

production

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1 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 < 1m²)
- ✓ Clinical batch (liquid < 30,000 pcs/batch, lyophilizer < 5m²)
- ✓ Mass batch (liquid > 90,000 pcs/batch, lyophilizer > 5m²)

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



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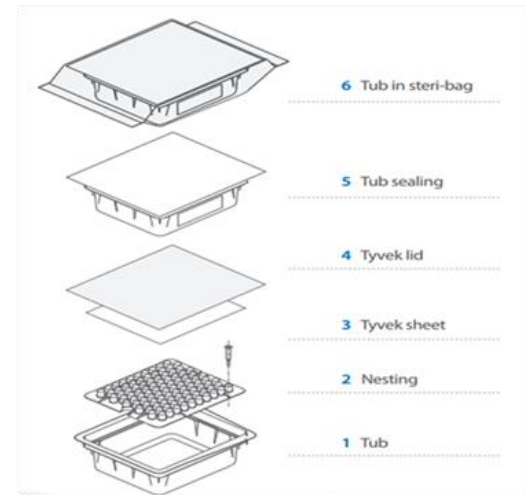
Detailed introduction of solution

1. For R&D and Clinical batch (liquid < 10,000 pcs/batch, lyophilizer < 1m²)

◆ For small batch

◆ Choose ready-to-use
containers will better

(Cancel wash machine and Tunnel)



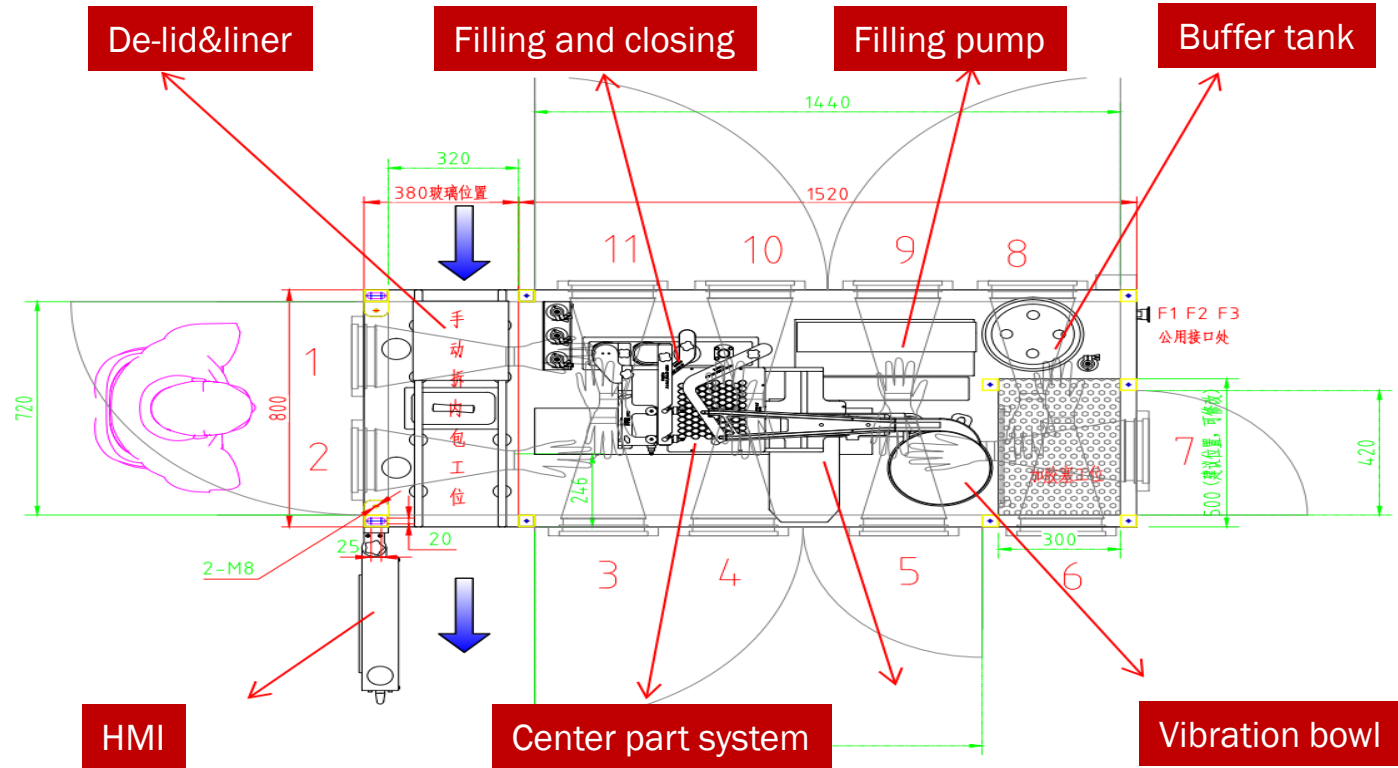
1. For R&D batch (liquid < 10,000 pcs/batch, lyophilizer < 1m²)

