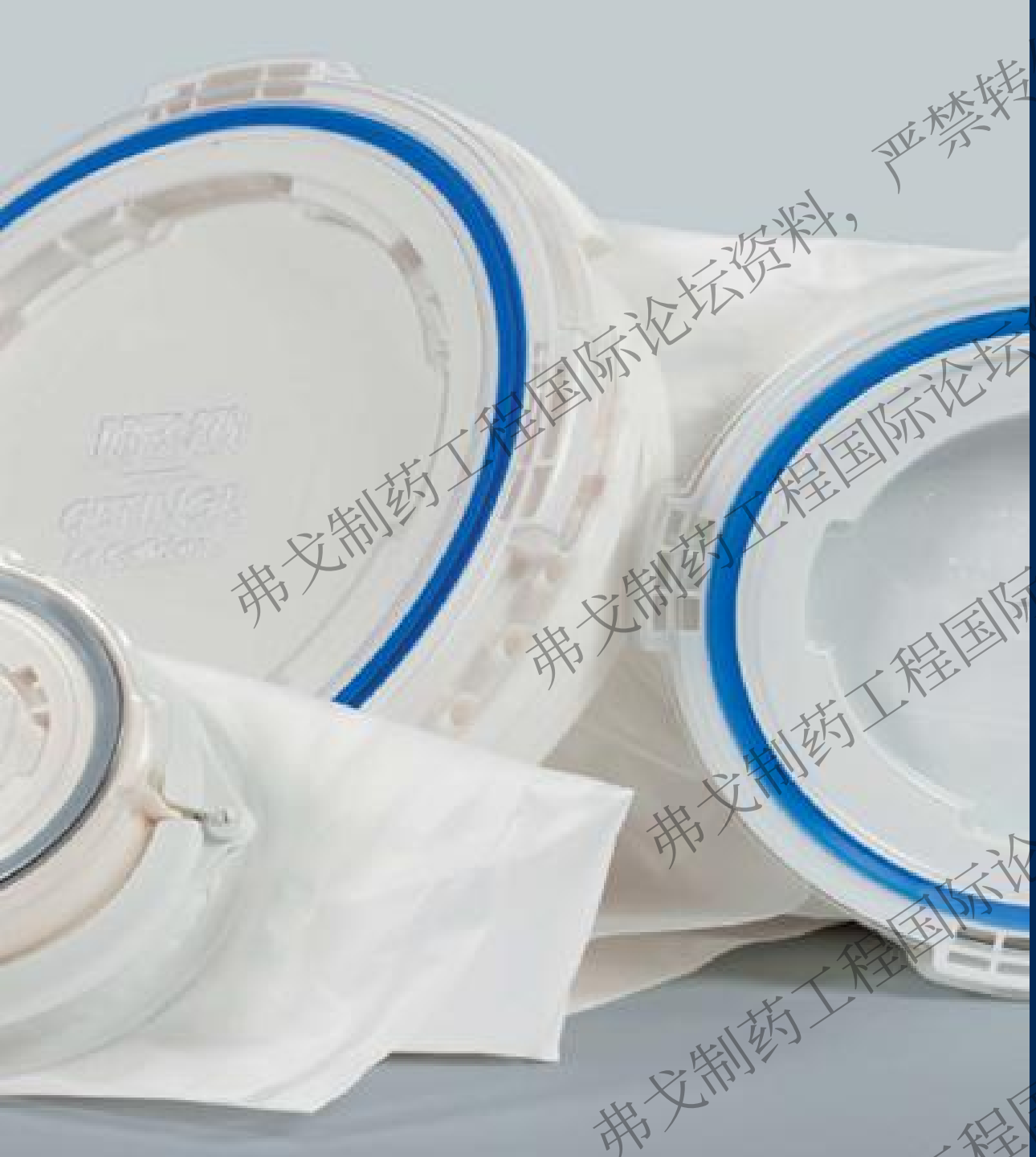


经典RTP转运方案
-DPTE®系统应用于受控环境的物料转运

Application of original RTP solution
- using DPTE® systems to transfer materials in contained environment

Vogel pharmaceutical弗戈制药论坛
Jane Jian简莎娜
20th of Sep

GETINGE

Agenda

I. Getinge

II. Protected processing area受保护的工作环境

III. How to ensure sterility / containment during the transfer of materials in classified rooms
如何在不同等级环境中保障物料转运的无菌和受控

   a. Transfer Systems for Clean Rooms, RABS & Isolators洁净室、RABS和隔离器的转运系统

   b. The DPTE® system has been developed originally for the nuclear industry为核工业开发的DPTE ®系统

   c. Transfer application多种转运应用

   d. DPTE-BetaBag®一次性方案

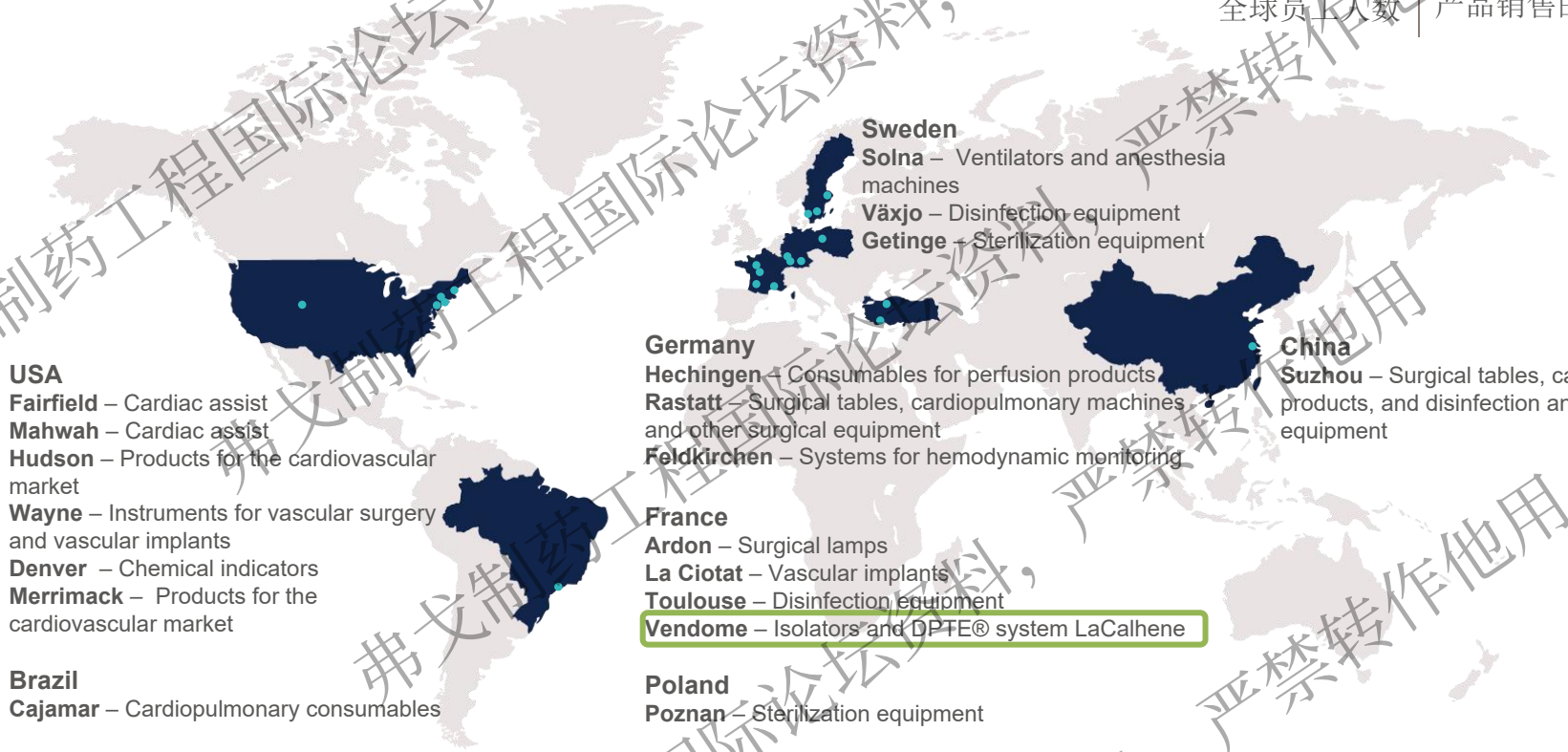
IV. Transfer Leak Tester TLT for DPTE® 完整性检测设备保障过程的完整

Getinge

公司简介

在8个国家内拥有21 个工厂

哥德堡, 瑞典	1904	+40 个国家
总部驻地	瑞典Getinge成立	独立运营
+10,000	**+150**	**26 BSEK**
全球员工人数	产品销售的国家	2019净销售额



USA
Fairfield – Cardiac assist
Mahwah – Cardiac assist
Hudson – Products for the cardiovascular market
Wayne – Instruments for vascular surgery and vascular implants
Denver – Chemical indicators
Merrimack – Products for the cardiovascular market

Brazil
Cajamar – Cardiopulmonary consumables

Sweden
Solna – Ventilators and anesthesia machines
Växjo – Disinfection equipment
Getinge – Sterilization equipment

Germany
Hechingen – Consumables for perfusion products
Rastatt – Surgical tables, cardiopulmonary machines, and other surgical equipment
Feldkirchen – Systems for hemodynamic monitoring

France
Ardon – Surgical lamps
La Ciotat – Vascular implants
Toulouse – Disinfection equipment
Vendome – Isolators and DPTE® system LaCalhene

Poland
Poznan – Sterilization equipment

Turkey
Antalya – Consumables for perfusion products
Ankara – Low temperature sterilization technology, and sterilization equipment

