# Downstream handling and Secondary Packging for BFS containers – some considerations

Peter Åkerman

Senior Advisor

AstraZeneca, Sweden Operations

# Content

- Regulatory requirements
- Examples of downstream handling
- Need for secondary packaging ?
- Integrated lines vs. Separated filling and packaging

# Regulatory Requirements

- Integrity testing
  - Several demands for Container Closure Integrity testing
  - FDA GMP for Aseptic Processing
  - EP 7:15
    *”Thightness of container is ensured by suitable means”*
  - EU GMP Annex 1, p117
    *”117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures”*
- Life cycle approach important
  - Product development and validation
  - Routine Manufacturing
  - Product Stability over shelf life should include Container integrity
- USP <1207.1, 1207.2 and 1207.3> contains valuable recommendations for choice of integrity test method

# Regulatory Requirements

- Visual Inspection (most commonly for injectables)
  - USP 40 <788>, <790>
  - EP 7:15
  - FDA GMP for Aseptic Processing
  - EMA GMP Annex 1, p124
    *”Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects”*

- Marking of units
  - Minimum demands for what information that are required on a single container varies for different markets
  - FDA demands
    *”…labeling…..by embossing or debossing is recommended”*

# Regulatory Requirements

- Secondary packaging
  - Several demands  also for secondary packaging
  - FDA ’Guidance for Industry – Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products  CMC documentation’
    *” Protective packaging (eg. foil overwrap) is recommended for inhalation drug products packaged in semipermeable containers (eg. LDPE)”*
    *”….mitigates conditions such as ingress of foregin contaminants, loss of solvent, exposure to oxygen”*
  - Similar demands can also be found in FDA ’Guidance for Industry – Container Closure Systems for Packaging of Human Drugs and Biologics’
    *”….Provides light protection for the packaging system…”*
    *”….an additional measure of microbioloical protection…”*
  - EMEA  ’Guideline on Plastic Immediate Packaging Materials’

# Examples of Downstream handling

- Punching / Deflashing
- Check weigher *(for filled containers)*
- Integrity testing
- Visual inspection and/or Cosmetic inspection
- Marking of containers
- In Process Control of BFS process
- Secondary packaging (Aluminium foil, Blister pack)
- Cartoning
- Check weigher (for cartons)
- Security seal, Serialization, Aggregation
- Considerations for Integrated lines vs. Separated packaging operation

# Punching (deflashing)

- Is the separation of the filled and sealed BFS container(s) from the excess plastic material that is needed during processing
- For modern BFS machines, the punching step is done outside the filling room
  - No risk for particles generated by punching in the filling room
  - Less need for operators to access filling room for adjustments
- Some models of punching equipment can also be equipped with a ”hot-stamp” unit to mark the containers with lot no. / expiry date and/or product code
- Excess plastic material can be milled into fine-grained material similar to granulate
  - Most common is to sell the vaste material for re-use for technical purposes
  - Some manufactures re-use the material in their BFS production, but this has to be carefully evaluated

# Check weigher for filled containers

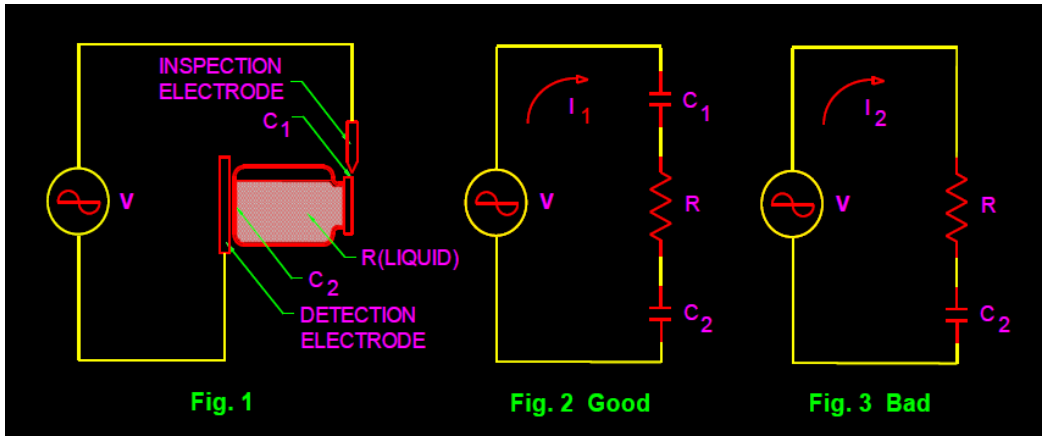
- For smaller containers (= ampoules in blocks), the main function of the IPC is to guarantee that no empty units are forwarded
  - Minor deviations in fill volume can’t be detected
- For bigger containers this IPC can reject any units with a fill volume outside acceptance limits

