The 'black' change room shall be provided with a hand-washing sink. The sink and its drain in the unclassified (first) change rooms may be kept clean all the time. The specially designed drain shall be periodically monitored to avoid presence of pathogenic micro-organisms. Change room doors shall not be opened simultaneously. An appropriate inter-locking system and a visual and/ or audible warning system may be installed to prevent the opening of more than one door at a time.

2. 7. For communication between aseptic areas and non-aseptic areas, intercom telephones or speak-phones shall be used. These shall be minimum in number.

2. 8. Material transfer between aseptic areas and outside shall be through suitable air-locks or pass-boxes. Doors of such air-locks and pass-boxes shall have suitable interlocking arrangements.

2. 9. Personal welfare areas like rest rooms, tea room, canteen and toilets shall be outside and separated from the sterile product manufacturing area.

2. 10. Animal houses shall be away from the sterile product manufacturing area and shall not share a common entrance or air handling system with the manufacturing area.

Air Handling System (Central Air-Conditioning) .–

3. 1. Air Handling Units for sterile product manufacturing areas shall be different from those for other areas. Critical areas, such as the aseptic filling area, sterilized components unloading area and change rooms conforming to Grades B, C and D respectively shall have separate Air Handling Units. The filter configuration in the air handling system shall be suitably designed to achieve the Grade of air as given in Table I. Typical operational activities for clean areas are highlighted in Table II and Table III.

3. 2. For products which are filled aseptically, the filling room shall meet Grade B conditions at rest unmanned. This condition shall also be obtained within a period of about 30 minutes of the personnel leaving the room after completion of operations.

3. 3. The filling operations shall take place under Grade A conditions which shall be demonstrated under working of simulated conditions which shall be achieved by providing Laminar Air flow work stations with suitable HEPA filters or isolator technology.

3. 4. For products, which are terminally sterilized, the filling room shall meet Grade C conditions at rest. This condition shall be obtainable within a period of about 30 minutes of the personnel leaving the room after completion of operations.

3. 5. Manufacturing and component preparation areas shall meet Grade C conditions.

3. 6. After completion of preparation, washed components and vessels shall be protected with "Grade D background and should be handled in such a way that they are not re-contaminated".

3. 7. The minimum air changes for Grade B and Grade C areas shall not be less than 20 air changes per hour in a room with good air flow pattern and appropriate HEPA filters. For Grade A Laminar Air Flow work stations, the air flow rates shall be 0.3 meter per second □□20 % (for vertical flows) and 0.45 meter per second □□20 % (for horizontal flows).

3. 8. Differential pressures between areas of different environmental standards shall be at least 15 Pascal (0.06 inches or 1.5 mm water gauge). Suitable manometers or gauges shall be installed to measure and verify pressure differential.

3. 9. The final change rooms shall have the same class of air as specified for the aseptic area. The pressure differentials in the change rooms shall be in the descending order from 'white' to 'black'.

3. 10. Unless there are product specific requirements, temperature and humidity in the aseptic areas "shall be 27 □□2 degree centigrade and relative humidity 55 % respectively".

(a) In order to reach the B, C and D air grades, the number of air changes shall be related to the size of the room and the equipment and personnel present in the room. The air system shall be provided with the appropriate filters such as HEPA for Grades A, B and C. The maximum permitted number of particles in the "at rest" condition shall approximately be as under:

Grade A and B *corresponds with Class 100 or M 3.5 or ISO class 5; Grade B with class 1000 or M 4.5 or ISO Class 6; Grade C with Class 10000 or M 5.5 or ISO Class 7; Grade D with Class 100,000 or M 6.5 or ISO Class 8.*

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(b) The requirement and limit for the area shall depend on the nature of the operation carried out

(c) Type of operations to be carried out in the various grades are given in Table

Types of Operations To Be Carried Out In The Various Grades For Aseptic Preparations Grade Types of operations for aseptic preparations.

A Aseptic preparation and filling.
B Background room conditions for activities requiring Grade A.
C Preparation of solution to be filtered.
D Handling of components after washing.

Types of Operations To Be Carried Out In The Various Grades For Terminally Sterilized Products Grade

Types of operations for terminally sterilized products.
A Filling of products, which are usually at risk.

C Placement of filling and sealing machines, preparation of solutions, when unusually at risk. Filling of product when unusually at risk.

D Moulding, blowing (pre-forming) operations of plastic containers, Preparations of solutions and components for subsequent filling.

Environmental Monitoring –
4. 1. All environmental parameters listed under para 3.1 to 3.10 shall be verified and established at the time of installation and thereafter monitored at periodic intervals. The recommended frequencies of periodic monitoring shall be as follows:
(a) Particulate monitoring in air – 6 Monthly
(b) HEPA filter integrity testing (smoke testing) – Yearly
(c) Air change rates – 6 monthly
(d) Air pressure differentials – Daily
(e) Temperature and humidity – Daily
(f) Microbiological monitoring by settle plates and/or swabs in aseptic areas – Daily, and at decreased frequency in other areas
Note : The above frequencies of monitoring shall be changed as per the requirements and load in individual cases.
4. 2. There shall be a written environmental monitoring program and microbiological results shall be recorded. Recommended limits for microbiological monitoring of clean areas "in operation" are as given in the table below :

(a) These are average values.
(b) Individual settle plates may be exposed for not less than two hours in Grade B, C and D areas and for not less than thirty minutes in Grade A area.

4. 3. Appropriate action shall be taken immediately if the result of particulate and microbiological monitoring indicates that the counts exceed the limits. The Standard Operating Procedures shall contain corrective action. After major engineering modification to the HVAC system of any area, all monitoring shall be re-performed before production commences.

