

# Capabilities & Limitations of Aseptic Processing



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# Understanding the Types of Aseptic Processing

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- **Filing Technologies**

- Traditional
- Modified Traditional
- Barrier Systems
- Modified Barrier technology
- Isolator systems
- Blow/Fill/Seal
- New Technologies



# Understanding the Types of Aseptic Processing

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- **Basic Aseptic Fill Line**

- Manual or automated system
- In-feed turntable and conveyer
- Manifold, fill pumps and needles
- Automated stopper and capper system with vibrating bowls
- Out-feed accumulating area
- Freeze dried or liquid products



# Understanding the Types of Aseptic Processing

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- **Basic Aseptic Fill Line**

- Manual or automated system
- In-feed turntable and conveyer for vials
- Infeed and scrolls for ophthalmic bottles
- Manifold, fill pumps and needles
- Automated stopper and capper system with vibrating bowls and hoppers
- Automated tip and cap system with vibrating bowls and hoppers



# Understanding the Types of Aseptic Processing

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- **Basic Aseptic Fill Line**

- Out-feed accumulating area
- Freeze dried or liquid products
- Auto loading freeze dryers
- Environmental monitoring
  - ❖ Active and passive air sample systems
  - ❖ Total particle, fixed and/or portable



# Understanding the Types of Aseptic Processing

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- **Traditional Fill Line**

- HEPA filters
  - ❖ Just over the critical areas
  - ❖ Over all door openings
  - ❖ Full HEPA ceiling in the fill room
- No hanging curtains
- No Lexan shields for barriers
- Dividing line on the floor for differentiating classified areas



# Understanding the Types of Aseptic Processing

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- **Traditional Fill Line**

- No physical barriers around critical areas
- Depends on air curtain and laminar flow, to protect critical areas
- Relies highly on aseptic techniques of fill operators
- Traditional sanitization methods and techniques used

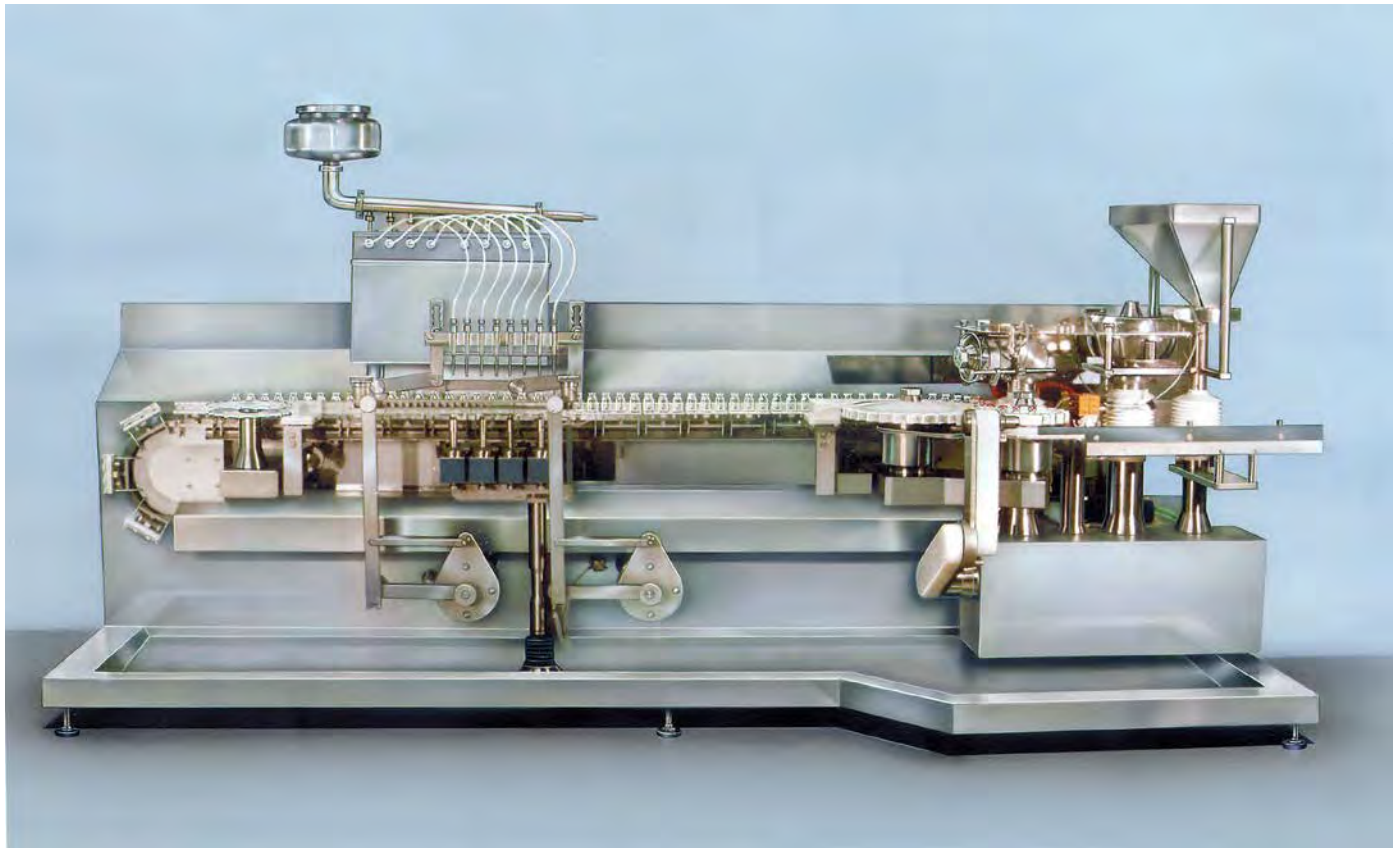
# Understanding the Types of Aseptic Processing



