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Achieving Sterility in Medical and Pharmaceutical Products

Nigel A. Halls

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Preface

The purpose of this book is to help practitioners in the field who manufacture sterile products, pharmaceutical products, and medical devices to understand what needs to be done to achieve sterility. It is not intended for experts in specific sterilization technologies; indeed, that would necessitate a multivolume, multiauthor work.

Achieving sterility is an important aspect of quality assurance. In the pharmaceutical industry, quality assurance is most often dominated by personnel in analytical chemistry. In the medical device manufacturing industries, engineers tend to be most strongly represented. Real expertise in sterilization, particularly in sterilization science, is often concentrated among a limited number of microbiologically qualified staff who have gained their knowledge through hands-on experience of specific technologies. This book attempts to cover a wider spectrum of sterilization technologies than most practitioners might ever encounter in a working lifetime with one company or organization. It is intended to increase the breadth of knowledge of the sterilization specialist beyond the boundaries of his or her hands-on experience and to assist in communicating the fundamentals of the main sterilization technologies to interested personnel who work in this area but do not have a strong microbiological background.

A further purpose of this book is to bridge the knowledge gap for students and recently qualified graduates who may be moving or wishing to move into the sterile products manufacturing industries. There are few sources of information

on achieving sterility lying between the general academic texts on microbiology and the level of detail and minutiae contained in advanced research papers, reviews, and guidelines on specific technologies.

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The Need for Sterility

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Why are some medical products required to be sterile? What distinguishes these products from other medical products that are not required to be sterile? What are the consequences of nonsterility?

Sterility is defined academically as the total absence of viable life forms. Some parts of the human body are always exposed to and contaminated by other forms of life. For instance, the external surfaces of the body, skin, hair, airways, etc., are unavoidably in contact with the general (microbiologically contaminated) environment. The buccal cavity and intestinal tract are regularly brought into contact with food- and water-borne microorganisms ingested with the diet. In many cases, some of these microorganisms colonize the surfaces of the human

body and exist in harmony with the human host, sometimes even beneficially. Internal tissues are, however, expected to be totally free from microbial contamination.

The external surfaces of the "normal," fit, healthy human being have evolved to be effective barriers against penetration by opportunistic microorganisms to internal tissues that might provide them with nourishment at the expense of the host. Sometimes the external physical barriers fail, and then other antimicrobial defense mechanisms come into play, the immune system for instance. These internal mechanisms are combating infection. The various symptoms of infectious disease are the result of the interaction between the attempts by the infecting agent to colonize the internal tissues of the body and the attempts by the body's defense mechanisms to overcome this invasion.

From the sterility standpoint, no distinction can be made between the microorganisms that are known to be specific causative agents of disease and those that are not. It would of course be a major disaster if a specific pathogen such as *Bacillus anthracis* (the causative agent of anthrax) were to be introduced into the human (or animal) body through the administration of a supposedly therapeutic agent. On the other hand, microorganisms that are frequently found on man or in man's immediate environment are often assumed to be harmless because they are not associated with any specific disease. However, this is a wholly invalid assumption once the body's antimicrobial defensive barriers are broken down, as they usually are in the administration of parenteral preparations. These microorganisms may often be opportunistic pathogens. This is particularly applicable in the case of weak and debilitated patients who are ill-equipped to resist infection, even from microorganisms that have not evolved to be specially invasive. Complete freedom from all microorganisms is the only criterion for sterility.

Many therapeutic procedures quite deliberately break down the body's external physical barriers. From the application of an ointment or cream to broken skin, to simple or complex surgery, to injection, to implantation of, say, a cardiac pacemaker, all of these procedures risk infecting the patient by breaking through the body's external physical barriers. Infection will only occur, however, if these procedures carry viable microorganisms to internal tissues. On the other hand, if the devices and substances that are brought into contact with internal tissues are free from viable microorganisms—in other words, "sterile"—there ought to be no infection. This is the first and most fundamental reason why some medical products are required to be sterile.

There are other reasons.