5. Garments
5. 1. This section covers garments required for use by personnel working only in aseptic areas. Outdoor clothing shall not be brought into the sterile areas.

5. 2. The garments shall be made of non-shedding and tight weave material. Cotton garments shall not be used. The garments shall shed virtually no fibers or particulate matter.

5. 3. The clothing and its quality shall be adopted to the process and the work place and worn in such a way as to protect the product from contamination. Garments shall be single piece with fastenings at cuffs, neck and at legs to ensure close fit. Trouser legs shall be tucked inside the cover boots. Suitable design of garments shall either include a hood (head-cover) or a separate hood which can be tucked inside the over-all. Pockets, pleats and belts shall be avoided in garments. Zips (if any) shall be of Plastic material. Garments with damaged zips shall not be used.

5. 4. Only clean, sterilized and protective garments shall be used at each work session where aseptic filtration and filling operations are undertaken and at each work shift for products intended to be sterilized, post-filling. The mask and gloves shall be changed at every work session in both instances.

5. 5. Gloves shall be made of latex or other suitable plastic materials and shall be powder-free. These shall be long enough to cover wrists completely and allow the over-all cuff to be tucked in.

5. 6. The footwear shall be of suitable plastic or rubber material and shall be daily cleaned with a bactericide.

5. 7. Safety goggles or numbered glasses with side extensions shall be used inside aseptic areas. These shall be sanitised by a suitable method.

5. 8. Garment changing procedure shall be documented and operators trained in this aspect. A full size mirror shall be provided in the final change room for the operator to verify that he is appropriately attired in the garments. Periodic inspection of the garments shall be done by responsible staff.

6. Sanitation –
6. 1. There shall be written procedures for the sanitation of sterile processing facilities. Employees carrying out sanitation of aseptic areas shall be trained specifically for this purpose.

6. 2. Different sanitizing agents shall be used in rotation and the concentrations of the same shall be as per the recommendations of the manufacturer. Records of rotational use of sanitizing agents shall be maintained.

6. 3. Distilled water freshly collected directly from the distilled water plant or water maintained above 70 degree centigrade from the re-circulation loop shall be used for dilution of disinfectants. Alternately, distilled water sterilised by autoclaving or membrane filtration shall be used. The dilution shall be carried
out in the ‘white’ change room.

6. 4. Where alcohol or Isopropyl alcohol is used for dilution of disinfectants for use as hand sprays, the preparation of the same shall be done in the bulk preparation area in grade C.

6. 5. Diluted disinfectants shall bear the label ‘use before‘, based on microbiological establishment of their germicidal properties. The solutions shall be adequately labeled and documents maintained.

6. 6. Formaldehyde or any other equally effective fumigant is recommended for the fumigation of aseptic areas or after major civil modifications. There shall be Standard Operating Procedures for this purpose. Its use for routine purposes shall be discouraged and an equally effective surface cleaning regime shall be followed.

6. 7. Cleaning of sterile processing facilities shall be undertaken with air suction devices or with non-linting sponges or clothes.

6. 8. Air particulate quality shall be evaluated on a regular basis and records maintained.

7. Equipment -
7. 1. The special equipment required for manufacturing sterile products includes component washing machines, steam sterilisers, dry heat sterilisers, membrane filter assemblies, manufacturing vessels, blenders, liquid filling machines, powder filling machines, sealing and labeling machines, vacuum testing chambers, inspection machines, lyophilisers, pressure vessels etc. Suitable and fully integrated washing-sterilizing- filling lines may be provided, depending upon the type and volume of activity.

7. 2. Unit-sterilisers shall be double-ended with suitable inter-locking arrangements between the doors. The effectiveness of the sterilization process shall be established initially by biological inactivation studies using microbial spore indicators and then at least once a year by carrying out thermal mapping of the chamber. Various sterilization parameters shall be established based on these studies and documented. For membrane filters used for filtration, appropriate filter integrity tests that ensure sterilization shall be carried out before and after filtration.

7. 3. Filling machines shall be challenged initially and then at periodic intervals by simulation trials including sterile media fill. Standard Operating Procedures and acceptance criteria for media fills shall be established, justified and documented. Special simulation trial procedures shall be developed, validated and documented for special products like ophthalmic ointments.

7. 4. The construction material used for the parts which are in direct contact with products and the manufacturing vessels may be stainless steel 316 or Borosilicate glass (if glass containers) and the tubing shall be capable of being washed and autoclaved.

7. 5. On procurement, installation qualification of each of the equipment shall be done by engineers with the support of production and quality assurance personnel. Equipment for critical processes like aseptic filling and sterilizers shall be suitably validated according to a written program before putting them to use.

7. 6. Standard Operating Procedures shall be available for each equipment for its calibration and operation and cleaning. Gauges and other measuring devices attached to equipment shall be calibrated at suitable intervals against a written program. Calibration status of equipment and gauges shall be adequately documented and displayed.

8. Water and Steam Systems –
8. 1. Potable water meeting microbiological specification of not more than 500 cfu/ml and indicating absence of individual pathogenic micro-organisms. *Escherichia coli*, *Salmonella*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* per 100 ml sample shall be used for the preparation of purified water.

8. 2. Purified water prepared by de-mineralization shall meet the microbiological specification of not more than 100 cfu per ml and indicate absence of pathogenic micro-organisms in 100 ml. Purified water shall also meet IP specifications for chemical quality. Purified water shall be used for hand washing in change rooms. Containers, closures and machine parts may be washed with potable water followed by suitably filtered purified water. Purified water shall be stored in stainless steel tanks or plastic tanks.

