Application of combo filling line for vaccine sterile production

Paddy . Peng
The existing problems
Multiple containers are used for vaccine small volume injections just now, such as ampoules, vials, prefilled syringes, cartridges, and so on… Different container needs different machines to filling product, such as:

- Ampoule filling line
- Vials filling line
- Syringe filling line
- Cartridge filling line

……
If one vaccine factory have many breeds vaccine being manufacture and filling into different container.

So drug factory had to build several factory and buy several different filling line to filling product into different container.

It is means more money, longer time, and low efficiency…

Actually, factory needs such a machine—automation, flexible, stable operation, safety, Small batch, quick turnover, compatible for product R&D and commercial production
2 How to solve the challenges
Combo Filling Line —

One filling line could filling multiple containers
Combo Filling Line —

➢ Smaller footprint
➢ Smaller clean room
➢ Lower clean room grade (> EU grade D / IOS 8)
➢ Decrease time to market
➢ Reduce cost
Combo Filling Line could used for

✓ R&D batch (liquid < 10,000 pcs/batch, lyophilizer < 1 m²)
✓ Clinical batch (liquid < 30,000 pcs/batch, lyophilizer < 5 m²)
✓ Mass batch (liquid > 90,000 pcs/batch, lyophilizer > 5 m²)
Combo Filling Line could used for

✓ Vaccine (common)
✓ Vaccine (toxicity)
✓ Vaccine (Active)
✓ Vaccine + adjuvant (suspension)
✓ Vaccine + adjuvant (viscose)
✓ Vaccine + adjuvant (oily)
➢ Combo filling line is a aseptic filling line integrated with full sealing isolator
➢ Combo filling line is specially designed for small scale injection filling. It can be used for R&D, clinic trial and commercial production
➢ Combo filling line is suitable for vaccine, Mabs, recombinant protein’s filling, and also suitable for the aseptic filling for toxic drugs, such as cytotoxin, live virus
Detailed introduction of solution
1. For R&D and Clinical batch (liquid < 10,000 pcs/batch, lyophilizer < 1 m²)

◆ For small batch
◆ Choose ready-to-use containers will better

(Cancel wash machine and Tunnel)
1. For R&D batch (liquid < 10,000 pcs/batch, lyophilizer < 1m²)

Combo Filler

For Syringe

For Cartridge

For R&D

De-lid&liner  Filling and closing  Filling pump  Buffer tank

HMI  Center part system  Vibration bowl
1. For R&D batch (liquid < 10,000 pcs/batch, lyophilizer < 1 m³)

**Mini KUFill**

For RTU tray vial

For R&D

<table>
<thead>
<tr>
<th>Package</th>
<th>Processing Machines</th>
<th>Pass-box with VPHP</th>
<th>Filling and Closing</th>
<th>Freeze Drying</th>
<th>Capper</th>
<th>External Washer</th>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
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2. For Clinical batch (liquid < 30,000 pcs/batch, lyophilizer < 5 m²)

Combo Fill Line (Two in one)

<table>
<thead>
<tr>
<th>Container type</th>
<th>Process machine</th>
<th>De-bagging machine</th>
<th>De-lid &amp; liner machine</th>
<th>Filling and stoppering</th>
<th>De-nesting</th>
<th>Capping</th>
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<td>—</td>
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<tr>
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<td>RTU Cartridge</td>
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<td>✓</td>
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<td>—</td>
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</table>
2. For Clinical batch (liquid < 30,000 pcs/batch, lyophilizer < 5m²)

Combo Fill Line (Three-in-one)
2. For Clinical batch (liquid < 30,000 pcs/batch, lyophilizer < 5m²)

Combo Fill Line (Four-in-one)

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<th>Container type</th>
<th>Process machine</th>
<th>De-bagging machine</th>
<th>De-lid &amp; liner machine</th>
<th>Filling and stoppering</th>
<th>De-nest machine</th>
<th>Loading &amp; unloading</th>
<th>Freeze dryer</th>
<th>Capping</th>
<th>Outer wall cleaning</th>
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</tr>
<tr>
<td></td>
<td>RTU Cartridge</td>
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<td>✓</td>
<td>✓</td>
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<td>—</td>
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<tr>
<td></td>
<td></td>
<td>PFS 1000</td>
<td>PFS 2000</td>
<td>PFS 5000</td>
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<tr>
<td></td>
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<td>900</td>
<td>2100</td>
<td>4500</td>
<td>8000</td>
<td></td>
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<tr>
<td></td>
<td>3ml</td>
<td>760</td>
<td>1700</td>
<td>3800</td>
<td>6800</td>
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<td>1570</td>
<td>3800</td>
<td>6000</td>
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<tr>
<td></td>
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<td>9000</td>
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<tr>
<td></td>
<td>10R</td>
<td>300</td>
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<td>2000</td>
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<tr>
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<td>20R</td>
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<td>3000</td>
<td>1000</td>
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</tr>
<tr>
<td>Cartridge</td>
<td>3ml</td>
<td>760</td>
<td>1700</td>
<td>5000</td>
<td>6000</td>
<td></td>
<td></td>
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</tbody>
</table>
The filling line integration by Stand Alone Machine as following:

- De-bagging machine: FB0102
- De-lid & liner machine: FL0202
- Filling and stoppering machine: FS0102, FS0202, FS0205, FS0210
- Nested vial de-nesting machine: FN0101
- Vial capping machine: FCVC 0501

