PRIMARY MANUFACTURING

PARENTERAL FORMULATION, FILTERING, AND FILLING

Learning Objectives

By the completion of this lecture and lab exercise, the participant will be able to:

- List some of the **unique requirements in a CGMP environment** designed to formulate, filter, and fill parenteral drugs and combination devices.
- Discuss how **CGMP regulatory requirements & aseptic processing** help protect sterile products and the patients who use them.

Learning Objectives

By the completion of this lecture and lab exercise, the participant will be able to:

- Identify **forms** that parenteral formulations may take.
- Describe some **different filling mechanisms** and some of the pros and cons of each.

Learning Objectives

By the completion of this lecture and lab exercise, the participant will be able to:

- Discuss some of the issues and challenges related to **filtering**.

- Compare **filter testing** by Bubble point and diffusive flow (lab exercise).

Learning Objectives

By the completion of this lecture and lab exercise, the participant will be able to:

- Describe some of the **challenges related to sealing, stoppering, and capping** parenteral products.

A Few Key Terms

Parenteral Drugs: Drugs administered by injection into a vein, muscle, or subcutaneous tissue.

A Few Key Terms

Aseptic Processing: the processes by which sterile products are filled and packaged in a manner that maintains sterility.

Bioburden: Degree of microbial contamination or microbial load; the number of microorganisms contaminating an object.

A Few Key Terms

CGMP: Current Good Manufacturing Practices, regulatory requirements designed to protect product SISPQ (Safety, Identity, Strength, Purity, Quality) and to maintain the CGMP environment in a consistent State of Control, in accordance to pre-determined Quality standards and systems.

Unique Requirements When Formulating or Filling Sterile Drugs

One Challenge Related to Aseptic Processing of Parenterals

After medical devices are assembled and packaged, they are usually sterilized by a variety of methods, including autoclaves and radiation. This intense sterilization is done at the very end of the production process, which is why it is called “terminal sterilization”.

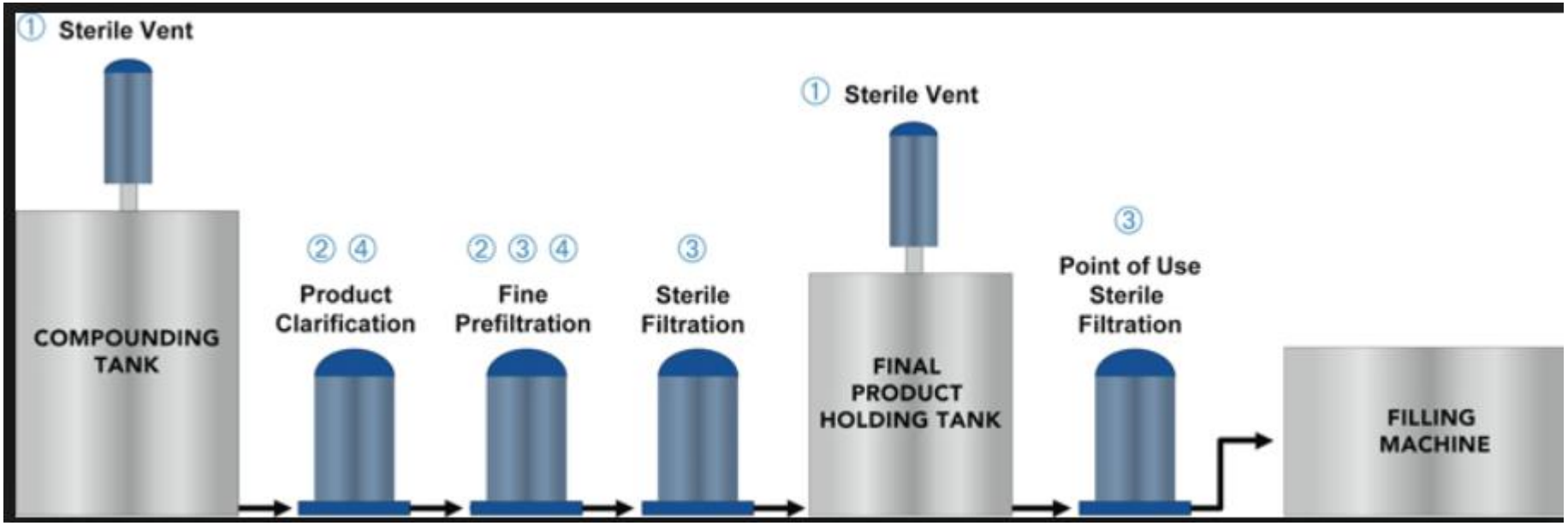
One Challenge Related to Aseptic Processing of Parenterals

Unfortunately, extreme heat and radiation would cause most parenteral drugs to deteriorate, which means that the drugs might not be as effective or safe as they were intended to be.

For that reason, processes are put into place to ensure sterility at each stage of production of parenteral drugs.

One Challenge Related to Aseptic Processing of Parenterals

A final filtration is designed to screen out microbes and particulates. Here is one filtering approach as illustrated by Amazon filters UK. We will learn more about filtering later.



