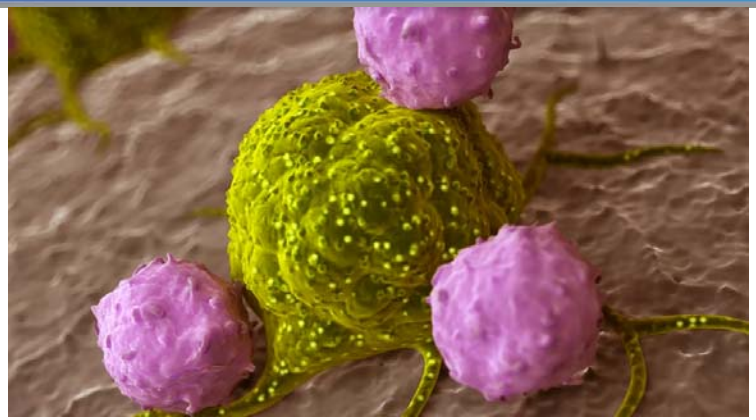
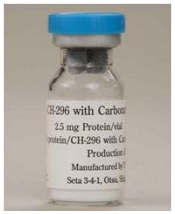
資料 1-2



再生医療等製品／遺伝子治療製品の製造施設

03/12/2015
峰野純一
タカラバイオ株式会社　バイオ産業支援事業部門

Takara Bio, Gene therapy supporting history



RetroNectin

Center for Cell & Gene Therapy (GMP)

HSV-TK ex vivo gene therapy clinical trial (JP)

TCR gene therapy clinical research (JP)

Center for Gene & Cell Processing (GMP)

1990

2000

2010

RetroNectin manufacturing (GMP)

CPCs (GMP)

HF10(oncolytic virus) clinical trial (USA)

MazF gene therapy clinical trial (USA)

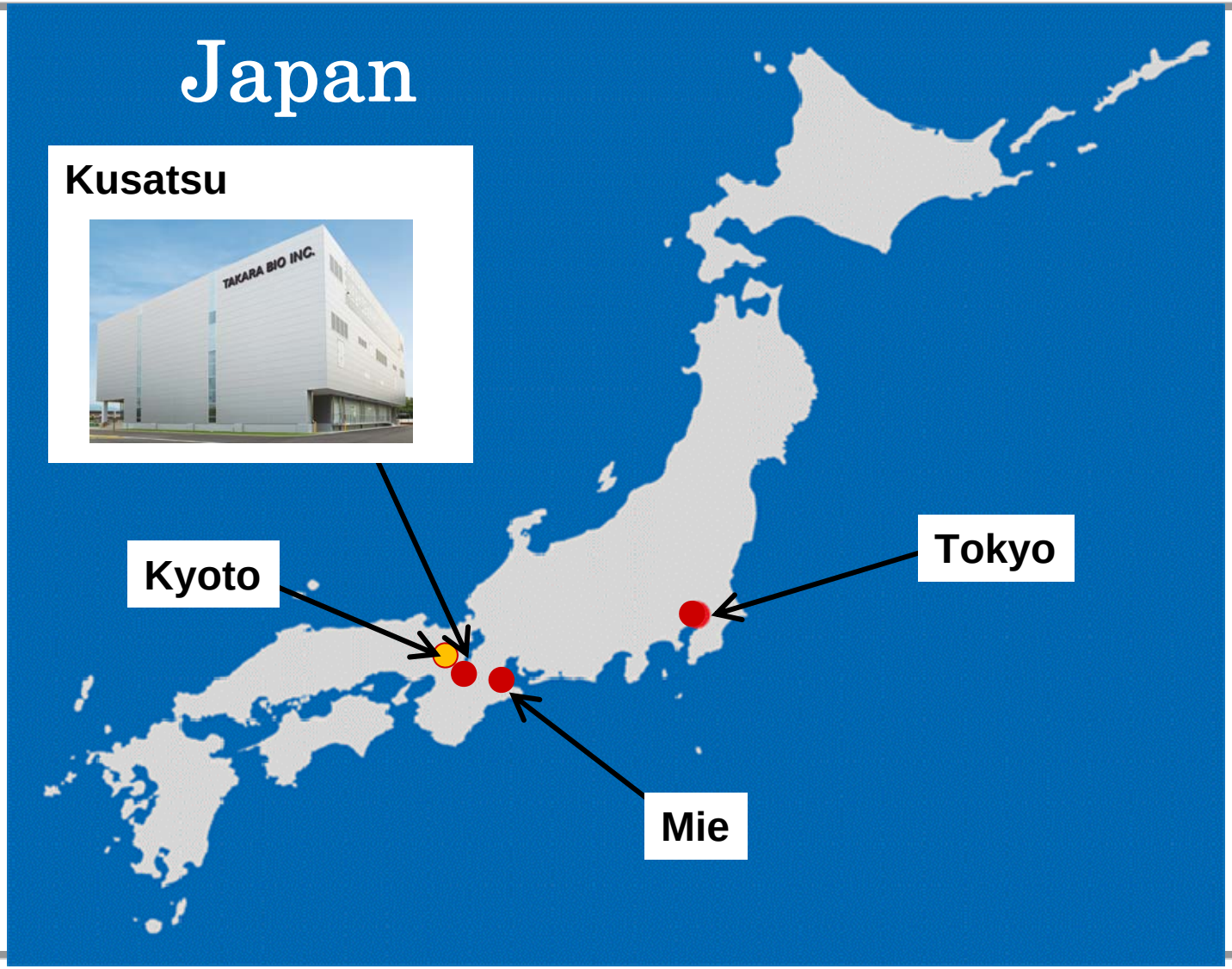
TCR gene therapy clinical trial (JP)