8. 3. Water for Injection (hereinafter referred as WFI) shall be prepared from potable water or purified water meeting the above specifications by distillation. Water for Injection shall meet microbiological specification of not more than 10 cfu per 100 ml. WFI shall also meet IP specification for Water for Injection and shall have an endotoxin level of not more than 0.25 EU / ml. Bulk solutions of liquid parenterals shall be made in WFI. Final rinse of product containers and machine parts shall be done with WFI. Disinfectant solutions for use in aseptic areas shall be prepared in WFI.

8. 4. Water for Injection for the manufacture of liquid injectables shall be freshly collected from the distillation plant or from a storage or circulation loop where the water has been kept at above 70 degree centigrade. At the point of collection, water may be cooled using suitable heat exchanger.

8. 5. Water for non-injectable sterile products like eye drops shall meet IP specifications for purified water. In addition, microbiological specification of not more than 10 cfu per 100 ml and absence of *Pseudomonas aeruginosa* and *Enterobacter coli* in 100 ml shall also be met.

8. 6. Water for Injection shall be stored in steam jacketted stainless steel tanks of suitable size and the tanks shall have hydrophobic bacterial retention with 0.22 vent filters. The filters shall be suitably sterilized at periodic intervals. The distribution lines for purified water and distilled water shall be of stainless steel 316 construction and shall not shed particles.

8. 7. There shall be a written procedure and program for the sanitation of different water systems including storage tanks, distribution lines, pumps and other related equipment. Records of sanitation shall be maintained.

8. 8. There shall be written microbiological monitoring program for different types of water. The results shall justify the frequency of sampling and testing. Investigation shall be carried out and corrective action taken in case of deviation from prescribed limits.

8. 9. Steam coming in contact with the product, primary containers and other product contact surfaces shall be sterile and pyrogen free.

9. Manufacturing Process –
9. 1. Manufacture of sterile products shall be carried out only in areas under defined conditions.

9. 2. Bulk raw materials shall be monitored for bio-burden periodically. Bio-burden of bulk solution prior to membrane filtration shall be monitored periodically and a limit of not more than 100 cfu per ml is recommended.

9. 3. The time between the start of the preparation of the solution and its sterilization or filtration through a micro-organism retaining filter shall be minimised. There shall be a set

maximum permissible time for each product that takes into account its composition and method of storage mentioned in the

Master formula record.

9. 4. Gases coming in contact with the sterile product shall be filtered through two 0.22 hydrophobic filters connected in-series. These filters shall be tested for integrity. Gas cylinders shall not be taken inside aseptic areas.

9. 5. Washed containers shall be sterilized immediately before use. Sterilized containers, if not used within an established time, shall be rinsed with distilled or filtered purified water and re-sterilized.

9. 6. Each lot of finished product shall be filled in one continuous operation. In each case, where one batch is filled in using more than one operation, each lot shall be tested separately for sterility and held separately till sterility test results are known.

9. 7. Special care shall be exercised while filling products in powder form so as not to contaminate the environment during transfer of powder to filling machinehopper.

MASTER FORMULA RECORD

batch records

All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

master formula

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master record

A document or set of documents that serve as a basis for the batch documentation (blank batch record).

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g.: equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

15. Documentation

15.1 *Principle*. Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

In-Patient

Traditional methods of distributing drugs in hospitals are now undergoing reevaluation, and considerable thought and activity is being directed toward the development of new and improved drug distribution systems. Some of the newer concepts and ideas in connection with hospital drug distribution systems are centralized or decentralized (single, or unit-dose) dispending, automated (mechanical and/or electronic) processing of medication orders and inventory control, and automated (mechanical and/or electronic) storage and delivery devices.

Several investigators are at work in each of these areas, and the results of their studies may greatly alter current practices and procedures. Because of the present state of uncertainty regarding the proper scope and optimum design of drug distribution systems for the modern hospital, and as an aid to pharmacists, nurses, physicians, and administrators who are faced with making decisions concerning drug distribution systems during this period of change, the following guidelines for evaluating proposed changes or new ideas or equipments are presented. Though some of the practices recommended may not be widespread at the present, the adoption of these practices is believed to be a desirable and practical goal. Therefore, it is urged that they be given prime consideration in the design of new drug distribution systems and in modifications of existing ones (particularly where such changes would commit a hospital to a considerable financial investment in a system not including, or not easily altered to include, the recommended practices).

1. Before the initial dose of medication is administered the pharmacist should review the prescriber's original order or a direct copy.

2. Drugs dispensed should be as ready for administration to the patient as the current status of pharmaceutical technology will permit, and must bear adequate identification including (but not limited to); name or names of drug, strength or potency, routes(s) of administration, expiration date, control number, and such other special instructions as may be indicated.

3. Facilities and equipment used to store drugs should be so designed that the drugs are accessible only to medical practitioners authorized to prescribe, to pharmacists authorized to dispense, or to nurses authorized to administer such drugs.

4. Facilities and equipment used to store drugs should be designed to facilitate routine inspection of the drug prior to the time of administration.

5. When utilizing automated (mechanical and/or electronic) devices as pharmaceutical tools, it is mandatory that provision be made to provide suitable pharmaceutical services in the event of failure of the device.

6. Such mechanical or electronic drug storage and dispensing devices, as require or encourage the repackaging of drug dosage forms from the manufacturer's original container, should permit and facilitate the use of new package, which will assure the stability of each drug and meet the standards for the packaging and storing of drugs, in addition to meeting all other standards of good pharmacy practice.