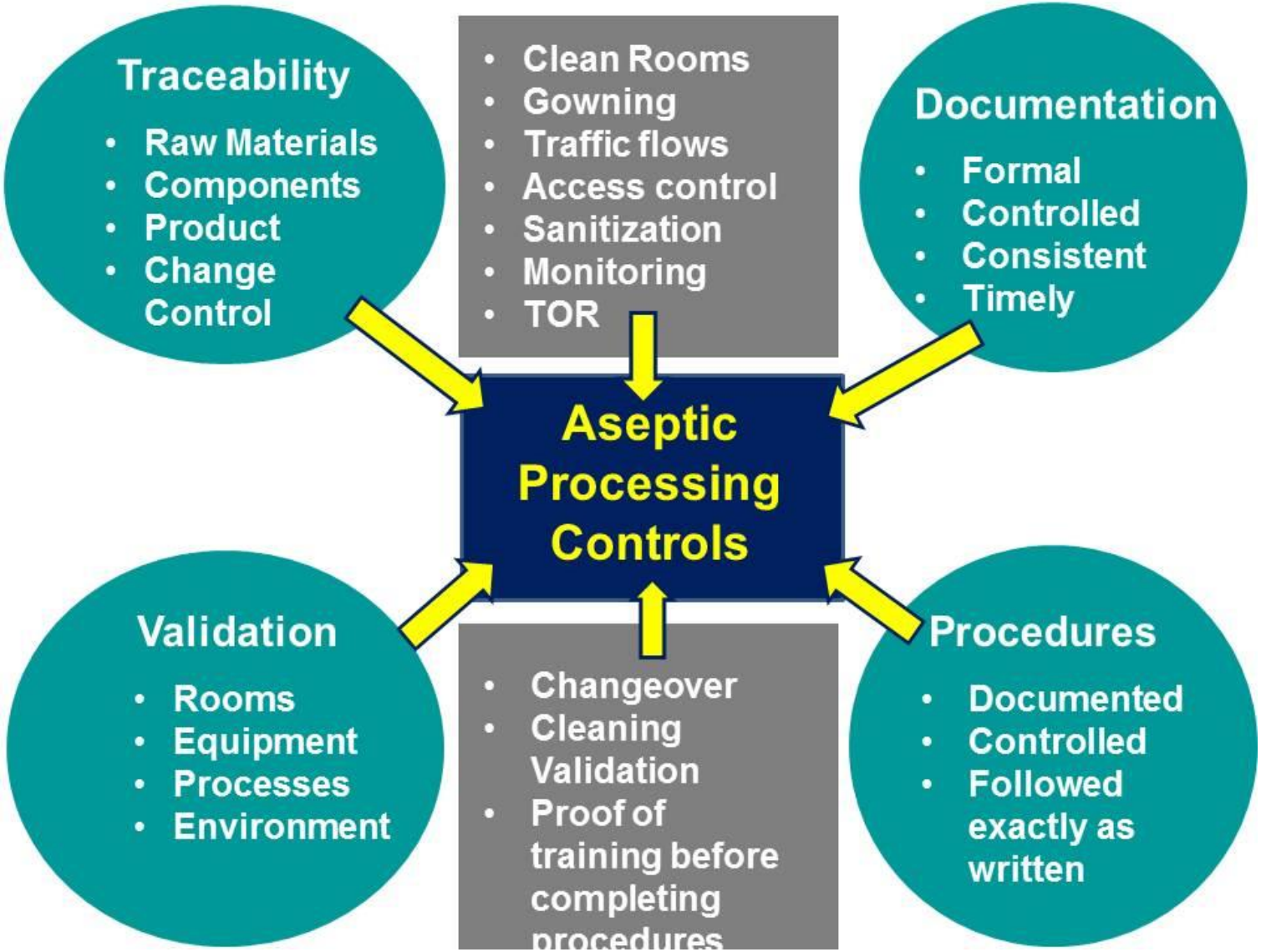
Parenteral Production – A Unique Environment

Exercise 1: Using what you've learned so far (and just common sense), what do you think some requirements might be for personnel who are working in parenteral manufacturing and for the rooms and equipment used to formulate, filter, and fill parenterals?

If I worked in parenteral primary production, I would need to know how to….

I imagine that some requirements related to the rooms and equipment used to produce parenterals include…..

