Medical Device Development

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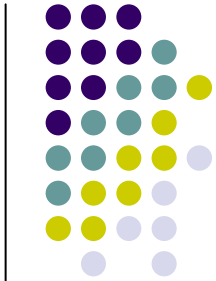
What is a Medical Device?

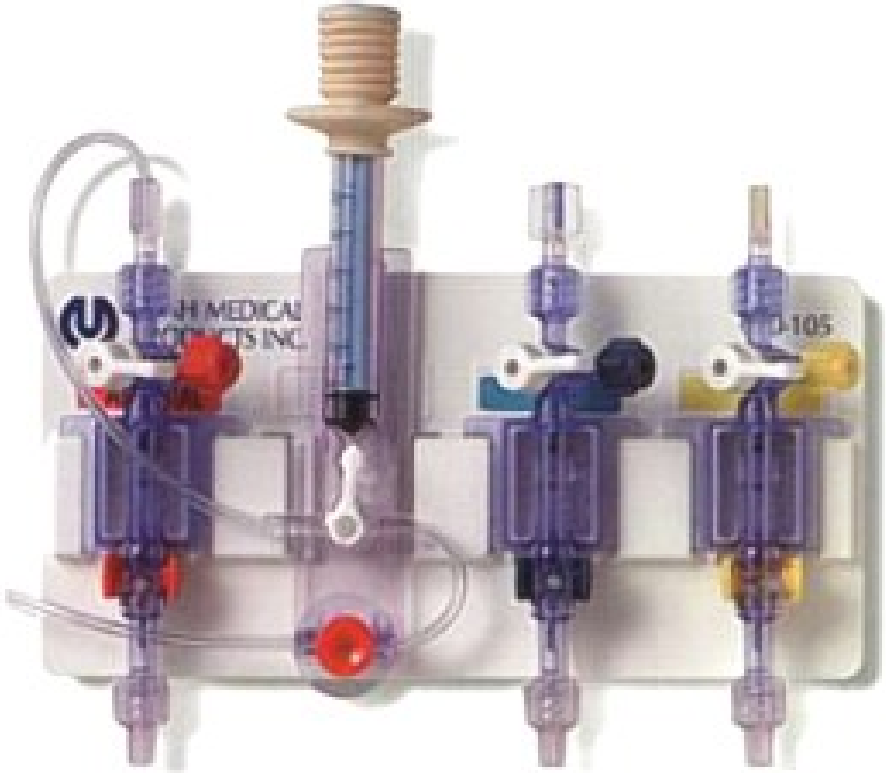
an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

1. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Medical Device Industry



- Global market for medical devices exceeds $200B
- US market ~ 42% of WW market
- US innovation drives the market (more US producers than rest of world combined)
- However.. it is increasingly difficult to commercialize
- Consumer v. agency regulation
- Increasing control improves safety and effectiveness at the expense of commercial progress
- Overseas manufacturing and product launch

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Medical Device Regulation

- 1976 Medical device amendments to the FD&CA
- 1978 GMP
- 1987 – 1989 Process validation, design control
- 1990 SMDA – 44% of recalls due to faulty design
- 1996 QSR – harmonization, FDA, MDD, ISO

The Big Picture - 21 CFR part 820
Quality System Regulation

Design Control

- Design & Development Planning
- Design input
- Design output
- Design review
- Design verification
- Design validation
- Design transfer
- Design changes
- Design history file

The Big Picture - 21 CFR part 820
Quality System Regulation

Subpart A – General Provisions
820.1 Scope
820.3 Definitions
820.5 Quality System

Subpart B – Quality System Requirements
820.20 Management Responsibility
820.22 Quality audit
820.25 Personnel

Subpart C – Design controls
820.30 Design controls

Subpart D – Document controls
820.40 Document controls

Subpart E – Purchasing controls
820.50 Purchasing controls

Subpart F – Identification and traceability
820.60 Identification
820.65 Traceability

Subpart G – Production and process controls
820.70 Production and process controls
820.72 Inspection, measuring and test equipment
820.75 Process validation

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820.170 Installation

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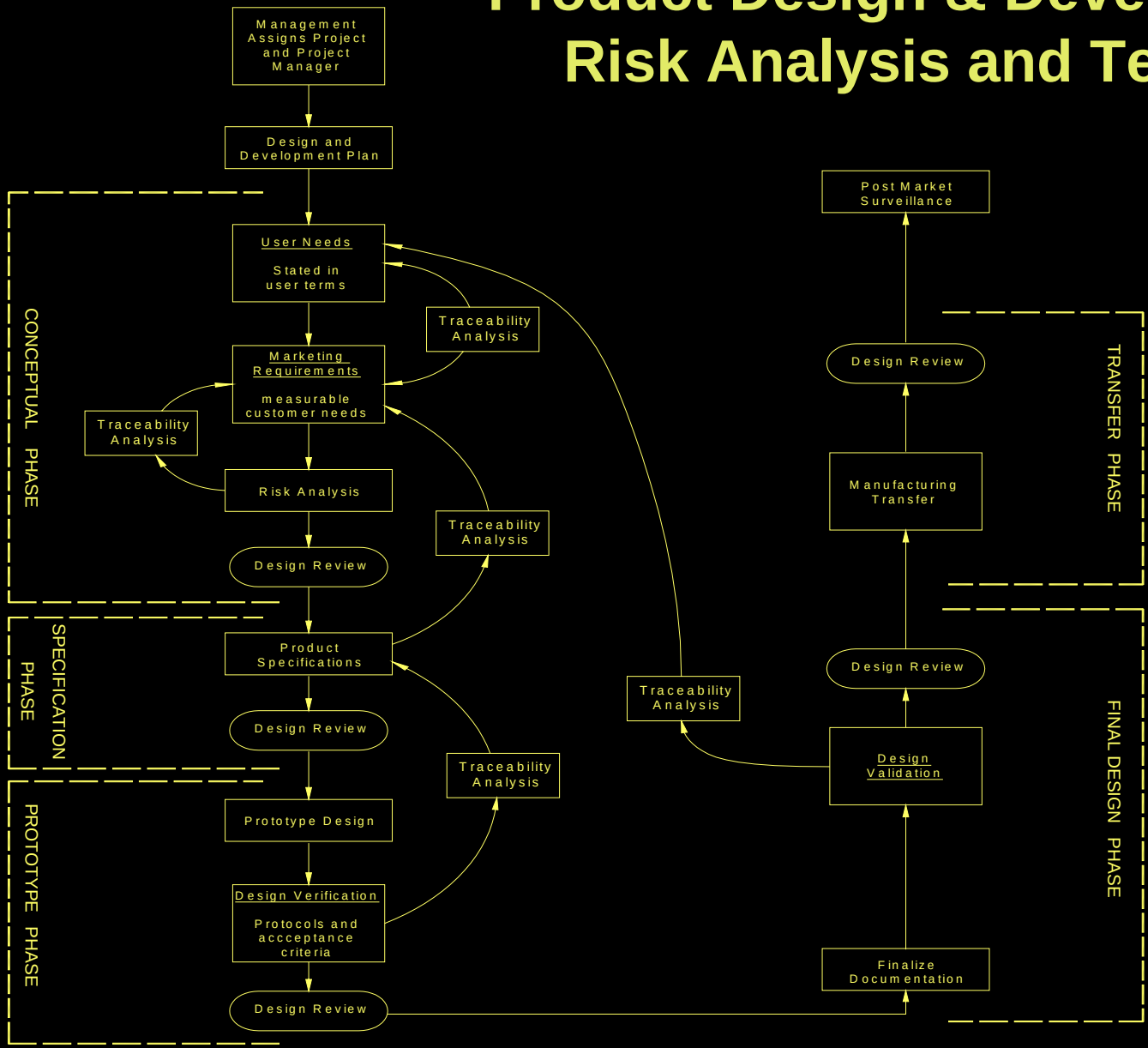
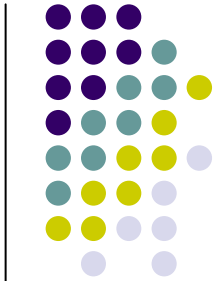
Product Design & Development Risk Analysis and Testing