China
Suzhou – Surgical tables, cardiovascular products, and disinfection and sterilization equipment

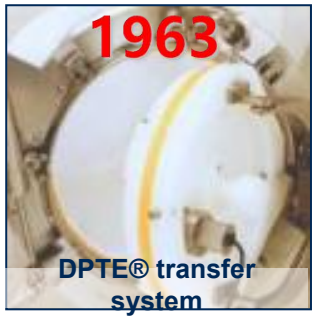
GETINGE

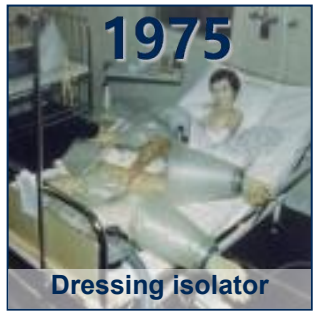
GETINGE La Calhène 隔离器和DPTE®生产中心

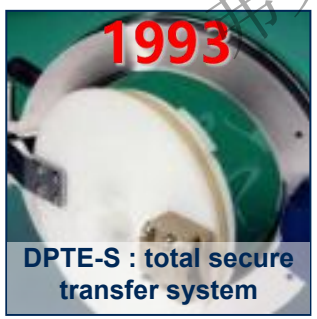
- 旺多姆 (法国, 41) Vendôme *(France, 41)*
- 8 600 m2 *(92,600 sqf)*
- 220 多名员工 More than 220 employees
- 1970年开始成为隔离器的生产中心 (3200+ 台隔离器在这里设计生产，并销售到世界各地)
- Center of Excellence for isolators since 1970 *(**3200+ isolators** designed and manufactured worldwide)*
- **DPTE®** 系统的创造者 The DPTE® inventor

GETINGE

50余年的研发创新，深厚的经验积累 50 years of innovations, a long journey!







GETINGE

Protected Processing Area

受保护的工作环境

Uses of protected areas in Pharma Industry受保护环境在药品生产中的应用

- Protection of product vs biological and particulate contaminations in ASEPTIC PROCESSING
  在无菌环境中保护产品免受生物和微粒污染
- Protection of people vs chemical contamination in CONTAINMENT PROCESSING
  在受控环境中保护人员免受化学危害
- Protection of Product & protection of people in ASEPTIC PROCESSING OF TOXIC PRODUCT
  毒性产品的无菌处理中，产品保护和人员保护
- Air leaktightness of an enclosure is very important, i.e.容器的气密性非常重要
  - To avoid any interference between inside and outside of the enclosure可避免容器内部和外部之间的干扰,
  - To be able to measure the level of contamination可测量污染程度,
  - To allow a cross protection people/product允许交叉保护人员/产品

ISO 14644-1

ISO 14644-1 defines the maximum concentration of particles per class and per particle size with the following formula :

ISO 14644-1使用以下公式定义每个级别和每种粒

$$C_N = 10^N \left(\frac{0.1}{D}\right)^{2.08}$$

度：

Where C_N is the maximum concentration of particles in a volume of 1m³ of airborne particles that are equal to, or larger, than the considered particle size which is rounded to the nearest whole number, using no more than three significant figures, N is the ISO class number, D is the size of the particle in µm and 0.1 is a constant expressed in µm. The result for standard particle sizes is expressed in the following table.其中C_N是等于或大于1m³体积的空气中对应粒径粒子的最大浓度，该粒径四舍五入到最接近的整数，使用不超过三个有效数字，N为ISO 等级数，D是以微米为单位的粒子尺寸，而0.1是以微米为单位的常数。 下表列出了标准粒径的结果。

Class	Maximum particles/m³ [a]						FED STD 209E equivalent
	≥0.1 µm	≥0.2 µm	≥0.3 µm	≥0.5 µm	≥1 µm	≥5 µm	
ISO 1	10						
ISO 2	100	24	10				
ISO 3	1,000	237	102	35			Class 1
ISO 4	10,000	2,370	1,020	352	83		Class 10
ISO 4,8 / 5	100,000	23,700	10,200	3,520	832		Class 100
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293	Class 1,000
ISO 7				352,000	83,200	2,930	Class 10,000
ISO 8				3,520,000	832,000	29,300	Class 100,000
ISO 9				35,200,000	8,320,000	293,000	Room air

EU GMP classification分级

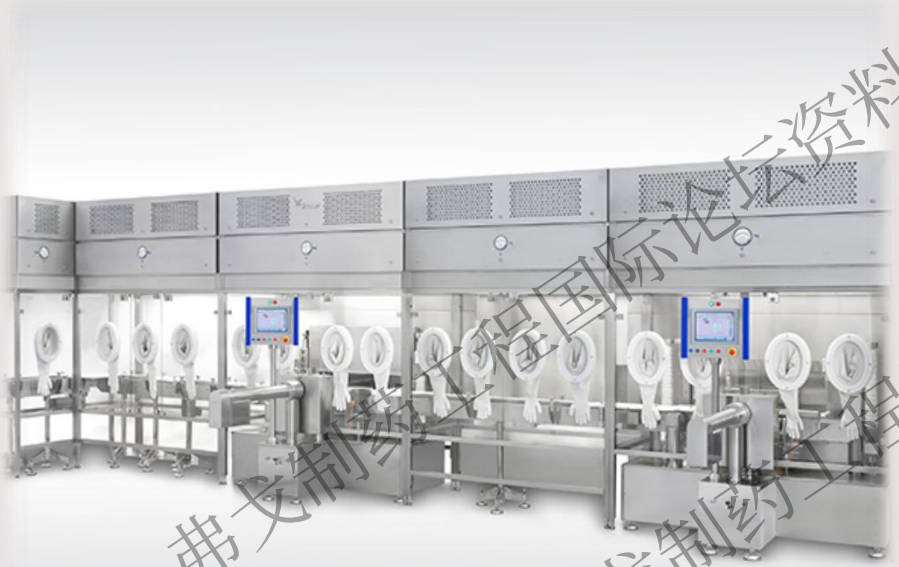
EU GMP guidelines are more stringent than others, requiring cleanrooms to meet particle counts at operation (during manufacturing process) and at rest (when manufacturing process is not carried out, but room air handling unit is on)
EU GMP准则比其他准则更严格，要求洁净室在操作时（制造过程中）和休息时（在不执行制造过程但室内空气处理装置开启时）要满足颗粒计数的要求.

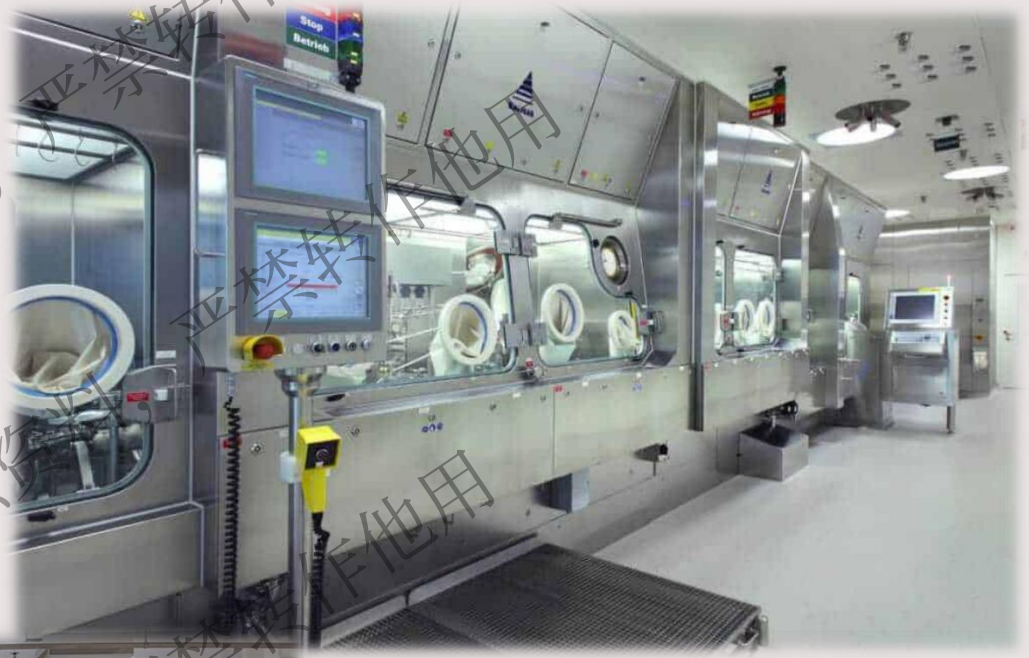
Class	Maximum particles/m^3[25]			
	At Rest		In Operation	
	0.5 µm	5 µm	0.5 µm	5 µm
Grade A	3,520	20	3,520	20
Grade B	35,200	29	352,000	2,900
Grade C	352,000	2,900	3,520,000	29,000
Grade D	3,520,000	29,000	Not defined	Not defined

3 main technologies 3种主要技术:

- Traditional clean room technology传统洁净室技术
- Barrier technology - RABS (Restricted Access Barrier System)屏障技术- -RABS(限制进入屏障系统)
- Barrier technology – Isolator屏障技术- -隔离器

Cleanrooms or classified room洁净室或符合规范的操作空间





GMPs requirements要求 (1)