Combo Filler

For Syringe

For Cartridge

For R&D

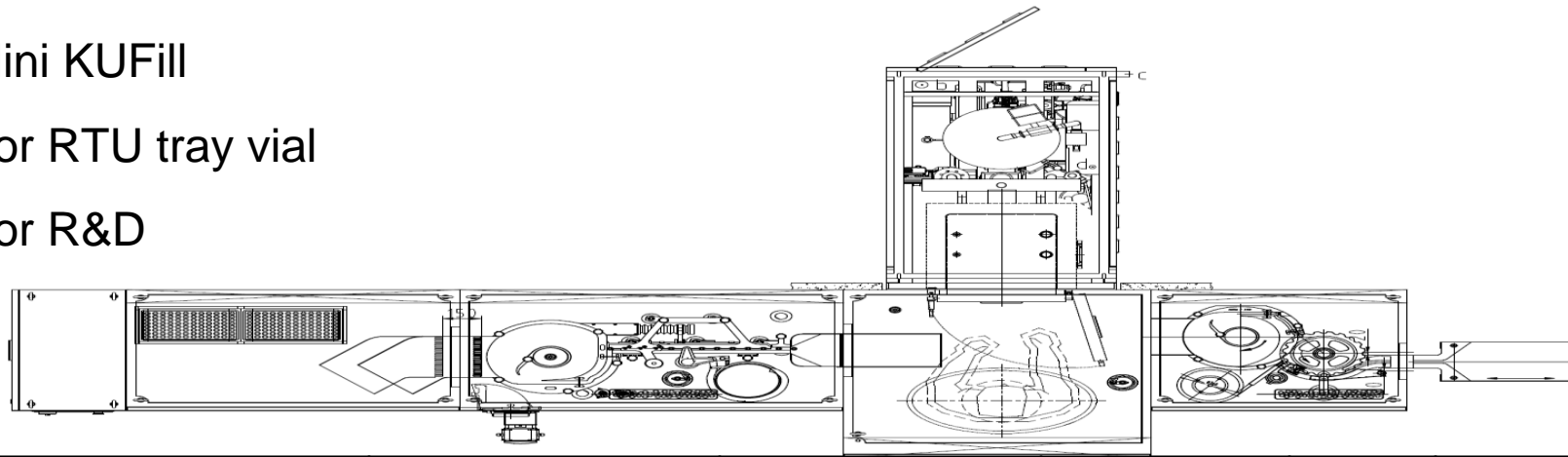


1. For R&D batch (liquid < 10,000 pcs/batch, lyophilizer < 1m²)

Mini KUFill

For RTU tray vial

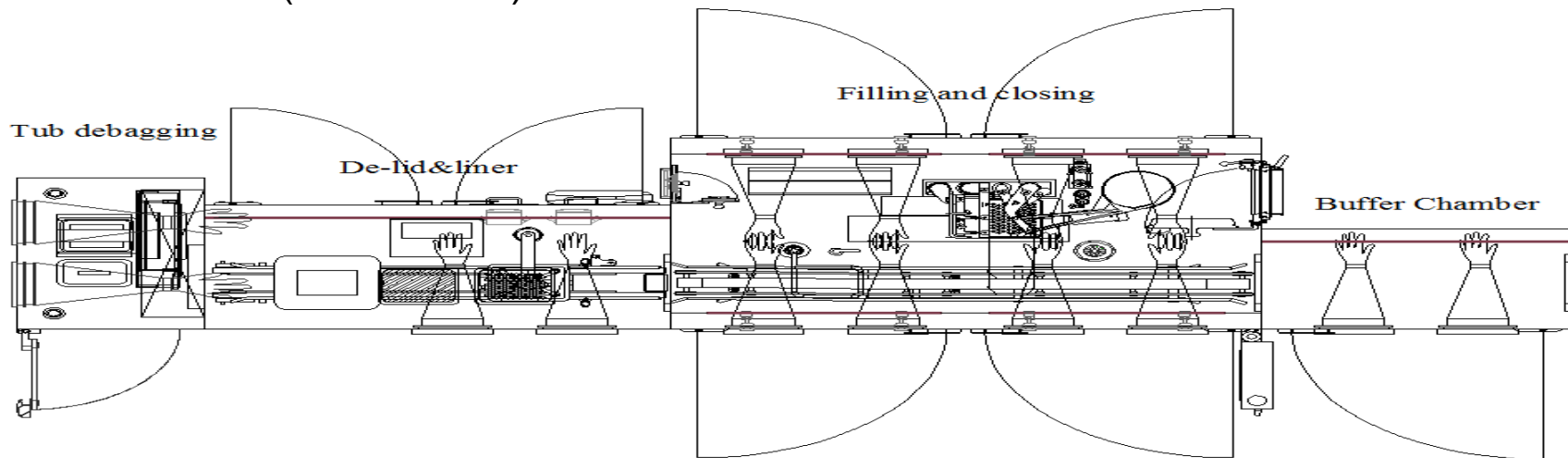
For R&D



Package \ Processing Machines	Pass-box with VPHP	Filling and Closing	Freeze Drying	Capper	External Washer
RTU Tray Vials (Aseptic)	√	√	√	√	—
RTU Tray Vials (Aseptic and Containment)	√	√	√	√	√