Three Key Elements

1. Design Input
2. Risk Analysis
3. Design Output

Design Input



- User Needs
  - what & why stated in user terms
- Marketing Requirements
  - measurable, engineering terms

Design Input – User Needs

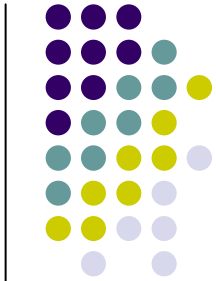
Over the Needle Catheter

- Infuse fluids into subcutaneous tissue
- Sharp enough to penetrate skin easily
- Simple to remove needle from catheter

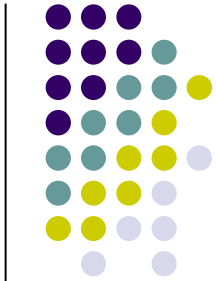
Design Input – Marketing Requirements

Over the Needle Catheter

- WFI infused at 100 ml/hr, backpressure not to exceed 10 psi
- Max insertion force through 5 mil latex = 3N
- Max force to remove needle = 1N



Regulatory Issues



Standards

Chapter 10

What are standards?

- Documents that represent consensus opinions on test methods, materials, devices or procedures (standardized).
- Timely review to keep them up to date.
- On going process-constantly evolving
- American Society for Testing and Materials (ASTM)

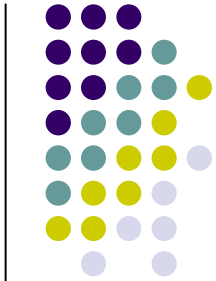
Test Method Standard

- Description of the specimen
- Test conditions
- Sample number
- Controls
- Method of analysis
- Stating that a test was “conducted in accordance with …ensures replication.

Representative Testing Standards

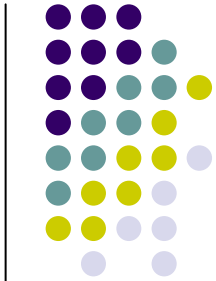
- ASTM D412 Test methods for rubber properties
- ASTM D638 Test method for tensile properties of plastics
- ASTM D695 Test method for compresive properties of ridgid plastics
- Standard test method for tensile properties of single textile fibers

A Material or Specification Standard



- Describes the chemical, physical an electrical properties of the material;

Representative ASTM Materials Standards



ASTM F75 Cast cobalt-chromium-molybdenum alloy for surgical implant applications

ASTM F451 Acrylic bone cements

ASTM F603 High-purity dense aluminum oxide for surgical implant applications

ASTM F604 Silicone elastomers used in medical applications

ASTM F603 High-purity dense aluminum oxide for surgical implant applications

2. Referenced Documents

C373 Test Method for Water Absorption, Bulk Density, Apparent Porosity, and Apparent Specific Gravity of Fired Whiteware Products
C1161 Test Method for Flexural Strength of Advanced Ceramics at Ambient Temperature
C1198 Test Method for Dynamic Young's Modulus, Shear Modulus, and Poisson's Ratio for Advanced Ceramics by Sonic Resonance
C1239 Standard Practice for Reporting Uniaxial Strength Data and Estimating Weibull Distribution Parameters for Advanced Ceramics
C1259 Test Method for Dynamic Young's Modulus, Shear Modulus and Poisson's Ratio for Advanced Ceramics by Impulse Excitation of Vibration
C1327 Standard Test Method for Vickers Indentation Hardness of Advanced Ceramics
E112 Methods for Determining Average Grain Size
F981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone
C1 Specification of General Requirements for a Quality Program
ISO 6474:1994 Implants for Surgery - Ceramic Materials Based on Alumina

Device Standard

- General design aspects;
- Dimensions and dimensional tolerances;
- Schematic drawings
- Perfomance such as fatigue life or biocompatibility requirements

Representative Device Standards

AAMI CVP3 Cardiac Valve prosthesis

AAMI VP20 Vascular graft prosthesis

AAMI RD17 Hemodialyzer blood tubing

ASTM ST8 Hospital Steam Sterilizers

ASTM F367 Holes and slots with spherical contour for metric cortical bone screws

ASTM F623 Foley catheters

A Procedure or Guidance Standard

- How to do something that is not generally considered a test
  - Surface preparation
  - Sterilization procedures for implants

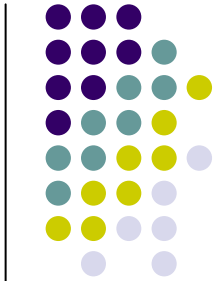
Who uses standards?

- Voluntary standards
- Manufacturers-precise description of the material
- Test laboratories
- Used as part of the regulatory approval process (FDA)-conformance standards expedite device review

Who writes standards?

- Association for the Advancement of Medical Instrumentation (AAMI)
- American Society for Testing and Materials (ASTM)
- International Standards Organization (ISO)
- American Dental Association (ADA)

Biocompatibility Standards



In Vitro Tests

F619. Practice for the extraction of Medical Plastics. A method for the extraction of medical plastics in liquids that simulate bodily fluids. The extraction vehicle is then used for chemical or biological tests. Extraction fluids include saline, vegetable oil and water.

F813. Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices

A cell culture test using American Type Culture Collection (ATCC) L2929 mouse connective tissue cells. This method or this type of cell culture method can be used as the first stage of biological testing.

F756. Assesment of Hemolytic Properties of Materials

An in vitro test to evaluate the hemolytic properties of materials intended for use in contact with blood. Procedure A is static; procedure B is performed under dynamic conditions.

Short-term In Vivo Testing

Primary Skin Irritation- Rabbits

Contact allergies-Guinea pigs

Subcutaneous injection-Mouse

Short-term screening in a particular tissue site

Long-term Testing In Vivo

F981. Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effects of Materials on Muscle and Bone. Long-term implantation of test materials in the muscle or bone of rats, rabbits and dogs. Two species are recommended. For rabbit muscle implants: the standard calls for four rabbits per time point, with test specimens placed in the paravertebral muscles. For bone implants in rabbits: the standard calls for three per femur.

New Products

Chapter 10

FDA

Center for Devices and Radiologic Health (CDRH)-maintains authority over medical devices.

Combination Products

- Device, biologic or drug
- drug eluting stent

Regulation

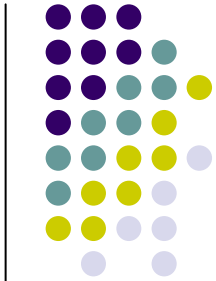
Biomaterials are regulated indirectly according to the intended use of the product incorporation the material and the relative risk of the use of the materials.

All regulations place the burden of proof upon the manufacturer to document quality of the biomaterials.

Typical Regulatory Control

1. Device specific requirements (guidance documents)
2. Material specifications
3. Validation and verification of material performance within the device
4. Manufacturing and purchasing controls

Consider Global Regulatory Requirements



The US and European requirements are not necessarily the same as in Japan or Canada or Australia.

