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Innovative Solutions for Aseptic Packaging

PRODUCT QUALITY USING BFS MACHINE

By Rajeev V. Kabbur

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THE EXPECTED PARAMETERS

Most important quality parameters of
a unit dose of IV solution or of injectable solution are:

- ✓ The solution should be sterile.
- ✓ Manufacturing process should be compliant to current regulations.
- ✓ Number of particles of a particular size should be less than prescribed limits in Pharmacopeia.
- ✓ Pyrogenic substances should remain within acceptable limits.
- ✓ Container closure should remain integral throughout the shelf-life of the product.
- ✓ Labelling of the product is compliant to the current regulations.
- ✓ Can be safely and easily administered

THE EXPECTED PARAMETERS

Most important quality parameters of a unit dose of IV solution or of injectable solution are:

Throughout the shelf-life →

- ✓ Quantity and concentration of the active ingredient within the container
- ✓ PH of the solution
- ✓ Substances leached into the solution by the container and closure material
- ✓ Container and closure system should act as a barrier against agents which can degrade the solution

} Must be in **compliance** with **Pharmacopeia**

THE BLOW FILL SEAL PROCESS

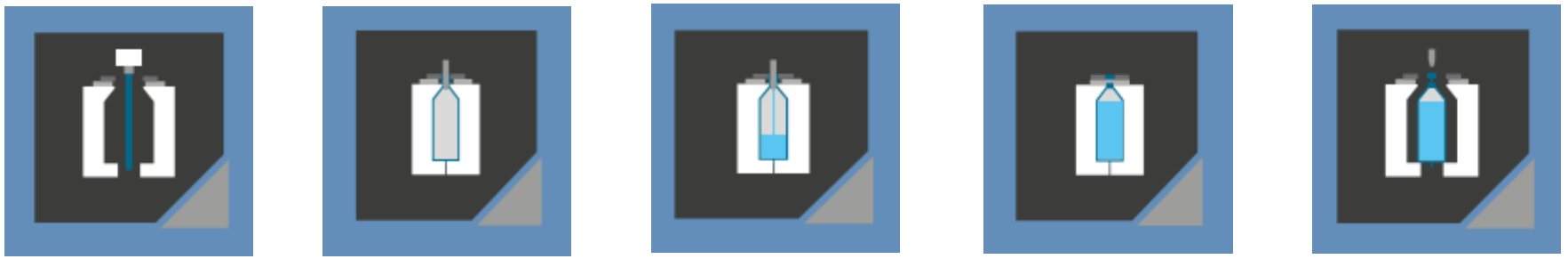
Blow-Fill-Seal technology is a pharmaceutical filling process in which containers are formed from a thermoplastic granulate, filled with product and then sealed in a continuous, integrated, automatic operation. BFS technology is being used in the manufacture of sterile pharmaceutical, medical device, biological, and veterinary products.

In the process, bulk solution/suspension is delivered to the filling machine, through the filling system to the filling nozzles.
Polymer granules are extruded under pressure (up to 500 Bar) as a hot (approx 200 C) mouldable plastic tubes also calld parisons.

2. *Blow-Fill-Seal* Technology

DEFINITION AS IT APPEARS IN **EU GMP:**

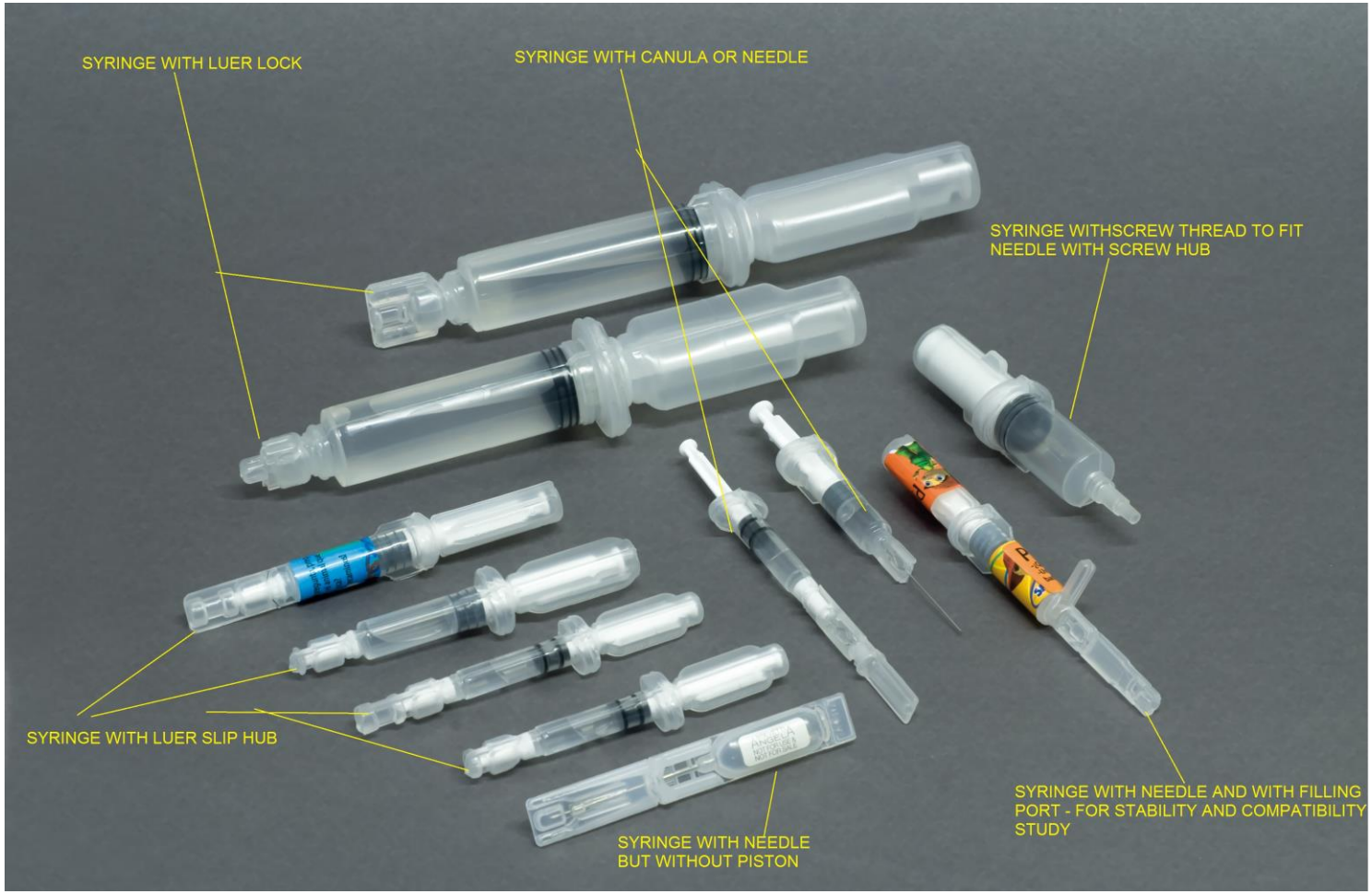
Blow-Fill-Seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine.



TYPES OF CONTAINERS:
2. BLOW FILL SEAL TECHNOLOGY

PARENTERALS – SMALL VOLUME & LARGE VOLUME

PREFILLED SYRINGES



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2. BLOW FILL SEAL TECHNOLOGY

