Tour of Manufacturing Building "FJ3" for Small and Mid-Size Molecule APIs at Fujieda Plant

26 February 2025

CHUGAI PHARMACEUTICAL CO., LTD.

API: Active Pharmaceutical Ingredient

Important Reminders

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Information regarding pharmaceuticals (including products under development) is included in this presentation, but is not intended as advertising or medical advice.

Agenda

01	Establishing the World Class Manufacturing System for Small and Mid-Size Molecules to Drive the Realization of TOP I 2030	Vice President, Head of Manufacturing Technology Div., Chugai Pharmaceutical Co., Ltd. Shinya Takuma
02	Pharmaceutical Technology for Mid-Size Molecule APIs	Head of API Process Development Dept., Pharmaceutical Technology Div., Chugai Pharmaceutical Co., Ltd. Dr. Kenji Maeda
03	Introduction of Fujieda Plant, Chugai Pharma Manufacturing Co., Ltd.	Head of Fujieda Plant, Chugai Pharma Manufacturing Co., Ltd. Kaichiro Koyama

Establishing the World Class Manufacturing System for Small and Mid-Size Molecules to Drive the Realization of TOP I 2030

February 26, 2025

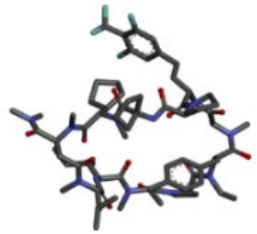
CHUGAI PHARMACEUTICAL CO., LTD

Vice President, Head of Manufacturing Technology Div.

Shinya Takuma

For the Sake of Patients - Innovations for the Next 100 Years -

- **Chugai will reach our 100th anniversary on March 10, 2025**
- **Since our founding, we have consistently carried on the spirit of "Creating drugs that benefit the world"**
- **Through bold challenges, we have relentlessly pursued drug discovery unique to us, for the benefit of medical community and human health around the world**
  - Constantly challenged to develop new drug discovery technologies, from small molecules to biologics, antibodies, and now mid-size molecules
  - Established technology-driven drug discovery that is unique to Chugai
  - Contributed to unmet medical needs for various diseases through innovative new drugs
- **For the next 100 years, we will continue to expand the benefit of medical community and human health around the world for the sake of patients**

1925	1970s	1980s	1990s	2000s	2010s	2025-
						**Expand the benefit of medical community and human health around the world for the next 100 years**
Founded in response to medicine shortage after the Great Kanto Earthquake	**Shift to in-house development of original new products**	**Challenge to biopharmaceuticals**	**Challenge to antibody drug discovery**	**Acceleration of drug discovery technology development**	**Challenge to mid-size molecules**	

Two Pillars of TOP I 2030

"Double R&D output" & “Launch global in-house products every year"

Global First-class Drug Discovery

- Expansion of existing technological bases and building a new technological foundation to materialize unique drug discovery ideas
- Maximization of the value of development projects by pursuing translational research and pharmaceutical technologies
- Accelerating innovation opportunities by strengthening collaboration with leading global players and leveraging digital technologies

Futuristic Business Model

- Dramatic improvement in product / patient value by restructuring business model, having digital utilization as a core
- Improve productivity of entire value chain by leveraging digital technologies.
- Development of PHC solutions to maximize the value of pharmaceuticals

Key Drivers ▶**DX** ▶**RED SHIFT** ▶**Open Innovation**

*RED: Research and Early Development, Translational Research: Research aimed at verifying scientific concepts generated in drug discovery in clinical settings
PHC solution: products/services to be able to provide best treatment options to each patient by diagnosing the disease or measure the treatment results

Summary of Five Reforms

1) Drug Discovery

- Expansion of existing technological platforms to realize unique drug discovery ideas and establish new technology platform.
- Acceleration of innovation opportunities by leveraging digital technologies and strengthening collaboration with leading global players.

2) Development

- Enhancement of Go/No-Go decision making and maximization of project value by integrating clinical development and human prediction capabilities
- Realization of advanced and efficient clinical development operations using digital technologies

3) Pharmaceutical Technology

- Establishment of world-class pharmaceutical technologies for antibody and mid-size molecule and acceleration of development
- Applying manufacturing technology to achieve world-class productivity and quality
- Establishment of supply systems that ensure both stable supply and high quality

4) Value Delivery

- Realization of further personalized medical care by the creation of unique evidence that addresses unmet healthcare needs in actual clinical practice
- Maximize customer value by innovative digital-based customer engagement model

⑤Foundation for Growth

- Realization of human resource management that encourages discovery, growth, and exercise of diverse individuals; acquisition, retention, and development of highly specialized human resources
- Realization of CHUGAI DIGITAL VISION 2030
- Realization of Mid-term Environment Goals 2030; enhancement of sustainability platform
- Achievement of QUALITY VISION 2030
- Provision of advanced proof and maximum value of pharmaceuticals through PHC solution

PHC Solution: Products and services that enable optimal treatment for individual patients by precisely diagnosing and measuring pathological conditions and therapeutic efficacy.

Five Reforms: Pharmaceutical Technology

Pursue world-class technologies to deliver drug discovery ideas to patients as pharmaceutical products; realize highly competitive pharmaceutical technologies in terms of quality, speed, and cost

	Direction of Reform	Goal
Pursuit of world-class technologies	• Manufacture highly unique compounds by strengthening collaboration with drug discovery and making full use of state-of-the-art technology • Evolution of the world's most advanced antibody/mid-size molecule technology and realization of development speed	Establish competitive pharmaceutical technologies World-class development speed
Establishment of robust and competitive supply systems	• Further efficiency gains by strengthening the manufacturing technology function, including the use of digital technologies and robotics • Pursuing stable supply and global standard quality through implementation of dual-site strategy	Apply production technologies and achieve world-class productivity and quality Establish supply systems that ensure both stable supply and high quality

Portfolio of Each Modality

Production capability/capacity that can accommodate a wide range of in-house developed products is necessary

As of January 30, 2025

Drug Discovery	Pre-clinical Development	Clinical	Launched

Antibody drugs, cellular and gene therapy products

25

AMY109
NXT007
DONQ52
RAY121
GC33
STA551
SOF10
ALPS12
SAIL66
ROSE12
BRY10

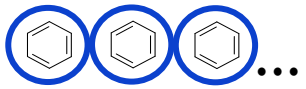
Enspryng (MOGAD, AIE, TED/P3)
PiaSky (aHUS/P3, SCD/P2)
GYM329 (SMA/P2/3, FSHD/P2, Obesity/P1)

Actemra
Hemlibra
Enspryng
PiaSky

Developments licensed out to 3rd parties excl. Roche

NEMLUVIO (AD, PN(filed in EU))
Mitchga (JPN)
NEMLUVIO (U.S.)

Small molecule drugs



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REVN24

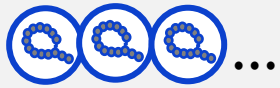
Alecensa (Maintenance treatment of NSCLC(stage III) after chemoradiotherapy/P3)

Alecensa
Edirol
Oxarol

Developments licensed out to 3rd parties excl. Roche

AP306 (Hyperphosphatemia/P2)
orforglipron (T2D, Obesity/P3)
avutometinib (LGSOC*, NSCLC, mPDAC/P1/2)
Deberza

Mid-size molecule drugs



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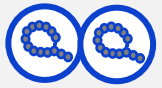


LUNA18

Blue: Joint development with Roche

*NDA was accepted under the accelerated approval pathway in the U.S.

Establishment of Manufacturing System for Small and Mid-Size Molecule APIs

- Acquired advanced technologies for EHS as well as small and mid-size molecule with high potency
- Build a consistent in-house supply system from manufacturing process development and early clinical development to initial commercial production

Pre-Clinical	Phase 1～Phase 2		Phase 3 to initial commercial
			
Ukima Research Laboratories	Fujieda Plant		
Start of operation: 2020	2003	Dec. 2022	Scheduled in Mar. 2025
Total floor area: 4,925 m^2	5,417 m^2	6,079 m^2	10,489 m^2
Total investment: 4.5 billion yen	7 billion yen	19.1 billion yen	55.5 billion yen

Establishing a stable in-house supply system from early clinical development to market launch leads to speedy development of mid-size molecule drugs and gaining competitive advantage

EHS: Environment, Health and Safety

Pharmaceutical Technology for Mid-Size Molecule APIs

February 26, 2025

CHUGAI PHARMACEUTICAL CO., LTD.

API Process Development Dept., Pharmaceutical Technology Div.