CGMP Requirements & Aseptic Processing

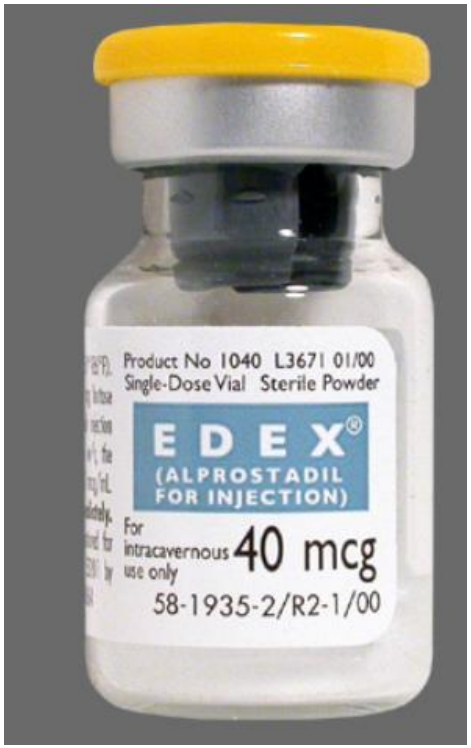


Forms of Parenteral Drugs

Liquid Solutions

Emulsions or Suspensions

Lyophilized Forms of Injectable Drugs



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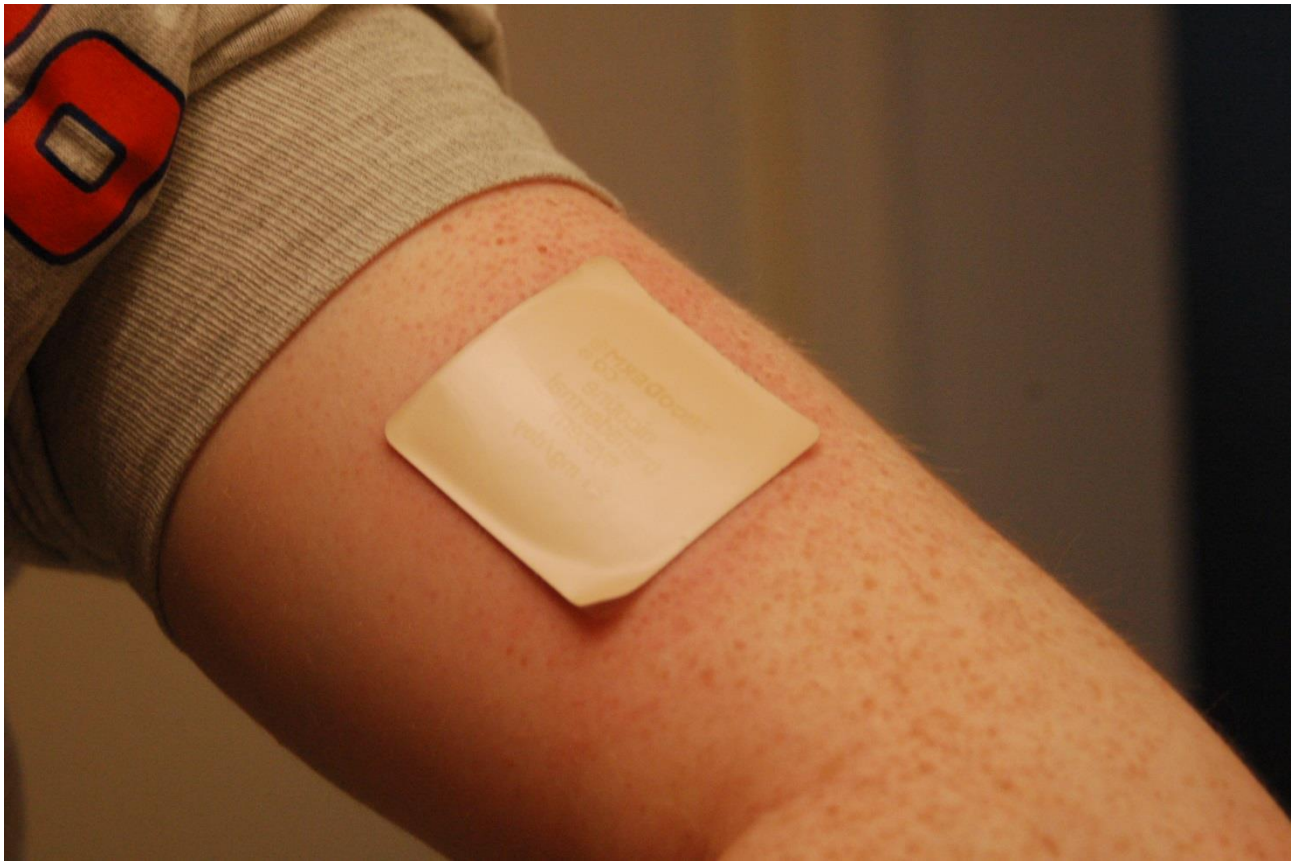
Trans-Dermal Patch



"Nicoderm". Licensed under CC BY 2.5 via Wikimedia Commons - https://commons.wikimedia.org/wiki/File:Nicoderm.JPG#/media/File:Nicoderm.JPG

Formulation

A Big Picture View of Formulation

The topic of parenteral drug formulation requires several semester-length courses to full understand, but take a look at your process map titled “Parenteral Drug Formation – A Big Picture View”.

It provides a big-picture view of many of the topics and challenges that are addressed during formulation.

A Big Picture View of the Filtration Process

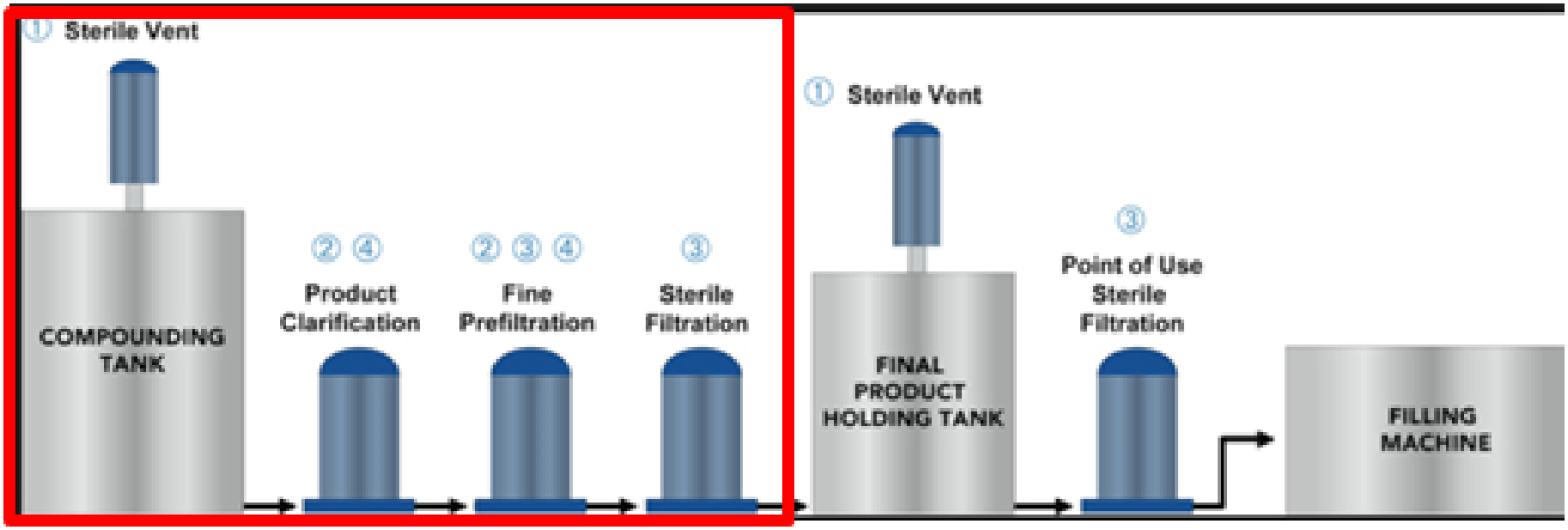
Filtration of Parenterals

Most of us are familiar with the use of filters when preparing a pot of coffee.

What do you think might be some differences between a filter used for brewing coffee and a filter used to purify large amounts of pharmaceutical parenteral solutions (formulated bulk solution)?

- Pharmaceutical filter is sterile, in a sterile system
- The holes in pharmaceutical filters are MUCH smaller
- Protection against contaminants & harmful microbes – impacts patient safety, not just a better-tasting coffee

Filtration of Parenterals During Formulation



Some of the purposes of early filtration are described on the next slide…

Filtration of Parenterals During Formulation

Filtration through a membrane and/or filtering processes using compressed gas and air are used in pharmaceutical manufacturing to remove unwanted material from the formulated bulk solution.