Traditional Open Fill Line Process



# Understanding the Types of Aseptic Processing



**Traditional Open Fill Line Process**

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# Understanding the Types of Aseptic Processing

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- **Modified Traditional Fill Line**

- Curtains are used as the primary barrier
  - ❖ Full or partial curtains that have overlapping surfaces to prevent airflow between each curtain
  - ❖ May/may not help direct the airflow
  - ❖ Defines critical areas from less critical areas



# Understanding the Types of Aseptic Processing

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- **Modified Traditional Fill Line**

- Creates a flexible barrier between personnel and filling equipment in the critical areas
- Personnel must move curtain to gain access to the critical areas
- In some cases, operators can go under the curtains to gain access to the processing areas



# Understanding the Types of Aseptic Processing

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- **Modified Traditional Fill Line**

- Curtains can touch various parts of the gown
- Difficult and time consuming to clean and sanitize
- Curtains may not be compatible with many disinfectants
- Still in wide use, but should minimize use of curtains

# Understanding the Types of Aseptic Processing



Traditional with Curtains

Courtesy of Bosch Filling and Jack Lysfjord. All property rights reserved



# Understanding the Types of Aseptic Processing



Traditional with Curtains

Courtesy of Bosch Filling and Jack Lysfjord. All property rights reserved



# Understanding the Types of Aseptic Processing

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- **Combination of Traditional & Barrier System Technology**
  - Areas with no protection between the people and the process
  - May have a line on the floor as to the Grade A and B designation
  - Relies on airflow and aseptic techniques
  - Many times the door does not open to a Grade-A Classification

# Understanding the Types of Aseptic Processing



Combination Traditional and Barriers





# Understanding the Types of Aseptic Processing

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- **Barrier System Fill Line**

- Lexan shield defines all critical areas from less critical areas
- Creates a rigid barrier between personnel and filling equipment in critical areas
- Personnel must open doors or move panels to gain access to the critical areas



# Understanding the Types of Aseptic Processing

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- **Barrier System Fill Line**

- Lexan shields surround equipment along the entire filling line
- There must be sufficient area, at the bottom of the enclosure, to allow air to exit the enclosure
- Lexan shield may/may not help direct the airflow



# Understanding the Types of Aseptic Processing

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- **Barrier System Fill Line**

- No hanging curtains
- Time consuming to sanitize but easier to clean/sanitize than curtains
- Some variation of this configuration is widely in use