Devices that are intermediates in the delivery of therapeutic substances to internal tissues, say infusion sets or catheters, ought to be sterile. It is quite obviously inappropriate to convey a sterile fluid from its sterile reservoir to internal tissues by a nonsterile route.

Garments, gloves, drapes and other operating theater paraphernalia ought to be sterile to prevent transfer of microorganisms to exposed internal tissue during surgical procedures.

Ophthalmic preparations, eye drops and eye ointments, ought to be sterile. There are three basic reasons for this. First, the cornea and other transparent parts of the eye have a particularly poor supply of blood and therefore a less responsive immune reaction than other parts of the body. Second, the transparency of these parts of the eye may be irreversibly damaged as a result of infection, with resultant permanent loss of vision. Third, infectious damage to the optic nerve is irreparable.

Numerous items of laboratory equipment, for instance pipettes, petri dishes, tissue culture plates, etc., have to be sterile. It is not within the scope of this text to address these, except to indicate striking similarities or differences in passing. In medical laboratory sciences particularly, containers for collection of tissues and body fluids for diagnostic analysis ought to be sterile. This is to ensure true results. Microbial contamination may pervert biochemical test results. Microbial contamination in containers may prevent accurate diagnosis of infectious conditions.

Numerous other medical products are not required to be sterile. Medicines to be taken by mouth, enemas, inhalations, most topical products, etc., need not be sterile. In some cases there may be a need to ensure that these products are microbiologically "clean," or free from specific pathogens or from microbiological contamination indicators, but there is no obligation to sterility.

Sterility is, however, required in some unusual circumstances for medical and nonmedical products that would not normally be associated with this type of need. For instance, you may consider sterile diets for hospital patients who are being treated with immunosuppressive therapeutic agents.

The scale of manufacture/preparation of sterile medical products and the complexity of sterile products is extremely wide ranging. Nothing is truly typical, nor can any text claim to be genuinely comprehensive. In this text we shall be addressing industrial manufacture of sterile products because governmental regulatory agencies and other ethical purchasing organizations have led industry to a certain consistency of approach that allows sensible generalizations to be made.

I. STERILE PHARMACEUTICAL PRODUCTS

Although it is conceivable that there are occasions when almost any pharmaceutical product may be required to be sterile, there are only two broad groups of sterile pharmaceutical products, parenteral products and ophthalmic products.

The *European Pharmacopoeia* is particularly succinct in its definition of preparations for parenteral use. It states that they are sterile preparations

intended for administration by injection, infusion, or implantation into the human or animal body. Further, parenteral preparations are supplied, according to the *European Pharmacopoeia,* in glass ampoules, bottles, or vials, or in other containers such as plastic bottles or bags or as prefilled syringes.

This colorless but clear definition of parenteral products has pretty well universal acceptance and is likely almost timeless as well: current United States FDA thinking is that no new forms of presentation of sterile parenteral products are likely to be approved without strong justification of their being of benefit to the patient. Commercial reasons are not acceptable.

Nonetheless, there is a huge variety and wide range of parenteral products. Some parenteral dosage forms may be filled into their presentation forms or systems of containment under controlled but nonsterile conditions and then exposed to a sterilization process; these are referred to as terminally sterilized products. Terminal sterilization must be the method of first choice for all sterile pharmaceutical products. This is good sense and reflects current FDA thinking. There are a variety of terminal sterilization processes, thermal, chemical, or by ionizing radiation, but quite frequently dosage forms cannot withstand any of these treatments without loss of efficacy. In these cases, recourse is made to aseptic manufacture. With aseptic manufacture, product contact components making up the system of containment are sterilized before filling; the dosage form is sterilized before filling, preferably by filtration but possibly by some chemical treatment that may or may not be part of its initial synthesis, and the whole final presentation is filled and sealed in a sterile or as near sterile as possible environment.

The first broad division among parenteral products is between those used for infusions and those used for other forms of administration. Infusions are principally intended for administration in large volumes and are frequently referred to as large volume parenterals (LVPs). With the exception of sterile *Water for Injection,* LVPs are usually made to be isotonic with blood, for example saline, dextrose, etc.