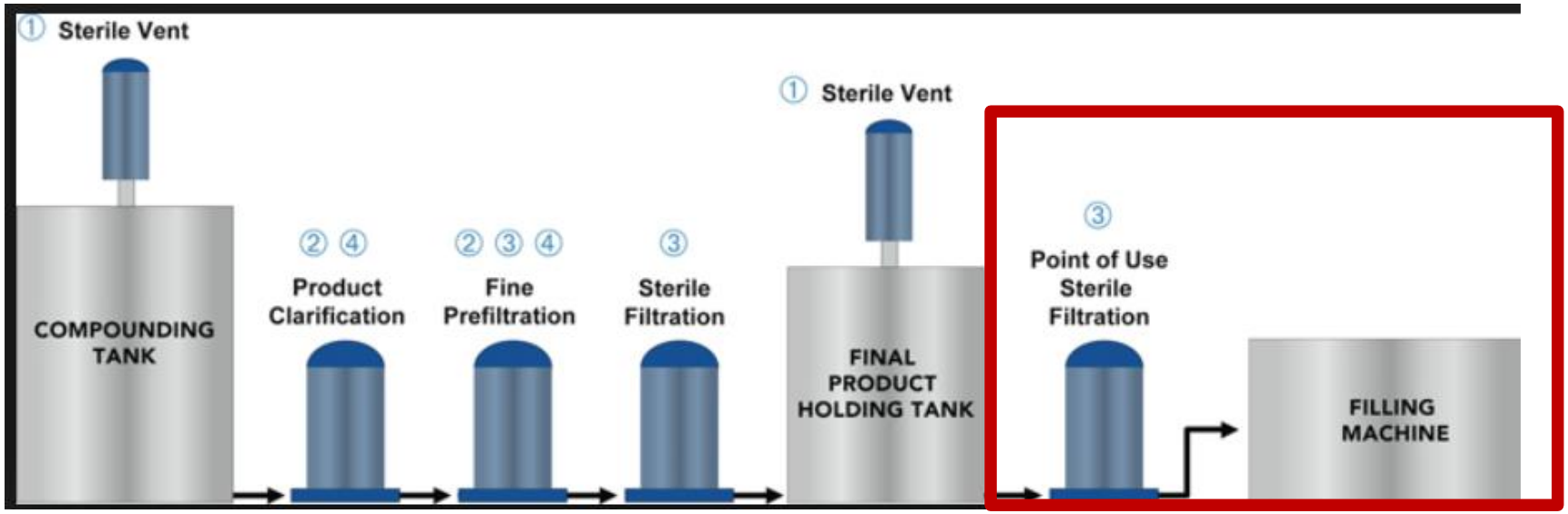
The first step in any filtration process is the removal of the largest suspended matter, either organic or inorganic.

- Serves to clarify the solution.
- Makes further processing more efficient by removing substances that might interfere with those processes.
- Helps protect expensive downstream equipment & the final sterilization filter from unnecessary damage from large particles.

Filtration of Parenterals

Final sterilization plays an essential role by removing undesirable elements (harmful microbes, particulates, etc.) while maintaining the identity and strength of the final product.

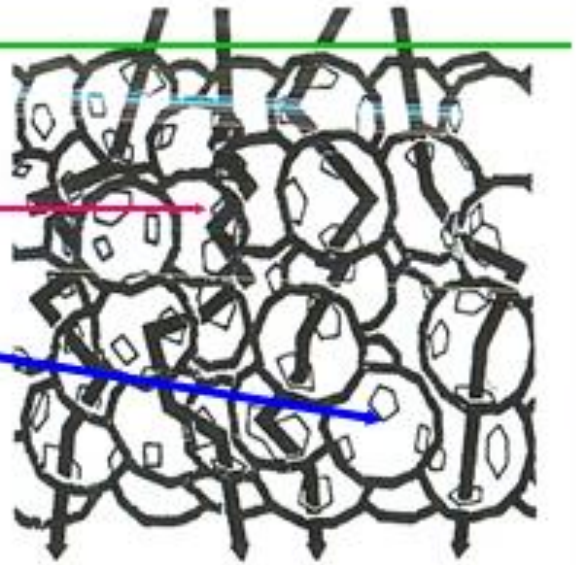
- Separates microbes & particulates from the rest of the product
- Size of filter pores based on size of possible contaminants



The Filtering Process

Membrane Filter Characteristics

- 65-75% porous
- High flow
- Particles retained either by:
- Sieving
- Entrapment
- Adsorption



Courtesy of EMD Millipore

Strict Regulatory Controls Related to Filtering of Parenterals

Stringent Regulatory Controls Related to Sterile Filters

Manufacturers who filter parenterals during aseptic processing must be able to demonstrate that:

- The company has scientific documentation of the levels and effects of the pre-filtration bioburden.
- The sterile condition of the filter, its housing and associated tubing has been scientifically qualified (usually by the manufacturer of the filters and related components).
- Validation studies demonstrate that the combination of the filter, product, and processing conditions results in a sterile filtrate (sterile, filtered product). This is done by the manufacturer of the parenteral drugs.

Source: Provantage Services & EMD Millipore, 2014

8 Elements of a Sterile Filtration Validation

Types of Sterile Filters

Categorization Based on Size of Pores in Membrane

Filter Type	Size Range (microns)	Examples of What Is Removed by this Filter Type
Particle	10 to 200	• Pollens • Particles • Some bacteria
Microfilter	0.1 to 10	• All bacteria • Yeasts • Colloids
Ultrafilter	0.001 to 0.1	• Most viruses • Large organic compounds (> 10,000 Daltons
Nanofilter (Reverse Osmosis)	Less than 0.001	• Small organic compounds • Ions

Sterilizing filter commonly used in industry

Microfilters

- Porosity of microfilters range from 0.1μm to 10 μm
- Used to remove all bacteria, yeast & colloidal forms
- Can be integrity tested

Examples: Millipore Express SHC 0.5 / 0.2 μ m PES filters

Categorization Based on Behavior with Water

Hydrophobic

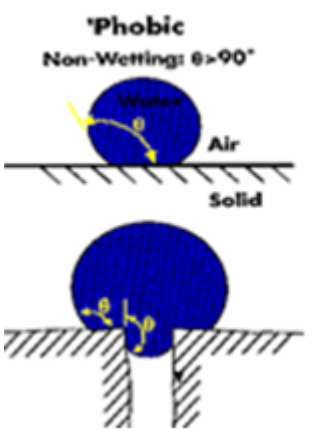


Figure 1

Image courtesy of EMD Millipore Corporation

Example of Hydrophobic Stacked Disc Membrane

These Millex filter units with hydrophobic Fluoropore membrane are used for sterilizing gases, venting sterile containers, and sterilizing or clarifying organic solutions.