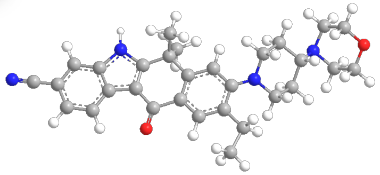
Dr. Kenji Maeda

Agenda

Chugai's Modality Strategy

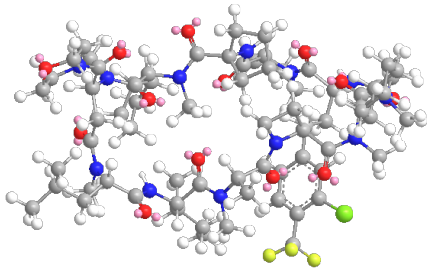
Chemical drugs

Small molecule drugs



ALECENSA®
2014

Mid-size molecule drugs



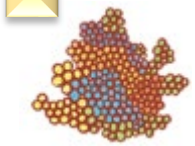
Cyclic peptide
LUNA18
2021 P1-

CHUGAI

Roche Group

Biological drugs

Polymer drugs

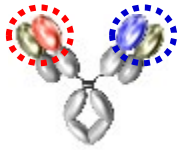


ESA

EPOGIN®
1990

Antibody

ACTEMRA®
2005

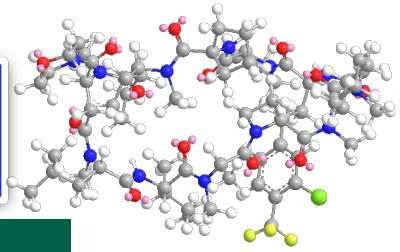


Engineered Antibody

HEMLIBRA®
2018

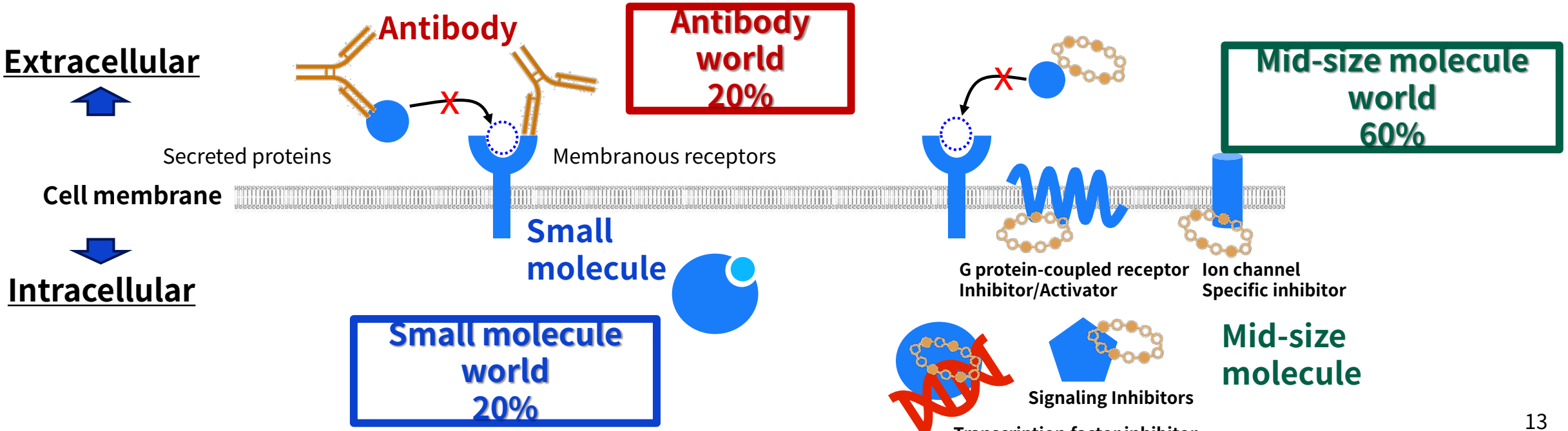
"There is much unexplored territory within the cell."

The Potential of Cyclic Peptide (Mid-Size Molecule) Drugs



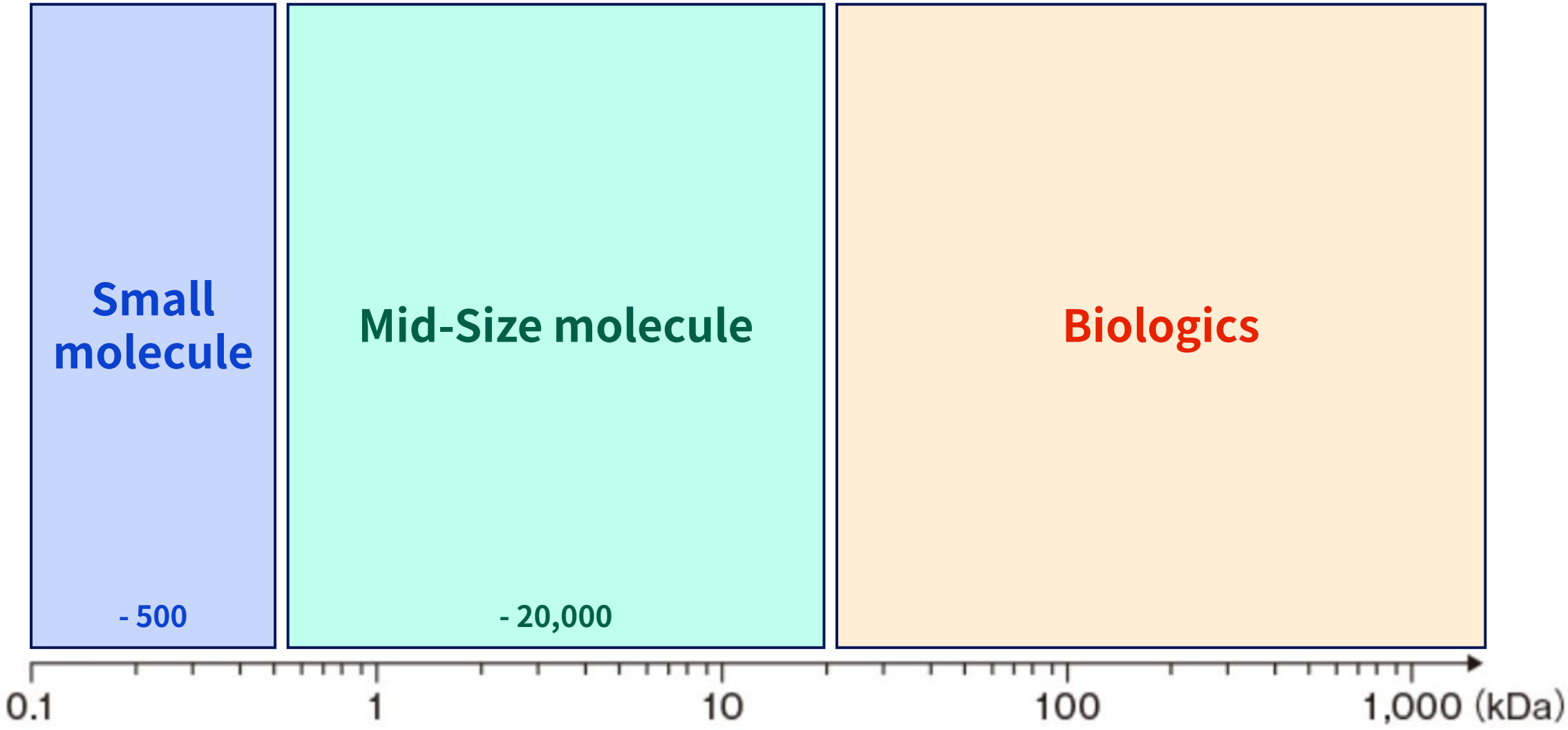
- ✓ >50% of drug discovery targets cannot be targeted by either antibodies or small molecules
- ✓ Mid-sized molecules are a modality with the potential to target these unexplored targets

Biologic (antibody) drugs	Small molecule drugs	Mid-size molecule (cyclic peptide) drugs
Extracellular target	Extra- and intracellular target with pocket	Extra- and intracellular target without pocket

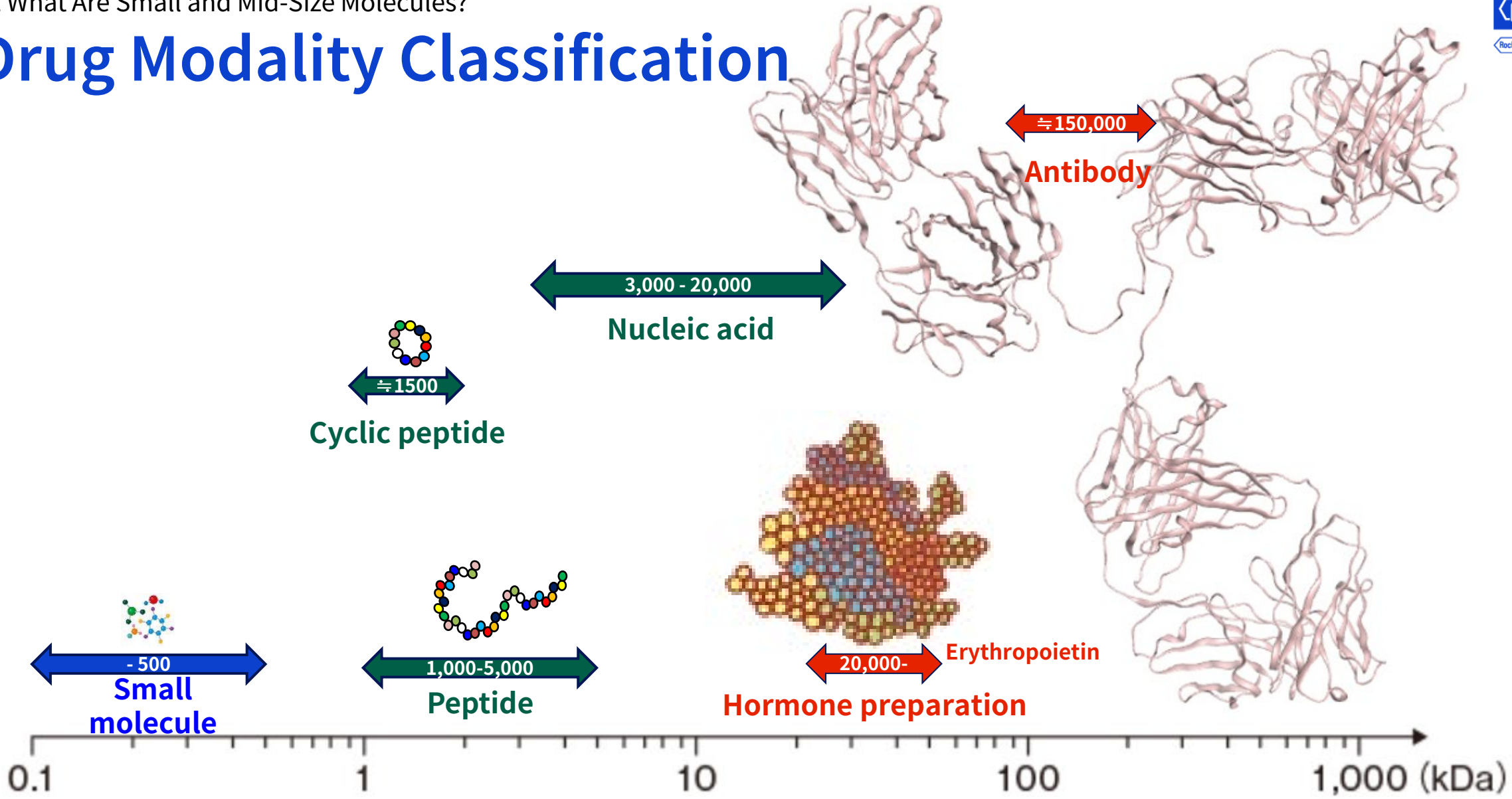


What Are Small and Mid-Size Molecules?