2. For Clinical batch (liquid <30,000 pcs/batch, lyophilizer <5m²)

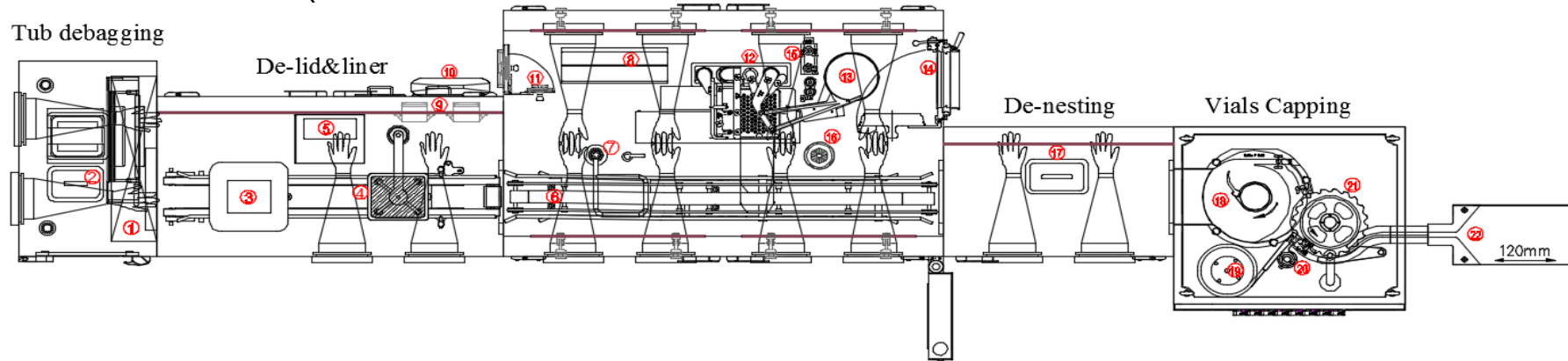
Combo Fill Line(Two in one)



Process machine		De-bagging machine	De-lid & liner machine	Filling and stoppering	De-nest ing	Capping
Container type	RTU Syringe	√	√	√	—	—
	RTU Cartridge	√	√	√	—	—

2. For Clinical batch (liquid < 30,000 pcs/batch, lyophilizer < 5m²)

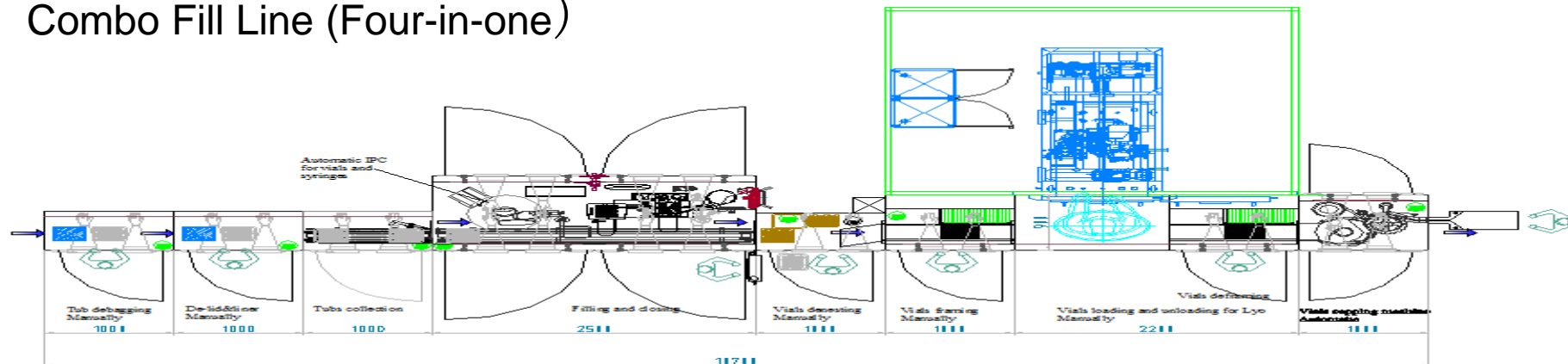
Combo Fill Line (Three-in-one)