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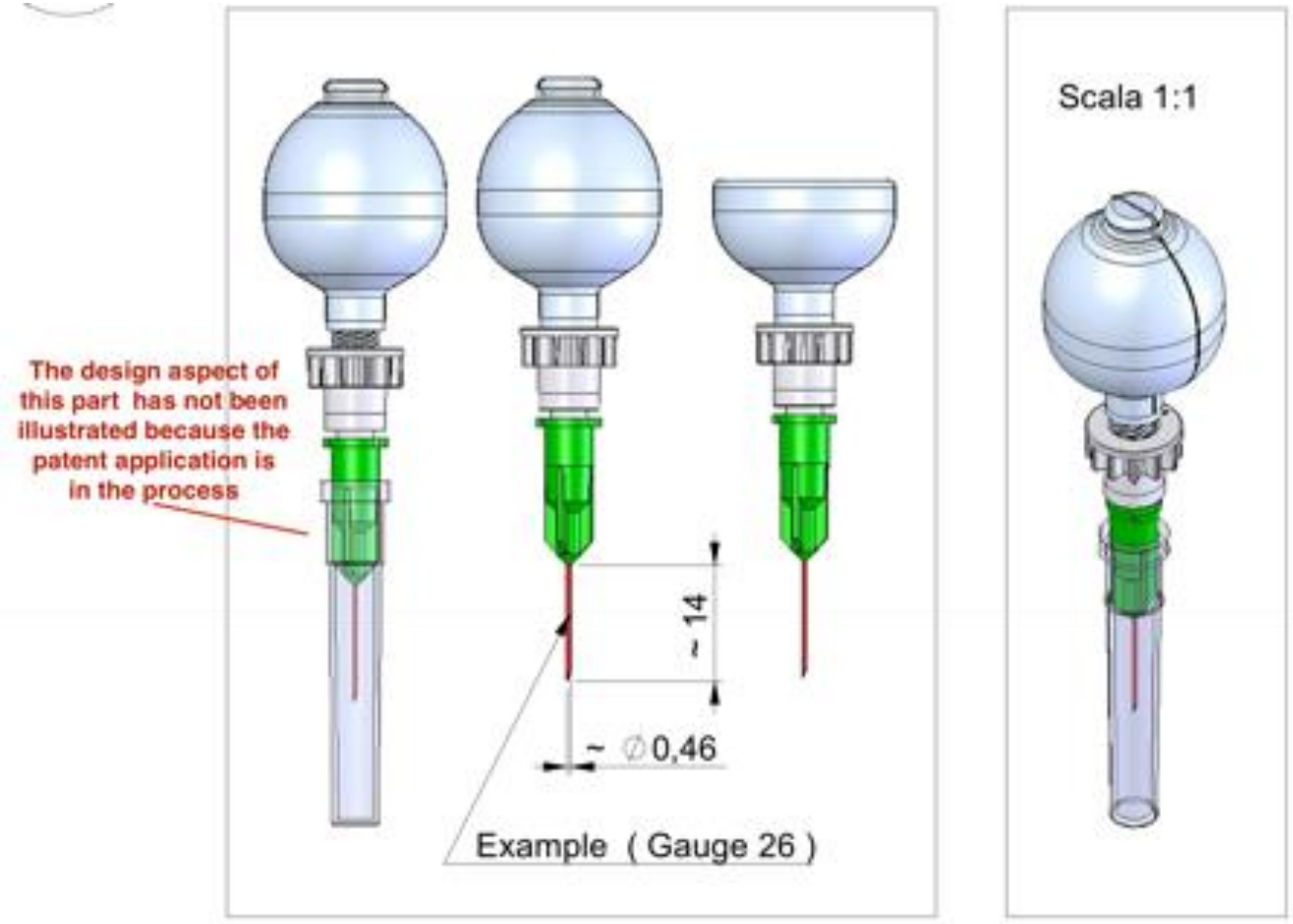


THE BLOW FILL SEAL PROCESS - ADVANTAGES

Blow-Fill-Seal technology offers 2 highly significant advantages over “traditional” aseptic filling operations.

1. In BFS operations, personnel should not normally be present in the filling area during the filling process, thereby removing the greatest potential source of microbial contamination from the operation.

2. For shuttling machines the containers are formed immediately before filling, are filled under controlled conditions, and are sealed immediately after filling. Therefore the exposure time to the environment for any individual product units is only a few seconds.
By elimination the major source of contamination (human operators), and reducing the exposure time, risk of product contamination is greatly diminished, as compared to typical aseptic processing.
By definition, if all interventions into the zone surrounding the BFS machine are minimized or eliminated while the machine is filling, and appropriate procedures are in place to assure removal of airborne particles following any intervention, it can be argued that BFS is an advanced aseptic process. (Agallaco J, Akers J, Madsen R. (2006)).

ENSURING QUALITY PRODUCT FROM A BFS OPERATION

WHERE TO FOCUS, WHEN TO FOCUS

	DESIGN	AT THE TIME OF FAT & START UP	ROUTINE MAINTENANCE
BFS Equipment	Well thought URS could be very useful	FAT Equipment qualification and validation	Training Routine Maintenance Preventive Maintenance
Container design	Trials on Pilot mould URS	FAT to verify product design Determine parameters to be controlled during IPQC	Maintain the machine to respect limits set in the IPQC. Adjust machine operating parameters to respect IPQC limits
Facility	URS	FAT Facility qualification	Training Routine Maintenance Preventive Maintenance

POINTS FROM URS - ABOUT PRODUCT AND CONTAINER

PRODUCT:

1. EYE DROPS Single use and multi use.
2. Suspension as well as solution
3. Could be also high viscosity
4. Cannot be terminally sterilized
5. Some products could be photosensitive
6. Volume of containers – Single use – 0,4 ml
7. Volume of containers – Multi use – 5 ml and 10 ml
8. Volume of containers – injection – 5 ml & 10 ml
9. One injection product is temperature sensitive (Vaccine)

CONTAINER DESIGN CONSIDERATIONS

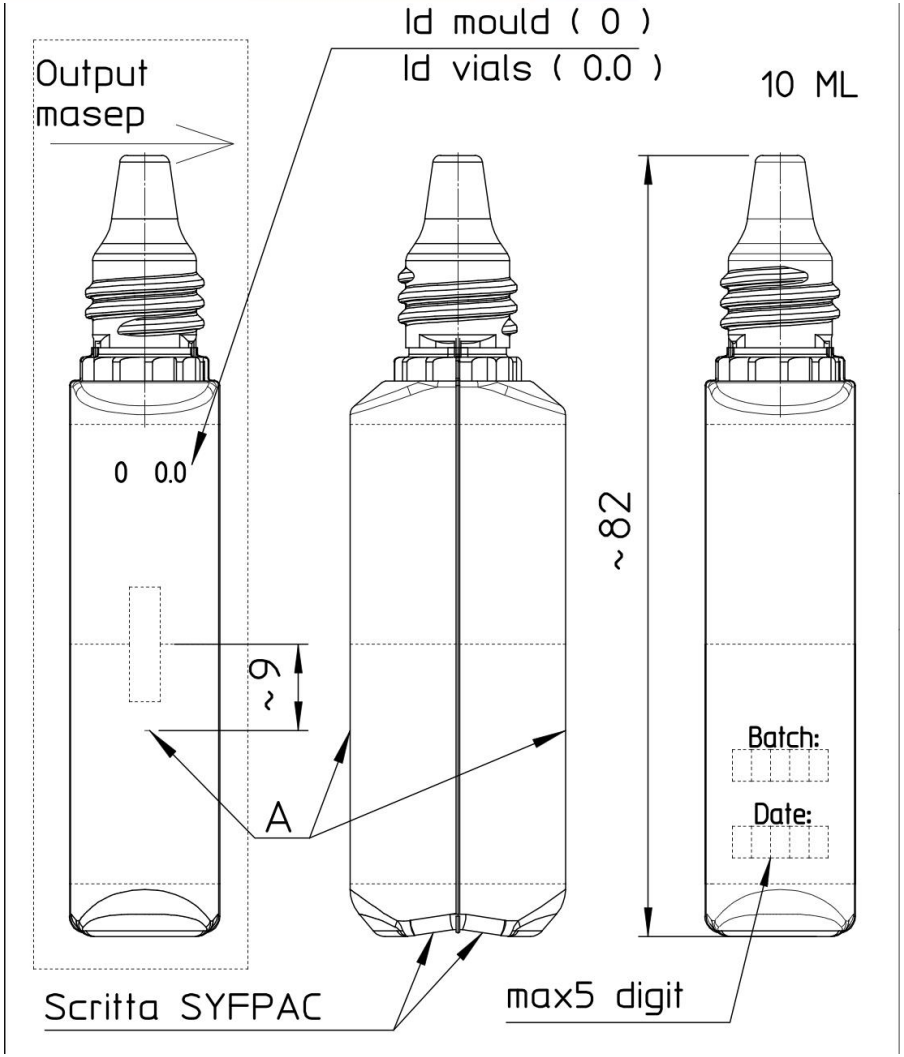
A total of 3 moulds to produce containers with following characteristics:

1. 0,4 ml single use Eye drop – 40 cavity configuration made using PE – for squeezablity
2. 5 ml and 10 ml injection – 40 cavity configuration, made using PP – for terminal sterilization
3. 5 ml and 10 ml injection – 40 cavity configuration, with connecting tab to monitor temperature made using PE – because stability has already been established in PE containers
4. 5 ml and 10 ml multi use container with screw head to fit cap
5. The 0,4 ml volume is too big for to be utilized in single use, so design the container such that the twist off could be used to re-close the bottle after first use.
6. Design the screw head such that two kinds of caps can be used, one cap for regular eyed drop and another for two piece metered eye drop caps – with saw tooth to lock the piercing cap
7. Volume of containers – Single use – 0,4 ml
8. Volume of containers – Multi use eye drop – 5 ml and 10 ml
9. Volume of containers – injection – 5 ml & 10 ml
10. Polymer to be used LDPE because the containers have to be squeezable

MULTI USE EYE DROP

Multi use eye drop container

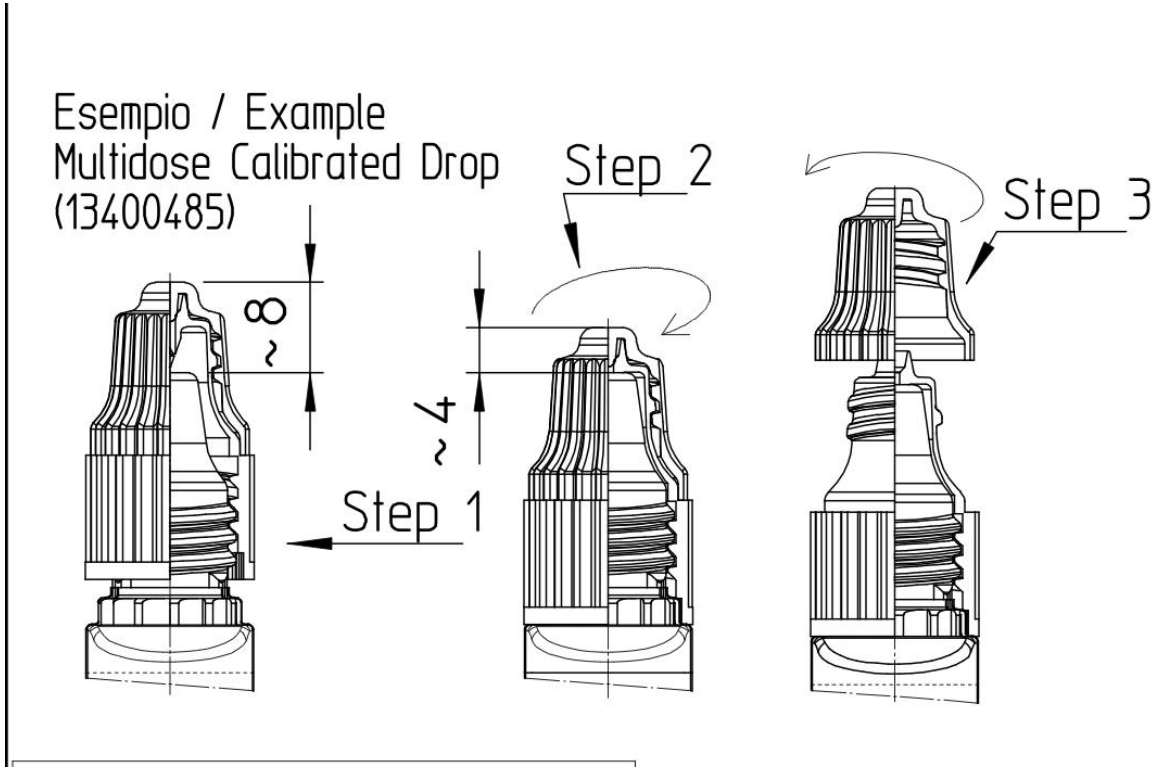
- Thread for screw cap
- Saw tooth serrations to lock the two piece cap
- Place to emboss company logo
- Arrangement to emboss batch number and expiry date



MULTI USE EYE DROP

Metered dose 2 piece cap

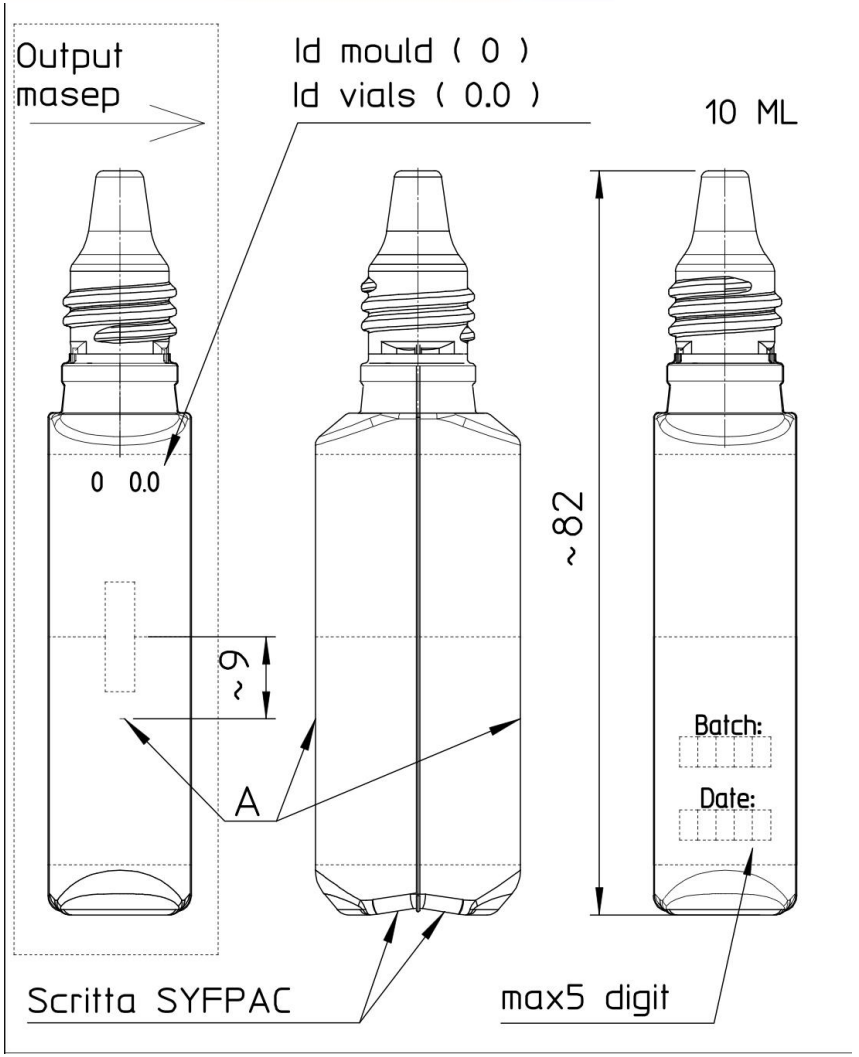
- Lower cap has a spike to pierce the bottle
- Lower cap also has a calibrated hole to dispense metered dose
- Upper cap is to close the bottle after use



MULTI USE EYE DROP

Multi use eye drop bottle with one piece cap (NOT METERED DROP)

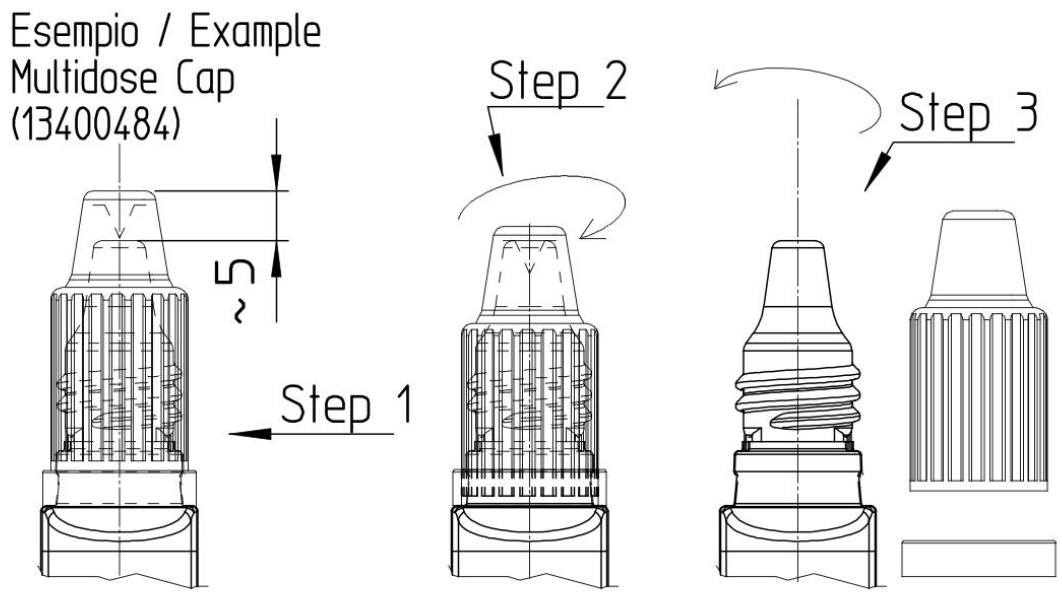
- Thread for screw cap
- Saw teeth serrations absent
- Place to emboss company logo
- Arrangement to emboss batch number and expiry date