# Understanding the Types of Aseptic Processing



Barrier Fill Line Process

# Understanding the Types of Aseptic Processing



Barrier Fill Line Process

# Understanding the Types of Aseptic Processing



Barrier Fill Line Process

# Understanding the Types of Aseptic Processing



Barrier Fill Line Process



# Understanding the Types of Aseptic Processing

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- **Passive Restricted Access Barrier System (RABS)**
  - HEPA filters over just the critical areas or full HEPA ceiling in the fill room
  - Lexan shields surround entire filling line
  - Fill line is accessed only through ports/holes that are spaced along the fill line
  - Glove ports are rarely placed in the proper locations to access all critical areas



# Understanding the Types of Aseptic Processing



Passive RABS Iris Design



# Understanding the Types of Aseptic Processing

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- **Active Restricted Access Barrier System (RABS)**
  - In most cases sterile gloves are not installed prior to each use
  - Gloves are extremely difficult to sanitize
  - Must evaluate for holes and/or damage pre and post use integrity testing
  - Single or multiple piece gloves



# Understanding the Types of Aseptic Processing

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- **Active Restricted Access Barrier System (RABS)**
  - Average glove size is 8.5
  - Hard to use for small hands
  - Glove material of construction typically CSM (formally Hypalon™)
    - ❖ High Resistance to UV Rays/Ozone
    - ❖ Particularly Adapted when Hydrogen Peroxide and Per Acetic Acid are Used



# Understanding the Types of Aseptic Processing

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- **Active Restricted Access Barrier System (RABS)**
  - Glove ports may not be placed on optimal positions
  - In most case filler setup is performed with the door open
  - Some variation of this configuration is in limited use

# Understanding the Types of Aseptic Processing



Active RABS Design

# Understanding the Types of Aseptic Processing



Active RABS Design

# Understanding the Types of Aseptic Processing



Active RABS Design



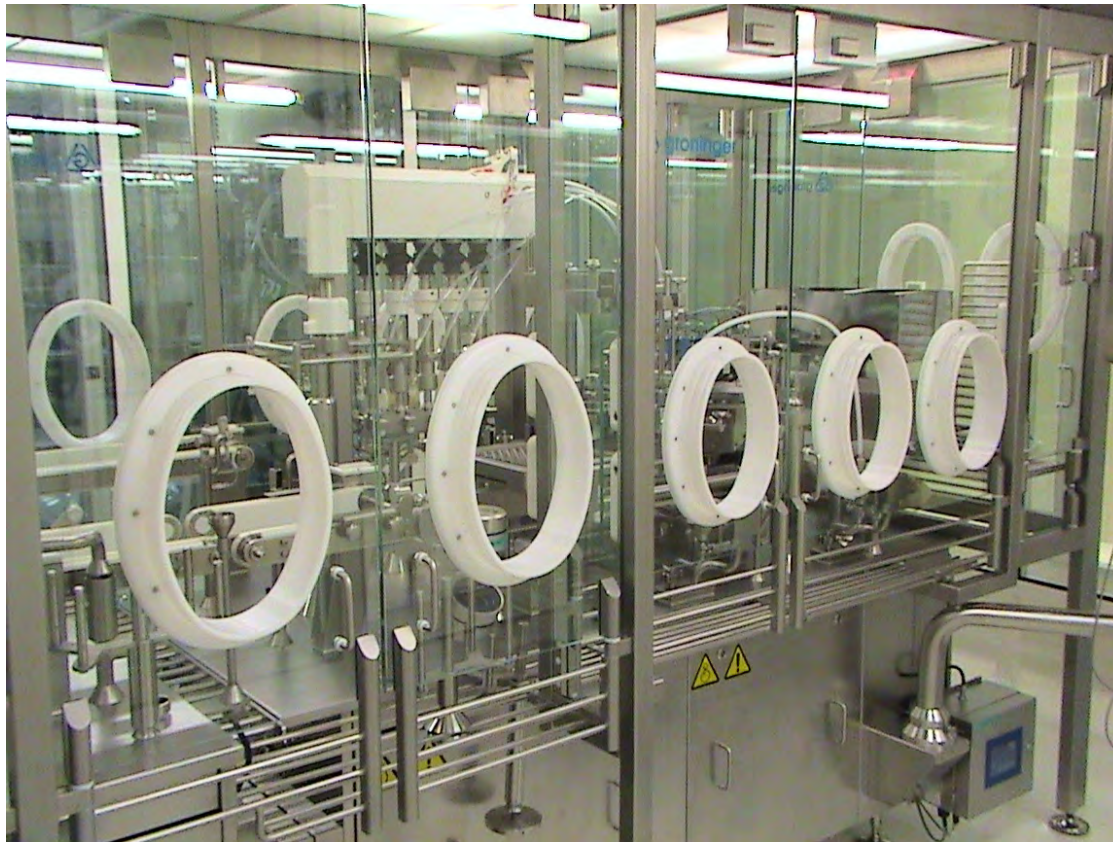
# Understanding the Types of Aseptic Processing