Drug Modality Classification



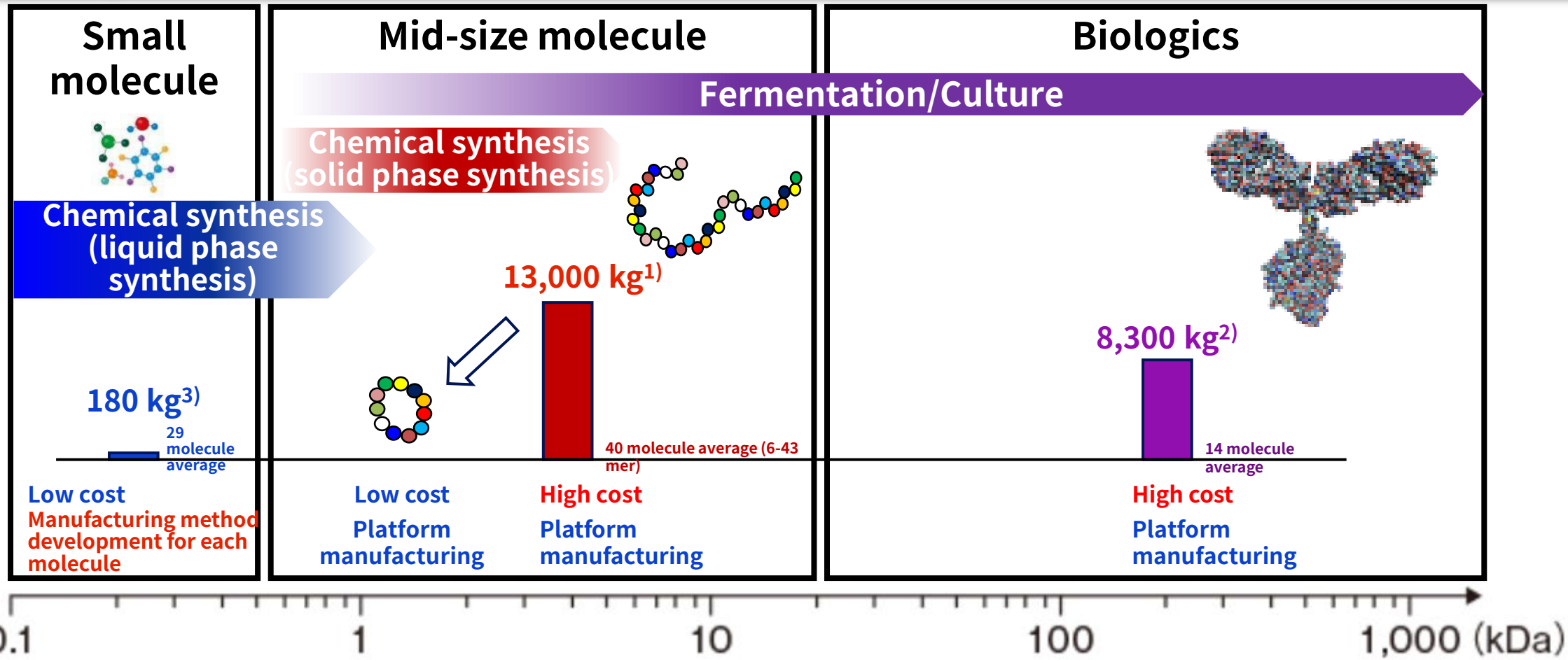
Drug Modality Classification



Method and Issues of Synthesizing Mid-Size Molecules

Manufacturing Method and Amount of Waste (per kg of API) of Each Modality

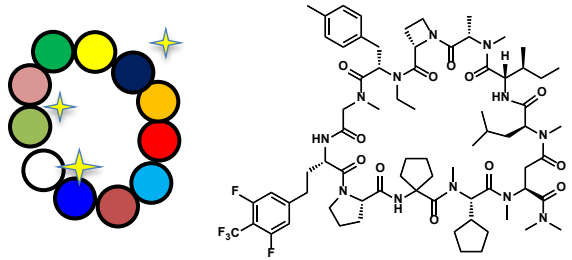
- ✓ Conventional manufacturing methods for peptide drugs (solid phase synthesis) produce large amounts of waste and manufacturing costs arise
- ✓ To commercialize Chugai cyclic peptides, a unique manufacturing method (liquid phase synthesis) was developed by making full use of technology cultivated for small molecules



PMI: Process Mass Intensity : Total mass of materials used to manufacture a specified mass (1kg) of product

1) *J. Org. Chem.* **2024**, *89*, 4261. 2) *New Biotechnol.* **2019**, *49*, 37. 3) *ACS Sustainable Chem. Eng.* **2022**, *10*, 5148.

Cyclic Peptide Synthesis



Intermediate process

API process

1) Non-natural amino acid synthesis

Chemical synthesis

Enzyme reaction

2) Peptide synthesis

Liquid phase synthesis

Solid phase synthesis

3) Cyclization

Cyclization

Crystal

Amorphous

4) Purification/Isolation

Crystallization

Drying

Column purification

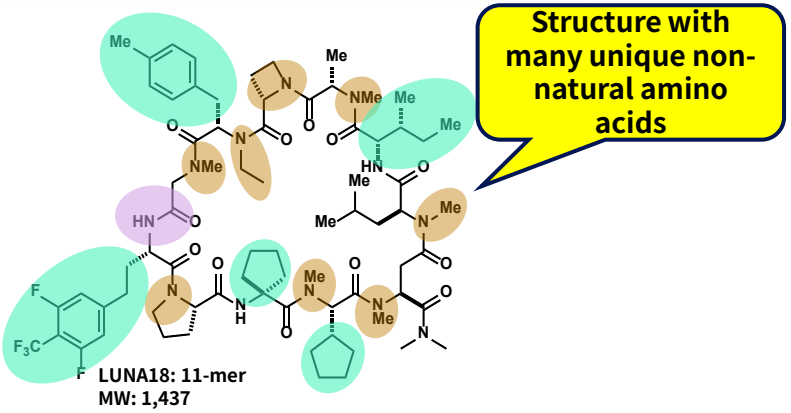
Freeze-drying or Spray drying

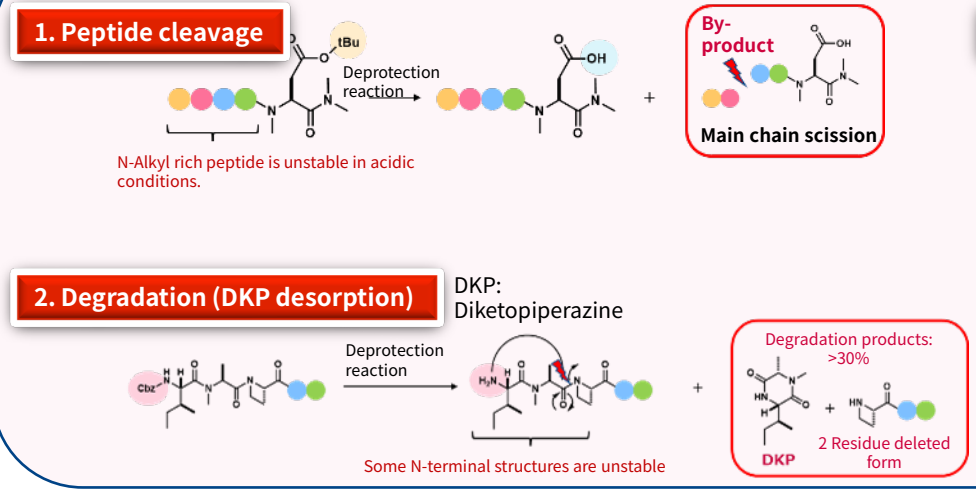
API

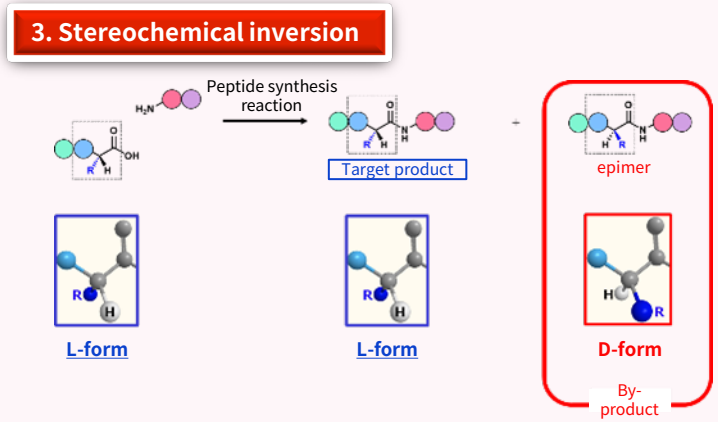
Difficulties in Chugai Cyclic Peptide Synthesis 1: Complex Structure