Categorization Based on Behavior with Water

Hydrophilic water loving, spontaneously wets when exposed with water.

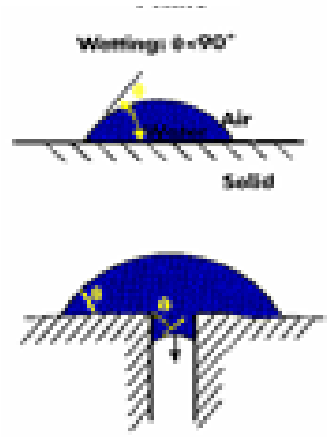


Figure 2

Millipore Integritest 4 AFIT
Image courtesy of EMD Millipore Corporation

Example: Durapore 0.45 µm Hydrophilic Cartridge Filter

More about Filter Testing and Validation

Destructive & Non-Destructive Testing

Key Term – Microbial retention

- The ability of a filter to remove bacteria from the filtrate, thereby providing a sterile solution.

Destructive Testing

- Used to qualify filter initially
- Includes three main tests:
  - Bacterial retention using actual final formulation of the parenteral product
  - Filter extractables / leachables
  - Compatibility of filter with parenteral product

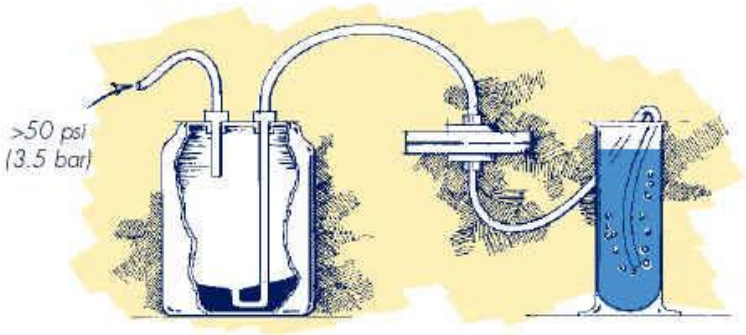
Non-Destructive Testing – testing prior to and after using the filter in batch production **(Typically bubble-point and diffusive flow)**

Question: Why do you think a non-destructive method is used during production?

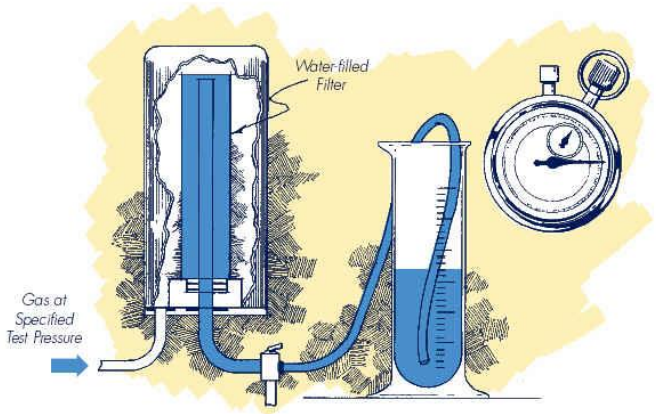
Integrity Testing

Surface Tension

Bubble point testing

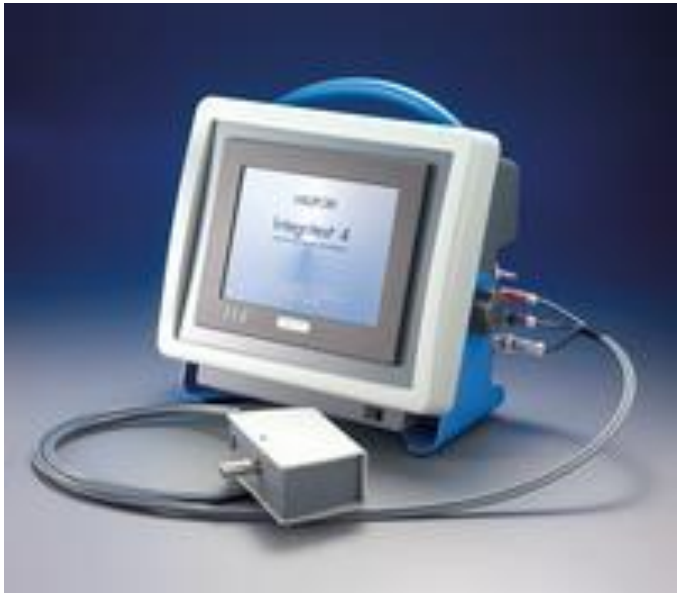


Diffusive Flow testing



Figures courtesy of EMD Millipore and WikiMedia

Automated filter Integrity Testing



Millipore Integritest 4 AFIT
Image courtesy of EMD Millipore Corporation,
Integritest is a registered trademark of Merck KGaA

Automated filter integrity testing has many advantages:

- Elimination of operator to operator variability.
- Increased sensitivity; you can easily determine the bubble-point of a large filter using AFIT, while it would be impossible to manually detect mass flow of gas (bubble-point) while the normal diffusive flow of the large membrane surface area is on-going.
- AFIT provides improved testing consistency and reproducible results.

Filtering Challenges

- **Wetting**- all of the filter's pores must be filled with liquid
- **Plugging**- material in the product blocking the filter's pores-stopping the flow
- **Filter Failure**
  - Integrity test **suppression** - **False failure**
  - Integrity test **failure-** the filter is damaged

Filling Mechanisms

A Big Picture View of Filling Operations

Look at your legal –sized, colored, two-sided illustration of syringe-filling and vial filling.