Harmonization committee and organizations

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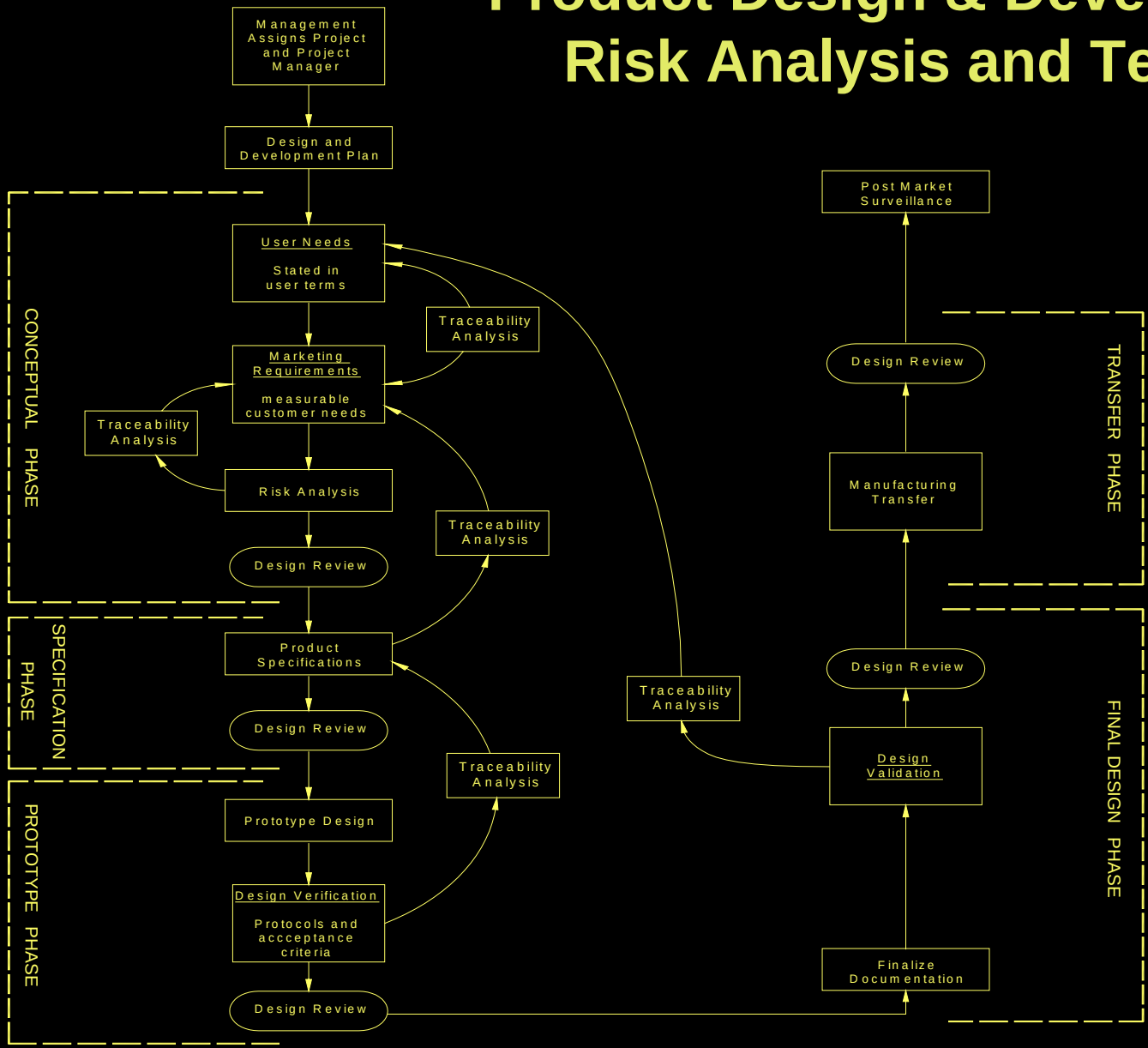
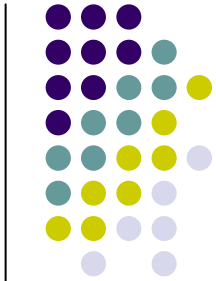


Typical Plan

1. Concept Phase
2. Development Phase
3. Clinical Evaluation
4. Market Introduction

Premarket Approval

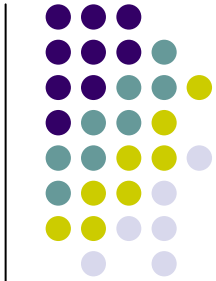


Premarket Approval Application (PMA): demonstration saftey and efficacy of new device, unless it is shown to be substantially equivalent to a product on the market in the US. [510(k)].

Final review by the Clinical Advisory Board

- Statistical proof of efficacy

Clinical Trials



IRB, protocols, patients rights, privacy

Investigational Device Exemption (IDE)-allows study in human patients

- A protocol or study plan
- Informed consent
- Training in the use of the product
- Financial disclosure
- IRB approval
- Reports of adverse events
- Performance claims of device need to be validated

Implant Associated Infections & Sterilization Methods

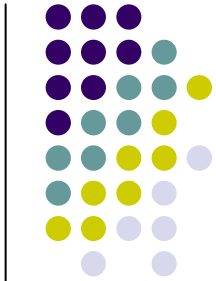
Infectious Agents

microscopic organisms, including

- bacteria,
- viruses,
- Fungi, and
- animal parasites,

they penetrate the body's natural barriers and multiply to create symptoms

Implant associated Infections



- The benefits of implanted devices are often limited by the occurrence of infections associated with the devices, even when the best aseptic techniques are practiced;
- Each year, as many as 2 million hospital patients in the United States develop device related infections at a cost of nearly $11 billion annually**;**
- Approximately 80% of the 80,000 annual deaths in this country that result from infections that are device related;

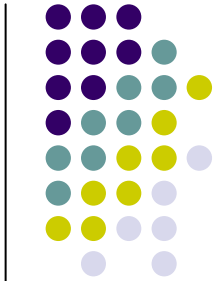
Nosocomial Infections

- Infections that are acquired while a patient is in a hospital are referred to as nosocomial infections; a term derived from 'nosos' the Greek word for 'disease'.
- Nosocomial infections are diseases that heath care professionals give to their clients.
- Device-related infection results from the introduction of organisms, primarily bacteria, during the device insertion or implantation procedure, or from attachment of bloodborne organisms to the newly inserted device and their subsequent propagation on its surface.

Nosocomial Infections - continued

- Good clinical practice—such as thoroughly cleaning and disinfecting the area prior to insertion, proper prepping by the clinical staff, and care in handling the device to maintain sterility prior to insertion—will reduce but not eliminate the occurrence of infection.
- Infection also can occur after insertion, either from bacteria in the blood or urine attaching to the device or, in the case of externally communicating devices, from bacteria that use the device as a pathway into the body, in some cases long after the device has been inserted.

Urinary Catheters



- Urinary-tract infections occur in about 20% of patients with Foley catheters in place for more than 10 days;
- and in more than 40% of patients with Foley catheters in place for more than 25 days.
- There are approximately 500,000 cases of these infections in U.S. hospitals each year, and most are associated with catheters.

Central Venous Catheters

- bloodstream infections in the United States number more than 100,000 per year, with annual mortality ranging from 10,000 to 20,000 and cost of treatment estimated at $1 billion;
- At least 50,000 cases of these infections are associated with central venous catheters; and,
- Other IV devices, such as midline catheters and peripherally inserted central catheters (PICCs), also cause for significant level of infections.