Schedule for clinical development of gene medicine of Takara Bio

	対象疾患	前臨床試験	第Ⅰ相臨床試験	第Ⅱ相臨床試験	第Ⅲ相臨床試験	商業化
(i) 腫瘍溶解性ウイルスHF10	悪性黒色腫	米国・第Ⅱ相臨床試験（2016年度終了予定）				2018年度
	悪性黒色腫、扁平上皮癌等	国内・第Ⅰ相臨床試験（2016年度終了予定）				2018年度
(e) MazF 遺伝子治療	HIV感染症	米国・第Ⅰ相臨床試験（2015年度終了予定）				2022年度
(e) MAGE-A4・TCR 遺伝子治療	食道癌等	三重大学等・第Ⅰ相臨床試験（医師主導治験）（2015年度終了予定）				2021年度
(e) NY-ESO-1・TCR 遺伝子治療	固形癌	三重大学等・第Ⅰ相臨床試験（医師主導治験）（2017年度終了予定）				2021年度

Takara Bio Center for Gene & Cell Processing

Where it is



Center for Gene & Cell Processing
(Kusatsu, Shiga, Japan)

Total floor space: 6,500 m^2,

1st floor:

- **Cell banking (e.g. *E. coli*)**
- **Plasmid vector manufacturing**
- ***E. coli* culture for protein production**
- **QC test (sterility, Mycoplasma)**
- **Cell bank storage**

2nd floor:

- **Viral vector production**
  gamma retrovirus, lentivirus, HSV, adenovirus, AAV, HVJ , etc.
- **Cell culture, Media preparation**
- **Protein purification**
- **Aseptic filling**

3rd floor:

- **Cell processing**
- **QC test (test for cells & viruses, qPCR, bio assay, etc.)**

Center for Gene & Cell Processing laws and guidelines

- **Standards for Manufacturing Control and Quality Control, etc. of Investigational Products (Investigational Products GMP) (PFSB Notification No. 0709002)**
- **Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs (MHLW Ministerial Ordinance No.179)**
- **Regulations for Buildings and Facilities of Pharmacies, etc (MHLW Ministerial Ordinance No.10)**
- **Guide to Good Manufacturing Practice for Medical Products (2013 PIC/S)**
- **Current Good Manufacturing Practice for Finished Pharmaceuticals（Code of Federal Regulations title 21, part 211）**
- **EU guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use**