The widest range of parenteral products are however, the small volume parenterals (SVPs). These may be sterile solutions for injecting directly into the patient. They may be concentrated solutions or suspensions or emulsions or even solids (solid dosage forms may be anhydrous, crystalline, or freeze dried [lyophilized]) for dilution or reconstitution in LVPs for direct injection or infusion into the patient.

Table 1 lists some examples of sterile parenteral products classified as LVPs or SVPs, as aseptically filled or terminally sterilized, and as solutions, suspensions, or solid dosage forms.

The therapeutic application of sterile parenteral products is almost boundless. Some products can only be administered via the parenteral route; others may be administered orally, as suppositories, intranasally, etc. This begs the

Table 1 Some Examples of Sterile Parenteral Products

Product	Condition	Achievement of Sterility
LVPs		
Water for Injection USP	"Solution"	Terminal (steam)
Dextrose Injection USP	Solution	Terminal (steam)
SVPs		
Ranitidine Injection USP	Solution	Aseptic fill
Suxamethonium Chloride Injection BP	Solution	Terminal (steam)
Progesterone Injection BP	Solution	Terminal (dry heat)
Epinephrine Oil Suspension USP	Suspension	Aseptic fill
Sterile Ceftazidime USP	Solid	Aseptic fill
Diamorphine Injection BP	Solid (lyophilized)	Aseptic fill

question of why they are being manufactured for parenteral administration at all. The answer may lie with the product's efficacy, with the acuteness of the condition it is being used to treat, or with the speed at which relief of symptoms is required.

Taking the products listed in Table 1, Ceftazidime has only two entries in the USP, *Ceftazidime for Injection* USP and *Sterile Ceftazidime* USP. Both are restricted to parenteral administration because of loss of efficacy when delivered by other routes.

Ranitidine, on the other hand, has entries as *Ranitidine Injection* USP and *as Ranitidine Tablets* USP. Epinephrine has entries as an inhalation aerosol, an injection, an inhalation solution, a nasal solution, an ophthalmic solution, and an oil suspension.

The question of which Ranitidine preparation to use for ulcer treatment is based primarily on the acuteness of the condition and with regard to convenience for maintenance therapy after the condition has been brought under control. Parenteral administration is in the main restricted to acute symptoms under hospital supervision; oral administration is used for maintenance of the condition once stabilized.

Epinephrine is rather more complicated, because it may be used in connection with a variety of symptoms. Subcutaneous or intramuscular injection may be life-saving for anaphylactic shock or acute allergic reactions, or it may

be used to control bronchial spasm in acute attacks of asthma. The other preparations are used for local application in less extreme circumstances. For instance, the ophthalmic solution may be used for pupillary dilation in connection with ophthalmic treatment or glaucoma.

Sterile Epinephrine Ophthalmic Solution USP takes us out of the realm of sterile parenteral products into ophthalmics. The manner of presentation of ophthalmics (i.e., as drops or ointments) is likely to be quite familiar. For the most part (but not exclusively) they are in multidose presentations. As such, most formulations include some form of preservative to control proliferation of any microorganisms that may by chance contaminate the product on one or other of the occasions when it is open, or during the time when it is left standing on the bathroom shelf. The inclusion of preservatives in a multidose formulation of an ophthalmic (or parenteral) is not a primary part of the process of achieving sterility. It has quite a separate purpose.

Even when preservatives are included in single-dose presentations (as they often are), their efficacy against particular types of microorganisms can never be legitimately used as an excuse for tolerating in-process contamination by preservative-sensitive types. Nor can the inclusion of preservatives in products be used to shorten or reduce the intensity of sterilization processes applied to products or their containers to lower than normal levels of sterility assurance. Preservatives are supplementary, not intrinsic to industrial-scale processes of achieving sterility.