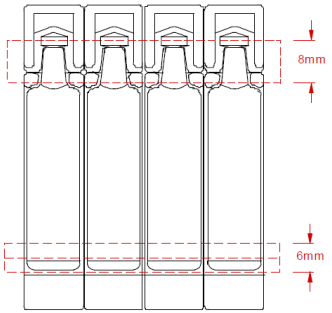
# Integrity testing of containers

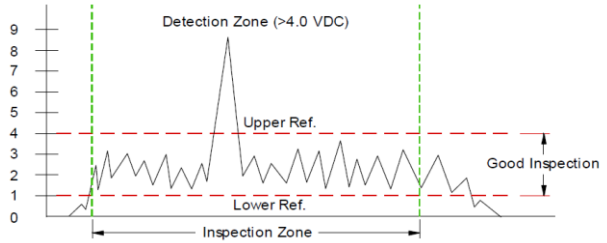
- For all sterile products 100 % integrity testing is mandatory
- Two major techniques are available;
  - High Voltage Leakage Detector
  - Vacuum chamber / Pressure decay
- Technique to be selected depending on product characteristics
- Manual testing by mechanical pressure on random samples can be used complementary
- All automated leakage detection processes has to be carefully validated and also verified for functionallity every day of production
  - Small holes can be made by laser beam or fine acupuncture needles
  - A reference method is recommended to be used (ex. blue dye bath)
- Line design consideration; test direct after filling or before packaging ?

# Integrity testing of containers

- High Voltage Leakage Detection



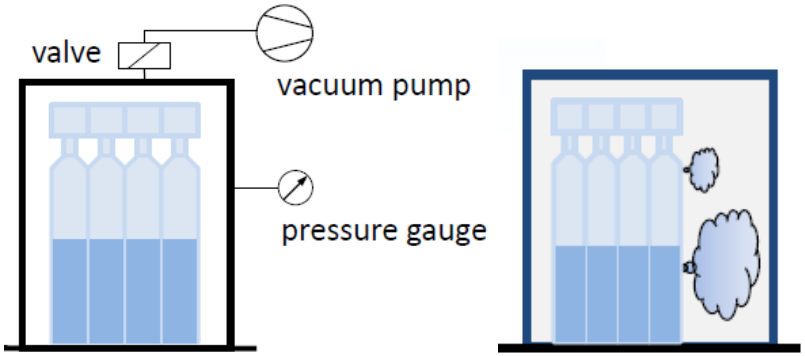



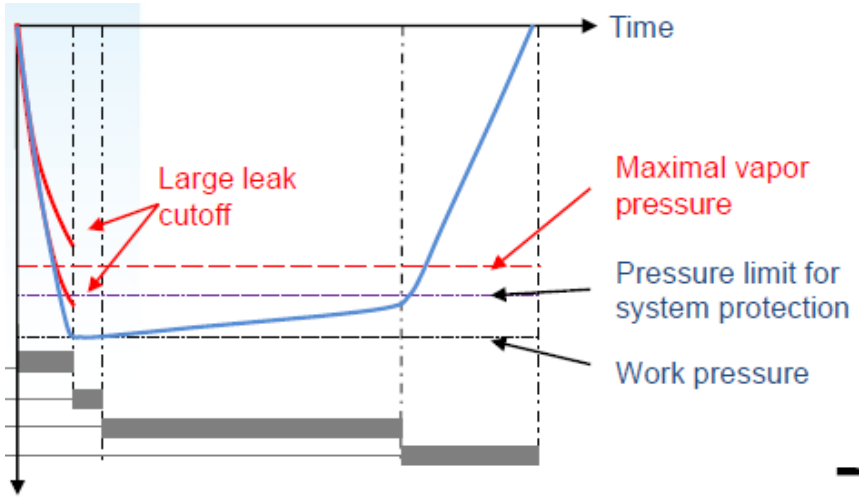




- Can operate at high speed
- Small foot print, not complicated
- Disadvantage – only critical parts of container tested