- **Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms**

Facility construction step

1) making an user requirements specification (URS)
2) making a validation master plan (VMP)
3) designing the facility
4) design qualification (DQ)
5) construction
6) installation qualification (IQ)
7) operational qualification (OQ)
8) performance qualification (PQ)
9) process validation (PV)

system impact assessment (SIA)
quality risk management (QRM)

Classification of air cleanliness specified in ISO, FDA, EU, PIC/S and Japan guideline

ISO			FDA		EU, PIC/S, JP				
			In the vicinity of exposed materials/articles during periods of activity			At rest		In operation	
ISO Class	0.5 μm particles/ m^3 of air	5 μm particles/ m^3 of air	0.5 μm particles/ft^3 of air	≧ 0.5 μm particles/m^3 of air	EU Grade	0.5 μm particles/ m^3 of air	5.0 μm particles/ m^3 of air	0.5 μm particles/ m^3 of air	5.0 μm particles/ m^3 of air
5	3,520	29	100	3,520	A	3,520	20	3,520	20
6	35,200	293	1,000	35,200					
7	352,000	2,930	10,000	352,000	B	3,520	29	352,000	2,900
8	3,520,000	29,300	100,000	3,520,000	C	352,000	2,900	3,520,000	29,000
					D	3,520,000	29,000	Not defined	Not defined

Requirements for each grade

Grade A:

Critical and/or high risk operation area where sterilized products and materials as well as their surfaces are directly exposed to the environment.

e.g., filling, aseptic connections, stopper bowls, open ampoules and vials, sterile ingredient additions.

Grade B:

Direct support and/or supporting clean area that is a background environment for the grade A zone.

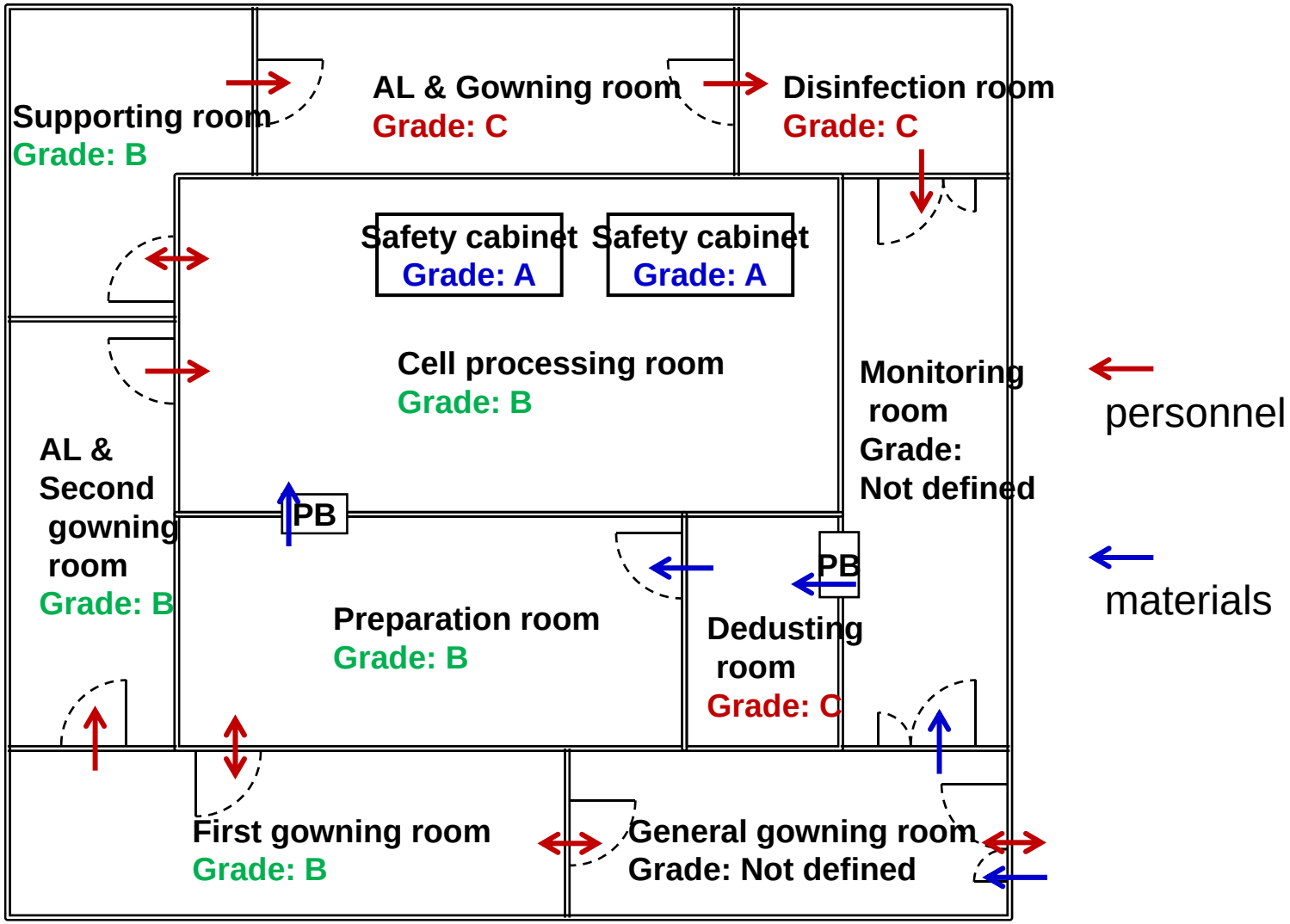
e.g., working areas for personnel who operate machines installed in the critical area and also routes for the transfer of sterilized products, materials, and equipment to the critical area or for moving sterilized products from the critical area, and where non-sterile components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred.