An important distinction to draw between sterile parenteral products and sterile ophthalmic products concerns pyrogens. We will discuss pyrogens in some detail at a later stage in this text. They are substances that induce fever when injected into mammals. As such, all sterile products for parenteral administration are expected to be pyrogen free, and if dilution is required they must be diluted in a sterile pyrogen-free diluent. The tie-up between sterility, absence of pyrogens, and administration by injection is reflected in the USP distinction between the two types of water recommended for ingredient purposes, *Purified Water* and *Water for Injection*. The former is not required to be pyrogen free, and only the latter is to be recommended for use in preparations intended for parenteral administration.

Sterile ophthalmic products have no requirement to be pyrogen free.

II. STERILE MEDICAL DEVICES

The term *medical device* includes instruments, apparatus, implements, contrivances, implants, or other similar or related articles used in medical treatment. A medical device does not achieve its principal intended purpose through chemical or pharmacological action within or on the body. Some medical devices need to be sterile.

For the most part (measured as numbers of devices used per annum), sterile medical devices are for single use only ("use once and then discard"). Hypodermic products and infusion sets are probably the most familiar types of single-use medical device. They are a comparatively modern concept that had its origins in economics and in an increasing concern over hospital-acquired infections in the "antibiotic era." Before the 1950s, most medical devices were washed, resterilized, and reused repeatedly. As antibiotics became widely available in that decade, "background" infections diminished in proportion to those that were associated with the reuse of equipment. At the same time the cost of labor for reprocessing was increasing while the cost of plastics was decreasing. Single-use industrially sterilized plastic medical devices grew from a practical alternative to be the current norm.

There are a huge range of different types of medical device. Approval to market is, as with pharmaceuticals, subject to regulatory control. Most sterile devices in the U.S.A. would require premarket approval and fall into Class III of Part 860 of the *Code of Federal Regulations.* This classification places great emphasis on devices that are life-supporting or life-sustaining, or those that are of substantial importance in preventing impairment of human health, or those that present potential unreasonable risks of illness or injury.

Less formally, sterile devices may be classified in terms of the severity of the consequences of their nonsterility.

(a) Devices making no direct contact with patients. Mainly we are thinking here of diagnostic devices, bearing in mind that contamination could affect the patient through adversely influencing the outcome of the diagnostic process.

(b) Devices that contact intact external surfaces, such as sterile dressings, or heavily contaminated internal surfaces such as the gut, for instance examination gloves. Patients are not really likely to die as a result of nonsterility of these products unless a chance contaminant has unusually invasive properties competitive with the innate microflora. Their sterility is of greater significance with susceptible patients, an example being those with severe burns, where infection is a major and possibly life-threatening issue. The range of products in this category is impossible to exemplify, but it may be of value to consider sterile cellulosic dressings. Almost inevitably, cellulosics are microbiologically contaminated, often with bacterial endospores, and therefore pose a severe challenge to whatever sterilization process is being applied.

(c) Devices that contact directly or indirectly with the intravascular system, say "giving" sets. Here we are talking about a vastly important route of administration, often for severely ill patients. The consequences of microorganisms being delivered directly to the blood, with the risk of them

being carried throughout the body and inducing generalized infection, is self-evident. The principal portion of a "giving" set is tubing, possibly rubber but nowadays more likely extruded plastic tubing. The temperatures reached in plastic extrusion processes are quite high enough to bring about significant reductions in numbers of vegetative microorganisms. However, cooling in water and subsequent assembly and packing may lead to recontamination.

(d) Invasive devices. This category probably contains the largest number of items marketed, because it embraces hypodermic needles and syringes, scalpel blades, catheters, etc. These are the mechanisms that break down the body barriers. If we take hypodermic syringes as an example of this type of device, we can consider a variety of different types of manufacturing technology versus their effects on microorganisms. The characteristic single-use disposable hypodermic syringe is made up of three pieces; the barrel, the plunger, and the plunger tip ("stopper"). Plastic plungers and barrels are almost always injection-molded; rubber "stoppers" are compression-molded. The temperatures achieved with these technologies kill most microorganisms. Like "giving" sets, contamination may occur during assembly and packaging; the numbers and types of microbial contaminants on packaged hypodermic syringes prior to sterilization are very largely related to the number of manual steps involved in these processes. In modern automated high-volume manufacture the final biological challenge *(bioburden)* on these products tends to be quite low [1].