7. In considering automated (mechanical and/or electronic) devices as pharmaceutical tools, the distinction between the accuracy required in accounting practices versus that required in dispensing practices should be clearly distinguished.

There are four systems in general use for dispensing drugs for **inpatients.** They may be classified as follows:
(i) Individual Prescription Order System.
(ii) Complete Floor Stock System.
(iii) Combination of (i) and (ii).
(iv) The unit dose method.

Individual prescription order system
As has been previously stated, this system is generally used by the small and/or private hospital because of the reduced manpower requirement and the desirability for individualized service. *Inherent in this system* is the possible delay in obtaining the required medication and the increase in cost to the patient. *Advantages of this system:*
(i) All medication orders are directly reviewed by the pharmacist.
(ii) Provides for the interaction of pharmacist, doctor, nurse and patient.
(iii) Provides closer control of inventory.

Complete floor stock system
Under this system, the nursing station pharmacy carries both "charge" and "non-charge" patient medications. Rarely used or particularly expensive drugs are omitted from floor stock but are dispensed upon the receipt of a prescription or medication order for the individual patient. Although this system is used most often in governmental and other hospitals in which charges are not made to the patient or when the all inclusive rate is used for charging, it does have applicability to the general hospital. Obviously, there are both advantages and disadvantages to the complete floor stock system.

Advantages of complete floor stock system:
(i) Ready availability of the required drugs.
(ii) Elimination of drug returns.
(iii) Reduction in the number of drug order transcriptions for the pharmacy.
(iv) Reduction in the number of pharmacy personnel required.

Disadvantages of complete floor stock system:
(i) Medication errors may increase because the review of medication orders is eliminated.
(ii) Increased drug inventory on the pavilions.
(iii) Greater opportunity for pilferage.
(iv) Increased hazards associated with drug deterioration.
(v) Lack of proper storage facilities on the ward may require capital outlay to provide them.
(vi) Greater inroads are made upon the nurse's time.
To be borne in mind by the student is the fact that in some hospitals the complete floor stock system is successfully operated as a decentralized pharmacy under the direct *supervision* of a pharmacist.

Obviously, when this occurs, many of the disadvantages associated with such a system disappear. In addition, the use of the decentralized pharmacy concept provides for a "home base" for the clinically oriented pharmacist.
In the past, floor stock containers were pre-labeled multiple dose units. Today, the floor stock is in unit-of-use packaging thereby assuring better packaging, control and identity of the medication.

Charge floor stock drugs and non-charge floor stock drugs

Each pavilion in the hospital, regardless of its size or specialty care, has a supply of drugs stored in the medicine cabinet even though the nursing unit is serviced by a unit dose system. However, the use of floor stock medications should be minimized. In addition, research has shown that the system of drug distribution has an effect upon the incidence of adverse drug reactions. These medications may be classified under two separate headings, each of which serves a specific purpose. Drugs on the nursing station may be divided into "*charge floor stock drugs*" and "*noncharge floor stock drugs*".

Definitions

Charge floor stock drugs may be defined as those medications that are stocked on the nursing station. *Charge floor stock drugs* represent that group of medications that are placed at the nursing station. It is the responsibility of the hospital pharmacist, working in cooperation with the nursing service, to develop ways and means whereby adequate supplies of each are always on hand and, in appropriate situation that proper charges are made to the patients account.

Combination of Individual prescription order system and complete floor stock system

Falling into this category are those hospitals which use the individual prescription or medication order system as their primary means of dispensing, but also utilize a limited floor stock. This combination system is probably the most commonly used in hospitals today and is modified to include the use of unit dose medications.

Unit dose system

Unit-dose medications have been defined as: "Those medications which are ordered, packaged, handled, administered and charged in multiples of single dose units containing a predetermined amount of drugs or supply sufficient for one regular dose application or use."

Advantages of unit dose system:

(1) Patients receive improved pharmaceutical service 24 hours a day and are charged for only those doses, which are administered to them.
(2) All doses of medication required at the nursing station are prepared by the pharmacy thus allowing the nurse more time for direct patient care.
(3) Allow the pharmacists to interpret or check a copy of the physician's original order thus reducing medication errors.
(4) Elimination excessive duplication of orders and paper work at the nursing station and pharmacy.
(5) Eliminates credits.
(6) Transfers intravenous preparation and drug reconstitution procedures to the pharmacy.
(7) Promotes more efficient utilization of professional and nonprofessional personnel.
(8) Reduces revenue losses.
(9) Conserves space in nursing units by eliminating bulky floor stock.
(10) Eliminates pilferage and drug waste.
(11) Extends pharmacy coverage and control throughout the hospital from the time the physician writes the order to the time the patient receives the unit-dose.
(12) Communication of medication orders and delivery systems are improved.
(13) The pharmacists can get out of the pharmacy and onto the wards where they can perform their intended function as drug consultants and help provide the team effort that is needed for better patient care.

Unit dose dispensing procedure

The characteristic features of centralized unit-dose dispending are that all in-patient drugs are dispensed in unit-doses and all the drugs are stored in a central area pharmacy and dispensed at the time the dose is due to be given to the patient. To operate the system effectively, electronic data processing equipment is not required, however delivery, systems such as medication carts and dumbwaiters are needed to get the unit-doses to the patients; also suction tube system (called pneumatic tube) or other means are required to send a copy of the physician's original medication order to the pharmacy for direct interpretation and filling.

The decentralized unit-dose system, unlike the centralized system, operates through small satellite pharmacies located on each floor of the hospital. The main pharmacy in this system becomes a procurement, storage, manufacturing and packaging center serving all the satellites. The delivery system is accomplished by the use of medication carts. This type of system can be used for a hospital with separate buildings or old delivery systems.