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- **Innovative Idea for Active Restricted Access Barrier System (RABS)**
  - Remove all the gloves
  - Use sterile gloves and sleeves to enter the cabinet
  - Optimized the airflow within the cabinet
  - Need to justify to the regulatory agencies the unique approach

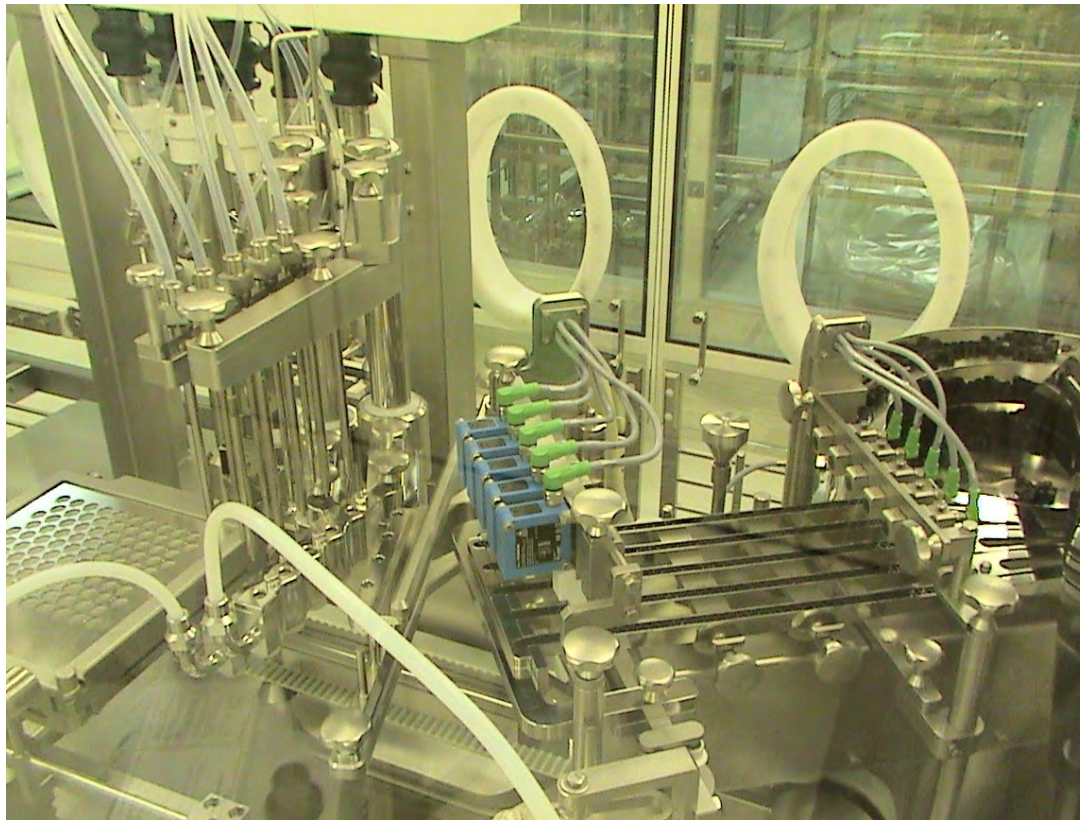


# Understanding the Types of Aseptic Processing



Passive RABS Open Design no Gloves

# Understanding the Types of Aseptic Processing



Passive RABS Open Design no Gloves



# Understanding the Types of Aseptic Processing

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- **Isolator System**

- Sealed enclosure for the aseptic processing areas
- Remote HEPA filters to supply air
- Personnel access through
  - ❖ Glove ports or full body suites
  - ❖ Very comfortable for operators to use
  - ❖ Usually placed in a Grade B area