FDA – Guidance for Industry “Sterile Drug Products...”, 2004

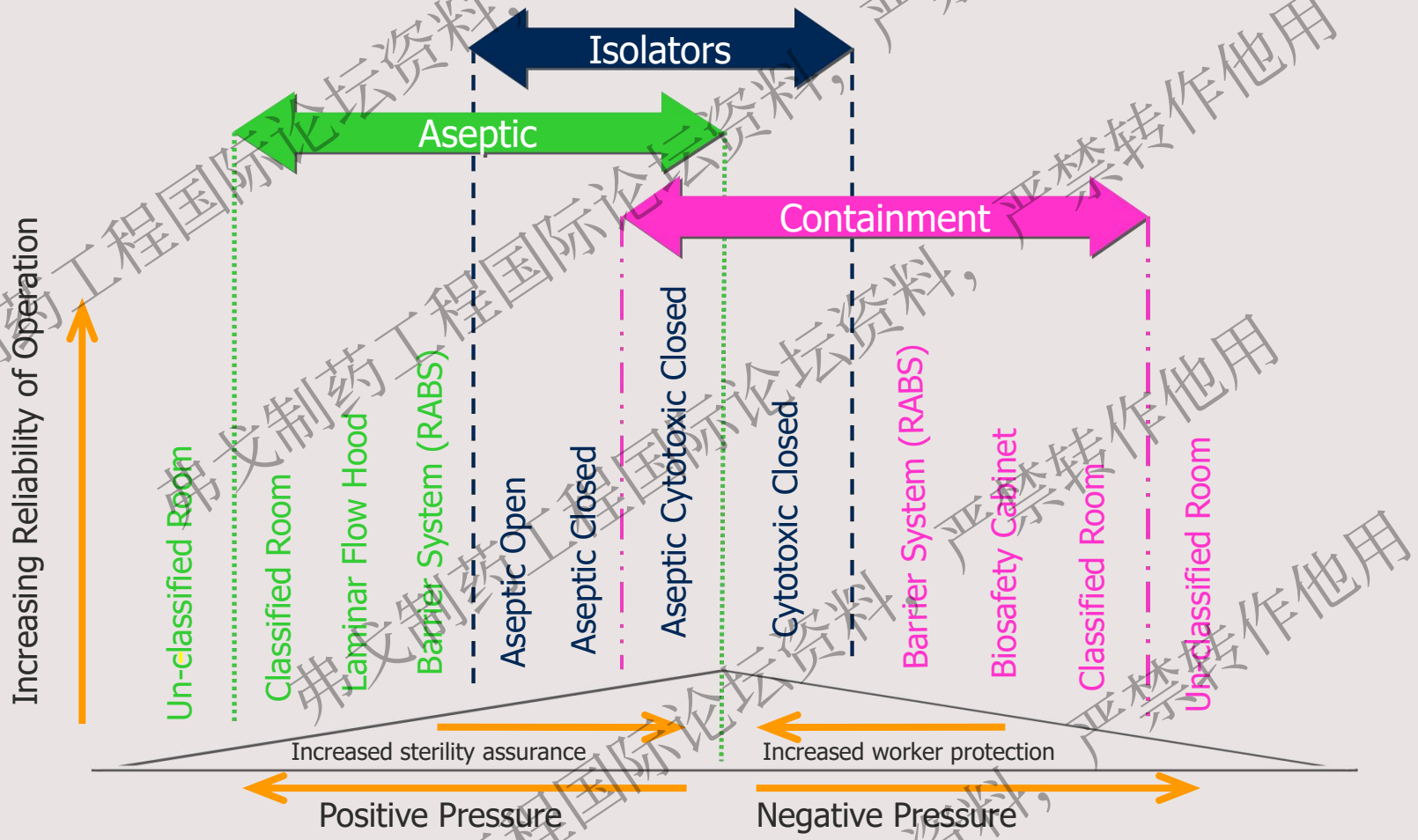
- An essential part of contamination prevention is the adequate separation of areas of operation. To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas. It is vital for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness.防止污染的重要步骤是适当隔离操作区域。 为了保持空气质量，重要的是要确保从较高清洁度区域到相邻较不清洁区域的适当气流。 对于空气清洁度较高的房间，相对于相邻的空气清洁度较低的房间，要有相当大的正压差至关重要
- Aseptic processing using isolation systems separates the external cleanroom environment from the aseptic processing line and minimizes its exposure to personnel. A well-designed positive pressure isolator, supported by adequate procedures for its maintenance, monitoring, and control, offers tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing.使用隔离系统进行的无菌处理将外部洁净室环境与无菌处理线分开，并最大程度地减少人员暴露。 设计良好的正压隔离器，辅以适当的维护，监控和控制程序，与传统的无菌工艺相比，具有明显的优势，包括加工过程中微生物污染的机会更少。

GMPs requirements (2)

EU Guidelines to Good Manufacturing Practice,
Annex 1 Manufacture of Sterile Medicinal Products, 2008无菌药品生产

[...] The utilization of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. [...] The isolator and the background environment should be designed so that the required air quality for the respective zones can be realized.隔离器技术的应用可降低过程中人为干扰，减少无菌产品生产中来自环境的微生物污染风险。[...]隔离器及其背景环境设计必须方便实现各个区域所需的空气质量。

Summary : Ultimate Level of Containment



Ensure sterility/containment during transfer of materials in classified rooms

如何在不同等级环境中保障物料转运的无菌和受控

Transfer Systems for Cleanrooms, RABS & Isolators
洁净室、RABS和隔离器的转运系统

Transfer systems - What is the application?转运系统的应用
What are the process requirements ?过程中要求

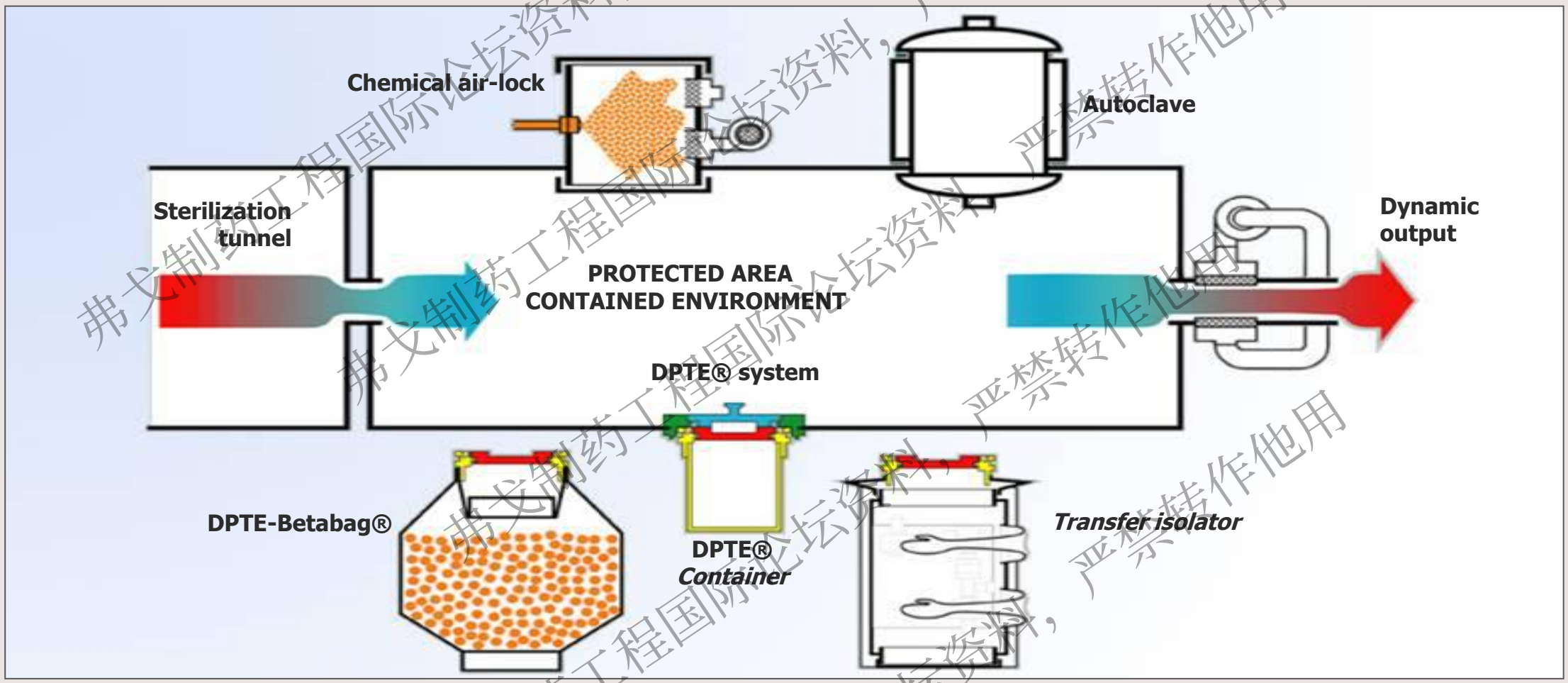
Frequent uses for Aseptic and/ or Toxic transfers:

- Inlet of liquid product 液体传入
- Powder transfer into formulation vessels, 粉末转入配制容器
- Bulk product transfer : powder 批量产品转运：粉末
- Inlet and outlet of Quality Control test devices 质量控制设备
- Inlet and outlet of tools, filling needles, spare-parts …工具等
- Inlet of closures for bottles or syringes, 包材
- Outlet of waste, rejects…废料
- Outlet of production samples for Quality Control,抽样
- Outlet of semi-finished product, 中间产物
- Material or machine part transfer 机器部件

- **Applicable to:**
  - Fine chemical production, 精细化工生产
  - Compounding, 配制
  - Filling, 灌装
  - Control (Sterility Testing) 质量控制（无菌测试）
  - Hospital pharmacies 医院药房
    - Parenteral Nutrition 肠外营养
    - Cytotoxic preparations 细胞毒性制剂
  - Research & Development.研发

Transfer Systems

How to introduce & exit products and components from a closed area without breaking containment?