Grades C and D

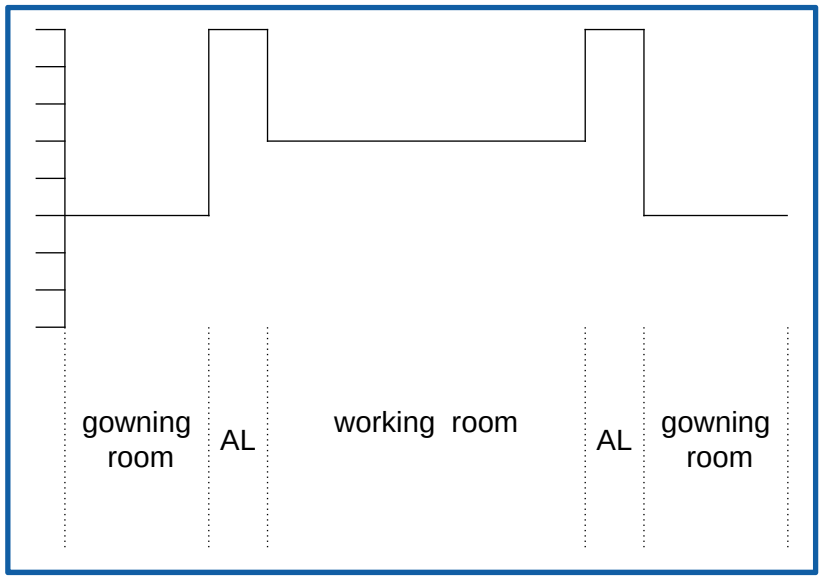
indirect support areas and/or clean areas for carrying out less critical stages

e.g., preparing drug solution prior to sterilization, washing and cleaning sterilization equipment and apparatuses, weighing and preparation processes.