Blood Stream Infections

- Migration of skin organisms at the insertion site into the cutaneous catheter tract with colonization of the catheter tip is the most common route of infection for peripherally inserted, short-term catheters;
- Contamination of the catheter hub contributes substantially to intraluminal colonization of long-term catheters;
- Occasionally, catheters might become hematogenously seeded from another focus of infection; and,
- Rarely, infusate contamination leads to BSI

Infectious Agents

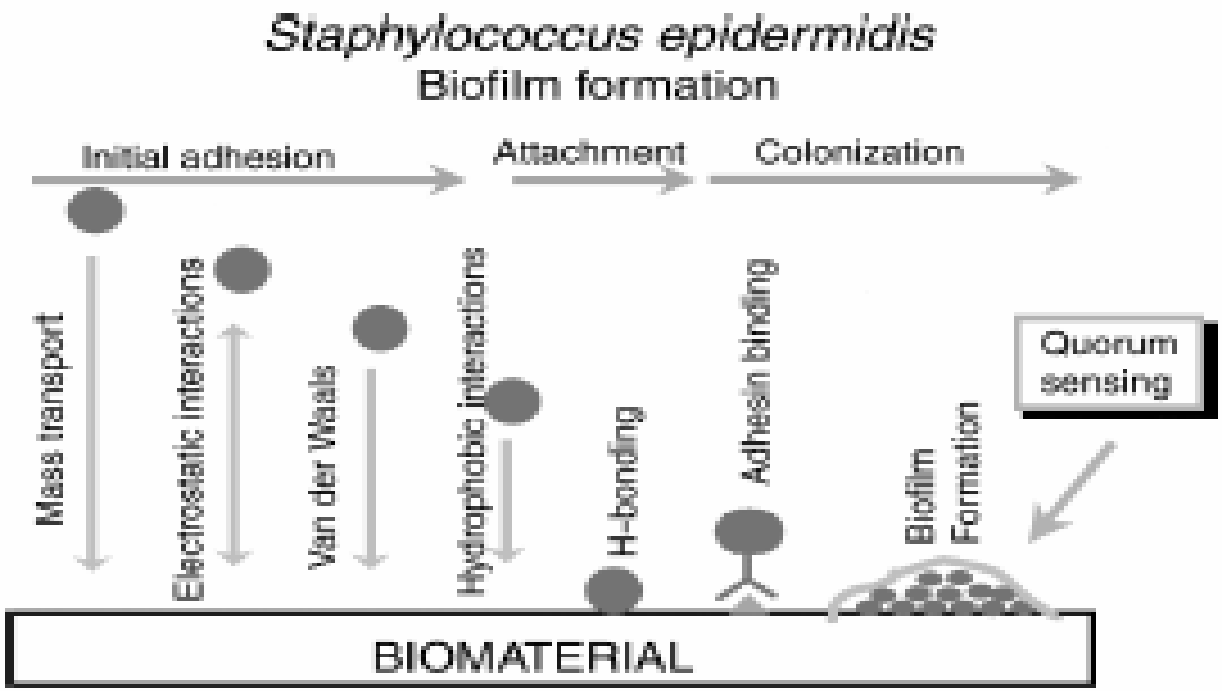
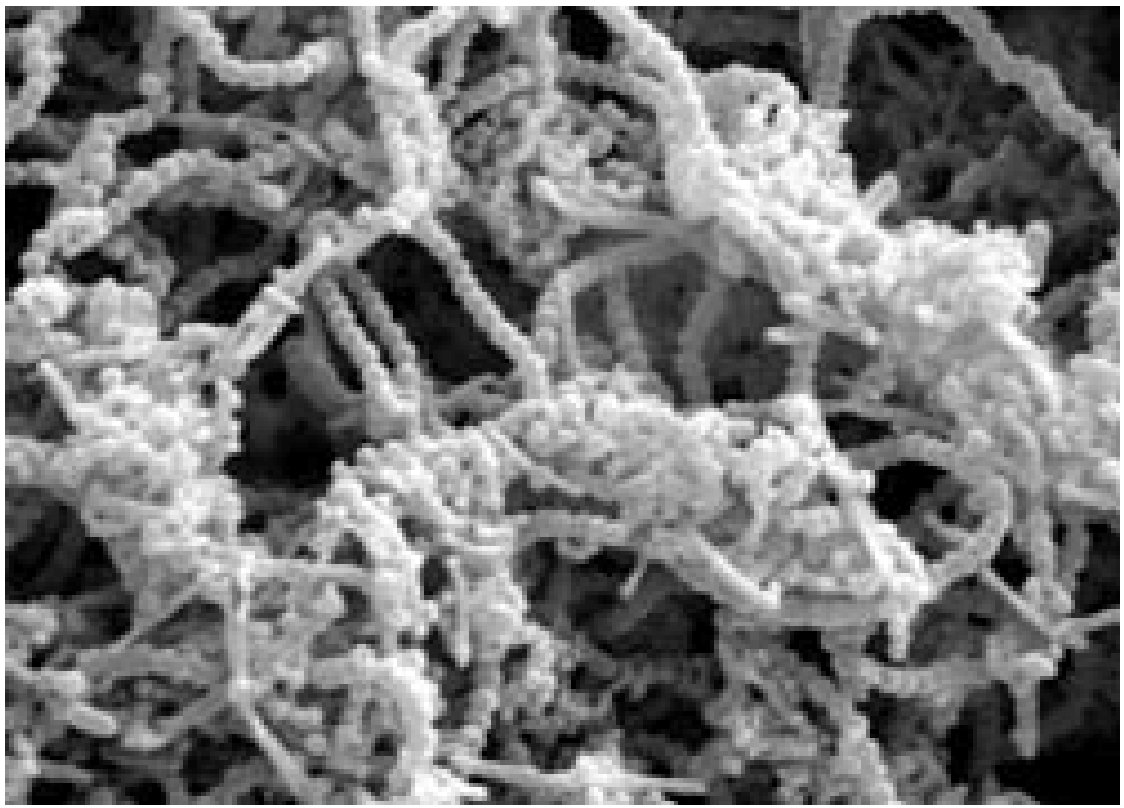
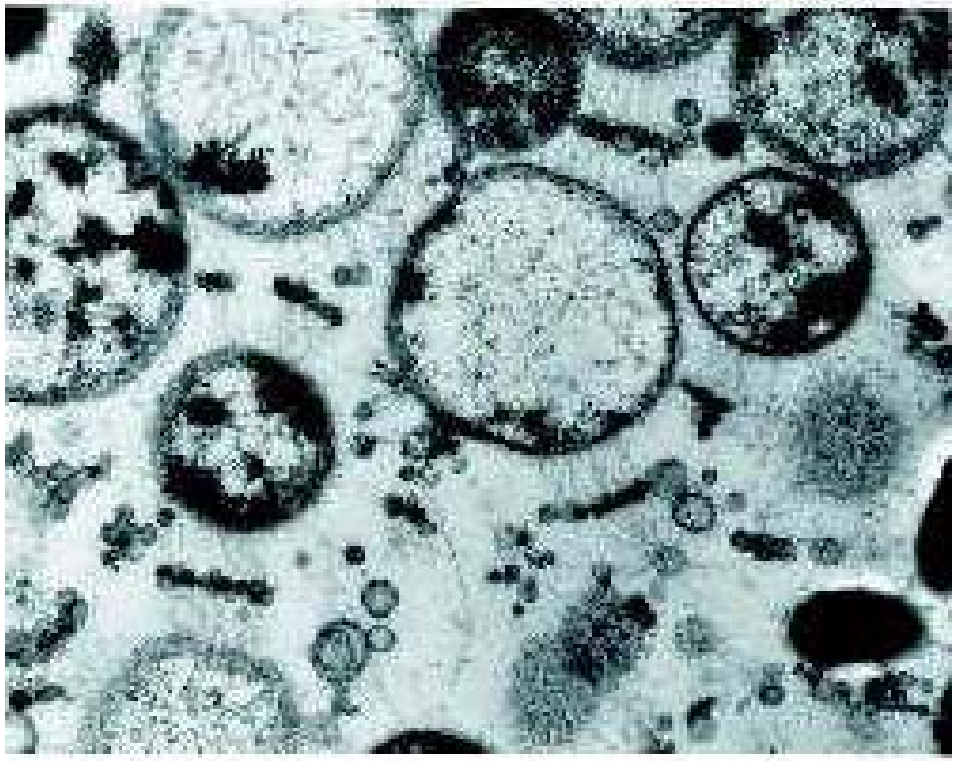


Figure 1 Factors involved in the colonization of a plastic biomaterial by *S. epidermidis*.