Transfer Systems: different types

- Sterilization tunnel
  - E-beam 电子束
  - Depyrogenation tunnel 去热源隧道
- Double doors systems 双门系统
  - Autoclaves 湿热灭菌柜
  - Oven 炉
  - Airlocks (materials, integrated or mobile) 传递窗
- Bag in / bag out system 袋进袋出系统
- RTP system 快速转运端口系统

GMPs requirements

EU Guidelines to Good Manufacturing Practice,
Annex 1 Revision: Manufacture of Sterile Medicinal Products (Draft)

Isolator or RABS technologies, and the associated processes, should be designed to provide protection of the Grade A environment. The entry of materials during processing (and after decontamination) should be minimized and preferably supported by rapid transfer technologies or transfer isolators.各种屏障技术提供A级环境，并通过快速传递技术或转运隔离器保障工艺过程中物品的传递。

Transfer systems - Air leak tight testing转运技术- -气密性测试

When a transfer system is attached onto the isolator (eg autoclave), it is tested with the same criteria as the isolator itself 气密性等同于隔离器

When the transfer system is mobile and can be disconnected (eg RTPs) the two parts have to be tested separately 可合并或独立进行测试

The DPTE® system has been developed originally for the nuclear industry

为核工业开发的DPTE ® 系统

DPTE® transfer system – History 历史

- The first DPTE® was marketed in 1963 and developed with the French Nuclear Agency (CEA) for nuclear application.研发
- DPTE® is an original LaCalhene (now Getinge) product, holding the patent until late 90's.专利
- DPTE® system allows immediate and safe connection between 2 closed volumes. 功能
- It is a mechanical and simple system and its design allows transfer without breaking the containment.性能
- Applied for pharmaceutical application late 70's.应用

1963

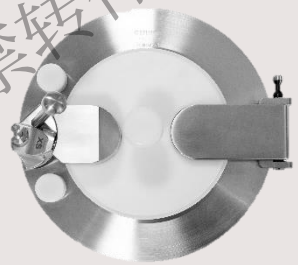
- 1st DPTE® Transfer System is developed by La Calhène for transfer of highly toxic nuclear material

1993

- DPTE®-S: Alpha door cannot open if the Beta component is not correctly connected or positioned.
- The devices cannot be separated if the Alpha-Beta door assembly is open

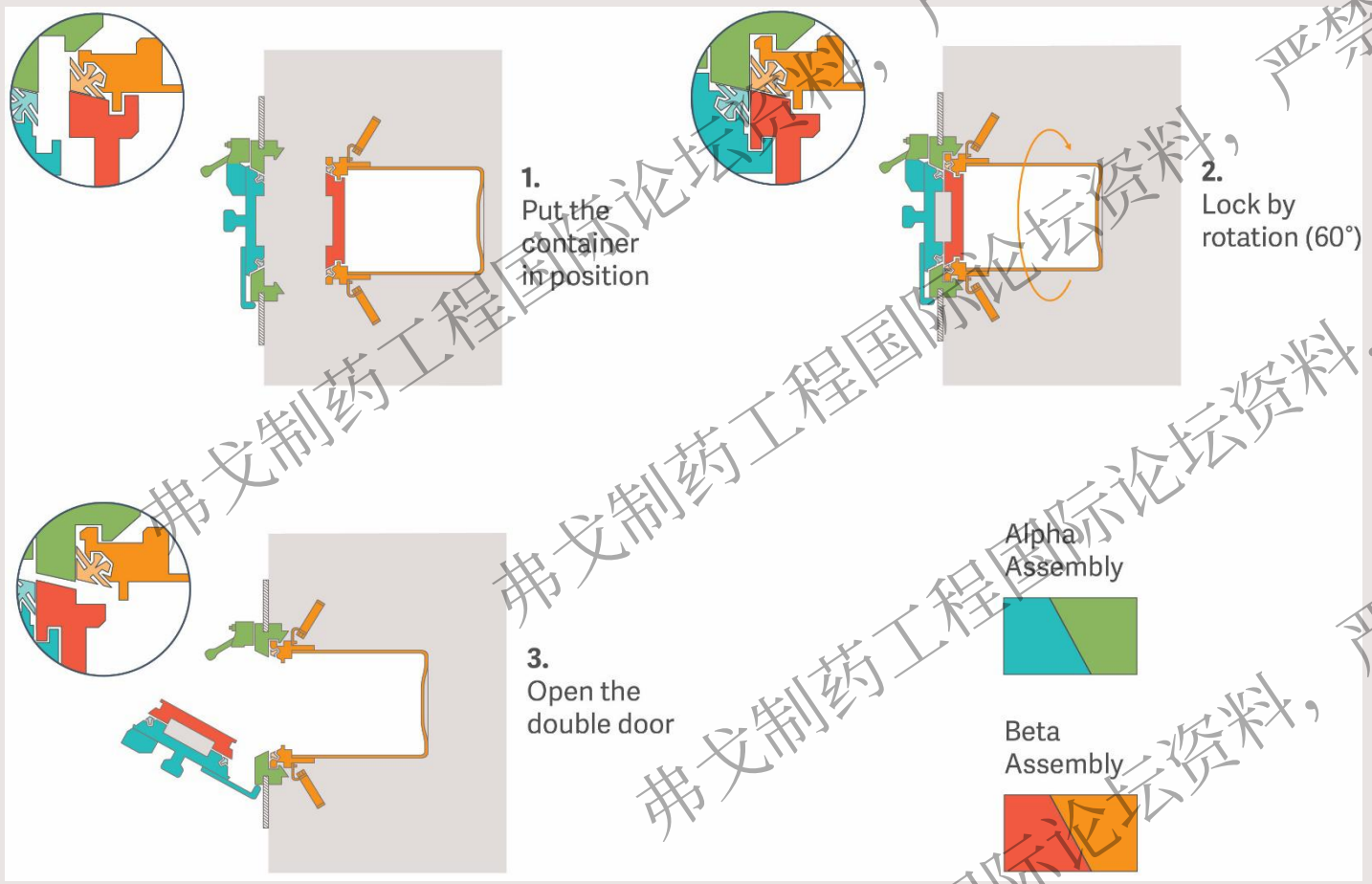
2012

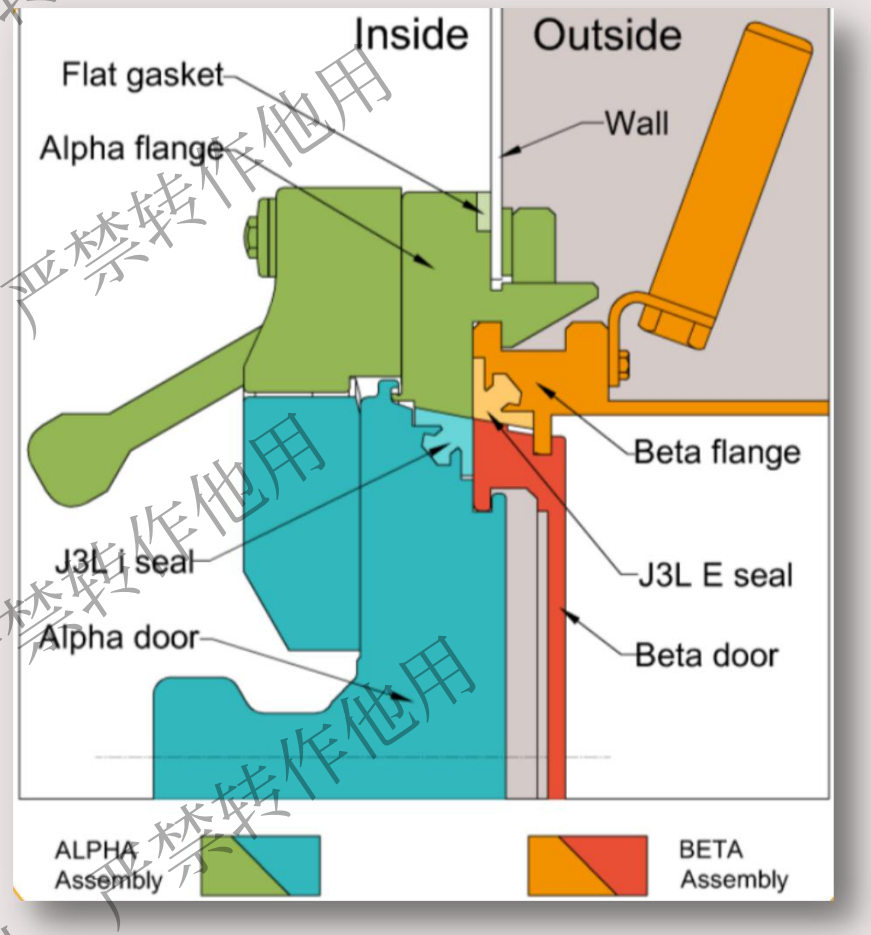
- DPTE®-XS is developed for an improved degree of safety with its locking system