Process machine Container type		De-bagging machine	De-lid & liner machine	Filling and stoppering	De-nest ing	Capping
RTU nest	RTU Syringe	√	√	√	—	—
	RTU Cartridge	√	√	√	—	—
	RTU Vial	√	√	√	√	√

2. For Clinical batch (liquid <30,000 pcs/batch, lyophilizer <5m²)

Combo Fill Line (Four-in-one)



Process machine Container type		De-bagging machine	De-lid & liner machine	Filling and stoppering	De-nest machine	Loading & unloading	Freeze dryer	Capping	Outer wall cleaning
RTU nest	RTU Syringe	✓	✓	✓	—	—	—	—	—
	RTU Cartridge	✓	✓	✓	—	—	—	—	—
	RTU Vial	✓	✓	✓	✓	✓	✓	✓	✓

Combo Filling Line Capacity

Packaging material	specification	Nest specification	Capacity (per hour)			
			PFS 1000	PFS 2000	PFS 5000	PFS 10000
Prefilled syringe	0.5ml	160	1000	2400	5200	9200
	1ml	100	900	2100	4500	8000
	3ml	100	760	1700	3800	6800
	5ml	64	670	1570	3800	6000
	10ml	42	360	840	3300	3200
	20ml	30	220	520	1800	2000
Vial	2R	120	1000	2200	5000	9000
	4R	120	850	1870	4200	7600
	6R	48	420	930	2100	3800
	8R	48	300	800	1500	2600
	10R	48	300	800	1500	2000
	20R	25	150	400	3000	1000
Cartridge	3ml	100	760	1700	5000	6000

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

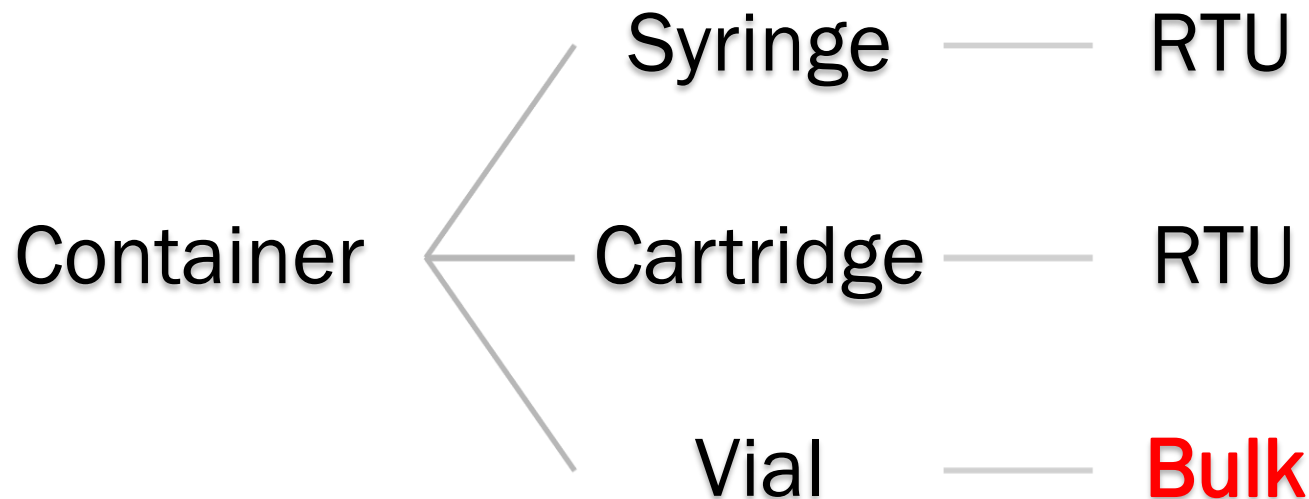
Containers specification:

Prefilled syringe: 0.5ml, 1ml long, 1ml, 2.25ml, 3ml, 5ml, 10ml, 20ml

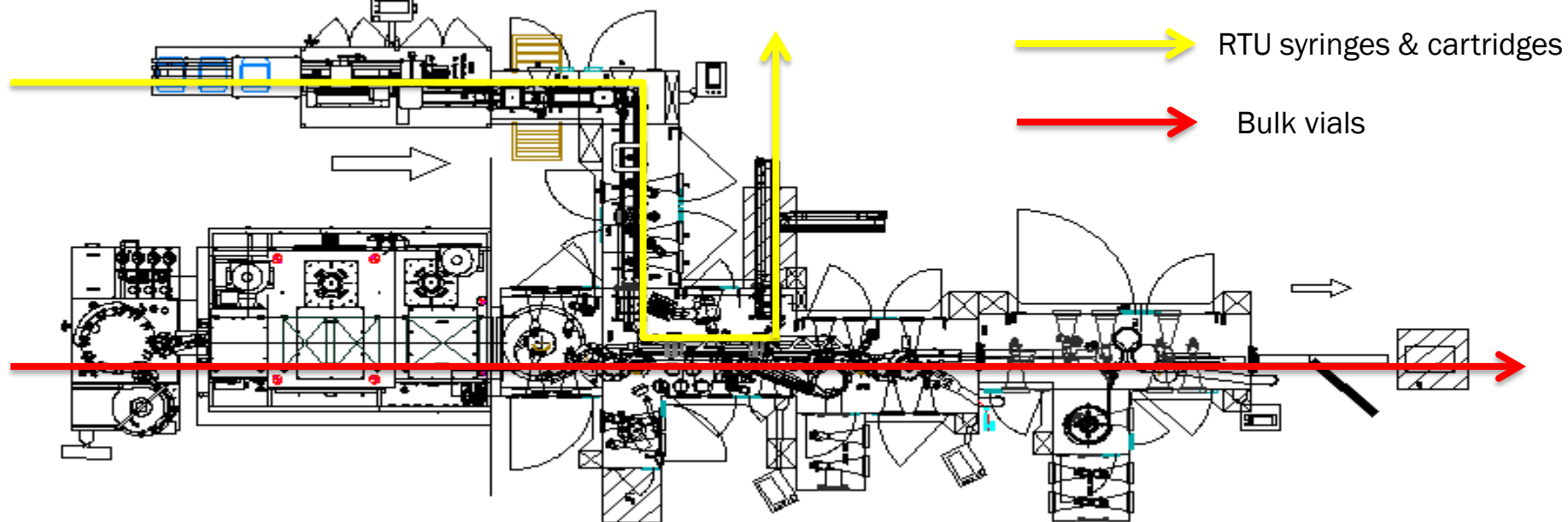
Vial: 2R, 4R, 6R, 8R, 10R, 20R

Cartridge: 3ml

3. For Mass batch (liquid > 90,000 pcs/batch, freeze dryer > 5m²)

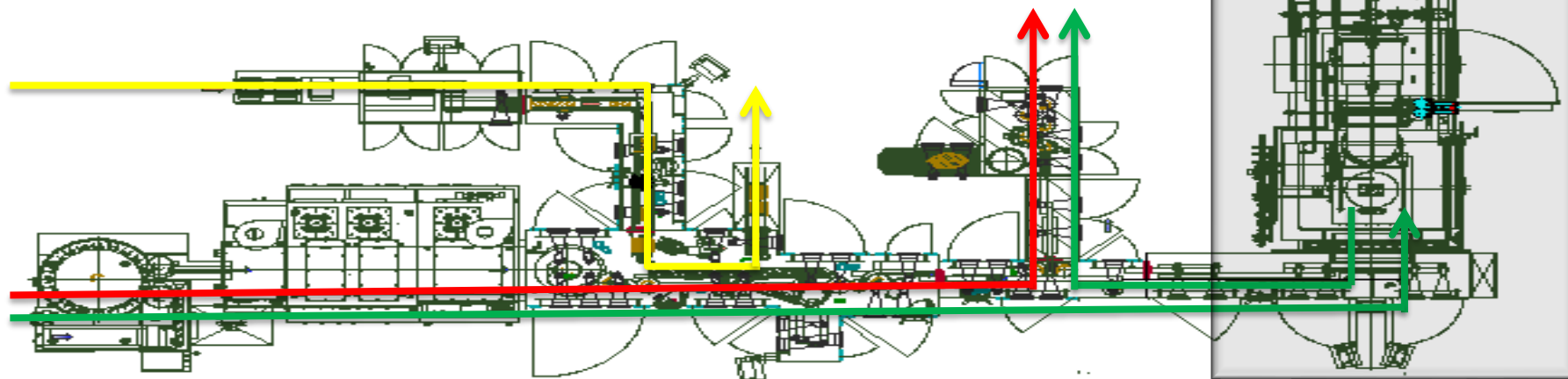
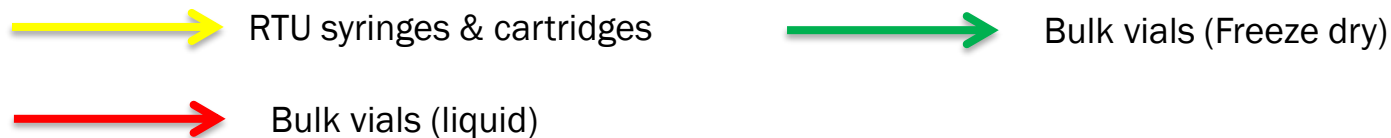


