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

- **Traceability**
  - Raw Materials
  - Components
  - Product
  - Change Control

- **Clean Rooms**
- **Gowning**
- **Traffic flows**
- **Access control**
- **Sanitization**
- **Monitoring**
- **TOR**

- **Documentation**
  - Formal
  - Controlled
  - Consistent
  - Timely

- **Validation**
  - Rooms
  - Equipment
  - Processes
  - Environment

- **Changeover**
- **Cleaning Validation**
- **Proof of training before completing procedures**

- **Procedures**
  - Documented
  - Controlled
  - Followed exactly as written
Forms of Parenteral Drugs
Liquid Solutions
Emulsions or Suspensions
Lyophilized Forms of Injectable Drugs
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
The topic of parenteral drug formulation requires several semester-length courses to fully 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.
8 Elements of a Sterile Filtration Validation

- Integrity Testing: Prove the filter’s bacterial retention capabilities with a non-destructive test.
- Fit for Use: Prove the filter meets all requirements within product & process conditions.
- Retention: Prove the filter removes bacteria from the stream per ASTM 838-05.
- Sterilization: Prove the sterilization method is effective and does not compromise the filter.
- Extractables/Leachables: Identify, quantify, and assess impact of compounds that migrate from filter to process stream.
- Stability: Prove the filter does not adversely affect the process stream.
- Compatibility: Prove the stream does not adversely impact the filter.
- Binding: Prove the filter does not remove stream components.

Source: Provantage Services & EMD Millipore, 2014
Types of Sterile Filters
## Categorization Based on Size of Pores in Membrane

<table>
<thead>
<tr>
<th>Filter Type</th>
<th>Size Range (microns)</th>
<th>Examples of What Is Removed by this Filter Type</th>
</tr>
</thead>
</table>
| 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 µm PES filters
Categorization Based on Behavior with Water

**Hydrophobic**

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.

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

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

<table>
<thead>
<tr>
<th>Driving Device</th>
<th>Filling Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravity (solids and liquids)</td>
<td>Gravimetric, time-pressure, fill by weight</td>
</tr>
<tr>
<td>(oldest &amp; most economical)</td>
<td></td>
</tr>
<tr>
<td>Piston (liquids and gases)</td>
<td>Rotary piston, Rolling diaphragm pump</td>
</tr>
<tr>
<td>Rotary pump (liquids and gases)</td>
<td>Rotary peristaltic</td>
</tr>
<tr>
<td>Auger screw or vibrator (solids)</td>
<td>Vibratory / Mechanical force</td>
</tr>
</tbody>
</table>
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 pharmiea.com](http://www.contract pharmiea.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.alibaba.com
Vial Stoppers for Vials

 Courtesy of Optima Corporation
Plungers for Syringes

Courtesy of Optima Corporation
Anatomy of a Pre-filled Syringe

PLUNGER
NEEDLE GUARD ACTIVATION CLIPS
BODY
VIEWING WINDOW
EXP 05 2023
LABEL
NEEDLE COVER
PLUNGER HEAD
NEEDLE GUARD WINGS
NEEDLE

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?