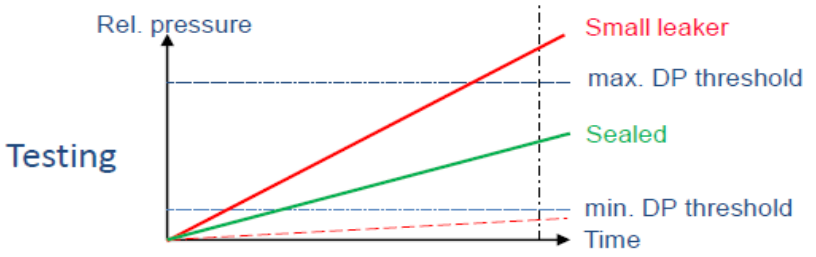
# Integrity testing of containers

- Vacuum chamber / Pressure decay




- Can operate at rather high speed
- Advantage – the whole container is tested
- Disadvantages – more expensive, bigger foot print, more moving parts



# Visual Inspection

- For all injectables 100 % visual inspection is mandatory
  - Check for visible particles in solution
    *(Sub visible particles will always have to be checked by QC lab)*
  - Particles in container wall
  - Cracks and defects during forming of container
  - Miscolouration of solution and plastic container
  - Fill volume
- Visual inspection is normally done manually for BFS products
  - BFS containers often comes in blocks or are non cylindrical
  - Only a few automated machines are available for BFS
- One challenge for inspection of BFS containers is the opaque plastic material

# ”Cosmetic” Inspection

- For all other BFS products a cosmetic inspection can be considered
- Cosmetic inspection can be done
  - Randomly - manual
  - 100 % - manual
  - 100 % - automated
- Items to look for are
  - Large particles in solution
  - Particles in container wall
  - Cracks and defects during forming of container
  - Miscolouration of solution and plastic container
  - Fill volume
- Automated inspection can easier be arranged for cosmetic inspection
  - For example a standard vision system can be installed on-line

# Marking of BFS containers

- Demands for what information that has to be marked on each container varies for different markets and type of product
- Minimum requirements are normally
  - Product name
  - Strength
  - Volume
  - Batch / Lot number
  - Expiry date
- Other local demands might be
  - Name of active ingredient
  - Route of adminstration
  - Manufacturer
- For ampoules in blocks information might also be available on end tabs or on a common bar that keeps the ampoules together

# Marking of BFS containers

- There are several techniques available for marking;
  - Embossing / Debossing
  - Hot-stamp / Laser engraving
  - Label
  - Pad printing
  - Ink Jet
- Considerations for choice of suitable technique depends on;
  - Type of BFS machine
  - Single or Multi-product line
  - Secondary package or not
- Batch / Lot number and Expiry date are regarded as variable data, and should therefore be easy to exchange

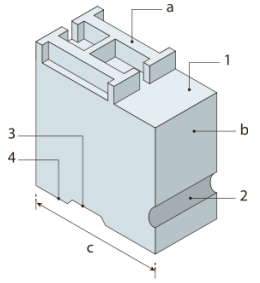
# Embossing / Debossing


- Engraving in the BFS mould

  or

- Exchangeable types of metal in the mould

- Suitable for shuttle type BFS machines, where mould / mould inserts and types can be exchange rather easily
- Might be used also for non-variable information on rotary machines, provided it is a single product line
- Advantage – no other material in contact with product
- Disadvantage – time consuming change over, risk for human mistakes when handling many small types
- Information can be difficult to read if not properly handled



# Hot-stamp / Laser engraving

- Hot-stamp uses heated metal types that are pressed into a tab of the BFS container
- The hot-stamp is done outside the filling room, normally in the punch / deflashing unit
- Normally only used for variable data
- All units that passes are marked, therefore suitable for rotary BFS machines
- Change over of types can be done rather easily
- An alternative that is becoming more suitable today is laser engraving

# Labels

- Most common method for product information
- For small ampoules a flat tab can be used to apply the label


# Labels

- Advantages
  - Clear information, easy to read
  - More information can be included, several colour can be used
  - Label can be printed with batch / lot no. and expiry date
    - no embossing and/or hot stamp needed

- Disadvantages
  - Separate labeller needed
  - Labels have to be ordered and stored
  - If label applied direct on ampoule – risk for migration of components in adhesive, lacquer or colour from label
  - If label applied on tab, and ampoule packed in aluminium pouch, there is still risk for migration of volatiles into the product