3. Combo Filling Line (liquid Bulk Vial & RTU Syringe & RTU Cartridge)



Process machine / Container type		De-bagging machine	De-lid & liner machine	Washing machine	Tunnel	Filling and stoppering	Capping
RTU nest	RTU syringe	√	√	—	—	√	—
	RTU Cartridge	√	√	—	—	√	—
	Bulk Vial	—	—	√	√	√	√

3. Combo Filling Line (Freeze dry Bulk Vial & RTU Syringe & RTU Cartridge)



Process machine Container type		De-bagging machine	De-lid & liner machine	Washing machine	Tunnel	Filling and stoppering	Auto- loading & unloading	Freeze dryer	Capping
RTU nest	RTU syringe	✓	✓	—	—	✓	—	—	—
	RTU Cartridge	✓	✓	—	—	✓	—	—	—
	Bulk Vial	—	—	✓	✓	✓	✓	✓	✓

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.

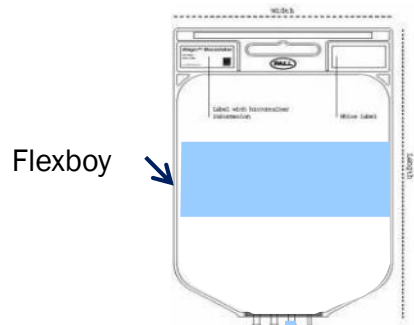
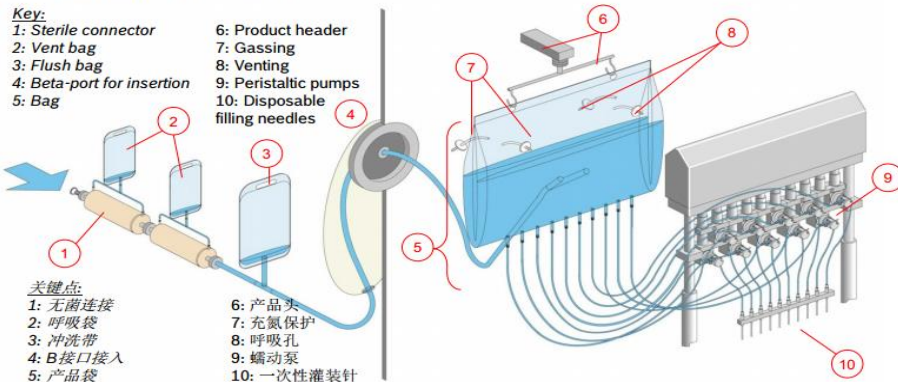
In addition to carefully cleaning and validating the cleaning results, we recommend that:

- ✓ 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

一次性灌装系统介绍



Flexboy

Pinch clamp

Sterile connector



Y-Dispensers

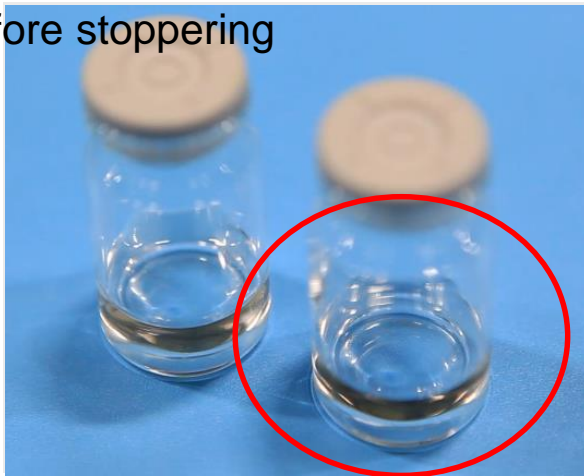
Filling heads

Risk 2- Product is oxidized

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

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

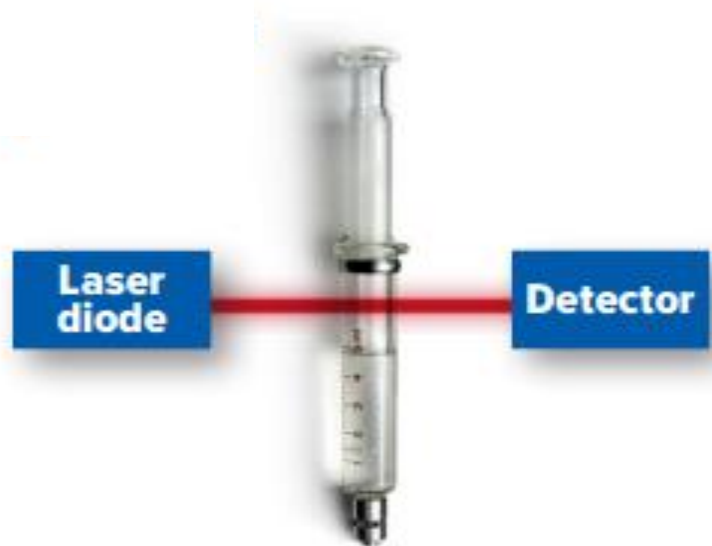


Bubble size
< 6 microlitre

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



西林瓶
Vials