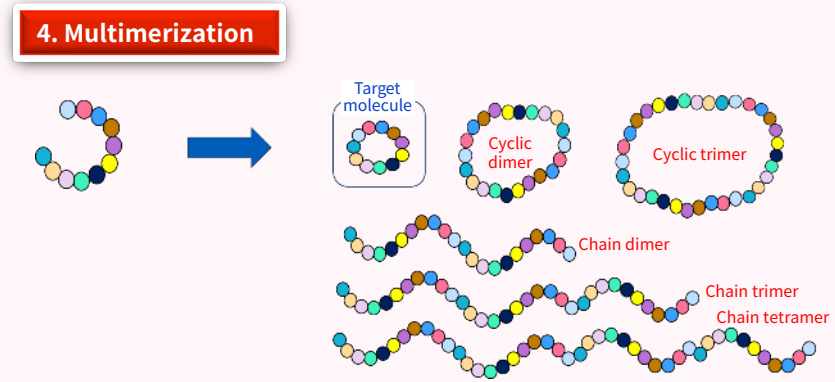
- ✓ In general, liquid phase synthesis has not been adopted as the manufacturing process for peptide drugs because it is a challenging method for development, and takes time for development and manufacturing
- ✓ Furthermore, Chugai cyclic peptides are composed of many non-natural amino acids, and their structural characteristics and physical properties differ greatly from those of conventional peptides. Therefore, various problems had to be overcome

1. **N-Alkyl rich structure:** Unstable under reaction conditions
   Low reactivity
2. **No polar functional groups:** Physical properties similar to those of small molecule compounds.
   Impurity removal by crystallization or liquid separation is relatively easy.
   Column purification and freeze-drying are difficult under typical peptide conditions.
   Complex side chain functional groups
3. **Amide cyclization structure:** Oligomerization (multimer formation) during cyclization



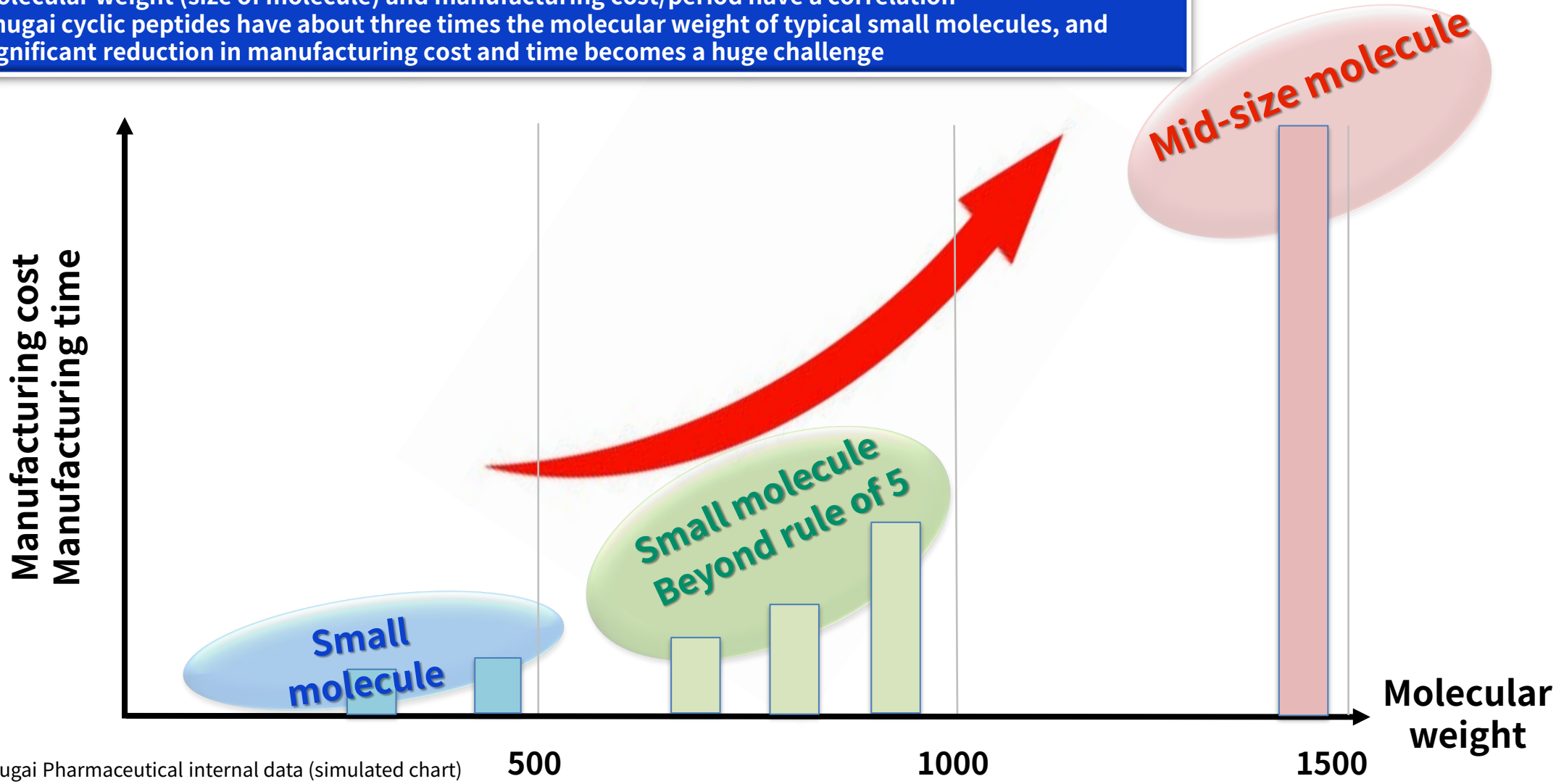






Difficulties in Chugai Cyclic Peptide Synthesis 2: Manufacturing Cost and Time

- Molecular weight (size of molecule) and manufacturing cost/period have a correlation
- Chugai cyclic peptides have about three times the molecular weight of typical small molecules, and significant reduction in manufacturing cost and time becomes a huge challenge



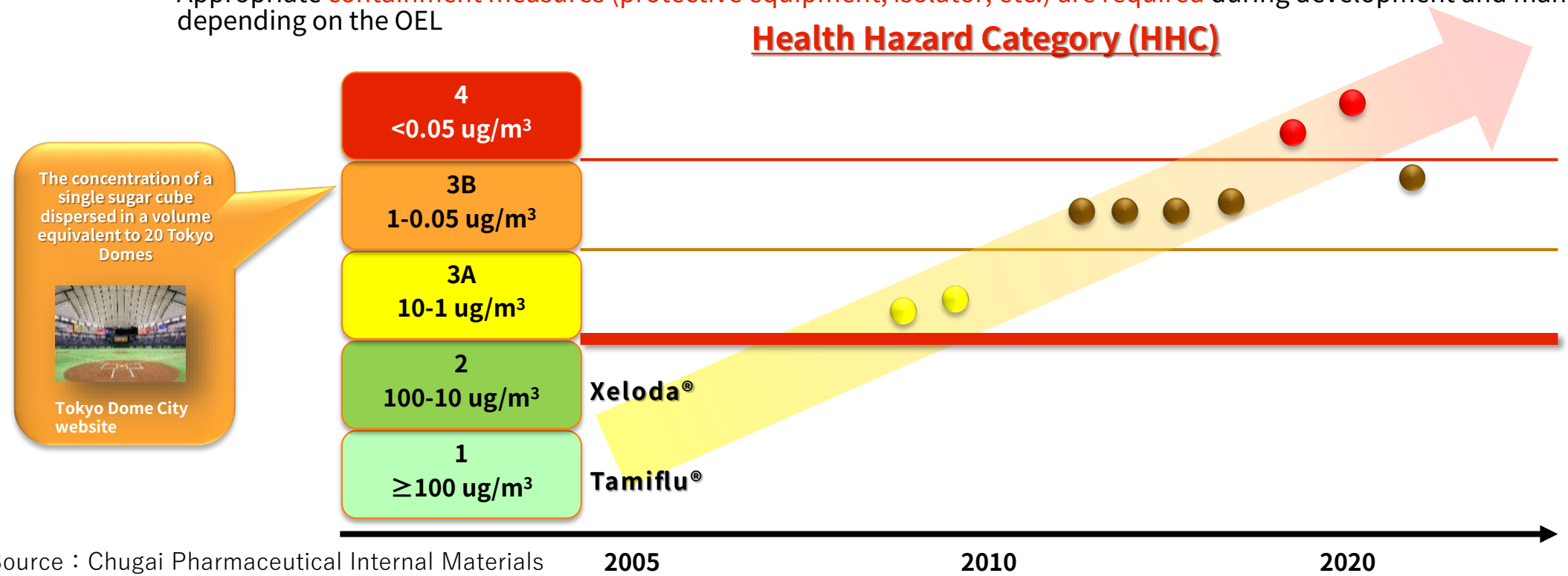
Source: Chugai Pharmaceutical internal data (simulated chart)