Possible Challenges Encountered During Filling

- Product splashing
- Product spills
- Product foaming and effect on dose accuracy
- Viscous product and potential problems with dose accuracy and uniformity
- Out of tolerance fill volumes/weight
- Receiving vessel overflows
- Receiving vessel over-pressurized
- Filling needles are bent
- Filling needles are plugged with product

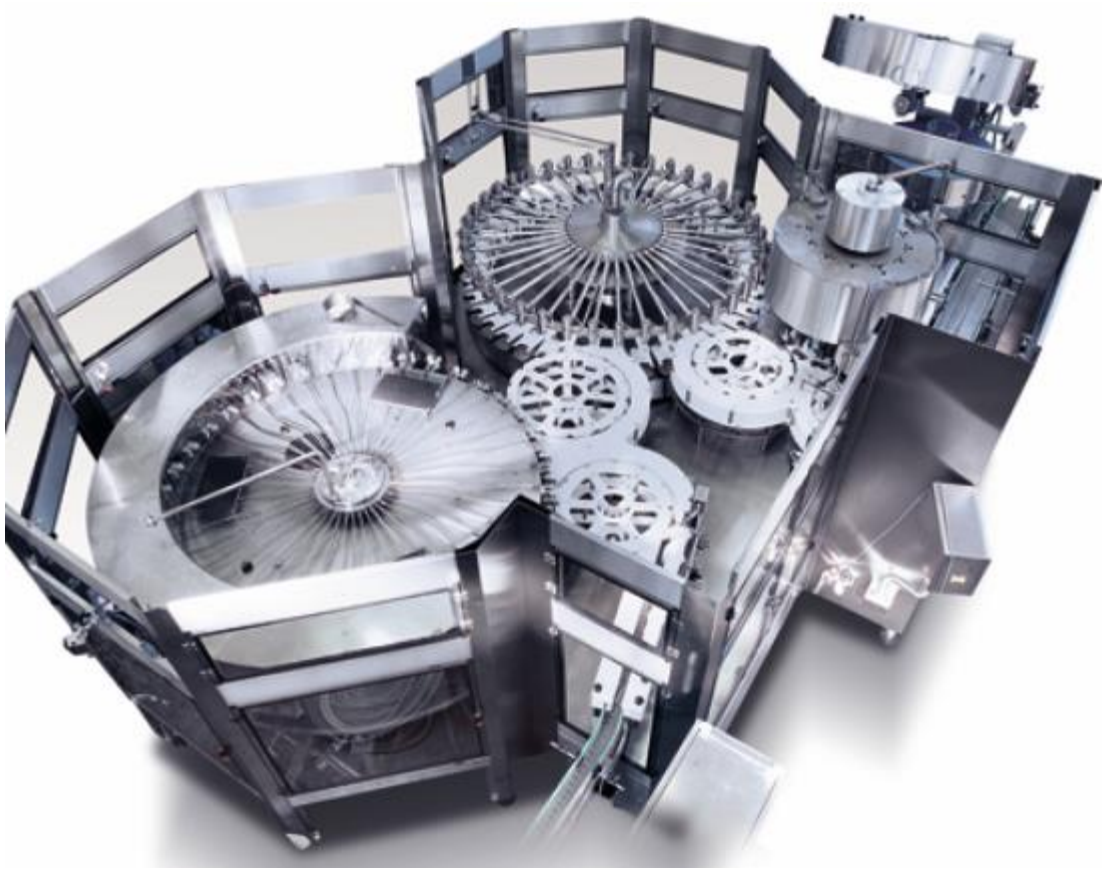
Possible Challenges Encountered During Filling

- Control of dose from container-to-container
- Adsorption of active ingredient on the surface of the tubing used with the filling machine.
- Protein aggregation due to tubing surface interactions
- Leachables from tubing
- Fill pump leak
- Power outage