DPTE® principle原理

https://www.youtube.com/watch?v=gBnQKd_SYRs





- Standard sizes are : 105 mm / 190 mm / 270 mm / 350 mm / 460 mm

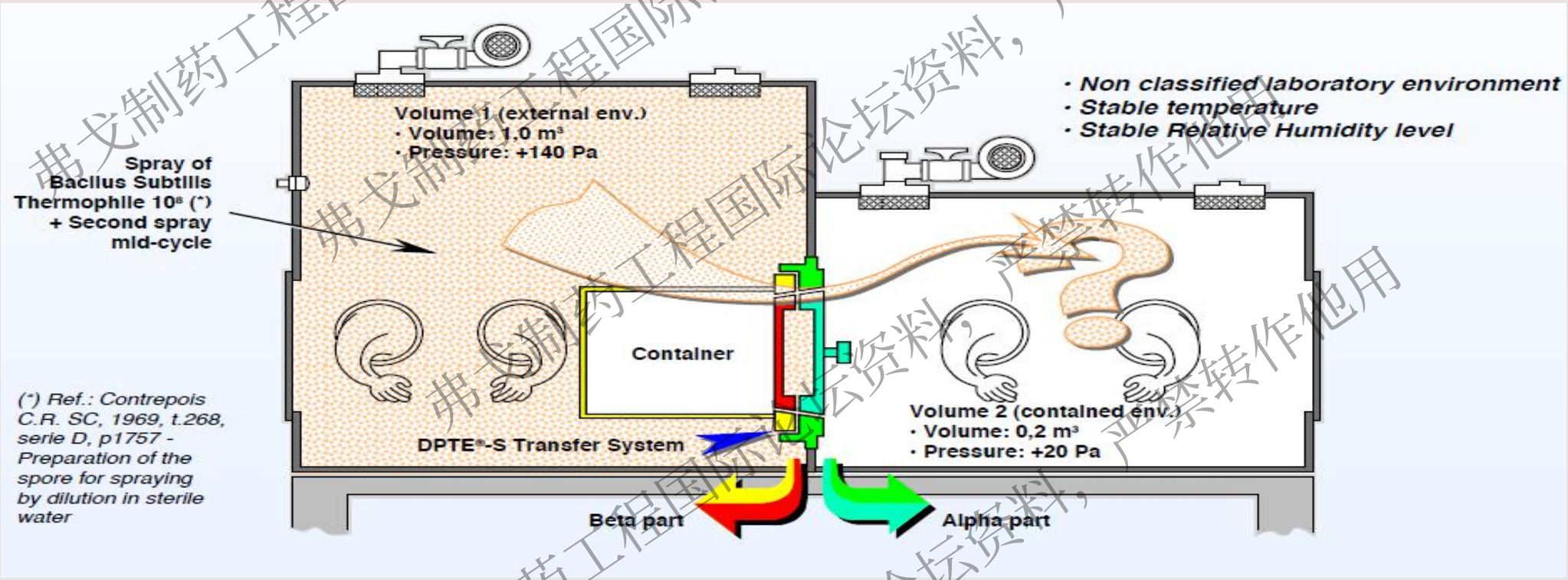
DPTE®-XS prevent from

- Opening the DPTE® alpha door when a DPTE ® beta part is not connected. 当Beta未对接时alpha无法打开
- Opening the DPTE alpha door when a DPTE beta part is not properly (completely) connected. 当Beta未正确操作时alpha无法打开
- Opening the DPTE alpha door when the DPTE beta part is not equipped with beta door.当beta门部分未对接时alpha门无法打开
- Disconnecting the DPTE beta part when the double door is not closed. 当双门未关闭时beta无法取下

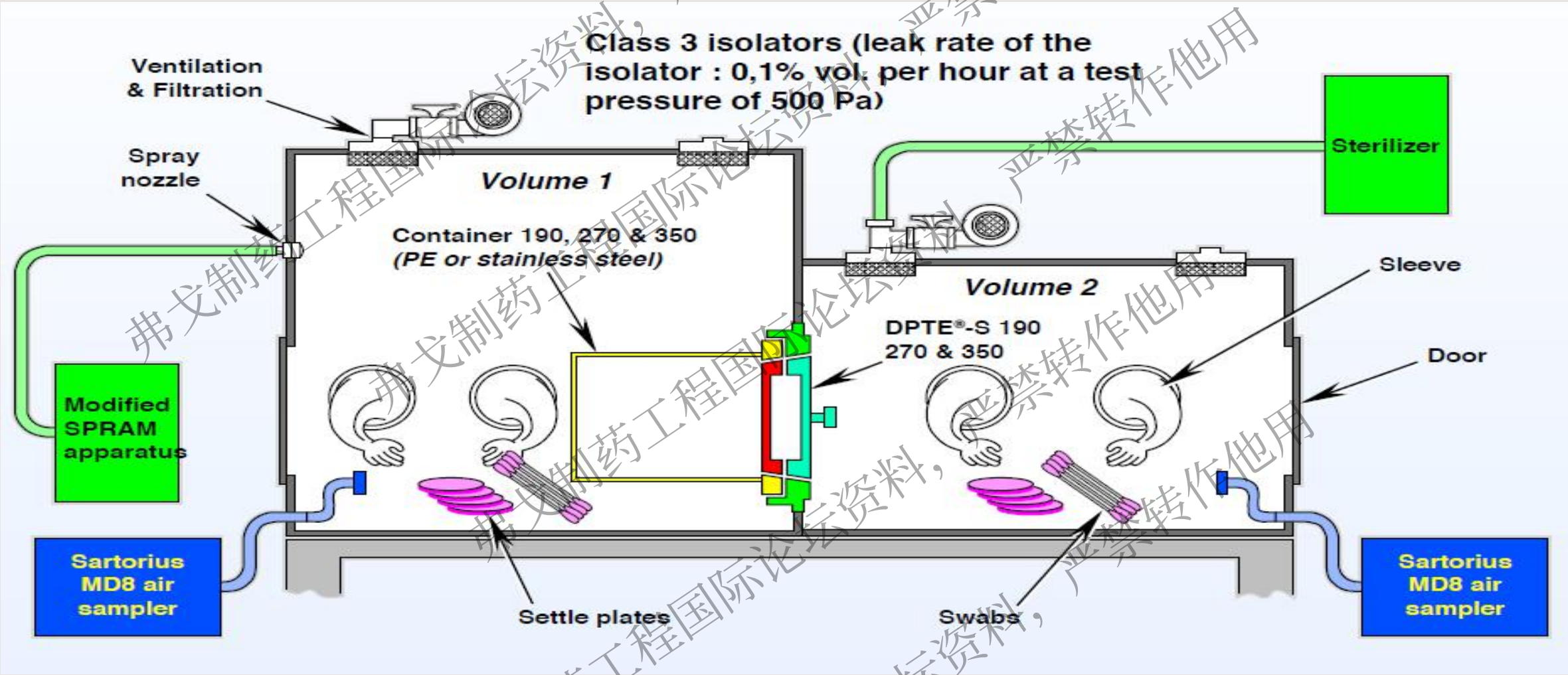
DPTE®-XS validation studies 验证实验(1/3)

FDA Guidance states that “integrity of a decontaminated isolator can be affected and impacted by the design of transfer ports” and that some RTPs may have “significant limitations, including marginal decontaminating capability”物料转运方式会影响隔离器的完整性，部分RTP具备有效密闭和防止污染的能力

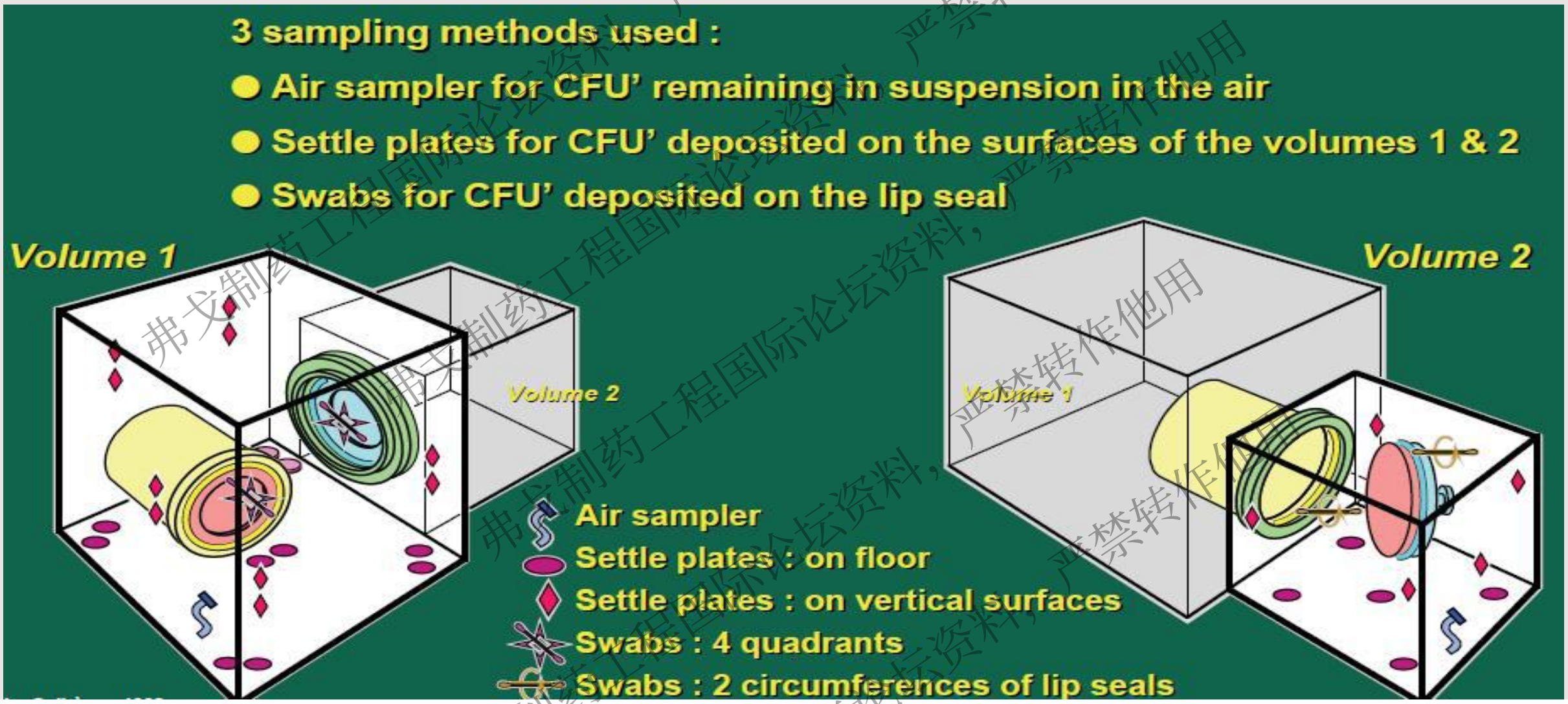
FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice



DPTE®-XS validation studies (2/3)

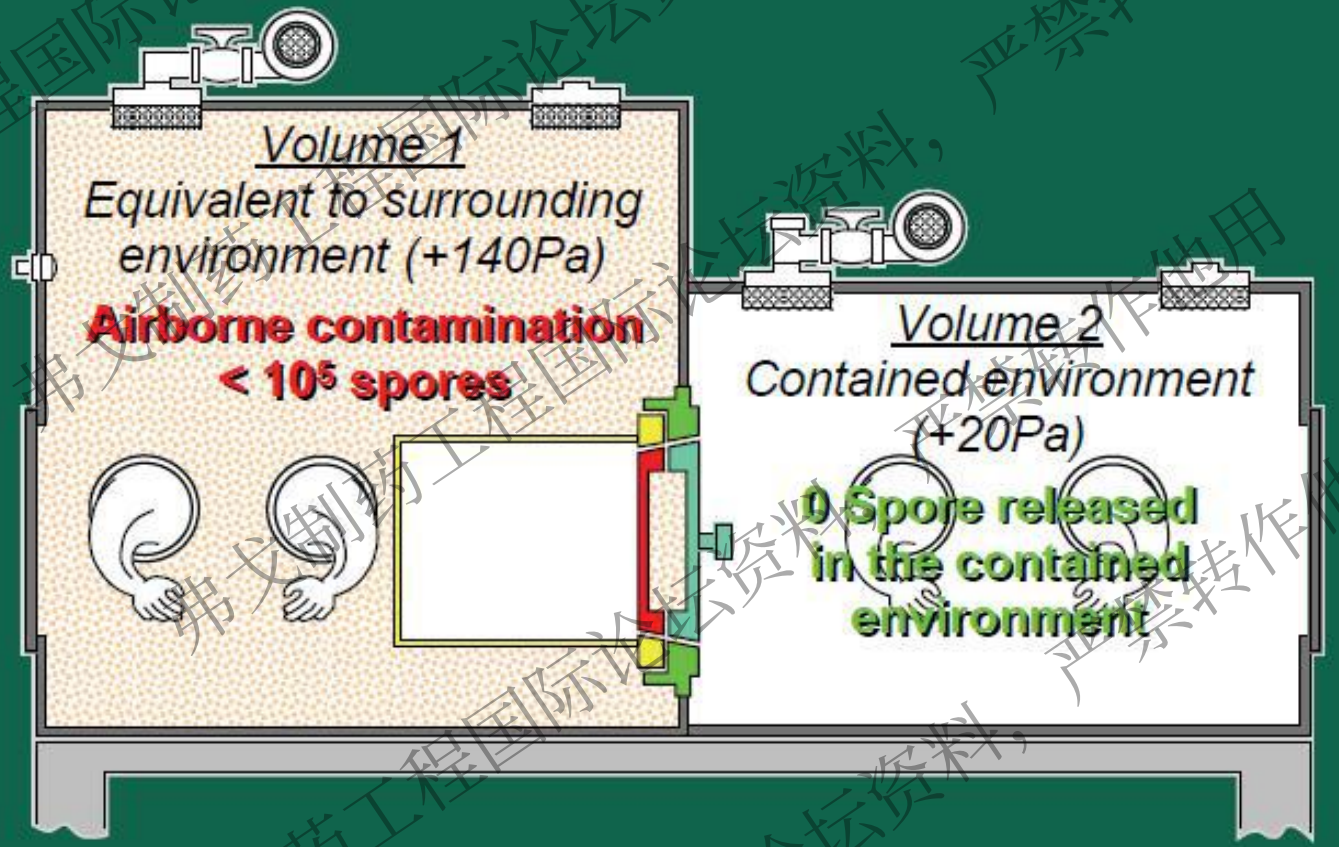


DPTE®-XS validation studies (3/3)



DPTE®-XS validation conclusions

- **No viable airborne contamination was measured in the volume 2 during 75 transfers, for a minimum level of viable airborne contamination in volume 1 < 10^5**

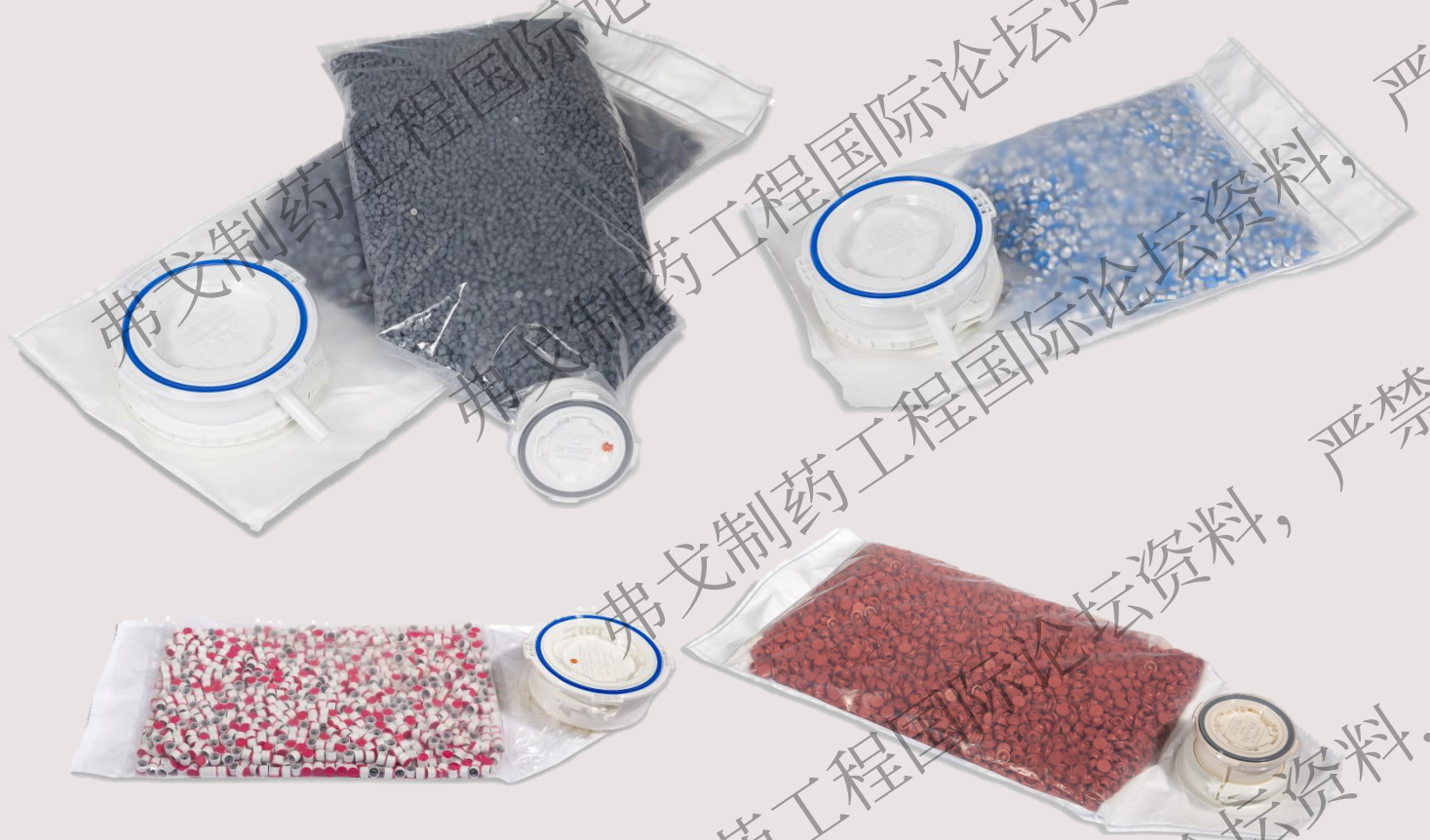


Transfer applications

多种转运应用

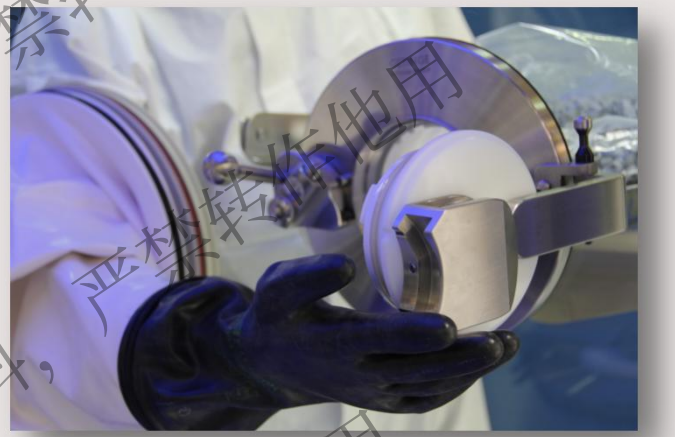
Inlet of closures (caps, stoppers, and plungers) for bottles or syringes包材传入