MULTI USE EYE DROP

Single piece cap for NON METERED dose

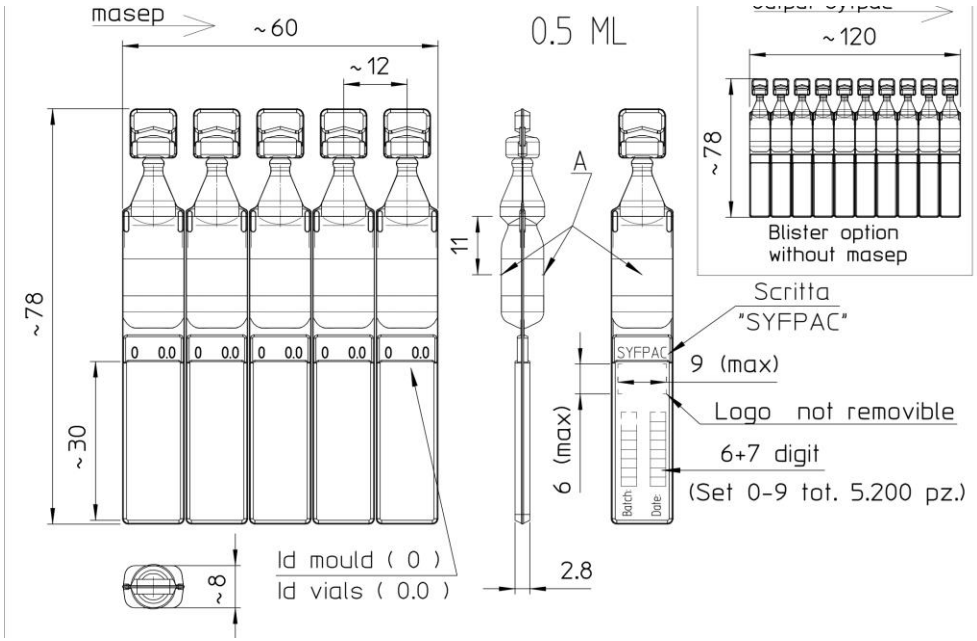
- Cap has a spike to pierce the bottle
- Once pierced, the bottle can dose non metered drops from the hole
- Cap can be used to close the bottles after use



SINGLE DOSE EYE DROP

Multi use eye drop bottle with re-closable twist off tab

- Twist off tab to open the container
- Dispensable volume is 0,4 ml, hence it is more then one dose, thus tab can be used to re close the bottle
- Arrangement to emboss batch number and expiry date



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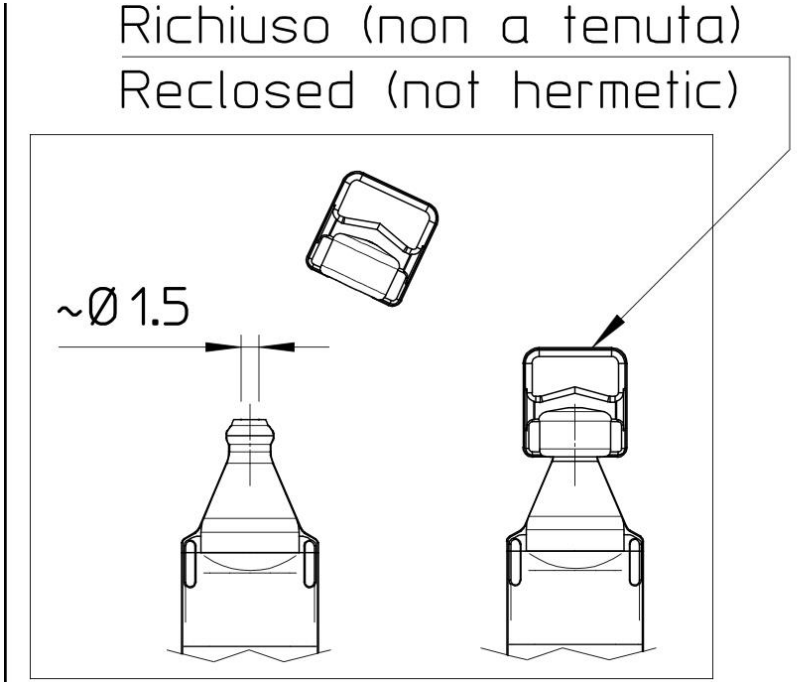
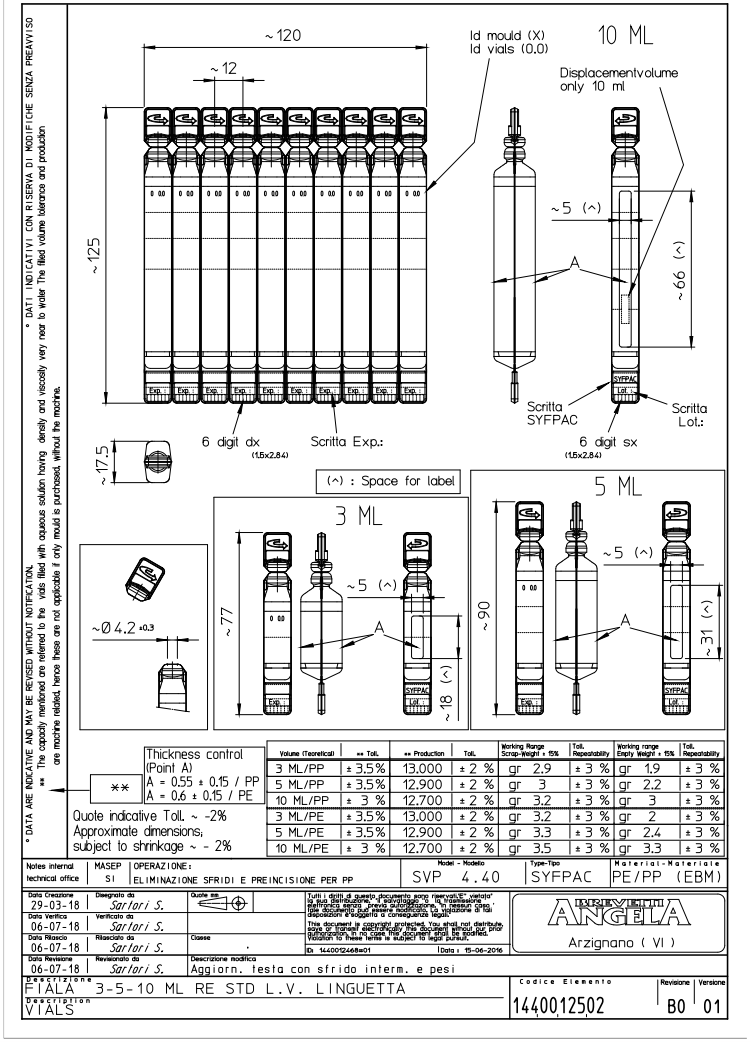