Difficulties in Chugai Cyclic Peptide Synthesis 3: Ultra-high Pharmacological Activity

- ✓ **Due to advances in drug discovery technology, all synthetic APIs, including mid-size molecules developed in-house in recent years, are classified as highly potent APIs**
- ✓ **To produce large quantities safely, it is essential to have manufacturing facilities with extremely high containment capabilities and advanced manufacturing technology for highly potent compounds**

Occupational Exposure Limit (OEL)

- ✓ The concentration at which most workers are considered not to suffer health damage, even if they breathe air containing a substance for 8 hours every day, 40 hours a week.
- ✓ Appropriate containment measures (protective equipment, isolator, etc.) are required during development and manufacturing, depending on the OEL



Source：Chugai Pharmaceutical Internal Materials

Chugai’s Peptide Synthesis Technology

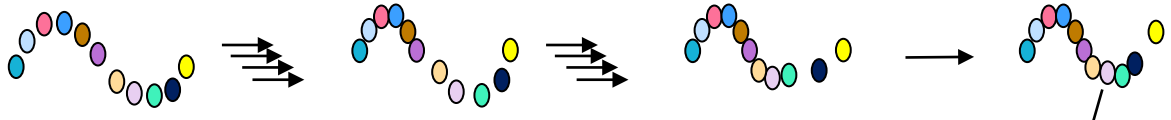
Strategy for Chugai Cyclic Peptide Manufacturing Technology

- ✓ We have adopted a technology strategy based on "liquid-phase synthesis," which maximizes our technologies and experience, including small molecule synthesis technologies and containment technologies for highly potent compounds.
- ✓ By adopting a simple liquid-phase synthesis method, we aim to significantly reduce environmental impact, manufacturing costs, and production time.

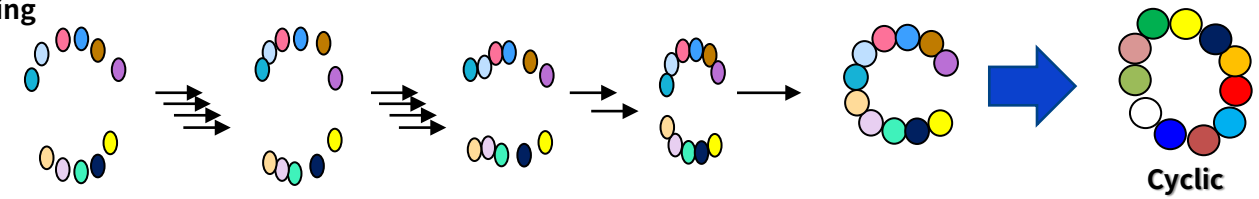
Chugai

A technology strategy based on simple "liquid-phase synthesis" that maximizes the utilization of small molecule API manufacturing technologies.

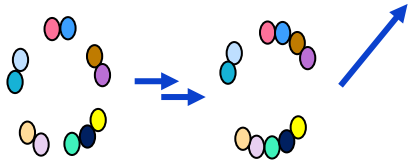
1. Linear synthesis route: Extending amino acids one by one, and then finally cyclizing



2. Convergent synthesis route: Extending amino acids one by one, fragmenting, and cyclizing

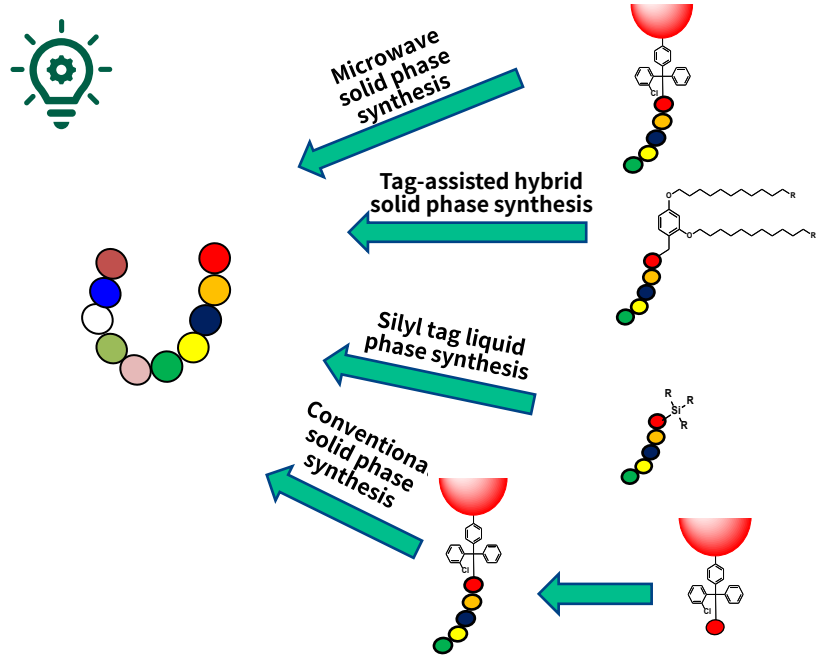


3. Highly convergent synthesis route: Extending 2 or 3 amino acids together, fragmenting, and cyclizing



Other companies and academia*

In addition to existing solid-phase synthesis technologies, various next-generation peptide synthesis technologies are being actively developed by companies and academic institutions.



*Pharmacia **2024**, *60*, 283

"There is a vast unexplored frontier in peptide synthesis technology"

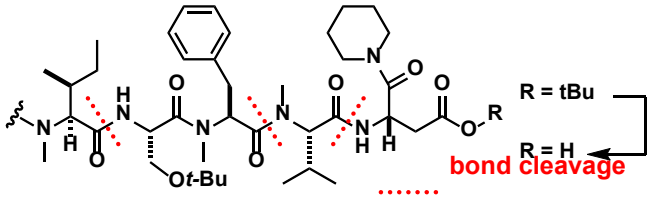
Examples of Newly Developed Peptide Liquid Phase Synthesis Technology

- ✓ Existing liquid phase peptide synthesis technology did not produce expected results
- ✓ **Various liquid phase peptide synthesis technologies at high yield and with high quality*** have been newly developed

*Even if each process has a 95% yield and purity, after 20 processes, both will drop below 40%.

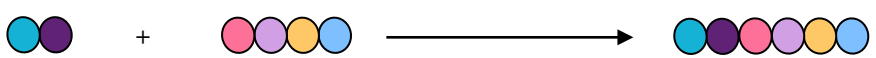
<Peptide synthesis reaction dilemma>
Increase reactivity → Becomes unstable (impurities increase)
Stabilize → Reaction does not proceed (yields decrease)

Technology to suppress peptide degradation



Conversion rate 100%, degradation 0%
(Existing method: Conversion rate 50%, degradation 28%)

Technology for coupling peptides



Technology A

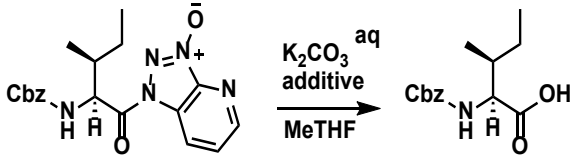
Conversion rate 100%, dr* 99.8/0.2
(Existing method: Conversion rate 92%, dr 34/66)

Technology B

Conversion rate 100%, dr 99.8/0.2
(Existing method: Conversion rate 100%, dr 80/20)

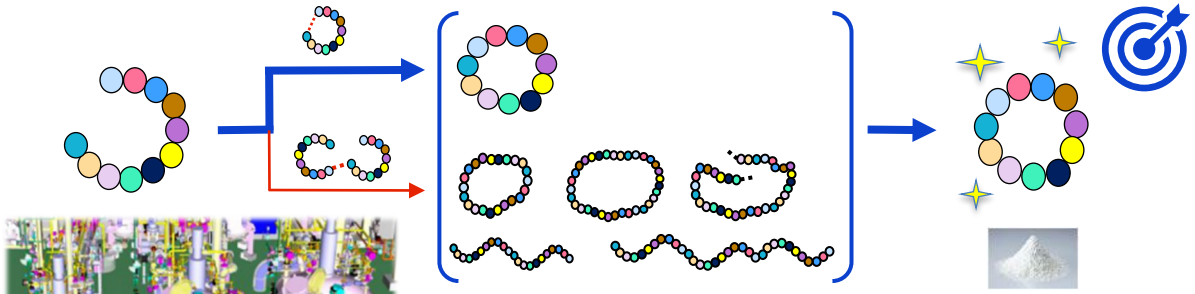
*dr: target compound / impurity

Technology for degrading unnecessary activated amino acids



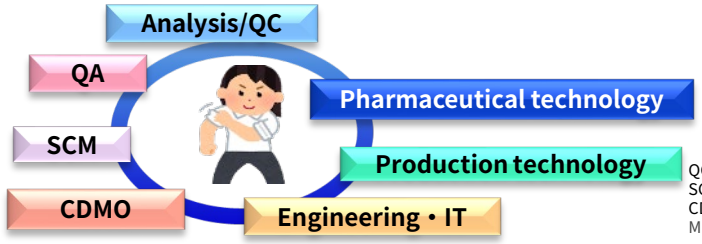
Residual rate <0.5%
(Existing method: Residual rate 84%)