(e) Implantable devices. Some of these may have a purely mechanical function, like the very widely used artificial hip- and knee-joints; others have more complex and life-sustaining functions, such as cardiac pacemakers. In both cases there is a critical necessity for sterility. Again the technologies of manufacture and the complexity of the devices are diverse. The technology of manufacture of cardiac pacemakers is that of the electronics industry, where cleanliness is of the highest importance to function as well as to the control of bioburden. The technology of manufacture of artificial hip-joints is the technology of the machine shop, casting, milling etc. Cleanliness is an additional constraint to the traditional practice of these crafts.

As with sterile pharmaceuticals, pyrogens are of significant importance to medical devices. Any device intended for administration of a sterile parenteral pharmaceutical must (like the pharmaceutical preparation) be pyrogen free. So must all invasive and implantable devices.

III. CONSEQUENCES OF NONSTERILITY

Hospital-acquired (nosocomial) infections are not uncommon. However, those that have been conclusively attributed to supposedly sterile but actually nonsterile pharmaceutical products or medical devices are quite rare. The consequences of these incidents have not confined themselves to the companies responsible for the failure to achieve sterility but have reverberated throughout the whole "steriles" industry. No company wishes to face the litigation, loss of sales, loss of goodwill, and generally bad publicity that accompanies nonsterility. Most of all, ethical companies are in the business of preserving life, not in the business of killing people—and death is often the consequence of nonsterility.

Although all the incidents described below occurred quite a long time ago and technology has changed and improved, and regulatory control has become more demanding and explicit, we believe that because sterility can only be achieved consistently by constant vigilance there are important lessons to be learned from reviewing them again.

A. The 1971/72 Devonport Incident in the U.K.

The Devonport Incident occurred in the U.K. Some postoperative patients who had been given supposedly sterile but actually contaminated infusion fluids died; others made unnecessarily long recoveries. The incident summarized below is described fully in a U.K. government enquiry, the *Clothier Report* [2].

A series of untoward reactions were seen among postoperative patients in the Devonport Section of Plymouth General Hospital in March 1972. Seven patients were involved; five died. A commonality among the patients was that all had received intravenous administration of *Dextrose Injection* BP (5% dextrose infusion fluid). All intravenous infusion fluids containing dextrose were promptly withdrawn from use, and samples were examined in the laboratory.

A batch of bottles of "sterile" *Dextrose Injection* BP manufactured by Evans Medical Ltd. (at that time a major U.K. producer of these types of products) was found to be contaminated by *Klebsiella aerogenes* and other gram-negative coliform bacteria. Approximately one-third of all of the bottles from the incriminated batch were found to be nonsterile. The concentration of bacteria in the bottles of fluid was sufficiently high to be visually perceptible to the naked eye; this would typically mean more than 10^6 bacteria per mL.

An urgent investigation was initiated. The possibility of other batches being contaminated could not be ruled out, and all Evans Medical infusion fluids were placed under U.K. government embargo.

The contaminated product was traced to incorrect operation of Evans Medical's sterilizing autoclaves. The Committee of Enquiry [2] concluded that too many people believed that sterilization of fluids was easily achievable with

simple equipment operated by men of little skill under a minimum of supervision.

What had happened was this. The sterilization process for bottles of *Dextrose Injection* BP was by exposure to saturated steam at a temperature of 116°C (specified as 240°F) for 30 min. Evans Medical's autoclaves were equipped with two temperature measuring devices. The first and most important of these was a recording thermometer located in the chamber drain. This is normally the coolest part of any autoclave, and it is from the sensor located at this point that the decision should be made that the autoclave has reached its specified operating temperature and exposure timing begun. The second temperature measuring device on the autoclaves was a dial thermometer located near the steam inlet pipe at the top of the chamber. This location usually reaches high temperatures more rapidly than any other location in the chamber. The recording thermometers in the chamber drains of Evans Medical's autoclaves were subject to faulty operation, and it had become "custom and practice" for the sterilizer operators to give more credence to the dial thermometers. It had been quite common for batches of autoclaved infusion fluids to be released as sterile despite the temperature recorder chart showing an inadequate cycle.