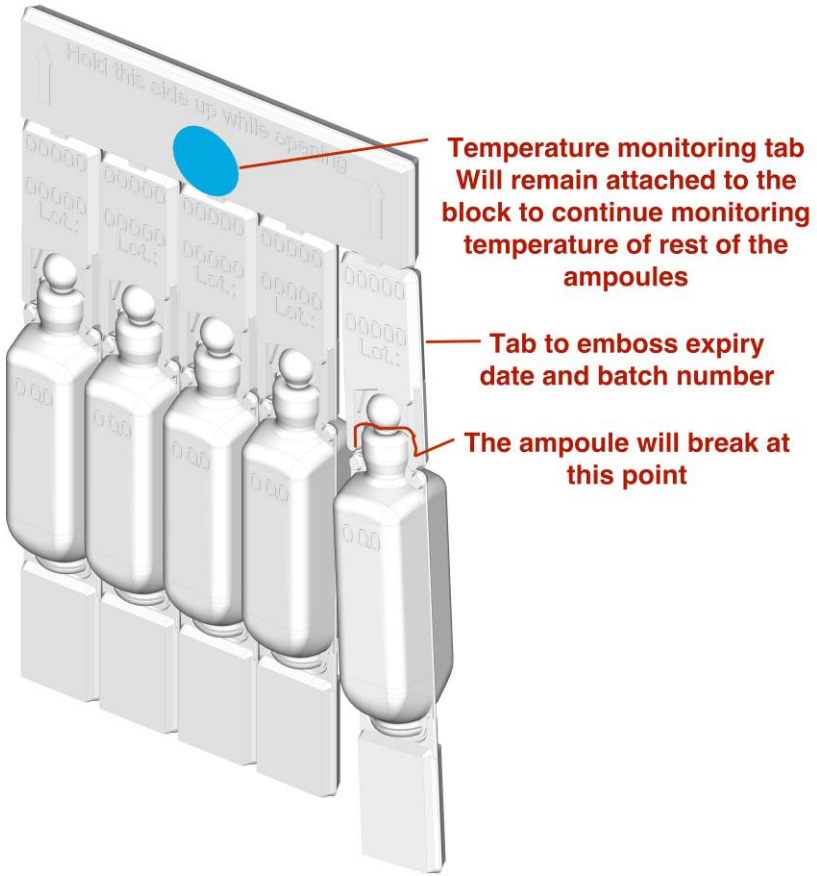
SINGLE USE CONTAINER FOR INJECTION

Single use ampoule for injection

- Twist off tab to open the container
- Hole size 4,2 mm for inserting the luer hub of the syringe
- Arrangement to emboss batch number and expiry date
- Space for label
- Space for company logo



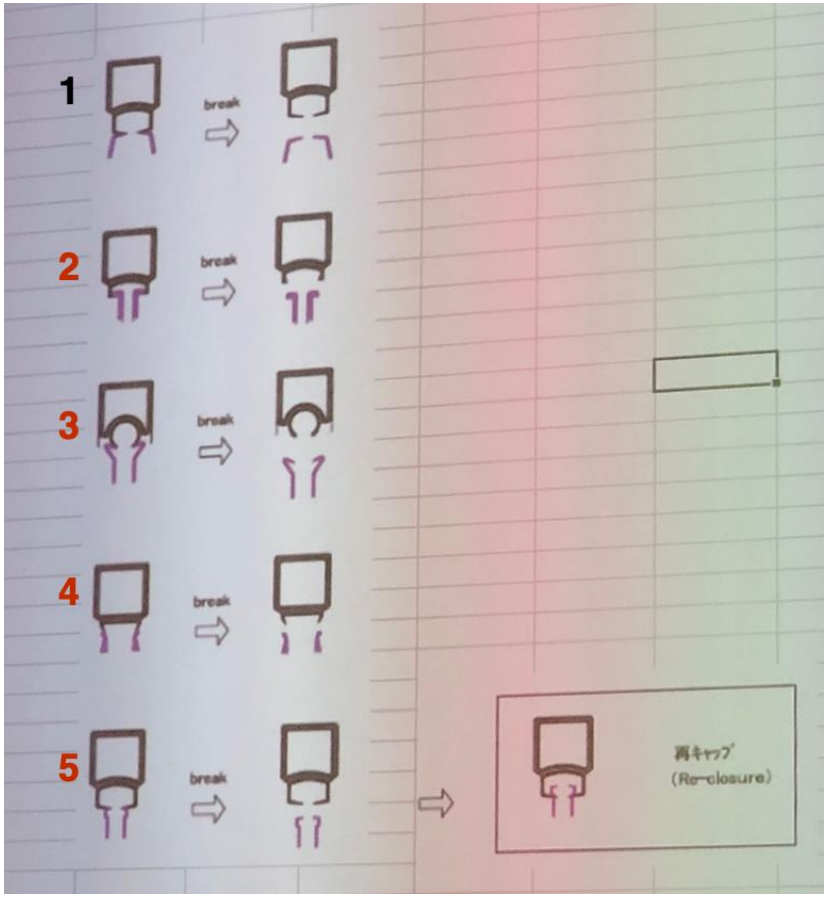
Injection Ampoule for, for heat sensitive Biological product with temperature monitoring label



TYPES OF TWIST OFF OPERNING FOR EYE DROP

At least 5 different type of twist off opening is possible. Each one has its own advantage and disadvantage.

Choose the right one to suit the application as well as client's ability to maintain the machine within working range



TYPE 2 OPERNING FOR EYE DROP – ADVANTAGE / DISADVANTAGE

Advantage:

Easy opening with different kind of polymers.

Force required for twist off to open within narrow range.

Clean opening without sharp burrs.

Disadvantage:

Machine alignment with filling nozzles should be well maintained.

Require skill.

Filling nozzles should not descend if there is cold plastic in the mould, requires special arrangement of cameras.

EQUIPMENT SHOULD BE CAPABLE OF PROCESSING WIDE RANGE OF POLYMERS

Select polymer in which products which are intended to be packed so that:

1. Product remain stable during entire shelf life
2. Container closure integrity is protected during entire shelf life
3. Lecheables remain within limits during entire shelf live
4. Container is sufficiently transparent to facilitate manual or automated particulate matter inspection
5. Container closure system should act as barrier against ingress of gases from environment and against loss of water or other solvent from the formulation.
6. Product pH and concentration remain within limits prescribed

IDEAL TEMPERATURE FOR STERILIZATION OF POLYMER CONTAINERS

- ✓ Only if the product **cannot sustain** high temperature, it should be sterilized at a lower temperature such that the product achieves **F0 Value >= 8**.
- ✓ Only if the product is heat liable, then it should be **sterilized by filtration**.
- ✓ Thus preferred temperature of sterilization is 121° C.
- ✓ The only commercial grade polymer, which can be sterilized at 121° C, and which is suitable for injectable containers and which is widely available is **Polypropylene**.
- ✓ **LDPE** (Low Density Polyethylene) **is no more suitable** to make containers of Injection/intravenous fluids because the containers made from LDPE cannot be sterilized at 121° C.

POINTS FROM URS - ABOUT EQUIPMENT DESIGN

EQUIPMENT SHOULD BE CAPABLE OF:

1. Producing All formats requested, container produced should perform as specified
2. Producing eye drop containers from PE and Injection ampoules from PP (Must for terminal sterilization at 121 Degree centigrade.)
3. Should be able to process viscous formulations
4. Should be able to process suspensions aseptically. Design re-circulation loop to operate without absolute filter.
5. Should be equipped with re-circulation loop to prevent suspension from settling
6. Re-circulation loop should occur as close to the filling nozzles as possible
7. Aseptic processing capability with or without absolute filter
8. Should be capable of producing container with colored masterbatch while filling photosensitive products
9. Product path cooling & product cooling to fill temperature sensitive product
10. Avoid condensation by design in critical processing zone

POINTS FROM URS - ABOUT EQUIPMENT DESIGN

GENERAL:

1. The design stage of a BFS project should take into account the following specific BFS equipment-related parameters.
    1. Airshower Design
    2. Design of critical zone and “zones of protection”
    3. Sanitization/sterilization requirements of critical zone
    4. Particle monitoring requirements
    5. Sanitization on non product contact surfaces
    6. Extruder performance
    7. CIP/SIP (air and product pathways)
    8. Filling system design
    9. Consider placing equipment such as hydraulics, coolant systems etc. in a separate area outside of the cleanroom.
    10. Ease of maintenance

POINTS FROM URS - ABOUT EQUIPMENT DESIGN

GENERAL CONTINUED:

1. Overall Equipment Efficiency (OEE)
2. Changeover time
3. Equipment Monitoring (process alarms)
4. Blowing/ballooning air/inert gas requirements
5. Exhaust system(s) (e.g. air removal from container during filling, removal of particles during knife cutting)
6. Mould design
7. Utilities (cooling, vacuum)
8. □ Polymer feed system
9. □ Deflashing system