Fig (2-2) nursing cart for use in unit dose system

Although each hospital introduces variations, the following is a step-bystep outline of the procedure entailed in a decentralized unit-dose system:

1-Upon admission to the hospital, the patient is entered into the system. Diagnosis, allergies and other pertinent data are entered on to the Patient Profile card.

2-Direct copies of medication orders are sent to the pharmacist.

3-The medications ordered are entered on to the Patient Profile card.

4-Pharmacist chicks medication order for allergies, drug –interactions, drug-laboratory test effects and rationale of therapy.

5- Dosage scheduled is coordinated with the nursing station.

6- Pharmacy technician picks medication orders. Placing drugs in bins of

a- Transfer cart per dosage schedule fig. (2-2) and (2-3).

7- Medication cart is filled for particular dosage schedule delivery.

8- Pharmacist checks cart prior to release.

9-The nurse administers the medication and makes appropriate entry on her medication record.

10-Upon returns to the pharmacy, the cart is rechecked.

11-Throughout the entire sequence, the pharmacist is available for consultation by the doctors and nurses. In addition he is maintaining surveillance for discontinued orders.

DRUG DISTRIBUTION AND CONTROL
(UNIT DOSE SECTION)

Medication distribution is the responsibility of the pharmacy. The pharmacist, with the assistance of the pharmacy and therapeutics committee and the department of nursing, must develop comprehensive policies and procedures that provider for the safe distribution of all medications and related supplies to inpatients and outpatients. For reasons of safety and economy, the preferred method to distribute drugs in institutions is the *unit dose system*. Though the unit dose system may differ in form depending on the specific needs, resources, and characteristics of each institution, for elements are common to all.

Elements of unit dose distribution:

(1) Medications are contained in, and administered from, single unit or unit-dose packages

(2) Medications are dispensed in ready-to-administer form, to the extent possible

(3) For most medications, not more than a 24-hour supply of doses is provided to or available at the patient care area at any time

(4) A patient medication profile is concurrently maintained in the pharmacy for each patient. Floor stocks of drugs are minimized and limited to drugs for emergency use and routinely used "safe" items such mouthwash and antiseptic solutions.

Writing the Order:

Medications should be given (with certain specified exceptions) only on the *written* order of a qualified physician or other authorized prescriber. Allowable exceptions to this rule (i.e., telephoned or verbal orders) should be put in written form immediately and the prescriber should countersign the nurse's or pharmacist's signed record of these orders within 48 (preferably 24) hours. Only a pharmacist or registered nurse should accept such orders. Provision should be made to place physician's order in the patient's chart, and a method for sending this information to the pharmacy should be developed. Prescribers should specify the date and time medication orders are written.

Medication orders should be written legibly in ink and should include:

- Patient's name and location (unless clearly indicated on the order sheet).
- Name (Generic) of medication.
- Dosage expressed in the metric system, except in instances where dosage must be expressed otherwise (i.e., units, etc)
- Frequency of administration.
- Route of administration.
- Signature of the physician.
- Date and hour the order was written.

Any abbreviations used in medication orders should be agreed to and jointly adopted by the medical, nursing, pharmacy, and medical records staff of the institution. Any questions arising from a medication order, including the interpretation of an illegible order, should be refer to the ordering physician. It is desirable for the pharmacist to make (appropriate) entries in the patient's medical chart pertinent to the patient's drug therapy. Also, a duplicate record of the entry can be maintained in the pharmacy profile. In computerized patient data systems, each prescriber should be assigned a unique identifier; this number should be included in all medication orders. Unauthorized personnel should not be able to gain assess to the system.

Medication Order Sheets:

The pharmacist (except in emergency situations) must receive the physician's original order or a direct copy of the order before the drug is dispensed. This permits the pharmacist to resolve questions or problems with drug order before the drug is dispensed and administered. It also eliminates errors, which may arise when drug orders are transcribed onto another form for use by the pharmacy. Several methods by which the pharmacy may receive physician's original orders or direct copies are:

1. Self-copying order forms. The physician's order form is designed to make a direct copy (carbon or NCR), which is sent to the pharmacy. This method provides the pharmacist with a duplicate copy of the order and does not require special equipment. There are two basic formats:

a. Orders for medications included among treatment orders. Use of this form allows the physician to continue writing his orders on the chart as he has been accustomed in the past, leaving all other details to hospital personnel.

b. Medication orders separated from other treatment orders on the order form. The separation of drug orders makes it easier for the pharmacist to review the order sheet.

2. Electromechanical. Copying machines or similar devices may be used to produce and exact copy of the physician's order. Provision should be made to transmit physician's orders to the pharmacy in the event of mechanical failure.

3. Computerized. Computer systems in which the physician enters orders into a computer, which then stores and prints out the order in the pharmacy or elsewhere, are used in some institutions. Any such system should provide for the pharmacist's verification ofany drug orders entered into the system by anyone other than an authorized prescriber.

Special Orders:

Special Orders (i.e., "stat" and emergency orders, and those for nonformulary drugs, investigational drugs, restricted-use drugs or controlled substances) should be processed according to specific written procedures meeting all applicable regulations and requirements.