Peptide cyclization technology and isolation/purification technology



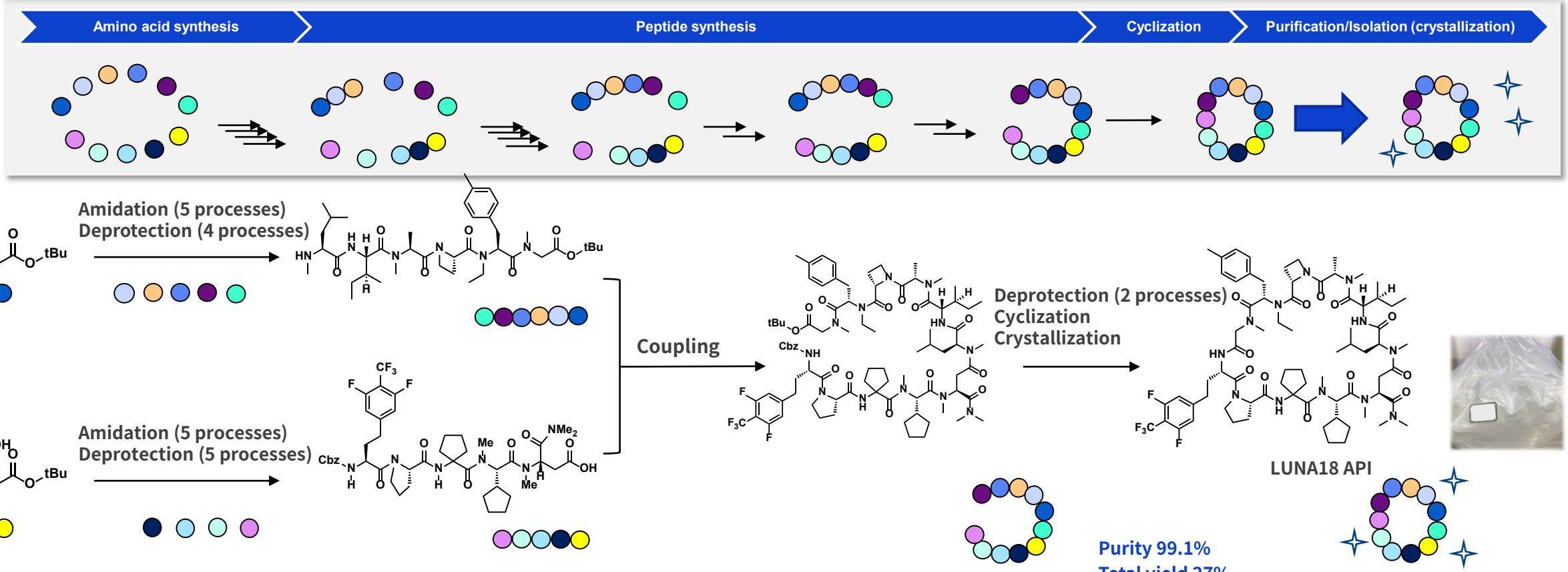
FJ3 cyclization reaction & equipment for isolation and purification

Development of Manufacturing Method for LUNA18 API, the First Mid-Size Molecule Drug



QC: Quality Control, QA: Quality Assurance
SCM: Supply Chain Management
CDMO: Contract Development and Manufacturing Organization

- ✓ We have successfully developed a process for the manufacture of LUNA18 API using convergent liquid-phase synthesis
  → Currently, we have succeeded in scaling up to about 50 kg/lot
- ✓ The technology has been further advanced for development into a platform and application to subsequent mid-size molecules

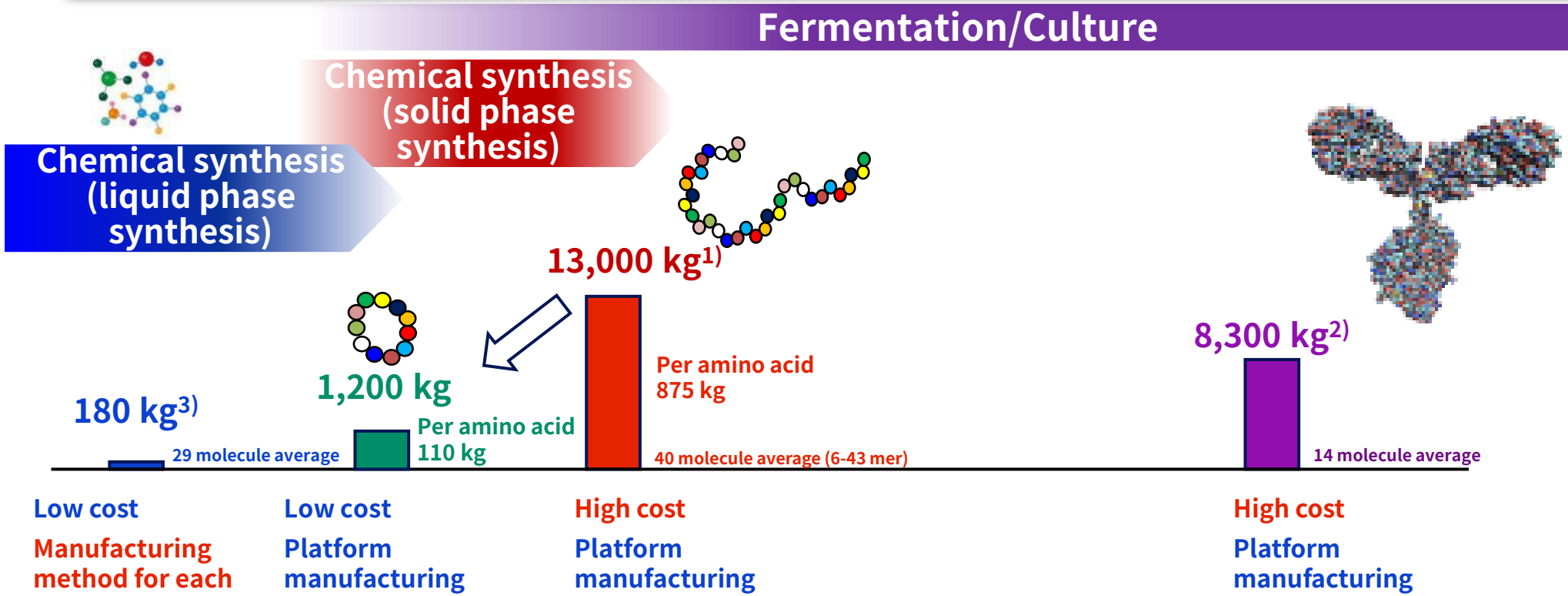


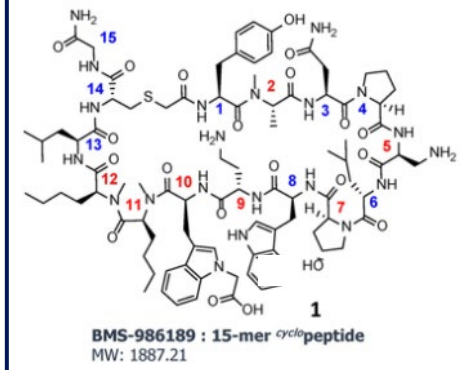
Purity 99.1%
Total yield 27%
(24 reactions, 1 isolation and purification step)

Pharmacia 2024, **60**, 283

Reduction Effect of Environmental Burden (Waste Volume per Kg of API)

- ✓ Convergent liquid-phase synthesis technology reduces waste to 1/10 or less of that required for conventional solid-phase synthesis
- ✓ The technology is being developed as an original platform technology to further reduce the environmental burden and costs





15-mer cyclic peptide
Solid-phase synthesis
PMI: 15,876kg4)

PMI: Process Mass Intensity : Total mass of materials used to manufacture a specified mass (1kg) of product

1) *J. Org. Chem.* **2024**, *89*, 4261−4282. 2) *New Biotechnol.* **2019**, *49*, 37−42. 3) *Acs Sustain Chem. Eng.* **2022**, 10 (16), 5148−5162. 4) *J. Org. Chem.* **2024**, *89*, 6651.

Overview of Mid-Size Molecule Manufacturing at FJ3

- API isolation process
- ASD* formulation process

Spray dryer

Amorphous API Isolation process

Spray drying

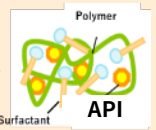
Amorphous API

Formulation and manufacturing ASD* process

Polymer surfactants, etc.