# Understanding the Types of Aseptic Processing

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- **Isolator System**

- Systems for introducing commodities into the isolator
  - ❖ Rapid Transfer Port (RTP)
  - ❖ Alpha-Beta sterile door system
  - ❖ Uses transfer isolators to move commodities from autoclave into process isolator



# Understanding the Types of Aseptic Processing

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- **Isolator System**

- Cleaning systems

- ❖ Traditional manual cleaning for non rigid isolators
- ❖ CIP system for rigid/stainless steel sealed systems
  - ✓ Spray-ball placement is extremely important to ensure proper cleaning of all surfaces



# Understanding the Types of Aseptic Processing

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- **Isolator System**

- Sanitization systems

- ❖ Vaporized Hydrogen peroxide (VHP)
    - ❖ Chlorine Dioxide Gas
    - ❖ Must check for leaks during sanitization
    - ❖ Air must be circulated during the sanitization phase



# Understanding the Types of Aseptic Processing

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- **Isolator System**

- Sanitization systems

- ❖ Interior must stay pressurized before during and after the sanitization process
- ❖ Gas/Vapor must contact all surfaces during sanitization





# Understanding the Types of Aseptic Processing

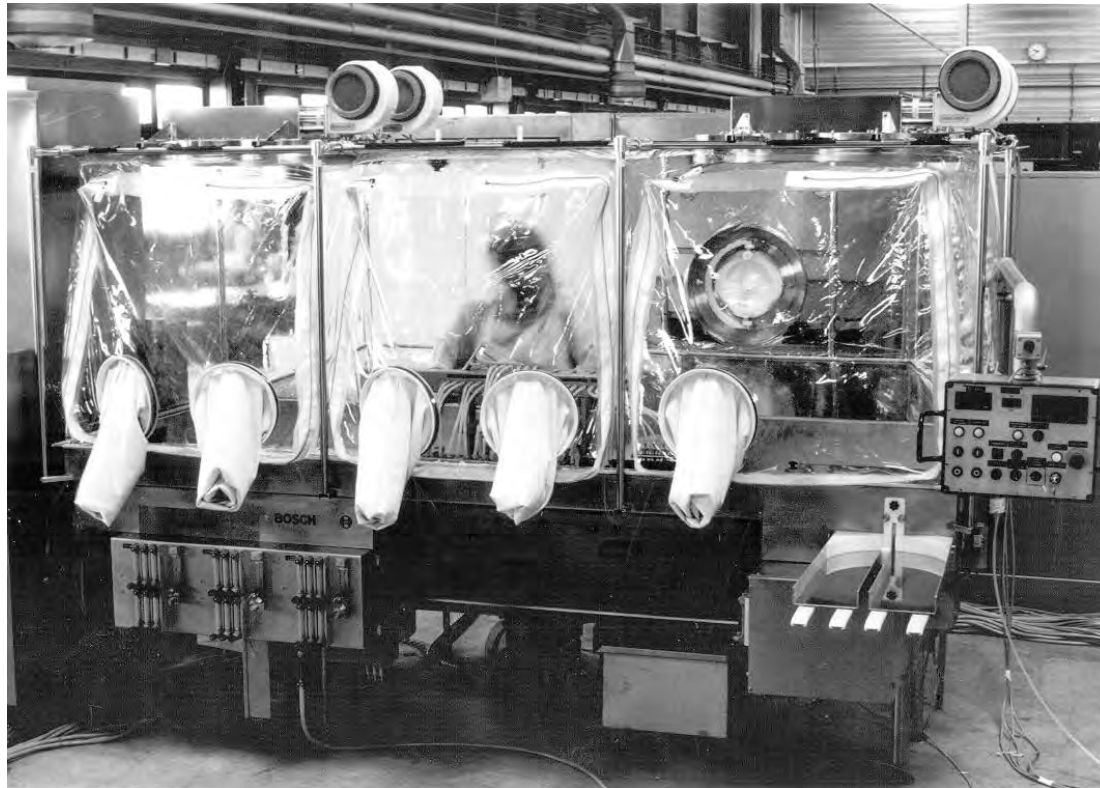
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- **Isolator System**