DPTE-BetaBag® - disposable / single use solution



DPTE-BetaBag® - transfer stages

Connection of the DPTE-BetaBag®



Opening of the DPTE® system (Alpha & Beta)

Unrolling of the inner sleeve

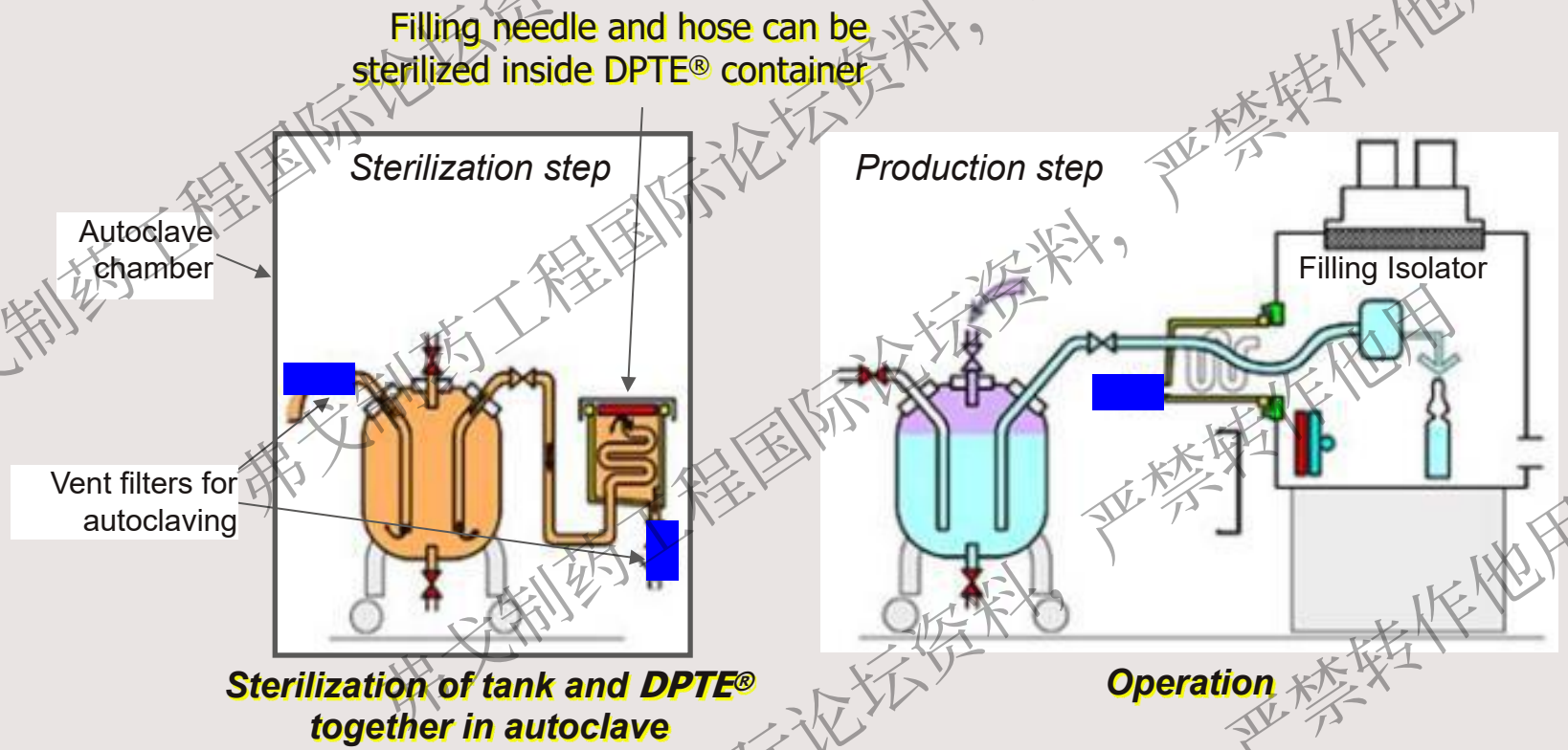
Discharging of the components

Inlet of liquid product

DPTE® Stainless steel reusable solution for Liquid Transfer

DPTE® Liquid Transfer Containers

Autoclave sterilization



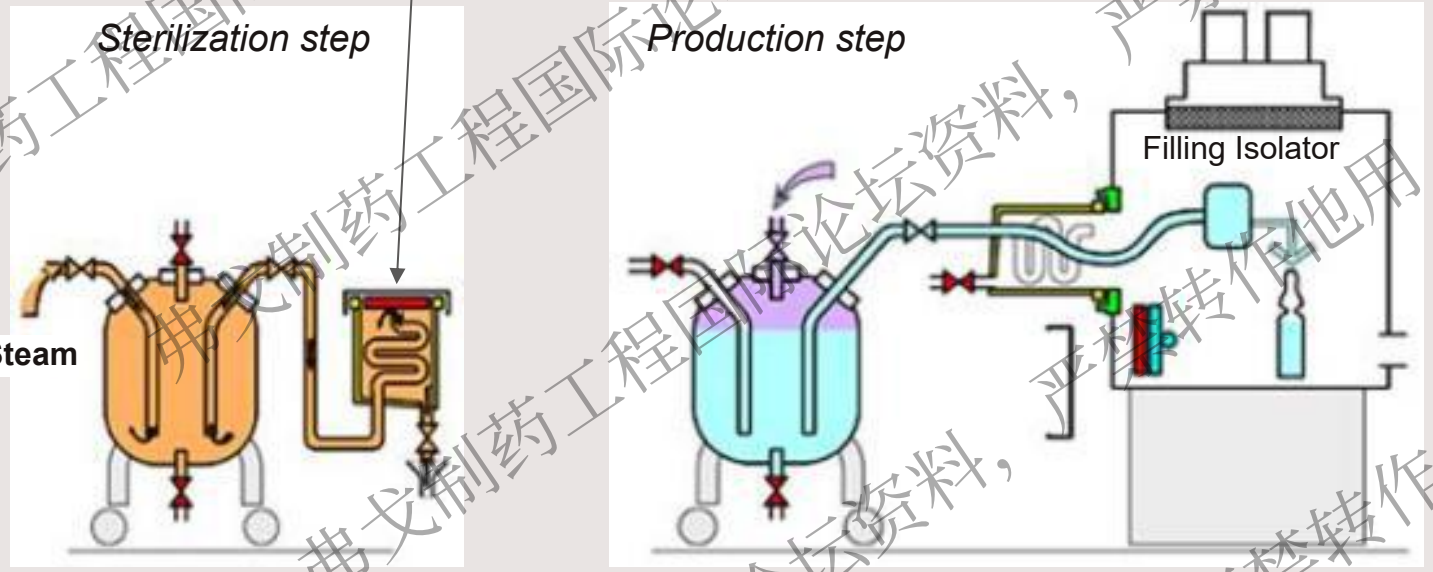
Sterilization of tank and DPTE® together in autoclave

Operation

DPTE® Liquid Transfer Containers

SIP sterilization

Filling needle and hose usually not sterilized inside DPTE® container



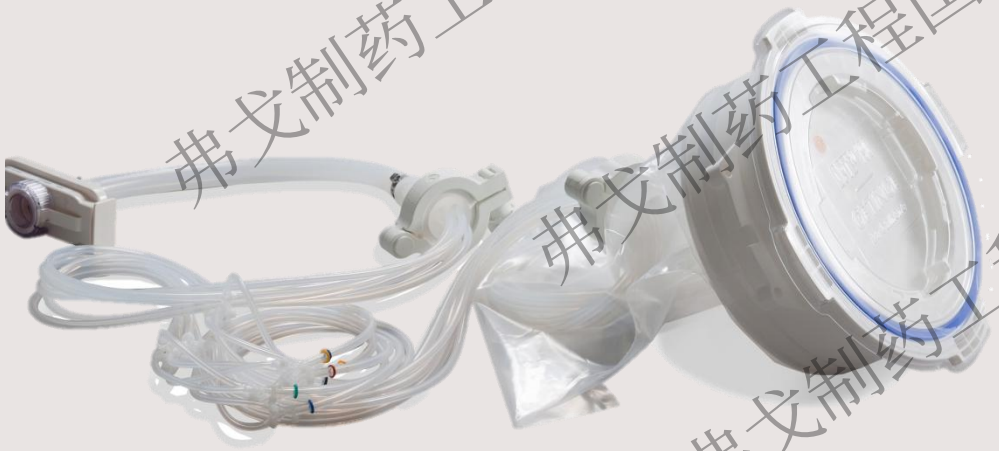
Sterilization of tank and DPTE® together