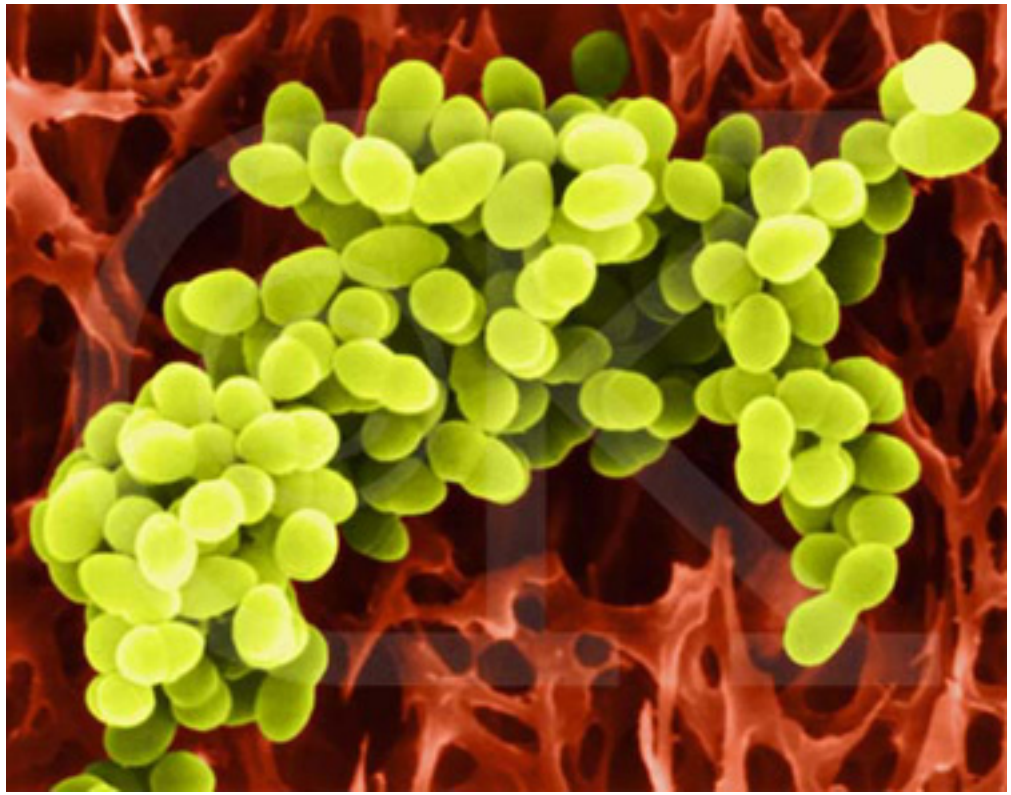
Biofilm on Dental Implant



TEM showing diversity in Biofilm

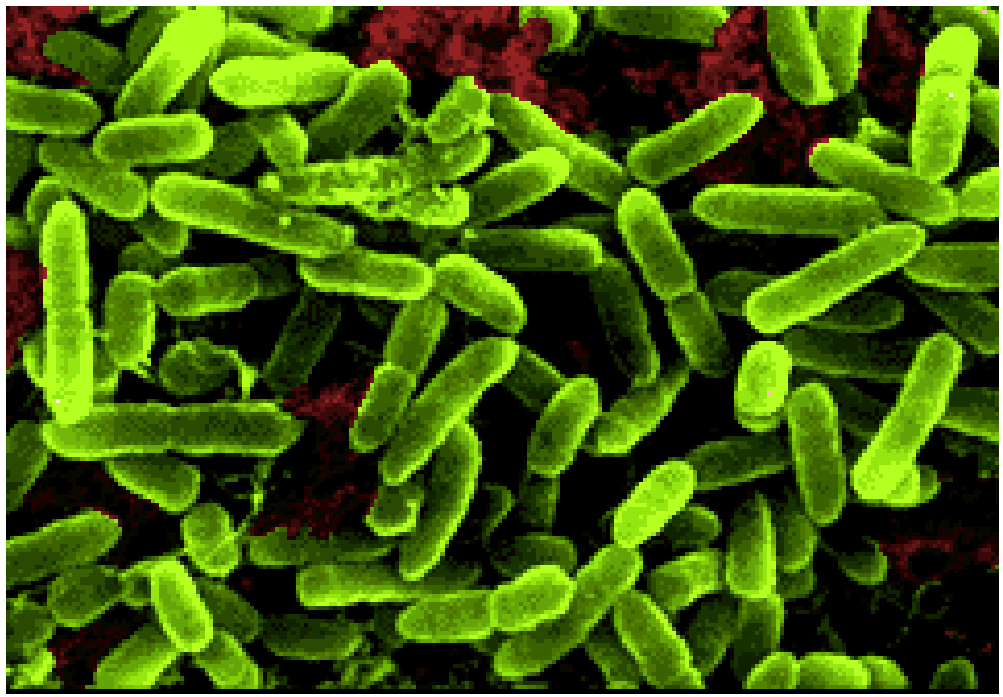


Aerobic, Gram-positive cocci



Staphylococcus aureus

Glucose-nonfermenting, Gram-negative rods



Pseudomonas aeruginosa

Types of Infectious Agents

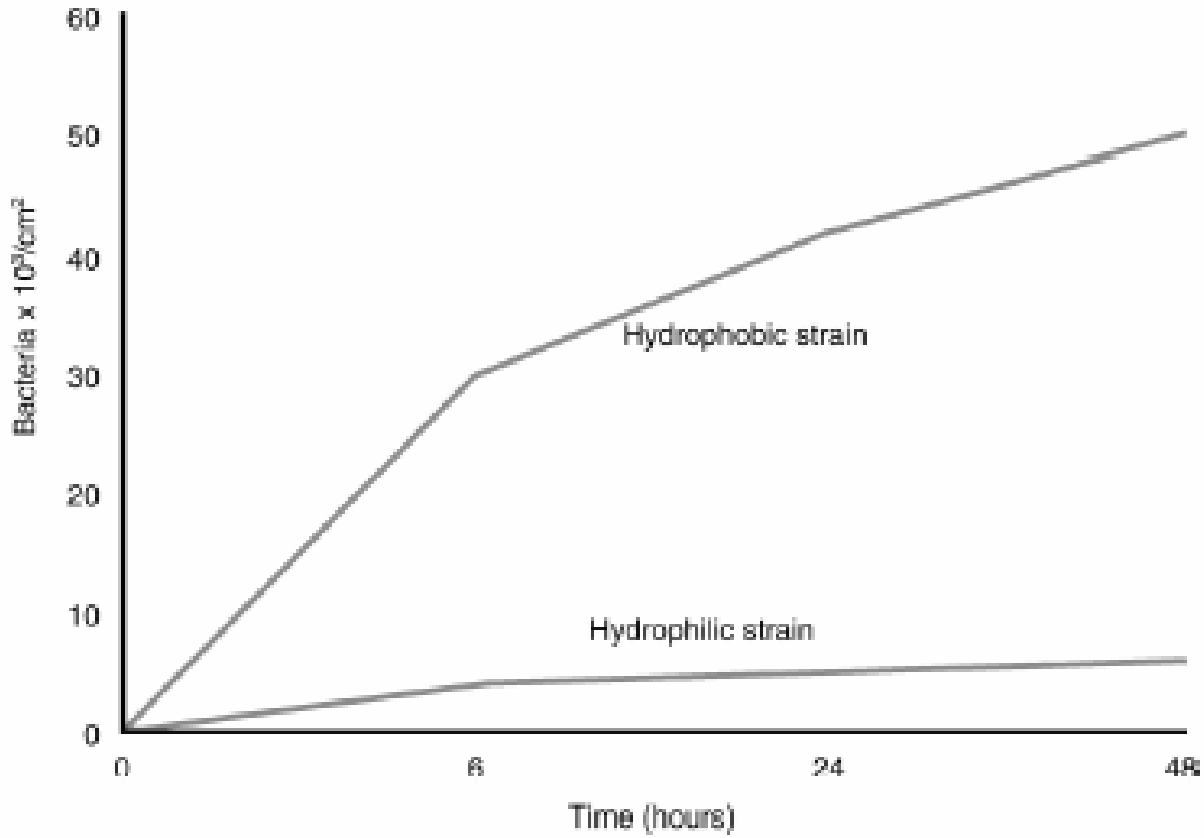
TABLE 3. Most common pathogens isolated from hospital acquired bloodstream infections