- Costly to purchase and validate
- Provides the most protection for a classical aseptic fill line
- Widely used in industry



# Understanding the Types of Aseptic Processing



Turbulent pos. pressure Softwall-Isolator on top of ampoule filler – 1989  
Courtesy of Bosch Filling and Jack Lysfjord. All property rights reserved

# Understanding the Types of Aseptic Processing



## Isolator Process

Courtesy of Bosch Filling and Jack Lysfjord. All property rights reserved

# Understanding the Types of Aseptic Processing



## Isolator Process

Courtesy of Bosch Filling and Jack Lysfjord. All property rights reserved



# Understanding the Types of Aseptic Processing



Transfer Isolator  
and Work Station  
Isolator.



# Understanding the Types of Aseptic Processing

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- **Blow, Fill & Seal Systems**

- Non-Classical aseptic filling operations
- Filling can be performed over days
- Reduces the number of parts/equipment to assemble, fill and package product.
- The technology is commonly used for ophthalmic and respiratory products and is being employed for dental, veterinary and parenteral products



# Understanding the Types of Aseptic Processing

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- **Blow, Fill & Seal Systems**

- The Process

- ❖ Granulated plastic is heated to 170 – 220 °C and becomes molten
    - ❖ The thermoplastic resin is extruded into a tubular shape called parison
    - ❖ When the parison reaches the proper length, the mold is closed and the top of the parison is cut



# Understanding the Types of Aseptic Processing

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- **Blow, Fill & Seal Systems**

- The Process

- ❖ The bottom of the parison is pinched closed and the top is held in place
- ❖ The mold is then conveyed to a position for the blowing and filling nozzle
- ❖ The blow-fill nozzle is lowered into the parison



# Understanding the Types of Aseptic Processing

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- **Blow, Fill & Seal Systems**

- The Process

- ❖ The container is formed by blowing sterile filtered compressed air into the parison and expanding it against the walls of the cooled mold cavity





# Understanding the Types of Aseptic Processing

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- **Blow, Fill & Seal Systems**

- The Process

- ❖ Sterile product is filled into the container through the fill nozzle which retracts after filling
- ❖ Separate sealing molds close to form the top and hermetically seal the container



# Understanding the Types of Aseptic Processing

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- **Blow, Fill & Seal Systems**

- The Process

- ❖ The mold opens and the formed, filled and sealed container is conveyed out of the machine



# Understanding the Types of Aseptic Processing

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- **Blow, Fill & Seal Systems**

- The Process takes place in a single machine under a controlled environment
- The container size can range from 0.5 ml to a maximum fill volume of 10 liters
- It enables the packaging of parenteral solutions in an aseptic manner



# Understanding the Types of Aseptic Processing

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- **Blow, Fill & Seal Systems**

- Advantages

- ❖ Less overall floor space requirements
    - ❖ Minimal personnel requirements
    - ❖ Lower clean room requirements
    - ❖ Lower logistical problems of storage of empty containers

# Understanding the Types of Aseptic Processing

- **Blow, Fill & Seal Systems**



# Understanding the Types of Aseptic Processing

- **Blow, Fill & Seal Systems**



bottelpack-system blows, fills and seals in one operation

# Understanding the Types of Aseptic Processing

- **Blow, Fill & Seal Systems**



# Understanding the Types of Aseptic Processing

- **Blow, Fill & Seal Systems**





# Understanding the Types of Aseptic Processing

- **Blow, Fill & Seal Systems**



*Blow-Fill-Seal bottelpack® Type 364*



*Blow-Fill-Seal bottelpack® type 360M*



*Respiratory Care Products*



*Small Volume Parenterals SVP*



*Large Volume Parenterals LVP*



# Understanding the Types of Aseptic Processing

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- **In-Tact Filling System**

- Non-Classical aseptic filling operations
- The technology uses vials which are sonically welded together with the stopper in place
- Vials are packaged in plastic trays that are double wrapped and gamma irradiated
- The fill line is a traditional line with the exception of the filling/sealing zone