# Pad-printing

- Ink from engravings in a cliché plate is transferred by soft rubber pads that are pressed to the surface of the BFS container


- Advantage – clear and easily legible text, one or two colours
  - can be used also for variable information
- Disadvantage – rather sensitive printing process
  - special equipment for preparing printing plates needed

# Ink jet

- Advantage
  - Very common technique for marking
  - Can be used for all information
  - Fast change over

- Disadvantge
  - Not perfect for surfaces of plastics like Polyethene or Polypropylene
  - Text not sharp enough for small fonts
  - Only one colour

- *Comment;*
  *- a new technology with UV cured ink jet printers is under evaluation*
  *- looks very promising, but still too early to recommend*

# In-Process Controls

- An important step to verify to performance of the BFS process is to perform frequent IPC checks during production
- The most common and recommended IPCs are;
  - Fill volume
  - Empty weight of container
  - Wall thickness
  - Ease of opening
  - Shape of aperture
  - Force needed for separation
- Frequency depends on conclusions from validation and experience based on long-time production and/or complaints
- IPC is normally done manually, but some equipment for automated and thus “operator independent” IPC exists

# Secondary Packaging

- One disadvantage for all plastic containers is the semi-permeable properties of the wall.
- Gases will be transported through the wall by diffusion
  - water vapour will leave the container, and other gases enter
  - also somewhat larger molecules might slowly migrate to the wall
- Therefore, in order to avoid evaporation of water that will affect the volume and concentration of the product a secondary package is needed
- This will also give a protection for oxygen-sensitive products to be exposed to the risk for degradation of the API
- An outer package can also offer a protection to light, which is important since the degradation of many APIs are caused by light.

# Secondary Packaging

- Most common is to use a foil including a thin layer of aluminium
- An aluminium foil consists normally of a heat seal layer, (polyethylene), aluminium and a stronger material such as PET
- These layers can be combined by lamination or extruded by heat
- Consideration must be taken to the risk for volatiles from adhesives for the different layers to enter into the BFS container
- For larger BFS containers, a secondary package is not needed, since the evaporation will be neglectable
- For smaller ampoules, they can be packed in blocks or as singles
  - if blocks are packed, they should normally refer to the number of units that are used within a rather short time frame
- A secondary package also have the advantage to offer more space for product information

# Secondary Packaging

- For ampoules where a sterile outside is required, these can preferably be packed in a blister before terminal sterilisation
- The blister bubble itself is then formed by polypropylene film, and the package then sealed with a lidding paper that allows steam to pass through
- The lidding paper can preferable be made of Tyvek material
  - better resistance to scrapes
  - better properties for steam penetration

# Cartoning & Check weigher

- There is no specific differences between cartoning of BFS products and other pharmaceutical products.
- Only if smaller containers are package directly without any secondary protection, consideration has to be taken to components in the carton material, such as paperboard constituents, glue, printing colours and lacquers.
- After cartoning, it is recommended to let the cartons pass over a second check weigher, that can verify that the correct number of units has been packed in the carton.

# Security Seal & Serialisation

- These steps are today a requirement for many markets.
- Since the application of a security seal and a unique number for serialisation can be considered as standard operations, there is nothing specific related to BFS here.

# Integrated lines vs. Separated filling / packaging

- Integrated lines have many advantges
  - All production of a product in one location
  - Product is completely finished when it leaves the line
  - No extra storage area for temporary staging necessary
  - Especially suitable for products that requires protective secondary package

- ….but also some disadvantages
  - For production to a high number of different markets, BFS process has to be stopped during change of packaging components and line clearance
  - Line efficiency often reduced due to addition of down time for all equipment in the line

# Integrated lines vs. Separated filling / packaging

- Advantages with Separation of filling / packaging
  - Higher efficiency of the BFS machine – less stop time on other equipment
  - Operators can focus on less different machine types
  - Customisation to be done later in the manufacturing process
    - more flexible production flow

- ….but also for this case some disadvantages
  - Handling system for loading and unloading product needed
  - Load carriers and Space for intermediate storage of semi-finished product needed
  - Not suitable for products that for example are sensitive to oxidation
  - Considerations for where to install Integrity testing
    - Valuable to perform as soon as possible after filling
    - A second integrity test might be needed if handling process can cause defects

# Thanks for your attention !

Any questions or comments ?