Pathogen	1986–1989 (%)	1992–1999 (%)
Coagulase-negative staphylococci	27	37
Staphylococcus aureus	16	13
Enterococcus	8	13
Gram-negative rods	19	14
Escherichia coli	6	2
Enterobacter	5	5
Pseudomonas aeruginosa	4	4
Klebsiella pneumoniae	4	3
Candida spp.	8	8

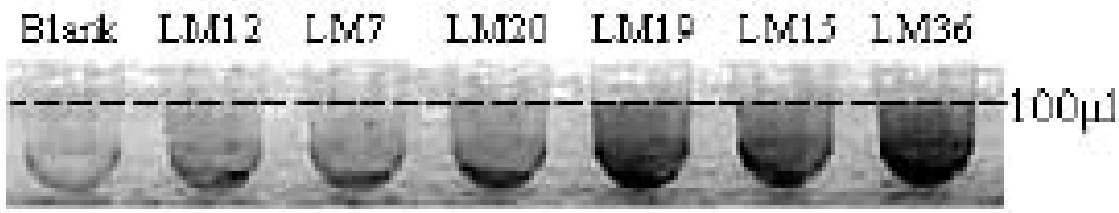
Devices and Types of Infections

- Sutures -*Staphylococcus epidermidis* and *S. aureus*
- Exit sites-*S. epidermidis* and *S. aureus*
- Contact lens-*P. aeruginosa* and Gram-positive cocci
- Urinary catheter-*E. coli* and other Gram-negative rods
- Peritoneal dialysis (CAPD) peritonitis -A variety of bacteria and fungi
- Endotracheal tubes -A variety of bacteria and fungi
- Mechanical heart valves-*S. epidermidis and S. aureus*
- Vascular grafts -Gram-positive cocci
- Orthopedic devices - *S. epidermidis and S. aureus*

Bacterial Adhesion to Biomaterials

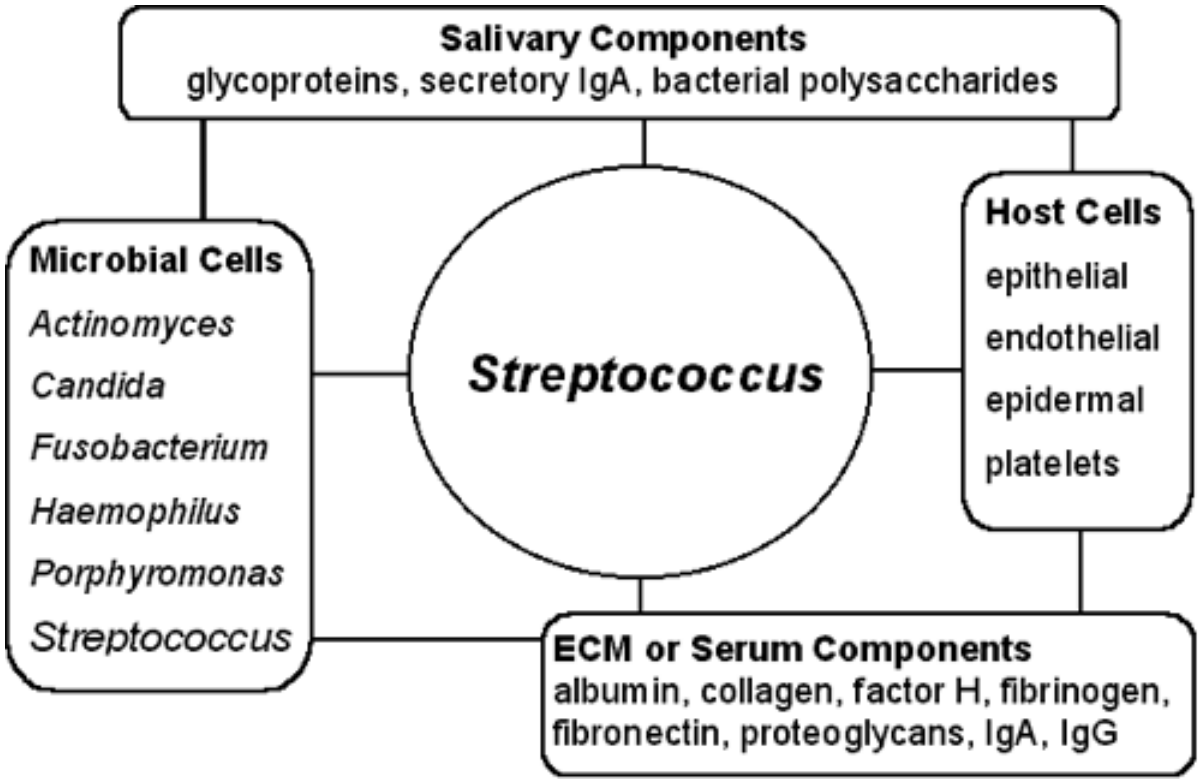


Biofilms of selected *L. monocytogenes* strains growing on PVC wells.



Levels of growth on solid surfaces can vary greatly between strains

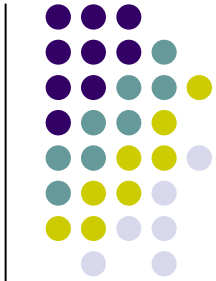
Binding Ability of Bacteria



Sterilization

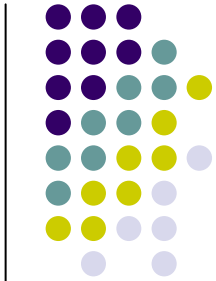
- Defined as a validated process used to render a product free from viable microorganisms,
- The presence of microorganisms on the individual items is expressed in terms of probability.
- While the probability may be reduced to a very low number, it can never be reduced to zero.
- The probability can be expressed as a Sterility Assurance Level (SAL), it means probability of a viable microorganism being present on the product unit after sterilization.

Historical Prespective



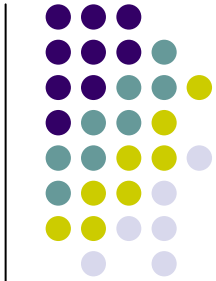
- In order to eradicate these infections, a new industry was developed—the disposable medical device industry.
- Nosocomial infections decreased significantly once this industry became regulated and sterilization processes became standardized.
- The new disposable products were created from a class of newly developed low cost plastics that were produced and packaged to maintain their sterile properties up to the time of use;
- Disposable plastic devices, such as syringes, blood transfusion kits, and hospital gowns could not be subjected to the traditional sterilization methods of dry heat or steam (autoclave) because they would melt.
- New methods of low temperature sterilization had to be developed in order to allow the use of these devices in a sterile environment.

Sterilization or Disinfection of Medical Devices: General Principles



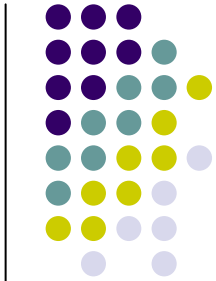
- In general, reusable medical devices or patient-care equipment that enters normally sterile tissue or the vascular system or through which blood flows should be sterilized before each use.
- Sterilization means the use of a physical or chemical procedure to destroy all microbial life, including highly resistant bacterial endospores.
- The major sterilizing agents used in hospitals are a) dry heat, b) moist heat by steam autoclaving, c) ethylene oxide gas, and, d) radiation.

General Principles-continued



- Disinfection means the use of a chemical procedure that eliminates virtually all recognized pathogenic microorganisms but not necessarily all microbial forms (e.g., bacterial endospores) on inanimate objects.