Containers specification:
- Prefilled syringe: 0.5ml, 1ml long, 1ml, 2.25ml, 3ml, 5ml, 10ml, 20ml
- Vial: 2R, 4R, 6R, 8R, 10R, 20R
- Cartridge: 3ml
3. For Mass batch (liquid > 90,000 pcs/batch, freeze dryer > 5m²)
3. Combo Filling Line (liquid Bulk Vial & RTU Syringe & RTU Cartridge)

<table>
<thead>
<tr>
<th>Process Container Type</th>
<th>De-bagging machine</th>
<th>De-lid &amp; liner machine</th>
<th>Washing machine</th>
<th>Tunnel</th>
<th>Filling and stoppering</th>
<th>Capping</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTU syringe</td>
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<td>✓</td>
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<tr>
<td>RTU Cartridge</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
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</tr>
<tr>
<td>Bulk Vial</td>
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<td>—</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
3. Combo Filling Line (Freeze dry Bulk Vial & RTU Syringe & RTU Cartridge)

- RTU syringes & cartridges
- Bulk vials (Freeze dry)
- Bulk vials (liquid)

<table>
<thead>
<tr>
<th>Container type</th>
<th>Process machine</th>
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<th>De-lid &amp; liner machine</th>
<th>Washing machine</th>
<th>Tunnel</th>
<th>Filling and stoppering</th>
<th>Auto-loading &amp; unloading</th>
<th>Freeze dryer</th>
<th>Capping</th>
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<tbody>
<tr>
<td>RTU nest</td>
<td>RTU syringe</td>
<td>✓</td>
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<td>✓</td>
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</tr>
<tr>
<td></td>
<td>RTU Cartridge</td>
<td>✓</td>
<td>✓</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>Bulk Vial</td>
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<td>—</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
4 How to control risks
Risk 1. Cross-contamination of different drugs

Use same machine to filling different vaccines production, cross-contamination is a big problem. In addition to carefully cleaning and validating the cleaning results, we recommend that:

✓ Avoid the production of two of mutually affected drugs on the same machine
✓ Available for using single-use drug solvent bag instead of stainless steel buffer tank to decrease cross-contamination risk and validating work
✓ peristaltic pump can be used, no need online or offline sterilization after the end of production
✓ If rotary piston pump need be used, you can choose to equip two sets piston filling pump
Single-use filling system introduction

Introduction of a single use filling system

Key:
1. Sterile connector
2. Vent bag
3. Hush bag
4. Beta-port for insertion
5. Bag
6. Product header
7. Gassing
8. Venting
9. Peristaltic pumps
10. Disposable filling needles

Flexboy
Pinch clamp
Sterile connector
Y-Dispensers
Filling heads
Risk 2 - Product is oxidized

If the product is lower anti-oxidation abilities, oxygen content should be controlled.

The method we can take:

- Fill the buffer tank with nitrogen to separate the surface of the liquid and the air
- Nitrogen flushing when filling product
- Nitrogen flushing before stoppering
- Vacuum stoppering
Risk 2 - Product is oxidized

Comparison of the size residual bubbles after stoppering for syringe

Bubble size

> 140 microlitre

Common stoppering

Bubble size

< 6 microlitre

Vacuum stoppering
Risk 2 - Product is oxidized

Oxygen content detection

**NOMINAL SPECIFICATIONS**

- Measurement Range: 0 to 21% Oxygen
- Measurement Time: 1 second
- Syringe Sizes: Up to 13.5 mm diameter
- Container Compatibility: Clear glass or transparent plastic
Risk 3 – How to ensure the sterility of the entire filling process

At any stage, we need to ensure the sterility of the vaccine product.

For the filling and stoppering equipment, you need to pay attention to the following points:

✓ Equipped with isolation systems that meet regulatory requirements, depending on the level of background environment and product characteristics (Grade B or grade C/D? Toxicity?)

✓ The inside of isolator chamber is design for easy cleaning

✓ Configuring particle and microbial detection systems in isolator

✓ All of parts contacting with product, containers’ inner surface and stoppers need to be sterilized

✓ Gas pipelines can be sterilized or aseptic
5 Cases Study
Case 1 Mini Combo Fill Line-PFS 1000M

France project, Syringe and vial, Isolator, CMO
Toxic product, Gread D, Area 14m²
Case 2 Mini Combo Fill Line - PFS 2000M

Malaysia project, Syringe + Vial + Cartridge

- Biopharmaceutical
- Toxic
- Isolator
- Lyo (0.5 m²) for vials
- Filling room 51.82 m²
- Lyo room 16.14 m²
- Processing room 10.71 m²
Case 3: Combo Fill Line- PFS 5000  Netherlands project, Syringe +Vial +Cartridge

- Biopharmaceutical
- Toxic
- Isolator
- Four in one
- Lyo (2m²) for vials
- Room size 14.1m*5.8m
Case 4: Super Fill Line- PFS 36000  Chendu OLYMVAX project, Syringe, ORABS

- Vaccine
- 0.3 Billion per year
- ORABS
- De-baging room 13.5 m²
- Filling room 48.96 m²
- Outfeed room 12.71 m²
Contents review

1. The problems faced by the R&D, pilot and small-scale production of macromolecular drugs: the need for flexible production equipment, saving upfront capital investment

2. How to solve the problem: use Combo Fill line

3. Combo Fill line is compatible with a variety of packaging materials, but based on RTU Nest/Tray packaging materials