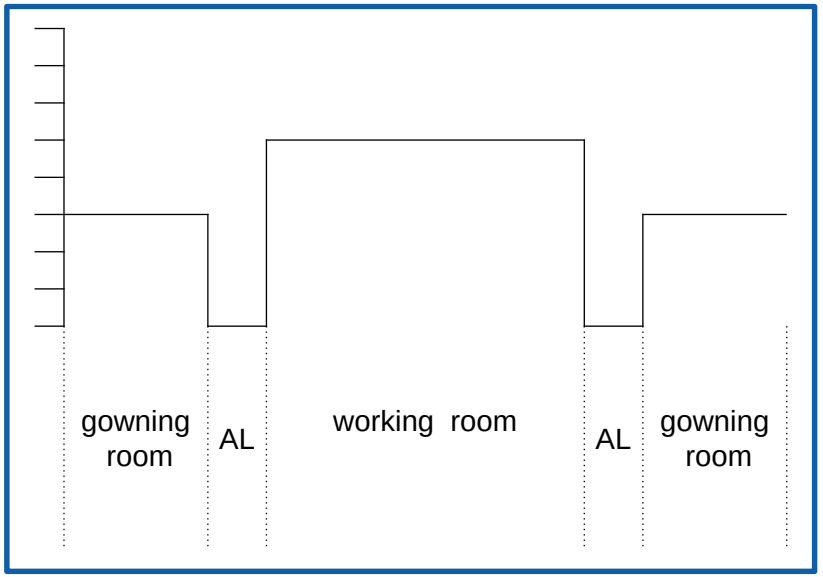
Typical cell processing room



Two types of AL (air lock): high pressure & low pressure

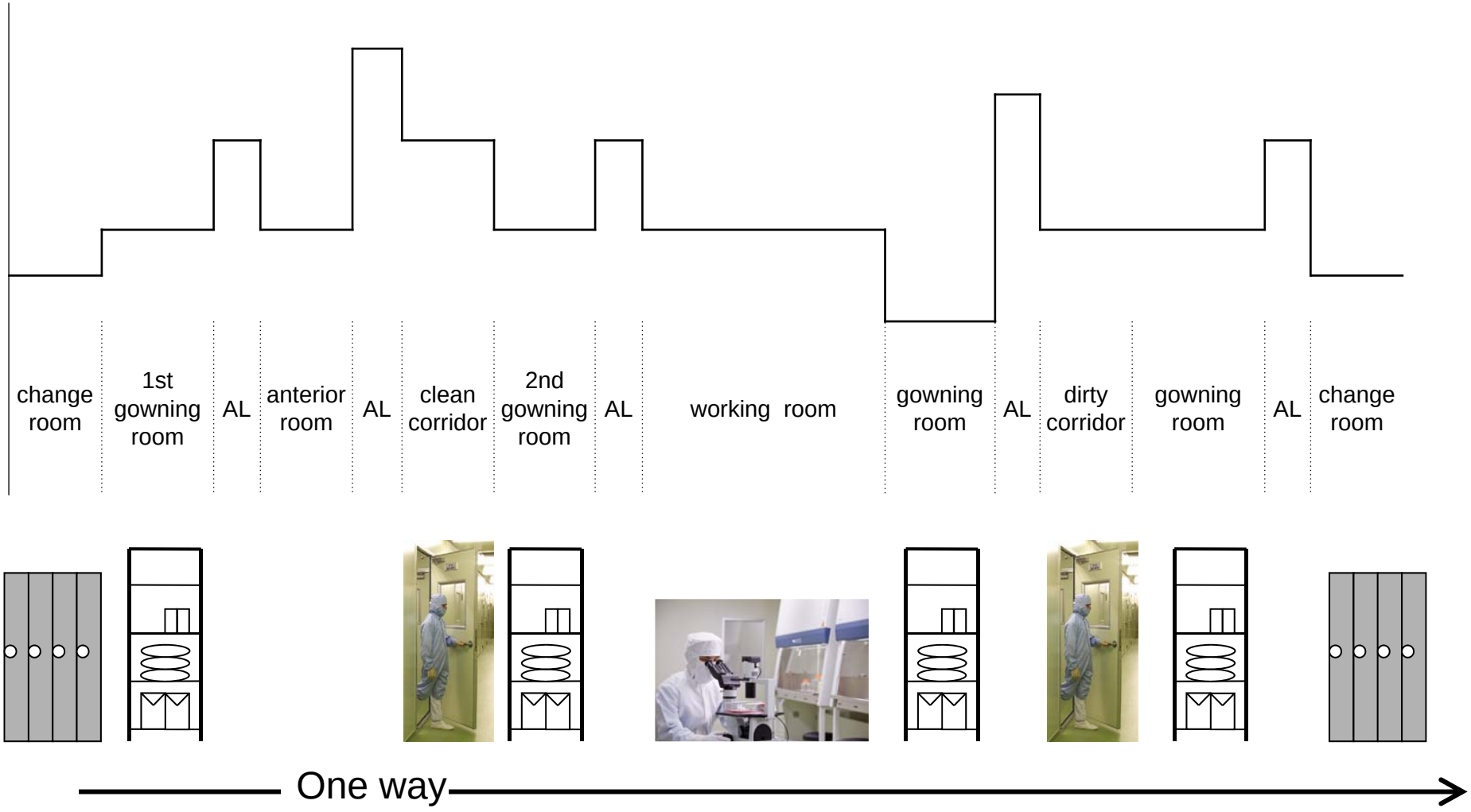


high pressure AL



low pressure AL

A design for strict control with paired high-pressure and low-pressure ALs



Designing the facility

Walls, floors, and ceilings should be designed to be easily cleanable.

- ✓ surfaces are polished, resistant to water and chemicals, especially cleaning agents and disinfectants, impermeable
- ✓ corners between floors and walls should be rounded, dust can be easily wiped off.

The location of equipment in the areas and rooms should also be carefully planned to minimize crossing of personnel, product, and material flows.

- ✓ stainless steel worktables with round legs and without drawers

Paper should not be brought into clean areas as much as possible to reduce the dust arising from paper

- ✓ dust-free paper
- ✓ paperless systems (manufacturing execution system)

Designing the facility

For the operators

- ✓ limited the low-temperature space for filling to laminar hoods, safety cabinets, and isolators to minimize the physical burden on operators.
- ✓ Placed many windows.
- ✓ Multiple emergency exits are necessary.
- ✓ In the cold room, a convenient video camera is placed to monitor the equipment from an outside room that is not cold.

1st floor equipments

E. coli culture (200 L)

Cell bank storage

Solid-liquid separation

Sterility test

2nd floor equipments

Automated aseptic filling (for vials)

Semi-automated aseptic filling (for bags)

Liquid chromatography

Cell culture

3rd floor equipments

Cell processing
for regenerative medicine & gene therapy