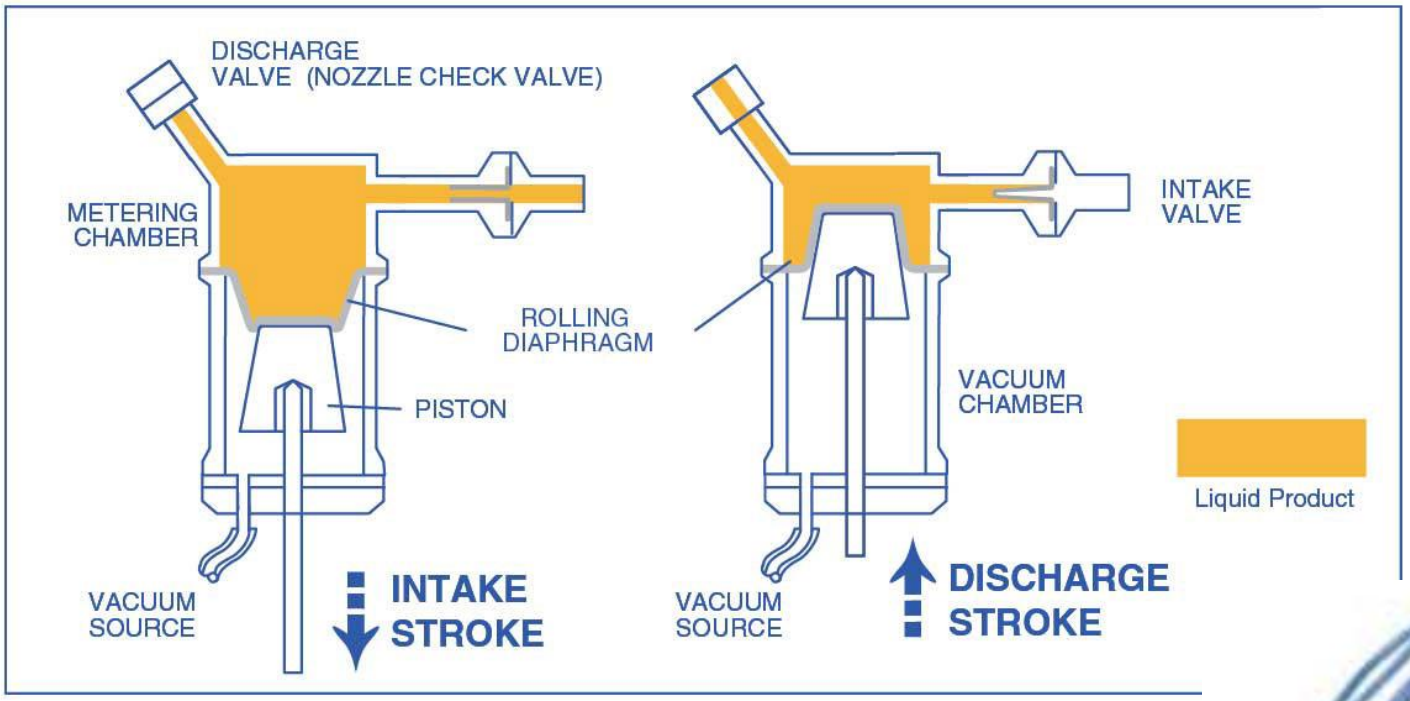
Different Approaches to Filling

Driving Device	Filling Mechanisms
Gravity (solids and liquids) *(oldest & most economical)*	**Gravimetric, time-pressure, fill by weight**
Piston (liquids and gases)	**Rotary piston, Rolling diaphragm pump**
Rotary pump (liquids and gases)	**Rotary peristaltic**
Auger screw or vibrator (solids)	**Vibratory / Mechanical force**

Gravimetric, time-pressure, fill by weight

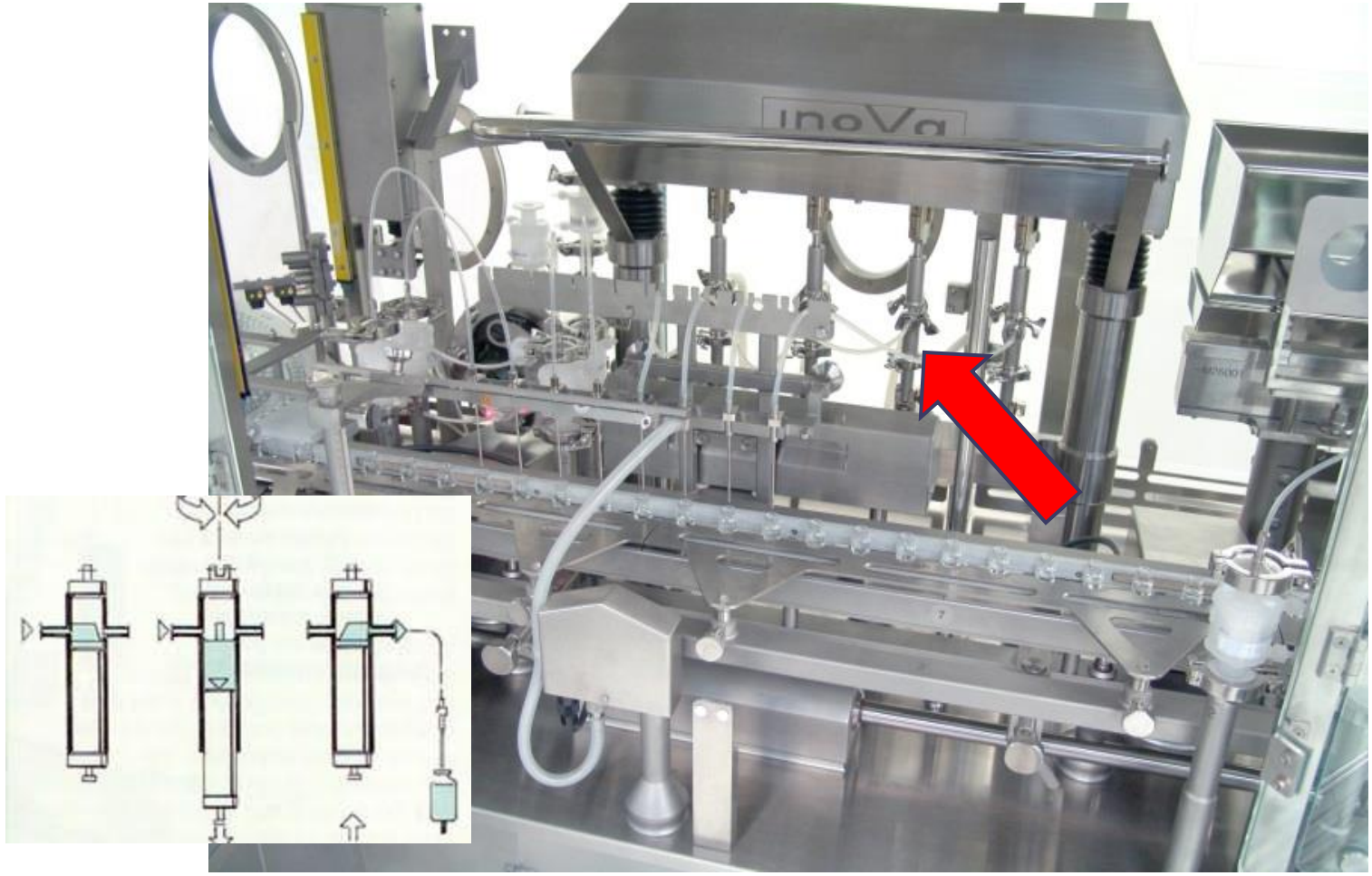


Filling via Piston Pump



Courtesy of www.filamtic.com and www.pharmaceuticalonline.com

Rotary Pump Aseptic Filler



Courtesy of OverLook Industries and Optima Corporation

Peristaltic Filling

Includes single-use components.

