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The manufacturer is subject to preapproval inspections and periodic GMP postapproval inspections by FDA. FDA also conducts inspections of the suppliers of active ingredients, both foreign and domestic, and certain inactive ingredients and packaging operations. The manufacture is subject to recalls of batches of product that do not meet quality requirements. In some cases a recall may result not from actual failed test results but from a lack of assurance that the product will continue to meet quality requirements through its shelf life.

Pharmacy Compounding

Compounding of individual patient prescriptions by pharmacists has been and continues in some areas to be an integral part of pharmacy practice. The need to routinely compound sterile ophthalmic products is no longer required with the broad range of commercially manufactured products available today. Most of the new and generic prescription ophthalmic products marketed today have been subjected to FDA's rigorous requirements for proof of safety and efficacy or bioequivalence as well as the above-described manufacturing and quality requirements.

If the pharmacist is requested to compound a prescription for a noncommercial product such as a preservative-free version or pediatric strength, he or she should be well versed in the preparation of sterile products, have the proper equipment and facilities and be knowledgeable about the special requirements for ophthalmic formulations and packaging. Reference information on the standards and technology for pharmacy compounding with special emphasis on preparation of sterile products should be consulted.[53, 54] The pharmacist must also consult the rules and regulations of the applicable state board of pharmacy concerning sterile pharmacy compounding as well as any federal regulatory requirements promulgated by the FDA. Congress included in the 1997 FDA Modernization Act certain legal conditions for which compounding as defined in the Act would be exempt from FDA regulation. The pharmacy compounding section of the Act was subsequently litigated and overturned in its entirety because it contained unconstitutional restrictions on commercial speech. FDA may seek new legislation to address their concerns regarding manufacturing in the guise of compounding. In the meantime, FDA has issued a guidance document on how the Agency intends to regulate pharmacy compounding of human drugs considered to be outside the bounds of traditional pharmacy practice and in violation of the Food, Drug and Cosmetic Act (www.fda.gov/cder/pharmcomp).

STERILIZATION

Common methods of sterilization include moist heat under pressure (autoclave), dry heat, filtration, gas sterilization, and ionizing radiation. Please refer to Chapter 40 where these sterilization procedures are described in detail.

DANGERS OF NONSTERILE MEDICATIONS—The possibility of serious ocular infection resulting from the use of contaminated ophthalmic solutions has been documented amply in the literature. Such solutions have been the cause repeatedly of corneal ulcers and even loss of eyesight. Contaminated solutions have been found in use in physicians' offices, eye clinics, and industrial infirmaries, and dispensed on prescription in community and hospital pharmacies. The microbe most frequently found as a contaminant is the Staphylococcus group. *Pseudomonas aeruginosa* is a less frequent contaminant, and the solution most often found contaminated is sodium fluorescein.

P. aeruginosa (*B. pyocyaneus; Pseudomonas pyocyanea;* blue pus bacillus) is a very dangerous and opportunistic organism that grows well on most culture media and produces both toxins and antibacterial products. The latter tend to kill off other contaminants and allow the *P. aeruginosa* to grow in pure culture. This gram-negative bacillus also grows readily in ophserious infections of the cornea. It can cause complete loss of sight in 24 to 48 hr. In concentrations tolerated by tissues of the eye, it seems that all the antimicrobial agents discussed in the following sections may be ineffective against some strains of this organism.

A sterile ophthalmic solution in a multiple-dose container can be contaminated in a number of ways unless precautions are taken. For example, if a dropper bottle is used, the tip of the dropper while out of the bottle can touch the surface of a table or shelf if laid down, or it can touch the eyelid or eyelash of the patient during administration. If the Drop-Tainer (*Alcon*) type of bottle is used, the dropper tip can touch an eyelash or the cap while removed to permit administration, or its edge may touch a table or finger, and that edge can touch the dropper tip as the cap is replaced.

The solution may contain an effective antimicrobial, but the next use of the contaminated solution may occur before enough time has elapsed for all of the organisms to be killed, and living organisms can find their way through an abrasion into the corneal stroma. Once in the corneal stroma, any residual traces of antimicrobial agents are neutralized by tissue components, and the organisms find an excellent culture medium for rapid growth and dissemination through the cornea and the anterior segment of the eye.

OTHER ORGANISMS—*Bacillus subtilis* may produce a serious abscess when it infects the vitreous humor. The pathogenic fungus considered of particular importance in eye solutions is *Aspergillus fumigatus*. Other fungi or molds may be harmful by accelerating deterioration of the active drugs.

With regard to viruses, as many as 42 cases of epidemic keratoconjunctivitis were caused by one bottle of virus- contaminated tetracaine solution. Virus contamination is particularly difficult to control because none of the preservatives now available is virucidal. Moreover, viruses are not removable by filtration. However, they are destroyed by autoclaving. The pharmacist and physician have not been made adequately aware of the dangers of transmitting viral infection via contaminated solutions. This is particularly pertinent to the adenoviruses (Types III and VIII), now believed to be the causative agents of viral conjunctivitis such as epidemic keratoconjunctivitis.

The danger of non-sterile preparations is exponentially increased for products intended to be injected within the eyeball. Endophthalmitis and loss of vision can occur within a short time of onset of a bacterial infection.

Methods

STEAM UNDER PRESSURE—Terminal sterilization by autoclaving is an acceptable, effective method of sterilization; however, the solution or suspension components must be sufficiently heat-resistant to survive the procedure. If sterilization is carried out in the final container, the container also must be able to survive heat and pressure. A recent addition to this technique is the so-called air-over-steam autoclave. This combination allows pressure adjustments to be made during the autoclave cycle. Pressure manipulations permit the autoclave sterilization of materials that while heat-resistant tend to deform (ie, polypropylene containers). The sterilization cycle for a product should be carefully validated and assure that sterilization temperature and time are monitored at the coldest spot of the autoclave load to assure sterility of the product.

FILTRATION—The USP states that sterile membrane filtration under aseptic conditions is the preferred method of sterilization. Membrane filtration offers the substantial advantage of room temperature operation with none of the deleterious effects of exposure to heat or sterilizing gas.

Sterilization by filtration does involve the transfer of the finished sterile product into previously sterilized containers, using aseptic techniques. The membrane filtration equipment itself

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