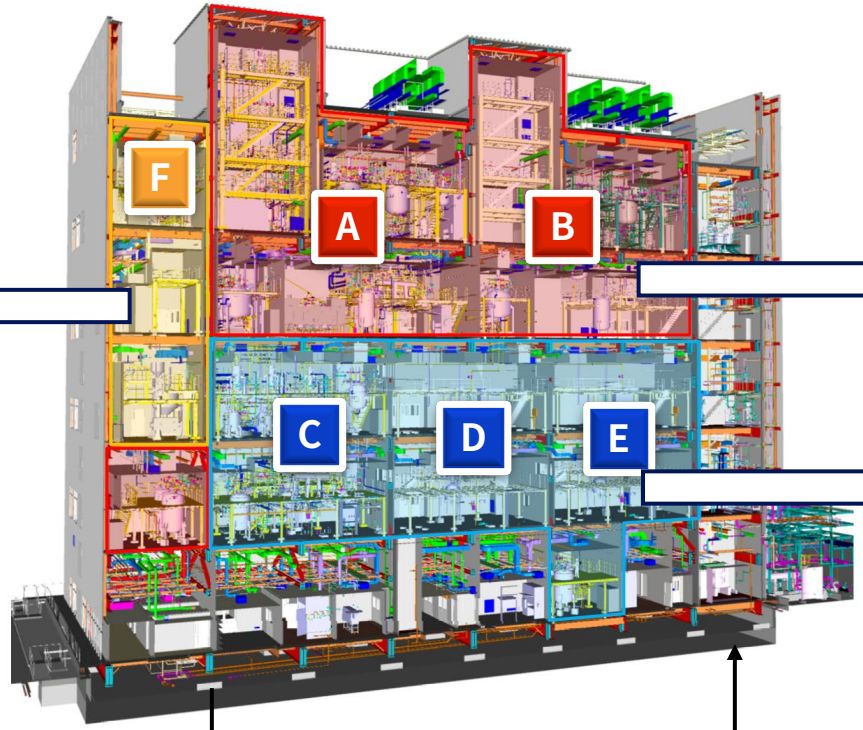
Spray drying

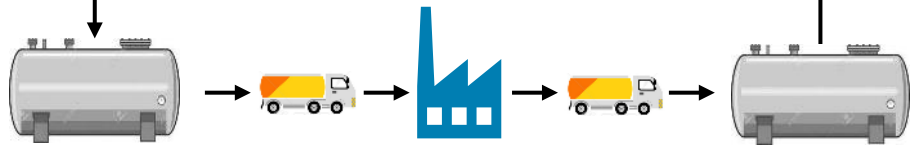
ASD Intermediate



*Amorphous solid dispersion

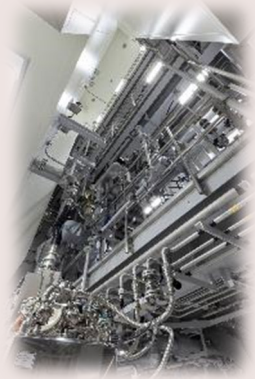
The world's largest production facility of ultra-high potency APIs





Solvent recovery tank — Distillation and purification company — Reusable solvent tank

Peptide synthesis process



High pressure reactor (Deprotection reaction using hydrogen)

Cyclization process

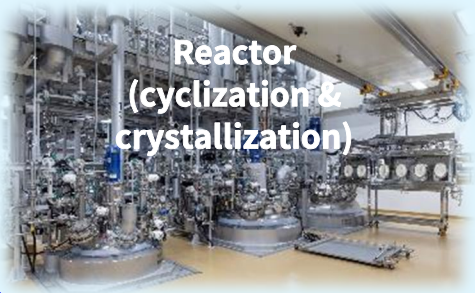
Cyclization

Impurities

Purification/Isolation process

Crystallization

API



Introduction of Fujieda Plant, Chugai Pharma Manufacturing Co., Ltd

February 26, 2025

Chugai Pharma Manufacturing Co., Ltd.

Head of Fujieda Plant

Kaichiro Koyama

Company Profile of Chugai Pharma Manufacturing Co., Ltd.

Company name: Chugai Pharma Manufacturing Co., Ltd.

Representative: Kenji Kamada

Established: May 2006

* Chugai Pharmaceutical's drug manufacturing business was transferred to Chugai Pharma Manufacturing through a company split.

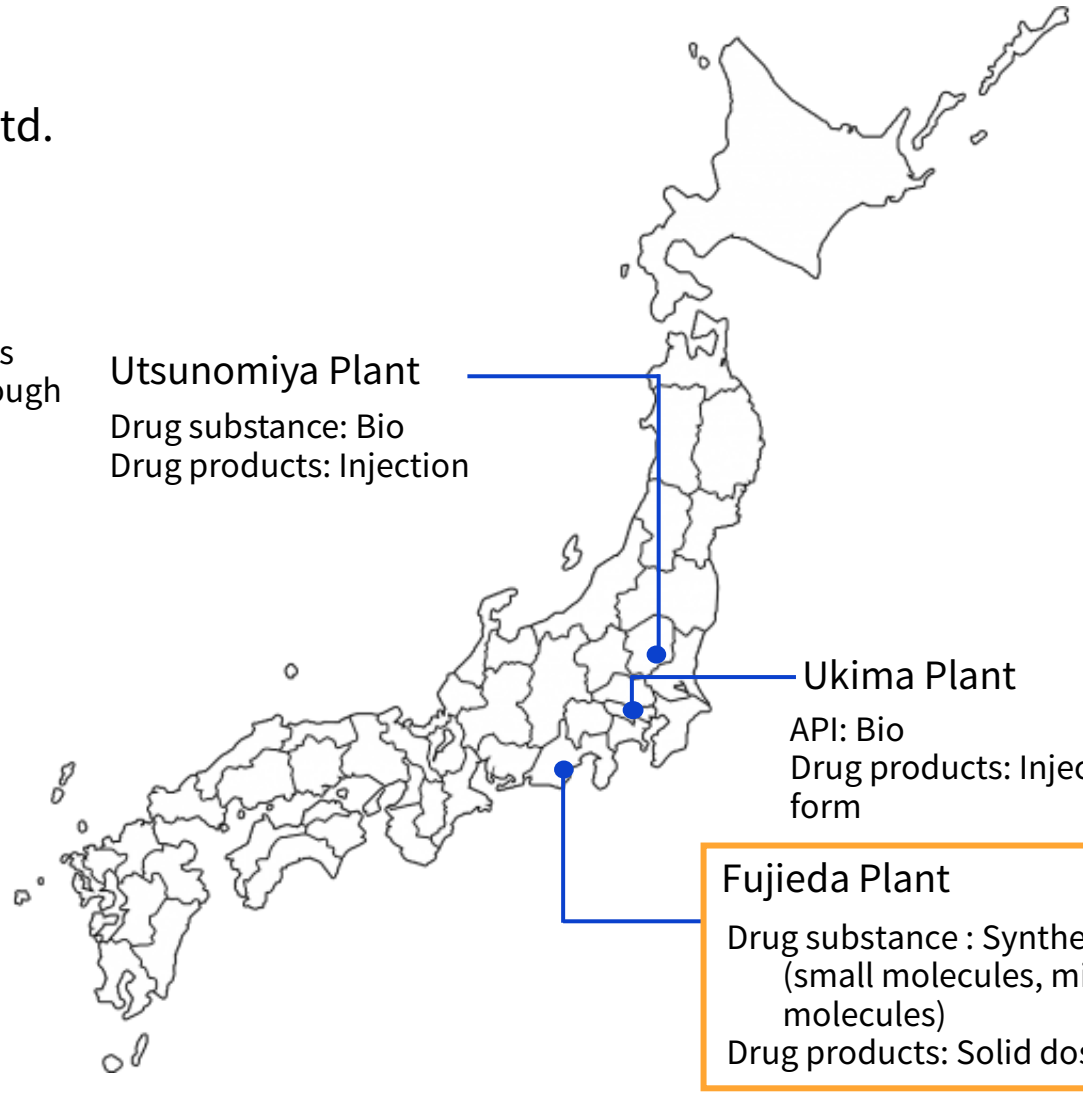
Business: Manufacturing of pharmaceuticals

Head Office: Ukima, Kita-ku, Tokyo

Number of employees: 1,599 (as of January 1, 2025)

Abbreviation: CPMC

→ **C**hugai **P**harma **M**anufacturing **C**o.,Ltd.



Overview of Fujieda Plant

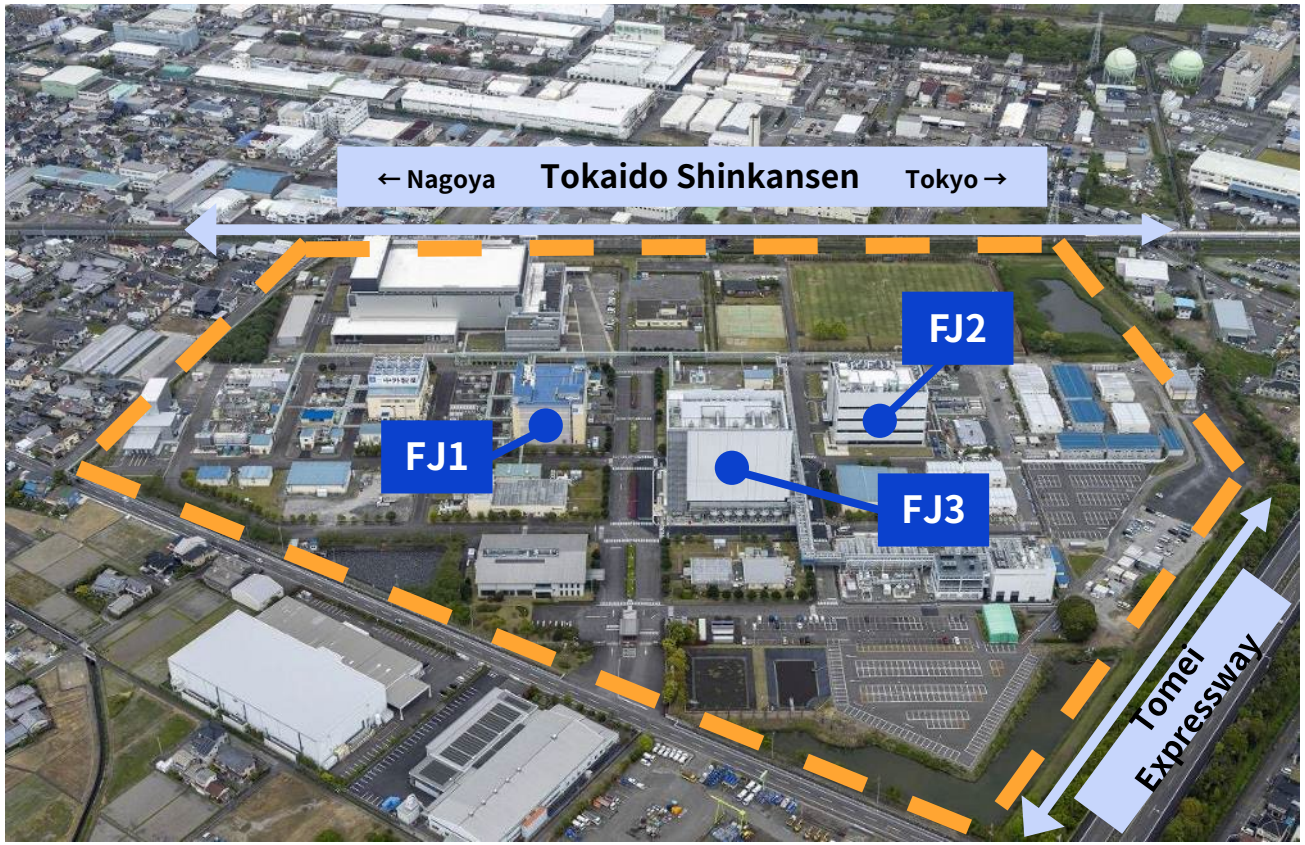
- Responsible for the production of APIs, which are the active ingredients of drugs, and the production of oral solid dosage forms, which involves forming raw materials into capsules or tablets and packaging them
- In addition, it will be the center of the production of mid-size molecule drugs, which are expected to be a pillar following small molecule and antibody drugs