Courtesy of Colanar and www.contract pharmica.com

Lyophilization

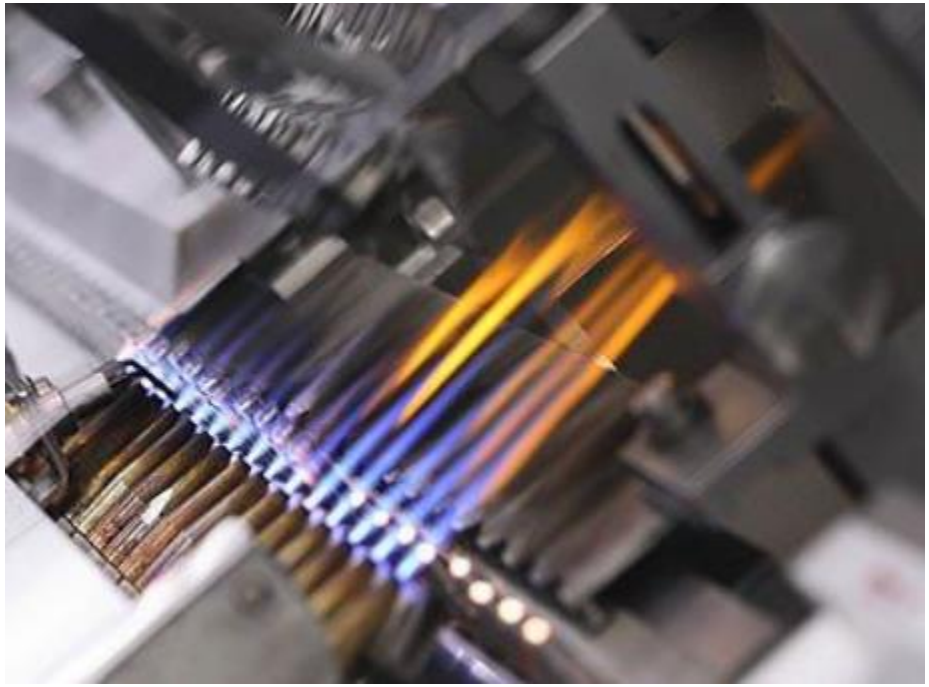
Exercise 2

Scenario: You are a new manager in a parenteral manufacturing company with aging equipment. Due to a recent round of retirements, many of your people are relatively inexperienced, so you are looking for something that is easy to maintain and change over. The Chief Financial Officer is especially sensitive about unexpected replacements of expensive parts. Some of your products include biologics. You are coming to realize that single-use components cut down the potential for contamination.

Based on the tables in Exercise 2 and this scenario, which filling method seems most attractive?

Sealing Mechanisms

Ampules – Sealed with a Flame



Courtesy of www.rotechmachinery.en.alababa.com

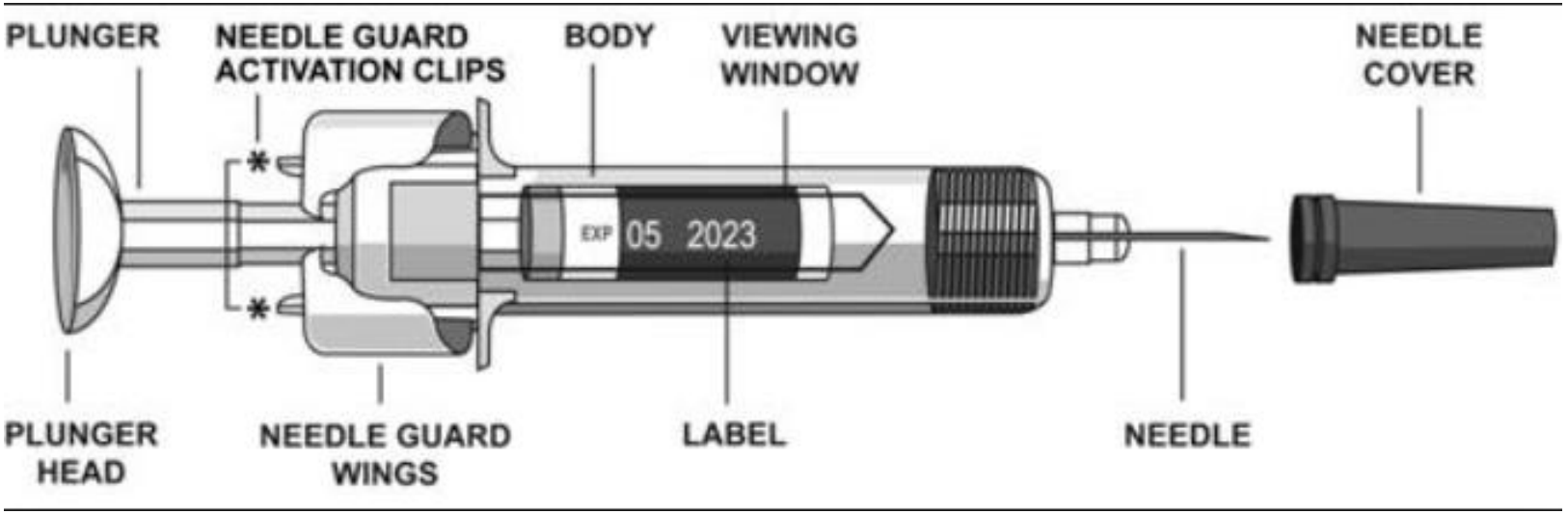
Vial Stoppers for Vials

Courtesy of Optima Corporation

Plungers for Syringes

Courtesy of Optima Corporation

Anatomy of a Pre-filled Syringe



Courtesy of www.drugs.com

Plunger Rods and Labels for Syringes

Plunger Rod Insertion and Labeling Machine

Courtesy of ima-pharma.com

Possible Challenges During Stoppering

- Too little or too much silicone on stoppers
- Misaligned or bent syringe stopper insertion rods or tubes
- Stoppers become jammed on the track
- Improper head space (syringes)
- Stoppers are not completely seated

Conclusion

Aseptic processing of parenterals involves a number of interesting challenges, including:

- Protecting the sterility of the product as it moves through several phases of formulation, filtering, filling, and packaging.
- Development of the experience and technical knowledge to trouble-shoot issues as they occur.
- Maintaining consistent compliance with CGMP regulatory requirements to protect product SISPQ.

Conclusion

There are also significant benefits related to successful parenteral drug production, including:

- Knowing that you helped produce medication that will save a life or will fight life-threatening diseases.
- Becoming a skilled employee with multiple options in the bio tech industry; an industry forecasted to continue to grow significantly in the future.

Any questions before we move on to the lab?