The batch implicated in the Devonport Incident had been sterilized in April 1971. The recording thermometer did not indicate the expected rise in temperature. On past experience, the manager of the area ignored this device and continued the process through reliance on the dial thermometer. With hindsight it is possible to conclude that all of the air had not been vented from the bottom of the chamber at the beginning of the cycle and consequently the correct operating temperature was not being achieved throughout the load; particularly it was not being achieved for bottles in the lower part of the chamber nor in the chamber drain. In other words, the recording thermometer had been operating correctly. If the correct procedure had been followed the process would not have been approved nor allowed to continue.

It is not pertinent to go into the detail of the likely technical problems that may have led to stratification of steam over air in the bottom of this autoclave, but details are given in the *Clothier Report* [2].

The contaminated bottles were not detected by end-product sterility testing. The batch was released to a wholesaler and distributed to the Devonport Section of Plymouth General Hospital in March 1972. The high concentrations of microorganisms found in the infusion fluid can be attributed to the period of time between sterilization, distribution, and final administration to the patients.

B. The 1970/71 Rocky Mount Incident in the U.S.A.

The Rocky Mount Incident, which began in July 1970, affected at least 378 patients in at least 25 US hospitals [3,4]. Forty patients died.

As with the Devonport Incident, the Rocky Mount Incident was caused by contaminated bottles of infusion fluids. The fluids were all made by Abbott Laboratories in their Rocky Mount, North Carolina, plant. The company's infusion products were recalled in March 1971.

The clinical features seen with patients who received these contaminated fluids included extreme fever, shaking chills, systemic toxicity, abdominal cramps, nausea, vomiting, diarrhea, delirium, and seizures. With hindsight these are the symptoms of gram-negative septicemia, but with sudden onset they were sometimes misdiagnosed [3]. Confirmed cases were mainly drawn from large hospitals, often university teaching hospitals, using significantly large volumes of infusion fluids. It is possible that many more patients in small hospitals were implicated, but the cases were not diagnosed or reported.

The microorganisms associated with the epidemic were identified with *Enterobacter cloacae, Enterobacter agglomerans*, and other *Enterobacter* species. The precise cause of the incident was traced to a program of gradual replacement of Gilsonite cap liners for the infusion fluid bottles with an elastomer cap liner (Fig. 1). The replacement program was operating only in Abbott's Rocky Mount plant and not on any other Abbott operating site.

Felts et al. [4] examined 93 bottles containing a variety of different infusion fluids. They looked for microbiological contamination of the closures.

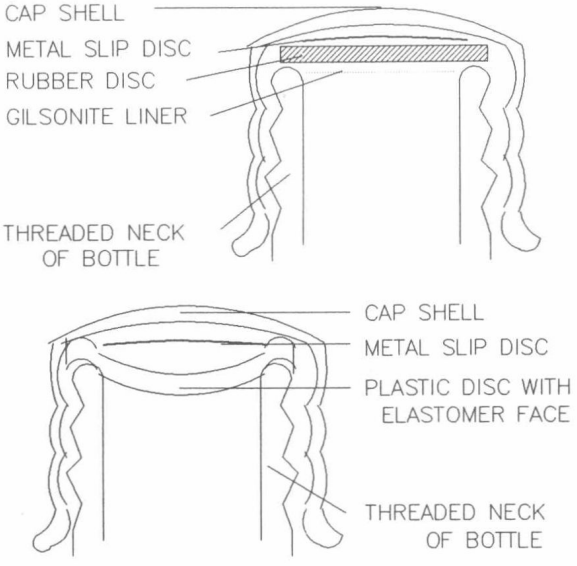

Fig. 1 Simplified drawings of bottle cap differences in Rocky Mount Incident (not to scale).