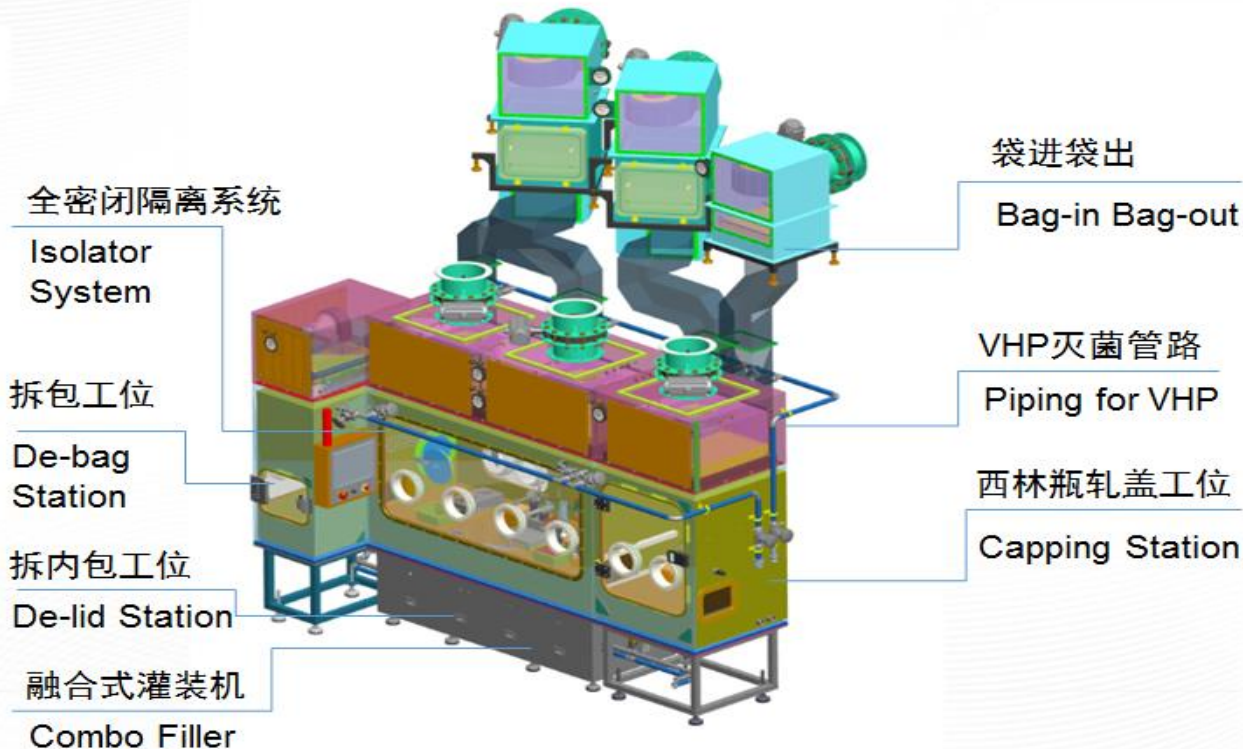


卡式瓶
Cartridge



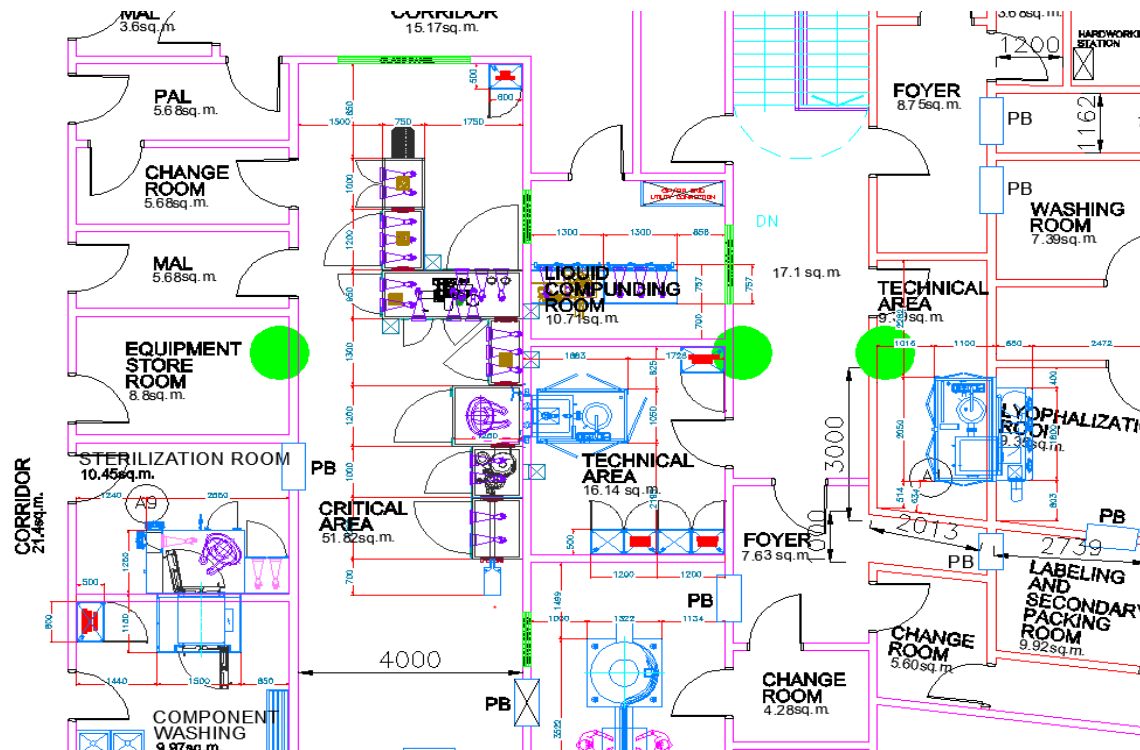
预灌针
PFS

注射剂柔性制造解决方案
Flexible Injectable Solution



Case 2 Mini Combo Fill Line- PFS 2000M

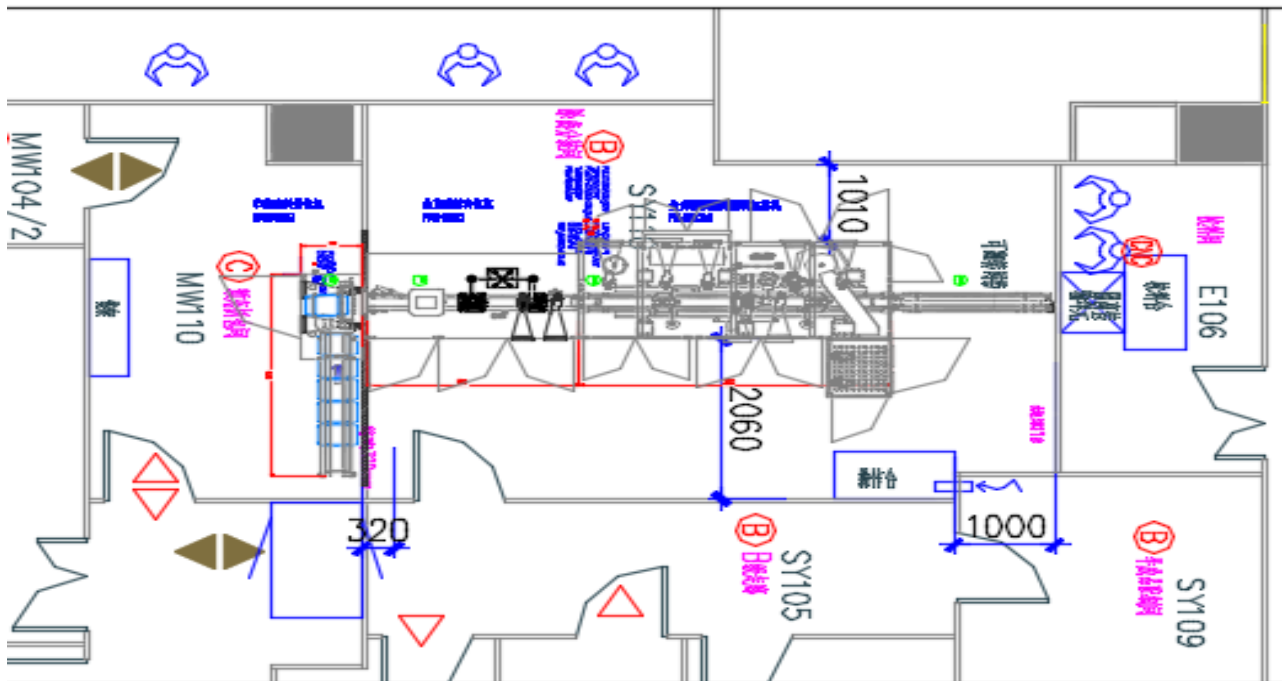
Malaysia project, Syringe +Vial +Cartridge



- ◆ Biopharmaceutical
- ◆ Toxic
- ◆ Isolator
- ◆ Lyo (0.5m²) for vials
- ◆ Filling room 51.82 m²
- ◆ Lyo room 16.14m²
- ◆ Processing room 10.71m²

- www.tofflon.com**

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