DISPENSING OF CONTROLED SUBSTANCES

Definitions:

- ***Addict:*** Any individual who habitually uses any narcotic drug so as to endanger the public morals, health, safety or welfare, or who is so far addicted to the use of narcotic drugs as to have lost the power or selfcontrol with reference to his addiction.
- ***Administer:*** The direct application of a controlled substances to the body of a patient or research subject by a practitioner or his agent or by the patient or research subject at the direction and in the presence of the practitioner.
- ***Controlled Substances:*** A drug or other substance, or immediate precursor, included in schedule I, II, III, IV or V of Part B of this title. The term dose not includes distilled spirits, wine, malt beverages or tobacco.
- ***Depressant Or Stimulant Substance:***

[A] a drug which contain any quantity of (1) barbituric acid or any of the salts of barbituric acid; or (2) any derivative of barbituric acid ;or

[B] a drug which contains any quantity of (1) amphetamine or any of its optical isomers; (2) any salt of amphetamine or any salt of an optical isomer of amphetamine; or (3) any substance which the Attorney General, after investigation, has found to be, and by regulation designated as habit-forming because of its stimulant effect on the central nervous system; or

[C] Lysergic acid diethylamide; or

[D] any drug which contains any quantity of a substance which the Attorney General, after investigation, has found to have, and by regulation designated as having, a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect.

- ***Narcotic Drug*:** means any of the following, whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis.

[A] Opium, coca leaves and opiates.

[B] A compound, manufacture, salt, derivative, or preparation of opium, coca leaves or opiates.

[C] A substance (any compound, manufacture, salt, derivative, or preparation thereof) which is chemically identical with any substance referred to in [A] or [B] above. Excluded are decocainized coca leaves or extracts of coca leaves, which do not contain cocaine or ecgonine.

SCHEDULES FOR CONTROLLED SUBSTANCES

(1) SCHEDULE I

[A] The drug or other substance has a high potential for abuse.

[B] The drug or other substance has no currently accepted medical use in treatment in the (United States).

[C] There is a lack of accepted safety for use of the drug or other substance under medical supervision.

(2) SCHEDULE II

[A] The drug or other substance has a high potential for abuse.

[B] The drug or other substance has recurrently accepted medical use in treatment in the (United States) or a currently accepted medical use with severe restrictions.

[C] Abuse of the drug or other substances may lead to severe psychological or physical dependence.

(3) SCHEDULE III

[A] The drug or other substance has a potential for abuse less than the drug or other substances in schedules I and II.

[B] The drug or other substance has a currently accepted medical use in treatment in the (United States).

[C] Abuse of the drug or other substances may lead to moderate or low physical dependence or high psychological dependence.

(4) SCHEDULE IV

[A] The drug or other substance has a low potential for abuse relative to the drug or other substances in schedules III.

[B] The drug or other substance has a currently accepted medical use in treatment in the (United States).

[C] Abuse of the drug or other substances may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.

(5) SCHEDULE V

[A] The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedules IV.

[B] The drug or other substance has a currently accepted medical use in treatment in the (United States).

[C] Abuse of the drug or other substances may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV.

REGULATIONS OF HOSPITAL CONTROLLED SUBSTANCES

Definitions:

1. "Order": The direction for the drug, strength and frequency of administration as written on the Doctor's Order Sheet of the patient's Medical Record.

2. "Prescription": The direction for the drug, strength, quantity, and frequency of administration as written on a prescription blank by a doctor for dispensing by the Pharmacy.

3. "Administer": The word "administer" is employed when a nurse or other properly qualified individual gives medication to a patient, pursuant to the order of a qualified practitioner.

4. "Dispense": The word "dispense" is employed when a pharmacist gives medication to a nurse or other properly qualified individual in accord with the directions of a properly written prescription.

5. "Doctor": This term is herein employed to indicate and individual who has qualified for and has received a number from the Drug Enforcement Agency.

Registration of doctors who can prescribe

Doctors (Practitioners), in order to prescribe narcotics for or order administered (dispensed) to their patients in the hospital, must be licensed to practice under the laws of the (state) and must be duly registered with the DEA.

INTERNS and RESIDENTS

Registration requirements were waived to allow interns and residents to dispense and prescribe controlled substances under the registration of the hospital by which they are employed.

Responsibility for controlled substances

The administrative head of the hospital is responsible for the proper safeguarding and the handling of controlled substances within the hospital. Responsibility for the purchase, storage, accountability and proper dispensing of bulk controlled substances within the hospital is delegated to the Pharmacist-in-Chief. The Head Nurse of a nursing unit is responsible for the proper storage and use of the nursing unit's controlled substances.

Preparation of orders

All controlled substances orders and records must be typed or written in ink or indelible pencil and signed in ink or indelible pencil.

Telephone orders

A doctor may order a controlled drug by telephone in case of necessity. The nurse will write the order on the doctor's order sheet, stating that it is a telephone order and will sign the doctor's name and her own initials. The controlled drug may then be administered at once. The order must then be signer by the doctor with either his signature or his initials within 24 hours.

Verbal orders

A verbal order may be given by a doctor in an extreme emergency where time does not permit writing the order. The nurse must write the order on the doctor's order sheet. The doctor must sign the order with either his signature or his initials within 24 hours.

Information on daily controlled drug administration sheet

The full information required on the Daily Controlled Drugs Administration Sheet is as follows:

1. Date.
2. Amount given.
3. Patient's full name
4. Patient's hospital number.
5. Name of doctor ordering.
6. Signature of nurse administering.

The following information is requested for auditing purposes and is not required by Federal law:

1. Number of tablets or ml administered
2. Filing out inventory column (to be retained for Pharmacy).

Prescribing controlled drug in out patient department

Prescriptions for Schedule II and other controlled substances drugs may be dispensed from Pharmacy and must include the following information.

a. Patient s full name

b. Patient's address or hospital number
c. Date
d. Name and strength of drug prescribed.
e. Quantity of drug to be dispensed
f. DEA number and signature of physician
g. Frequency and route of administration

The prescription must be written in ink or indelible pencil and shall not bear cross outs or erasures. Discharge prescriptions for Schedule II drugs must be picked up by a registered nurse.