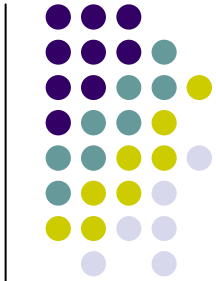
Sterilization Methods



There is no ideal sterilization process but in general:

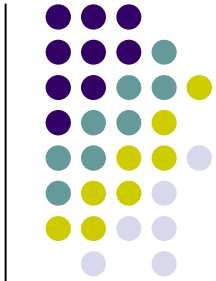
- For liquid products, where possible, utilize one of the variations of steam sterilization. Small volume parenterals, however, also might be compatible with radiation sterilization. Avoid aseptic filtration / fill unless absolutely dictated by product compatibility.
- For non-liquid products, steam, dry heat, and radiation sterilization are much preferred over EtO. The aforementioned processes are relatively simple, are amenable to parametric release, and do not leave toxic residues in the product.

Dry Heat



- Temperature: 140 -170°C
  Exposure Time: 60 -180 minutes
- Dry heat sterilization is a relatively simple process that involves exposure of the product to hot air in an appropriate sized chamber.
- To assure temperature uniformity in the chamber, the air is circulated via a fan/blower system.
- When glass vials or ampules are sterilized /depyrogenated prior to the asceptic filling of pharmaceuticals, special equipment is utilized that has particulate control systems to ensure that the load is exposed to class 100 conditions or better during the sterilization run.

Dry Heat-continued



- Typical products sterilized by dry heat, in addition to glass vials and ampules, include heat stable dry powder pharmaceuticals, oils, and products that are heat stable but either sensitive to moisture or not penetrated by moist heat.
- The principal advantages of dry heat sterilization are its simplicity, penetrating power, and lack of toxic residues.
- Its disadvantages are the relatively long processing time and the high temperature, which limits the types of products and packaging materials compatible with this process.

Steam under Pressure

- Sterilization by steam under pressure also is a relatively simple process which involves exposure of the product to steam at the desired temperature and pressure.
- The process usually is carried out in a pressure vessel designed to withstand the high temperature and pressure.
- To provide for uniform temperature distribution, it is important to remove the air from the sterilization chamber; this may be accompanied by gravity displacement or by a vacuum system.
- A vacuum system is generally preferred when compatible with the product/package system to ensure efficient air removal and optimum steam penetration.

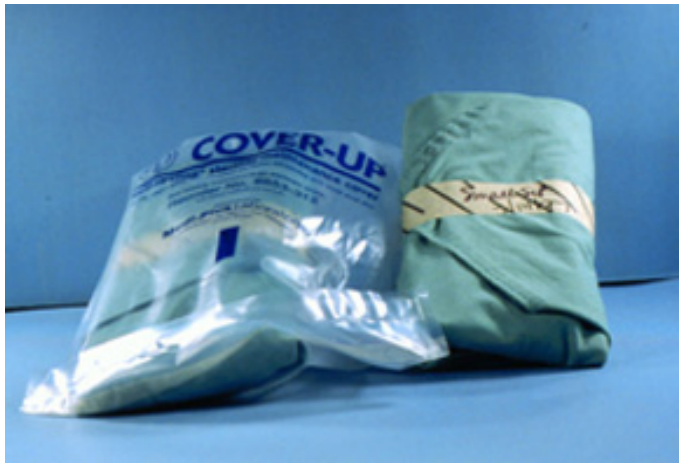
Steam Sterilization: Autoclaving

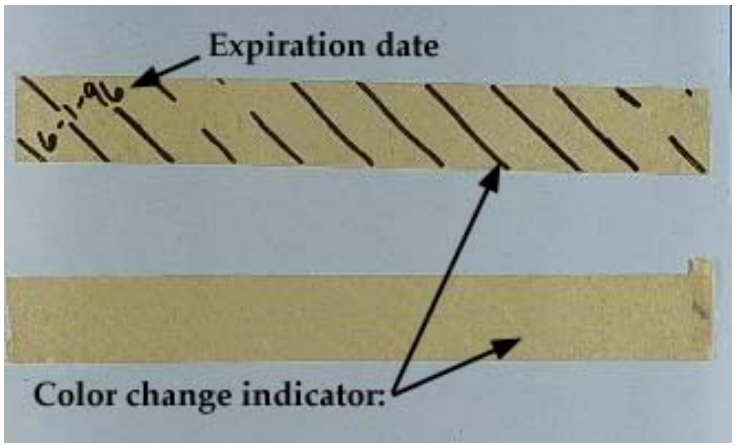
- An autoclave is a self locking machine that sterilizes with steam under pressure.
- Sterilization is achieved by the high temperature that steam under pressure can reach.
- The high pressure also ensures saturation of wrapped surgical packs.
- Ideal for metal instruments.

Operational Information

Autoclave Settings	Temperature (F)	Pressure (PSI)	Time (min)
General Wrapped Items	250	20	30
Bottled solutions	250	20	30
“Flashing”	270	20	4-7

Preparation for Sterilization



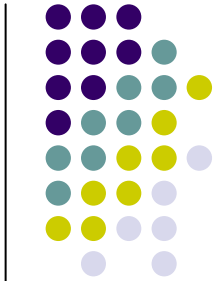


- All instruments must be double wrapped in linen or special paper or placed in a special metal box equipped with a filter before sterilization.
- 'Flashing' is often used when a critical instrument is dropped.
- The white stripes on the tape change to black when the appropriate conditions (temperature) have been met.
- Indicators should be on the inside and outside of equipment pack.
- Expiration dates should be printed on all equipment packs.

Steam under Pressure

- The principal advantages of steam sterilization are its simplicity, relatively short processing times, and lack of toxic residues;
- Parametric release, that is, the release of product for sale without conducting microbiological sterility testing, generally is easily validated;
- Its main disadvantage is the relatively high temperature (generally lower than dry heat, however) making it unsuitable for many plastic devices and lack of utility for products that are moisture sensitive or moisture impermeable.

Steam under Pressure-continued



- Products typically sterilized by steam under pressure include small and large volume parenterals (SVPs, LVPs), surgical dressings, water for injection, contact lenses, and so on.
- To be compatible with steam sterilization, a product must be stable with respect to temperature and moisture, and the product/package must be readily penetrated by steam.
- Without adequate steam penetration, sterilization can be impeded or defeated entirely.

Ethylene Oxide Sterilization: ETO Gas

- Colorless gas, **very toxic** and **flammable;**
- Requires special equipment with special venting requirements;
- Low temperature sterilization method of choice for heat sensitive instruments: plastics, suture material, lenses and finely sharpened instruments;
- Materials must be well aerated after sterilization;
- Materials/instruments must be dry.

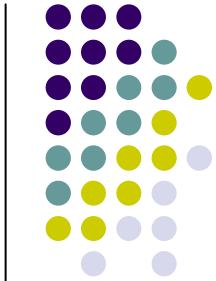
Ethylene Oxide

- Nonliquid products, contained in gas permeable packages not compatible with the heat or moisture of dry heat or steam sterilizaiton, and not compatible with radiation sterilization, are candidates for sterilization with EtO gas.
- Because it is toxic and potentially carcinogenic, the use of EtO is under ever increasing regulatory scrutiny and control.
- EtO is flammable and potentially explosive, so specialized equipment and damage limiting facilities are required.
- EtO can be used undiluted in its pure form or with nitrogen as a diluent.

Ethylene Oxide

- The primary advantages associated with the use of EtO sterilization are the low processing temperature and the wide range of compatible materials.
- The disadvantages relate to the toxicity of the gas, only useful as a surface sterilant unable to reach blocked-off surfaces, such as those found in hypodermic plunger/barrel interfaces in hypodermic needles, and residuals in the product and manufacturing environment are present after treatment.
- The increasing cost of the gas and of the various engineering and environmental controls required to assure safe low residual products and low personnel exposure has raised and will continue to escalate the cost of EtO sterilization.
- EtO is used for a wide range of products including blood oxygenators, catheters, tracheostomy tubes, mechanical heart valves, sutures, custom procedure kits, adhesive bandages, tubing sets, and so on.