EQUIPMENT DESIGN - CRITICAL PROCESSING ZONE

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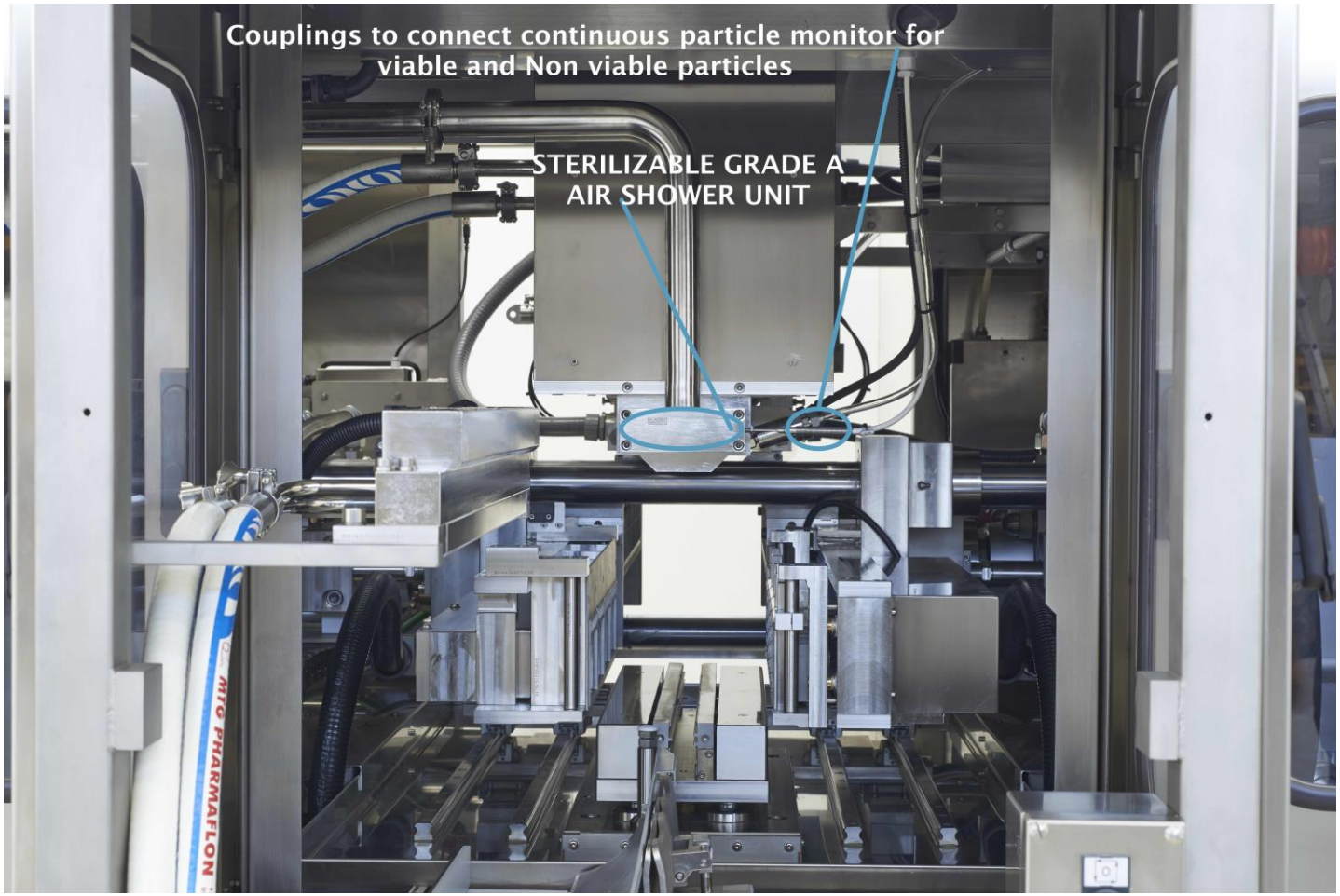
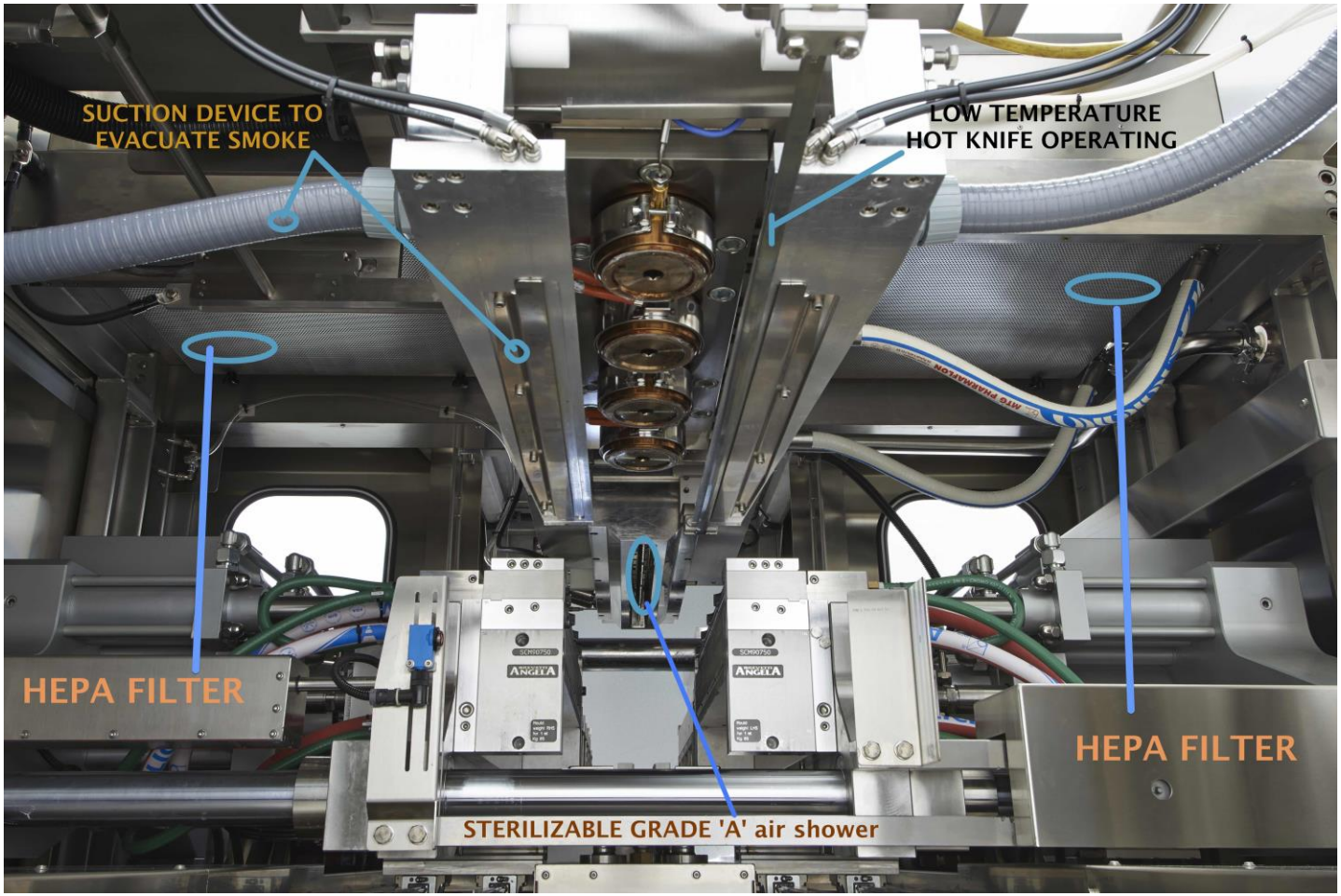
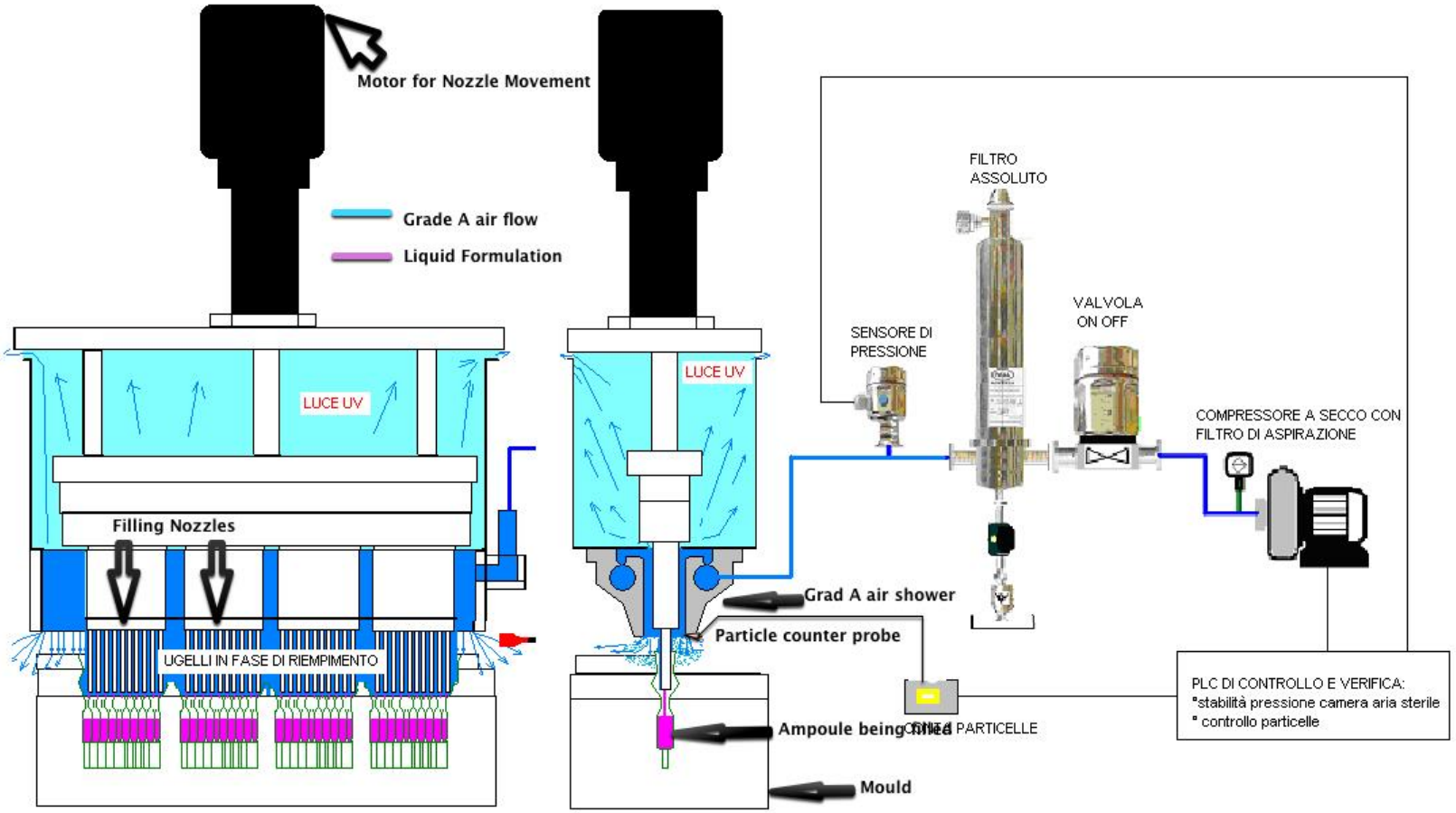