GMP organization

Manufacturing Unit

Manufacturing Control Manager — **Responsible Persons**

- Process Controls
- Hygienic Control and Maintenance
- Facility Maintenance
- Process Equipment Maintenance and Cleaning
- Materials Management
- Storage and Distribution

Quality Unit

Quality Manager

Quality Control Manager — **Responsible Persons**

- Hygienic Control and Maintenance
- Facility Maintenance
- Equipment Maintenance and Cleaning

Quality Assurance Manager

Responsible Persons

- Validation
- Personnel Training
- Deviation Control
- Quality Information Control
- Handling of Recall
- Self-inspection
- Document Control
- Change control

Visited facilities

Facility	Product	Facility	Product
Indiana University, USA	Vector	**Progenitor Cell Therapies**, USA	Cell
University of Pennsylvania School of Medicine, USA	Vector, GMC	**Cognate BioServices**, USA	Cell
Baylor College of Medicine CAGT, USA	Vector, GMC	**LONZA (Huston)**, USA	Vector, Cell
Children's Hospital of Philadelphia, USA	Vector	**City of Hope** , USA	Vector, Cell, Antibody
Cincinnati Children's Hospital Medical Center, USA	Vector, Cell	**Genethon**, France	Vector, Cell
Vivante, USA	Vector	**MolMed**, Italy	Vector, Cell
uniQure, Netherlands	Vector	**BioReliance**, Scotland	Bio-safety assay
SAFC, USA	Filling	**Vitrology Ltd.** , Scotland	Bio-safety assay
Areta international, Italy	Antibody	**Moredun Scientific Ltd.**, Scotland	Bio-safety assay

課題

ハードよりもソフト:

- ✓ 複数細胞を加工する際のクロスコンタミ対策、取り違え防止
- ✓ 洗浄・除染・滅菌方法、環境モニタリング方法
- ✓ 原材料提供会社の査察
- ✓ 試験委託先の査察
- ✓ 再生医療等製品提供先とのシステム作り

ICH Q9 “Quality Risk Management”の考え方を参考に。

Dawn of Japanese-made Gene therapy and Cell therapy

Clontech TaKaRa cellartis