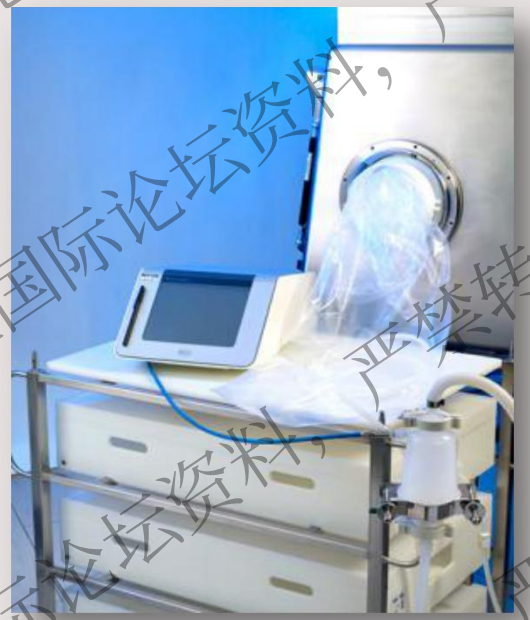
Operation

Inlet of liquid product

DPTE-BetaBag® - Disposable / Single Use Liquid Transfer

Courtesy Merck Millipore – PALL – …





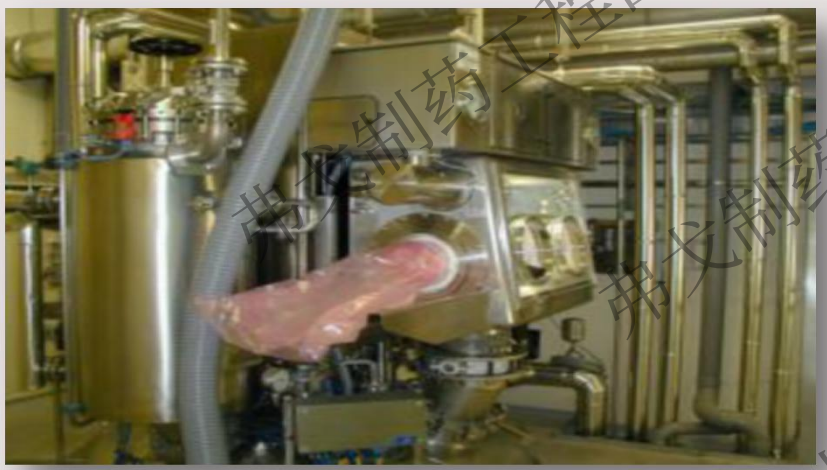
Bulk product transfer of powder – containment粉末传递

DPTE® PolyEthylene reusable solution PE桶

- Containers used to bring in, remove or transfer material from one isolator to an other one可用于传入传出
- J3L lip seals in EPDM (FDA 21CFR177.2600 compliant)材质合规
- HDPE door and flange, MDPE body, aluminium handles
- Can be sterilised by gamma radiation (or H2O2 / APA)灭菌
- Used mainly for potent material
- Exist in DPTE® 105, 190, 270, 350 & 460

Bulk product transfer of powder - containment

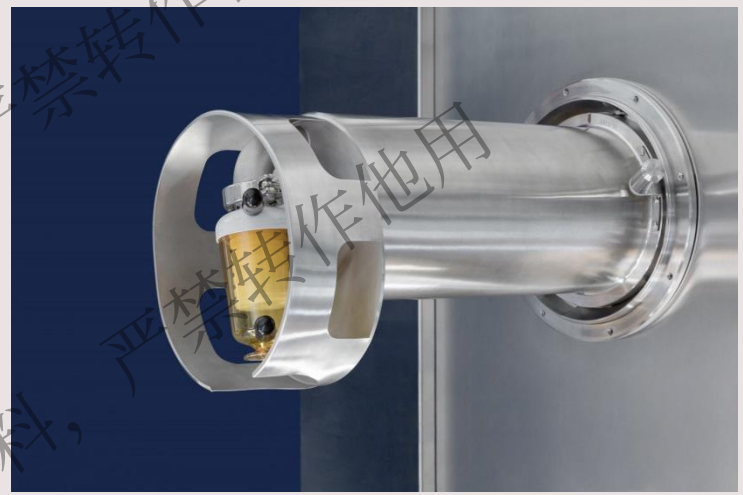
DPTE® disposable / single use solution



Inlet and outlet of tools, filling needles, spare-parts, machine parts, ….工具转运

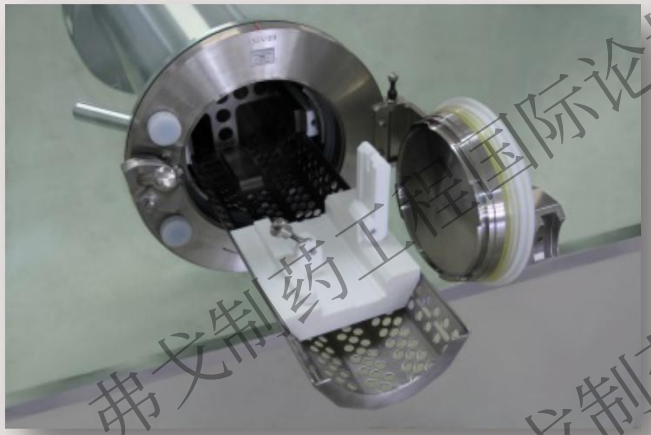
DPTE® Stainless Steel reusable solution 不锈钢重复使用方案

- These containers are used to sterilize material before bringing it into the isolator or to remove material from sterile environment无菌
- Silicon J3L seals
- AISI316L stainless steel (1.4404 / X2CrNiMo17-12-2) door, flange and body
- Sterilisation by autoclave with its protective cover and vent filter可反复灭菌



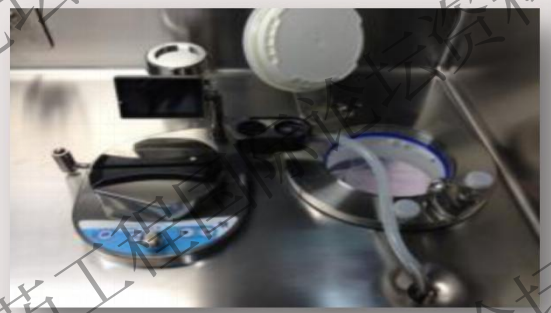
Inlet and outlet of tools, filling needles, spare-parts, machine parts, ….

DPTE® Stainless Steel reusable solution



Outlet of waste, rejects…废弃物剔除

DPTE® disposable / single use solution



Inlet and outlet of Quality Control test devices - Outlet of production samples for Quality Control and various application质量控制器具转运

Isobag® Merck Millipore

Transfer Leak Tester TLT for DPTE®

完整性检测设备保障过程的完整

DPTE® TLT (TRANSFER LEAK TESTER)

EU Guidelines to Good Manufacturing Practice,
Annex 1 Revision: Manufacture of Sterile Medicinal Products (Draft),

The materials used for glove systems (for both RABS and isolators), as well as other parts of an isolator, should be demonstrated to have good mechanical and chemical resistance. Integrity testing of the barrier systems, and leak testing of the glove system and the isolator should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined periods, at a minimum at the beginning and end of each batch, and should include a visual inspection following any intervention that may affect the integrity of the system.手套系统（用于RABS和隔离器）以及隔离器其他部件的材料应证明具有良好的机械和化学耐受性。屏障系统的完整性测试、手套系统和隔离器的泄漏测试应采用证明适合的方法进行。测试应在规定的时间内进行，至少在每批开始和结束时进行，并应在可能影响系统完整性的任何干预措施之后进行目视检查。

DPTE® TLT (TRANSFER LEAK TESTER)

Which types of RTPs can be tested?哪些RTP部分可被检测

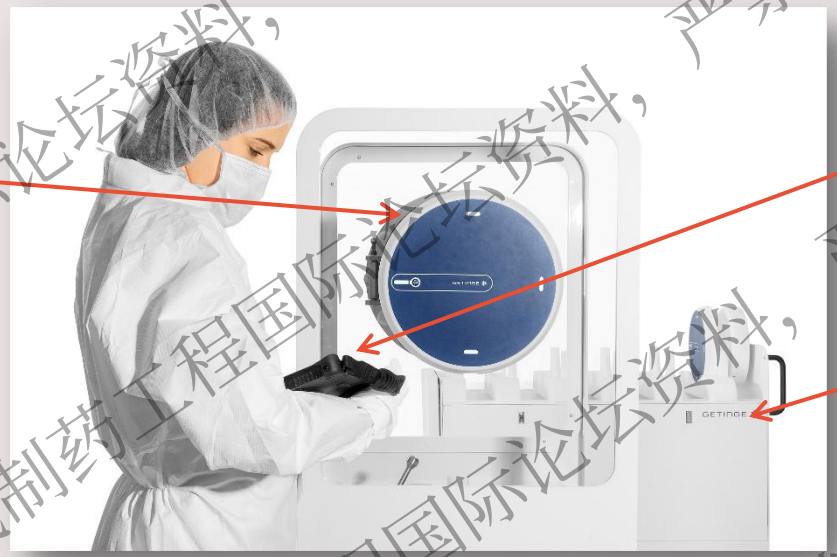
- Empty DPTE® containers
- Loaded DPTE® containers
- Getinge La Calhène DPTE® alpha parts///bags?
- All DPTE® parts mounted onto process

When performing the test?什么时候

- Beta part
  - Before and after each transfer when operator will preparation in-house
- Alpha part
  - Before starting each new batch process
  - After each batch process.

DPTE® TLT (TRANSFER LEAK TESTER)

Plug with inflatable gasket.



Tablet 11.9 inches for control and traceability.

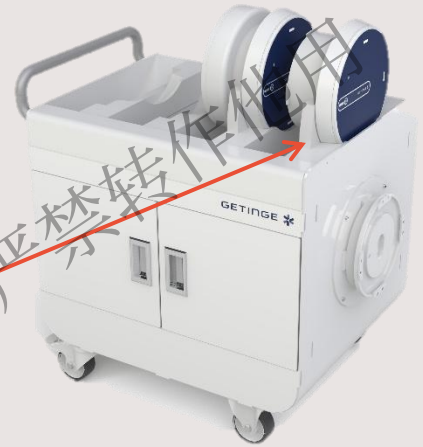
Windows 10 and SQL server 2016.

Trolley connected to electrical power and Ethernet port (available) for storage and batteries power loading

Push button for gasket command.

Lighting for information and battery status.

Dedicated support for storage and power loading



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PASSION FOR LIFE