EQUIPMENT DESIGN - CRITICAL PROCESSING ZONE



EQUIPMENT DESIGN - CRITICAL PROCESSING ZONE



EQUIPMENT DESIGN - CRITICAL PROCESSING ZONE

DESIGN OF CRITICAL ZONE:

1. The air flow pattern inside the BFS machine could influence the environment in the critical zone
2. The air flow within BFS machine is complex because of hot extruding zone, movement of knife, particles generation during knife cutting, particles rise due to mould movement
3. The air flow within BFS machine is complex because of HEPA filters, and suction devices to evacuate particles
4. Smoke study should be conducted to understand the air flow pattern inside the clean room

MONITORING

Equipment Monitoring, control and recording:

Monitoring functions for the BFS process SHOULD AT LEAST include the following:

1. Temperature of extruder and extruding head
2. Temperature of hydraulic oil
3. Temperature of probes in aseptic circuit during SIP & cip
4. Temperature of the formulation during filling of temperature sensitive products
5. Temperature and humidity in critical zone while filling of temperature sensitive products
6. Temperature of mould cooling water and vacuum pump cooling
7. Pressure. buffer vessel during filling and during SIP
8. Various Speeds (extruder, mould reciprocation, mould opening closing, cycle time)
9. Airflow, air pressure air shower, HEPA filter, air flow of supporting/ballooning air

FACILITY DESIGN

Aseptic Processing Area (APA).

Any aseptic BFS process should comply with the regulatory requirements of the specific market for pharmaceutical products or medical devices.

The environmental requirements of the FDA and EU guidance (Food and Drug Administration 2004, Commission of the European Communities 2009) are now aligned for aseptic BFS operation. Room classifications should reflect ISO 14644 International Standards Organisation.

The recommendation follows that the BFS filling machine should be located in an ISO Class 8 (Operational) / Class 7 (at rest) room, EU grade C, environment.

On open parison machines the area between parison cutting and mould sealing in the BFS process may be considered as a “Zone of Protection” which may suggest coverage by a flow of HEPA filtered or sterile air of appropriate quality to provide enhanced protection.

FACILITY DESIGN – ASEPTIC PROCESSING AREA

BFS ZONE	EU CLASSIFI-CATION	≥ 0.5 ⍰m particles/m3 ≥ 5.0 ⍰m particles/ m3 (Operational	≥ 0.5 ⍰m particles/m3 ≥ 5.0 ⍰m particles/ m3 (Operational	MICROBIOLOGICAL	
				ACTIVE ACTION LIMIT Cfu/meter cu	SETTLE PLATE LEVEL, DIA 90 CFU/4 hours
CRITICAL ZONE	A	3520	20	1	1
BACKGROUN G	C	3,520,000	29,000	100	50

CHECK DURING FAT – PERFORMANCE OF MULTI USE CONTAINER

USUAL CHECKS RELATED TO CONTAINER

1. Empty Container weight should be within limits shown in FAT protocol
2. Scrap weight should be within limits shown in FAT protocol
3. Fill volume tolerance should be within limits shown in FAT protocol
4. Container should be squeezable
5. Type of polymer match with FAT protocol

CHECK RELATED TO THREAD PERFORMANCE FOR SCREW HEAD

1. Torque required to fix cap without piercing should be within limits shown in FAT protocol
2. Torque required to pierce the container should be within limits shown in FAT protocol
3. Thread should not slip when slightly higher torque compared to opening torque is applied
4. Container should not leak when the cap is fixed

The above checks also provide information regarding checks to be carried out during IPQC to produce good quality containers

CHECK DURING FAT – PERFORMANCE OF INJECTION AMPOULE

USUAL CHECKS RELATED TO CONTAINER

1. Empty Container weight should be within limits shown in FAT protocol
2. Scrap weight should be within limits shown in FAT protocol
3. Fill volume tolerance should be within limits shown in FAT protocol
4. Container should be squeezable
5. Type of polymer match with FAT protocol

CHECK RELATED TO AMPOULE PERFORMANCE

1. Force required to Separate the ampoule from Block should be within acceptable limits
2. Torque required to Twist open the ampoule should be within acceptable limits
3. While opening the ampoule for biological product, it should open at desired point, keeping the tab for expiry date and batch number attached with the block

The above checks also provide information regarding checks to be carried out during IPQC to produce good quality containers