Dispensing controlled drugs for home use

Occasionally patients who require drugs for use at home are discharged from the hospital or released from The Emergency Ward during hours when the Pharmacy is closed. Whenever possible, a prescription signed by a member of the staff who has a License to practice medicine and a DEA number should be obtained. A staff physician whose DEA number is issued to an outside office should use his own prescription blank. If this is not available, then he must insert his office address on the hospital prescription blank. This will permit the patent or his relative to purchase the drugs at an outside pharmacy. If no physician is available, or during hours when the local pharmacies are closed, the following procedure is allowed, but only as an *EMERGENCY MEASURE:*

The attending doctor will calculate the smallest amount of the drug necessary to treat the patient until the Pharmacy opens. He will write a prescription for this amount and the nurse may dispense the medication from her stock supply. The prescription will be presented to the pharmacy the following morning for replacement of stock.

Procedure in case of waste, destruction, contamination etc

1. Aliquot Part of Narcotic Solutions Used for Dose:

The nurse shall use the proper number of tablets or ampoules from nursing stock. She shall record the number of tablets or ampoules used and the dose given in the proper columns on Daily Controlled Drugs Administration Form. She shall, in arriving at the proper aliquot part, expel into the sink that portion of the solution that is not used.

2. Prepared Dose refused by Patient or Cancelled by Doctor:

When a dose has been prepared for a patient but not used, due to a refused by the patient or because of cancellation by the doctor, the nurse shall expel the solution into the sink and record why the drug was not administered. Examples: "Discarded," "Refused by patient" or "order cancelled by Dr. ." The head nurse of the unit shall countersign the statement.

3. Accidental Destruction and Contamination of Drugs:

When a solution, ampoule, tablet etc., is accidentally destroyed or contaminated on a Nursing Unit, The person responsible shall indicate the loss on figure (2-4).

PREPACKING

Prepackaging of drugs is not a new concept to the profession of pharmacy. It has been in practice since the apothecary of old grew his own herbs and drugs and harvested and packaged them for sale. Many retail pharmacies purchase various over-the-counter tablets and syrups in bulk quantities and prepackage the material in smaller-sized containers.

In the hospital pharmacy, the concept of prepackaging is utilized in both the large and the small hospital for it is, oftentimes, the means of coping with the periods of peak demand for pharmaceutical service. In the small hospital, the pharmacist may prepackage only those items which he considers require too much time if filled only when called for. In some hospital pharmacies, items, which fall into this category, are narcotics, barbiturates oily products, heavy syrups or magmas. Most large hospitals have found it economical to prepackage all ward stock items as well as the often-prescribed tablets; capsules, syrups, ointments and creams used both by the in-patients as well as the outpatient clinics. Because of the scope of thus phase of a large hospital pharmacy operation, it often requires a separate work force, special equipment, and detailed control procedures to ensure against the possibility of errors.

Factors considered in prepacking

a. Demand for the product.
Is it a year 'round demand or is it a seasonal demand?
Is the demand one, which originates from the clinics or the pavilions?
Can this product be purchased in quantities to meet the demand, yet have it packaged in small units by the manufacturer at a price lower than the hospital cost to prepackage the same item in a similar container?
b. What size units should be packaged? How many of each size?
c. What type of containers and closures must be used in order to maintain therapeutic integrity?
d. What special labeling will be required?
e. Can the item be machine packaged or must hand counting be resorted to?
f. What is the stability of the product? Is it dated?
g. What will the unit cost of prepackaging amount to? Who should pay it?

STERILE MEDICATION DOSES AND I.V NUTRITION
Parenteral Hyperalimentation

Parenteral hyperalimentation is the intravenous administration of sufficient nutrients above the usual basal requirements to achieve tissue synthesis, positive nitrogen balance and anabolisin.
The preparation of parenteral hyperalimentation solutions must be considered as an integral part of the pharmacy department's manufacturing program irrespective of its size. The procedures employed are not unduly complicated and do not require extensive capital outlay for equipment. Most hospital pharmacists prepare these solutions by using a technique described as the "wet method" through the extemporaneous compounding techniques of an intravenous admixture program.
This consists of mixing the dextrose solution from one flask with the fibrin hydrolysate solution in another flask utilizing a solution transfer set. In the "dry method" the pharmacist adds the appropriate amount of anhydrous glucose to the fibrin hydrolysate solution. Both methods must be carried out under a laminar flow hood. Because of the nature of these products, the pharmacy must have available appropriate refrigeration equipment and the pharmacist must become familiar with membrane filtration processes in view of the fact that the heat associated with the normal sterilization process will cause caramelization of the dextrose contained in each formula.

Emergency medications
Because in most true emergencies time is of the essence, it is imperative that emergency drug or "Stat' boxes containing drugs and supplies be readily available for use by the bedside. The pharmacy and therapeutic committee should develop a list of supplies and drugs, which ought to be in an emergency box and instruct the pharmacist and nursing service supervisors of their joint responsibility to have the box ready for use at all times. Once the content of the box has been established and the responsibility for its stocking assigned, the units should be prepared and placed on each pavilion, in the clinic, in the emergency ward and in the special procedures room of the department of radiology. After the emergency boxes have been placed on the ward, it is mandatory that a program be developed whereby they are checked daily either by the hospital pharmacist or by the nursing supervisor responsible for the ward

OUT-PATIENT DISPENSING- Outpatient Drug Dispensing

While an important part of the continuum of care and a convenient service for patients, the outpatient pharmacy is also a valuable source of revenue for the hospital. For these reasons, maximizing operational efficiency is an important priority for outpatient pharmacies. Automating operations, such as medication dispensing and medication management, can help pharmacies meet their goals for improved workflows and better patient service.