# Understanding the Types of Aseptic Processing

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- **In-Tact Filling System**

- The Process

- ❖ The intact sterile vials are a closed sterile system while on the in-feed turntable and conveyer system
- ❖ The vials enter the filling zone
- ❖ The vials stop under the fill needles
- ❖ The needles pierce the stopper, fill the vial and is retracted



# Understanding the Types of Aseptic Processing

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- **In-Tact Filling System**

- The Process

- ❖ The stopper is a proprietary formulation which prevents coring and allows the stopper to close around the puncture site
- ❖ The vials move to the next step, the sealing zone



# Understanding the Types of Aseptic Processing

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- **In-Tact Filling System**

- The Process

- ❖ The sealing zone consists of one or two laser per vial
- ❖ The lasers heat up the puncture area and seals the vial
- ❖ If the laser temperature at the sealing point is below the set point, the vial is rejected.



# Understanding the Types of Aseptic Processing

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- **In-Tact Filling System**

- The Process

- ❖ Rejects are usually due to improper alignment of the lasers on the puncture zone
- ❖ Container closure testing was performed on representative vials using the dye leak test method. There were no positive vials



# Understanding the Types of Aseptic Processing

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- **In-Tact Filling System**

- Advantages

- ❖ Vials are never open in the classical sense
- ❖ Potential for contamination is significantly reduced
- ❖ Can revolutionize aseptic filling if the stoppers and vial configuration can show equivalence to classical systems

# Understanding the Types of Aseptic Processing

- **In-Tact Filling System**





# Understanding the Types of Aseptic Processing

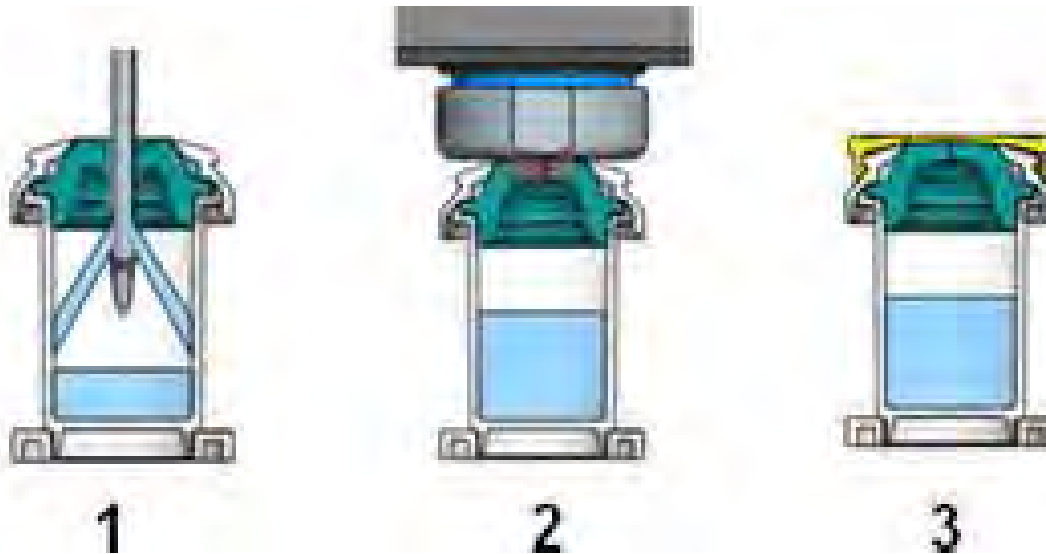
- **In-Tact Filling System**



Vial Construction

# Understanding the Types of Aseptic Processing

- **In-Tact Filling System**



Pierce the Stopper

Laser Seal

Cap and Crimp

# Understanding the Types of Aseptic Processing

- **In-Tact Filling System**



Filling

# Understanding the Types of Aseptic Processing

- **In-Tact Filling System**



Vial Laser Sealing



Capping



# Understanding the Types of Aseptic Processing

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## ■ Take Away Message

- All systems have their limitations
- To understand the issues, companies must understand what/where the risks are
- Airflow is critical to understand risk
- In particular, isolators must be challenged to their failure point when performing VHP qualification with BI's
- No system is perfect!