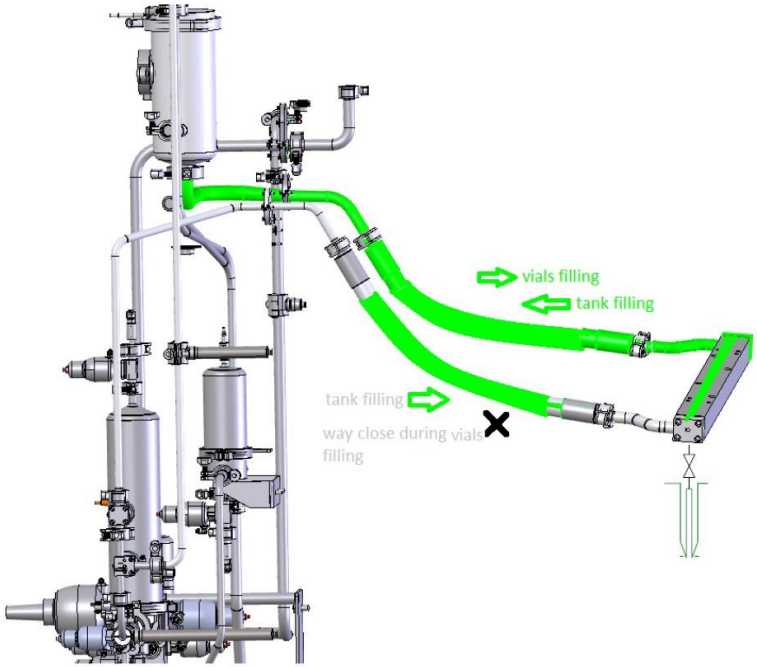
STANDARD OPERATOR TRAINING

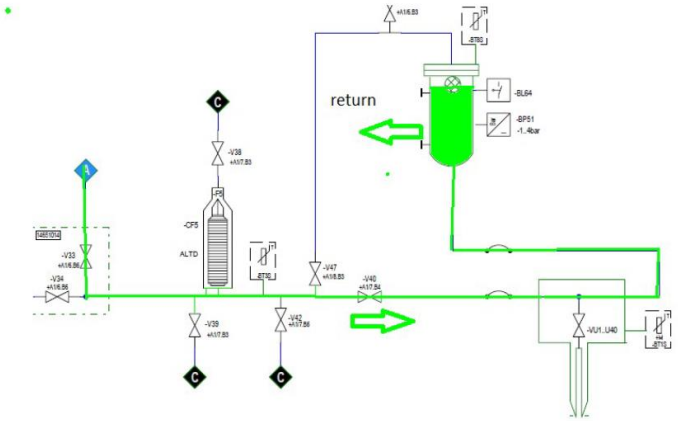
1. Standard operator training should include:
2. cGMP
3. Hygiene and microbiology training including appropriate gowning
4. Clean room pressure differentials, HEPA filter
5. Clean room cleaning and sanitization
6. Entry exit procedures

BFS SPECIFIC TRAINING

1. Working of BFS MACHINE
2. How and why sterility is assured in BFS process
3. Critical processing zones of BFS machine
4. Complexity of Air flow pattern within BFS machine
5. Particle generation source in BFS machine, viable (Human Dust)and non viable particles. (particles generated when knife cuts parison)
6. Interventions which are considered non critical – Opening rear door of the machine, and removing cut parisons or fallen containers
7. Intervention which are considered critical – Intervention in core aseptic zone to remove stuck plastic from nozzles
8. Alarm limits, and action to be take
9. Maintenance activities and effects
10. Preventive maintenance activity which has profound effect on maintenance of aseptic status

DESIGN OF RECIRCULATION LOOP TO FILL SUSPENSION

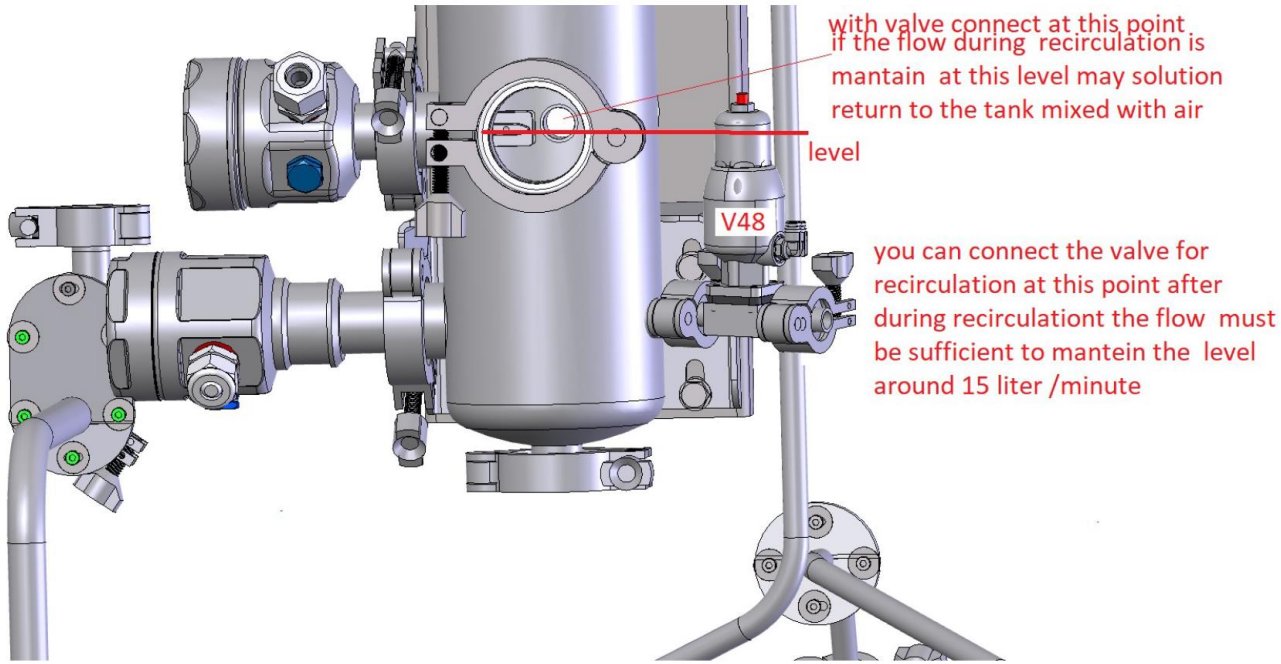




Re-circulation loop from Holding tank to filling nozzle manifold including buffer tank.

Use peristaltic pump (or diaphragm pump) instead of centrifugal pump. Centrifugal pump tend to separate the suspension.

DESIGN OF RECIRCULATION LOOP TO FILL SUSPENSION

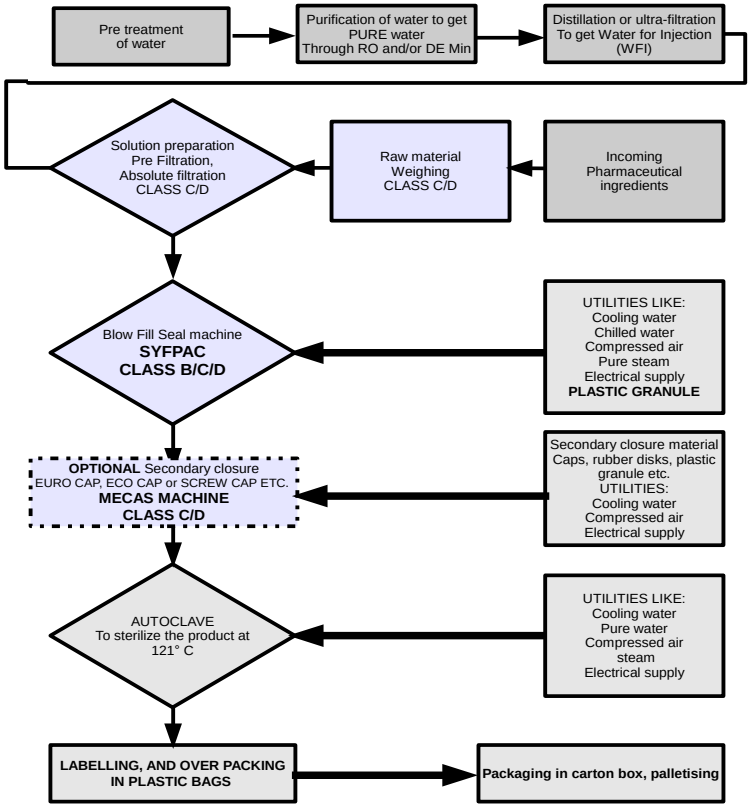


Connection of the return pipe to the buffer tank should be submerged under liquid level to avoid air entrapment in the suspension.

Air entrapment in suspension tend to separate suspended particles.

PROCESS FLOW DIAGRAM

PRODUCTION OF INTRAVENOUS FLUID – FLOW DIAGRAM



1		Optional items
2		Should be carried out under controlled envoronment
3		Closed area, not necessarily controlled environment

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INJECTION DEVICE: 3rd Generation

- ✓ Introduction of pre sterilized components.
- ✓ Maintaining sterility by the use of RTP ports and chamber for surface decontamination
- ✓ Decontaminating CRABS, Maintaining the CRABS aseptic
- ✓ Advantage of BFS technology is well known... and these syringes are made on SYFPAC® BFS Machine!

Thank you for your attention!

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