From medication labeling to incorrect packaging to dispensing the wrong medication, human errors can occur during the delivery of prescriptions. Swisslog's pharmacy automation solutions improve tracking and traceability as well as reduce manual tasks in order to ensure outpatient pharmacies are dispensing the right medication to the right patient.

To support the continuation of care upon discharge, outpatient pharmacies are tasked with providing more hands-on medication management. Patients depend on pharmacists to help them understand the appropriate use of their medication, possible side effects and the importance of medication compliance. Additionally, nurses and other staff also rely on these busy individuals to assist them with medication-related issues. By automating medication dispensing, management and inventory tasks, pharmacies can free their staff to focus on delivering more direct patient care.

Drug Dispensing System

An automated drug dispensing system, UniPick 2 reduces the manual dispensing process for outpatient medication – decreasing errors and increasing staff productivity. Pharmacists can now spend more time counseling patients on medication information and administration.

Save Staff Time and Money!

The In sty Meds system is the solution for hospital emergency departments to offer patients their acute prescription medication 24 hours a day, 7 days a week. Our revolutionary system provides this patient convenience without any extra work for your staff.

Reduces Staff Workload
With the InstyMeds system, staff is free to concentrate on other patient care responsibilities.

Once the prescription is prescribed using the InstyMeds Prescription Writer, InstyMeds will handle the rest.

Eliminates Starter Doses
Hospitals lose tens of thousands of dollars giving out starter doses to patients. With InstyMeds, patients can obtain their full prescription directly from the dispenser.

Complements existing pharmacy
InstyMeds safely performs outpatient dispensing functions freeing up pharmacists to assist other patients and deal with more complex issues.

Decreases Pharmacy Callbacks
InstyMeds will reduce the number of callbacks to prescribing physicians due to formulary rejections and handwriting interpretation questions. This will save the practice $5-$7 per call according to a 1999 study by the Institute of Medicine.

Improves Health Outcomes
Dispensing prescriptions quickly and conveniently at the point-of-care will improve medication compliance and eliminate handwriting errors.

Enhance patient care!

Convenience
Patients receive medication at the point-of-care rather than waiting an average of 30 minutes (often when sick or injured) at a pharmacy.

Access
Pharmacy services are difficult for patients to obtain during evenings, weekends, and holidays, or for those with transportation barriers.

Safety
Medications are dispensed from the InstyMeds dispenser using a triple bar code safety check system that ensures the correct medication is always dispensed.

TYPE OF DRUG DISTRIBUTION- The Drug Enforcement Administration (DEA) promulgates rules to enforce against the risk of drug diversion. DEA's "Office of Diversion Control" prevents, detects, and investigates the diversion of controlled substances from legitimate sources while ensuring an adequate and uninterrupted supply for legitimate medical needs. To accomplish this mission, the DEA sets forth regulations designed to prevent any such diversion.

Due diligence

Healthcare practitioners (physicians and pharmacists alike) should undertake proactive measures to ensure that a narcotic regimen is being used for legitimate medical purposes.

With respect to a pharmacist's responsibility, the DEA regulations state that "[a] prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription."

As a result, a pharmacist must "carefully review all purported controlled substance prescriptions to ensure that the prescription meets all of the legal requirements for a valid prescription. The pharmacist has a duty to inquire further as to any question surrounding the satisfaction of any or all of the legal requirements for a valid prescription, depending on the particular circumstances, including the requirement that the prescription be issued for a legitimate medical purpose by a practitioner acting in the usual course of professional practice."

By undertaking due diligence in this regard, a pharmacist will help ensure compliance with DEA requirements.

Verification

Additionally, DEA regulations dictate that the pharmacist must verify that a controlled substance prescription contains the patient name, address, drug name and strength, quantity prescribed, and directions for use, as well as the name, address, and DEA number of the issuing practitioner. The pharmacist must further verify that the prescription is dated as of, and signed on, the date that it is issued.

Factors that the DEA will review when determining the potential for drug diversion, include but are not limited to the following:

- Whether the pharmacy monitors and documents the physical proximity of patients who present for a controlled substance prescription
- Whether the patient has exhibited a history or evidence of "doctor shopping" or "pharmacy shopping" when seeking controlled substances
- Whether patients presenting to the pharmacy to fill controlled substance prescriptions include a disproportionate number of cash-payers
- Whether the pharmacy dispenses a disproportionate number of controlled substances when compared to total dispensed prescriptions
- Whether the pharmacy complies with DEA regulations pertaining to physician responsibility and pharmacist corresponding responsibility when verifying the legitimacy of patients and their prescriptions for controlled substances
- Whether the pharmacy complies with other DEA regulations such as those pertaining to record-keeping requirements and security requirements, among others.

Written agreements

Written patient agreements with physicians and/or pharmacies help the pharmacy monitor the legitimacy of a patient presenting for a narcotic prescription. At least one such company offers physicians, pharmacies, and patients alike the opportunity to electronically document such a relationship. The website of the Patient Physician Trust Partnership offers information in this regard and a product intended to ensure greater compliance in the treatment of patients with controlled substances.

This article is not intended as legal advice and should not be used as such. When legal questions arise, pharmacists should consult with attorneys familiar with the relevant drug and pharmacy laws.

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