Radiation (Co-60, Cs-137, accelerated electrons)



- Dose: 1.5-3.5 Mrad;
- Radiation sterilization, either by gamma rays from Co-60 or Cs-137, radioisotopes, or accelerated electrons, offers a simple sterilization alternative for moisture sensitive/thermolabile nonliquid products;
- Inactivation of microorganisms occurs either through direct ionization of a vital cellular molecule (DNA, key enzyme, etc.) or indirectly through the reaction of the free radicals produced in the cellular fluid;
- It also applies to small volume thermolabile liquid products that are radiation compatible;
- Products to be sterilized are exposed to gamma rays from a Co-60 or a Cs-137 source or to machine accelerated electrons until the desired dose is received.

Radiation

- No toxic agents are involved, and products may be released for sale on the basis of documentation that the desired dose was delivered; microbiological release testing generally is not required unless it is a local regulatory requirement.
- Gamma radiation is a penetrating sterilant.
- No area of the device or container is left with uncertain sterility. This includes prefilled containers.
- There is no need for specialized packaging.
- Since there is no requirement for pressure or vacuum, seals are not stressed.
- Gamma radiation is highly reliable due to its single variable to control—exposure time.
- Gamma processing has demonstrated lower overall costs. Both large and smallproduct volumes can be accommodated in a cost-effective manner.
- Many medical products are sterilized by radiation including sutures, gloves, gowns, face masks, dressing, syringes, surgical staplers, and so on.

Drawbacks

- Gamma radiation sterilization is not without its drawbacks.
- Recently, tests have shown that the gamma radiation provides an environment conducive to the oxidation of the UHMWPE (Wright Medical Technology, 1995 and Naidu et al., 1997).
- Many researchers have concluded that this oxidation process explains the diminished wear properties of the UHMWPE in the human body by changing the percent crystallinity of the UHMWPE (Naidu et al., 1997).

Asceptic Processing

- Many liquid pharmaceutical and biological products cannot withstand any form of thermal sterilization; so most of them are relegated to aseptic filtration and then filled into presterilized containers in a cleanroom environment.
- As mentioned above, a few thermolabile liquid products have been demonstrated to be compatible with radiation sterilization.
- Aseptic filtration involves passing the solution through a sterile 0.1 to 0.22 mm microbiological filter and capturing the filtrate in a presterilized bulk container.
- The liquid from the bulk container then must be aseptically dispensed in presterilized containers such as bottles, vials, ampules, or syringes.

Aseptic Processing-continued

- Many parenteral and diagnostic products are asceptically filtered and filled, including intravaneous drug solutions, ophthalmic drug solutions, blood banking reagents, antibiotic solutions, and so on.
- There is now increasing pressure in the United States not to approve asceptic filtration / fill processes for products unless terminal sterilization processes have been demonstrated to be deleterious to the product.
- Once an asceptic filtration / fill facility has been established and validated, it has been convenient to process subsequent products by this method even though they might, for example, be compatible with steam sterilization.

In - House Sterilization

- If one desires in house sterilization capability because of the benefits of increased control of the operation and lack of necessity for shipment of nonsterile product, steam and EtO processes can be installed for modest to moderate capital investments.
- The cost of a 350 ft3 steam sterilization system (installed) would generally range between $150,000 and $250,000.
- The cost of a similar sized EtO unit, owing to its increased complexity and requirement for emission control, would range from $175,000 to $300,000.
- This does not include the cost of reclamation equipment and damage limiting construction for potentially explosive EtO mixtures.

In - House Sterilization

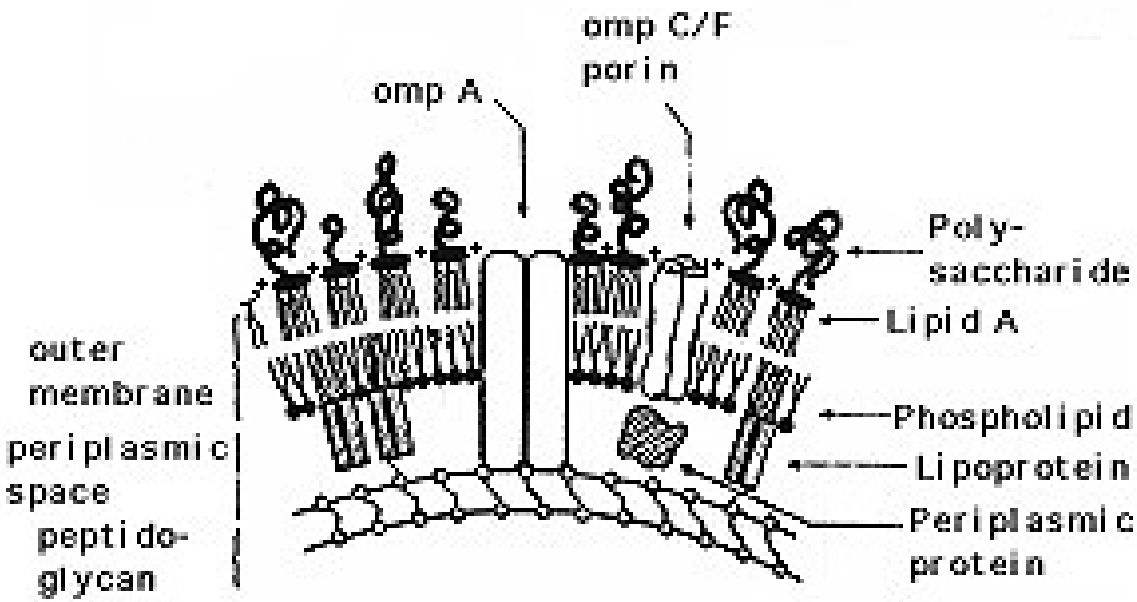
- The establishment of an asceptic filtration/filling facility would be considerably more expensive because of the need for sterilization and possibly depyrogenation equipment, in addition to the filtration and filling equipment and associated cleanrooms and laminar flow hoods.
- An asceptic filtration/fill area would cost between $500 and $800 per ft2, not including the associated filtration and filling equipment.
- Because of its extremely high capital cost, it is very unlikely that the average manufacturer would attempt to establish an in-house radiation sterilization capability.
- Electron beam and Co-60 requires large volumes of product to be cost effective; the cost of typical installations runs from $5,000,000 to $12,000,000.
- For this reason, a large number of manufacturers utilize contract radiation services.

Contract Sterilization

- Establishing a relationship with a contract sterilizer involves several activities:
- Assessing the capability of the contractor to ensure that the staff are technically qualified and the facility follows the applicable GMP regulations.
- Auditing the quality and computer based systems of the company for product receipt, traceability and reconciliation, and return shipment.
- Reviewing the records of the contractor for recent federal regulatory audits. Were adverse findings reported (483s) or regulatory letters received? What was the nature of the findings, and was corrective action promptly applied?
- If possible, meeting with current clients of the contractor and discussing both technical capability and business issues.
- Developing a plan and appropriate protocols for validation of the processes performed by the contractor.

BACTERIAL ENDOTOXINS

- **Endotoxins** are part of the outer membrane of the cell wall of Gram-negative bacteria. Endotoxins are invariably associated with Gram-negative bacteria whether the organisms are pathogens or not. Although the term "endotoxin" is occasionally used to refer to any cell-associated bacterial toxin, it is properly reserved to refer to the **lipopolysaccharide** complex associated with the outer membrane of Gram-negative bacteria such as *E. coli*, *Salmonella*, *Shigella*, *Pseudomonas*, *Neisseria*, *Haemophilus*, and other leading pathogens.



The biological activity of endotoxin is associated with the lipopolysaccharide (LPS). **Toxicity** is associated with the lipid component (**Lipid A**) and **immunogenicity** is associated with the **polysaccharide** components.