- Location: Fujieda City, Shizuoka Prefecture
- Start of operations: 1971
- Site area: 216,804 m^2
- Business overview: Production of APIs, manufacturing of solid formulations, packaging of pharmaceuticals, manufacturing of APIs for clinical studies

Manufacturing Building for APIs “FJ1”

Manufacturing Building for APIs “FJ2”

Manufacturing Building for APIs “FJ3”



Overview of FJ3

- Aims to address the manufacturing functions of small and mid-size molecule drugs with high potency, covering APIs for late-stage clinical trials and early commercial production after launch
- By adding FJ3 to the existing manufacturing buildings, FJ1and FJ2, Chugai will gain the capability to consistently supply APIs throughout early clinical development to early commercial production

<Facility Overview>

- Total investment: 55.5 billion yen
- Construction area: 2,205 m^2
- Total floor area: 10,489 m^2
- Structure: 5-story base isolated building
- Features:
  - World-class high potency containment technology
  - Environmental considerations (non-fluorocarbons design, energy saving/CO_2 reduction, waste reduction)
  - Safety considerations (safety design, base-isolation structure, etc.)

Role and Positioning of FJ3

- FJ3 is responsible for the large-scale manufacturing of APIs and formulations for late-stage development and early commercial production of small- and mid-size molecule drugs

PC → P1 → P2 → P3 → Initial production → Full-scale production

[P1 - 2 Investigational drug facility] [P3 - Early production facility] [Main production]

APIs

Speed

Laboratory building

Speed & flexibility

Speed & ultra-high potency drug facilities

CMO

Production volume

Drug product
Spray dry Intermediate

Speed

Laboratory building

Speed & ultra-high potency drug facilities

CMO

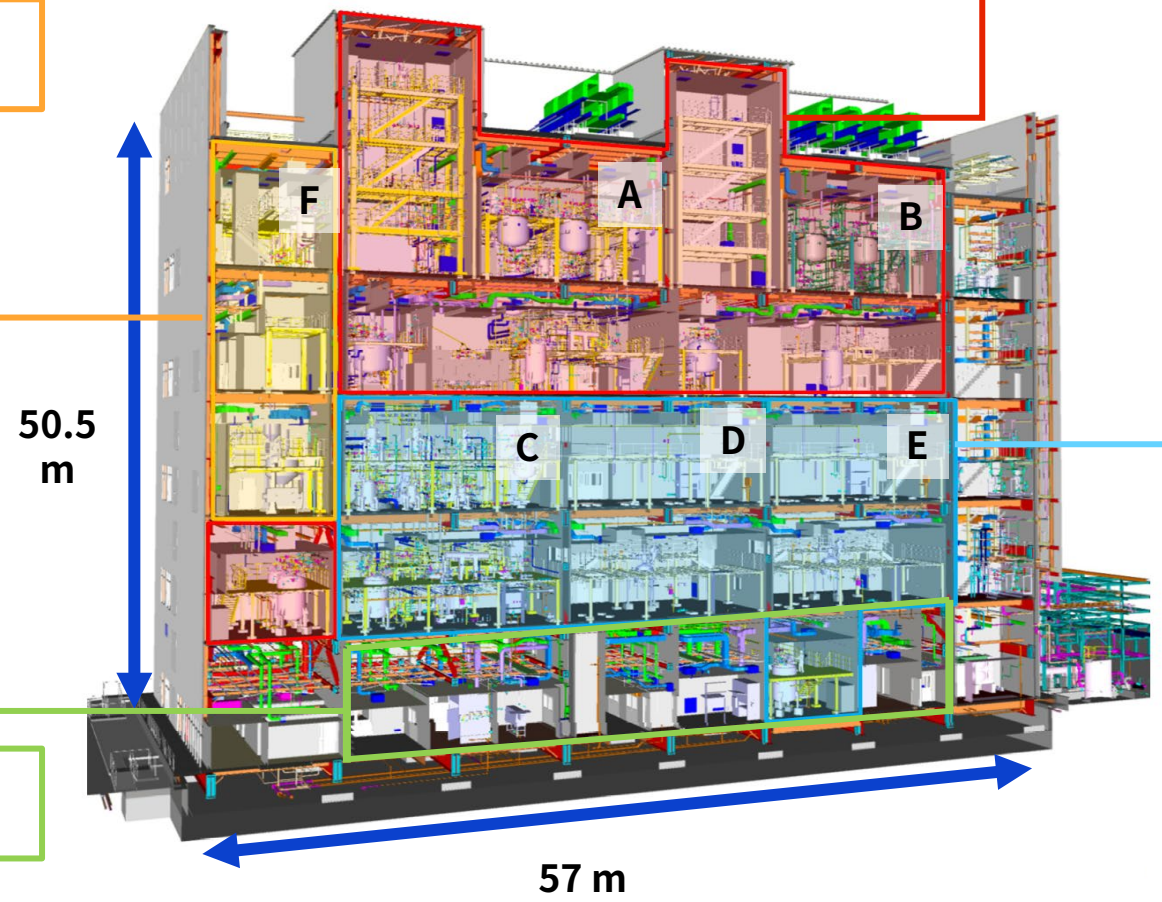
FJ3 Layout

- Simultaneous manufacturing of multiple products is possible with 2 lines for manufacturing intermediates, 3 lines for manufacturing APIs, and 1 line for spray drying.

Spray dryer:
1 line (F)

Intermediate manufacturing facilities:
2 lines (A, B)

Main facilities
- Reactors
- Hydrogenation reactors
- Filter dryers



API manufacturing facilities:
3 lines (C, D, E)

Main facilities
- Reaction chambers
- Crystallization vessels
- Filter dryers

Weighing room/
Storage cabinet

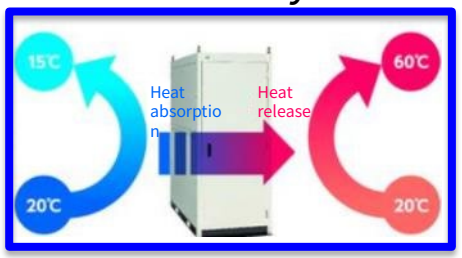
Features of FJ3: High Potency Containment, Environmental and Safety Considerations

- High potency: Containment capability corresponding to extremely potent drugs
- Environment: Non-fluorocarbons design, energy saving/CO_2 reduction, waste reduction
- Safety: Thorough safety design against explosions and fire, etc., and earthquake countermeasures with base-isolation structure

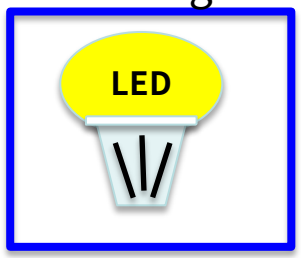
High potency containment

Natural refrigerants

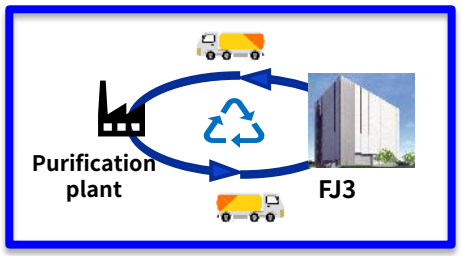
Exhaust heat recovery



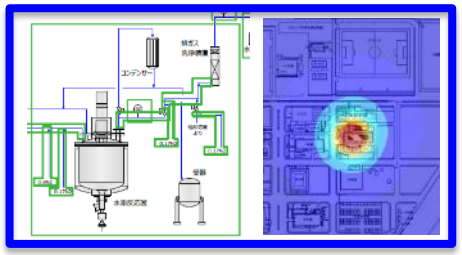
Electric energy saving



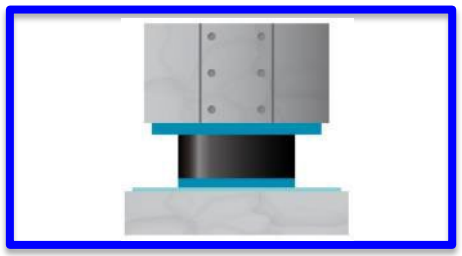
Organic solvent/ Catalyst recycling



Explosion safety



Base-isolation structure

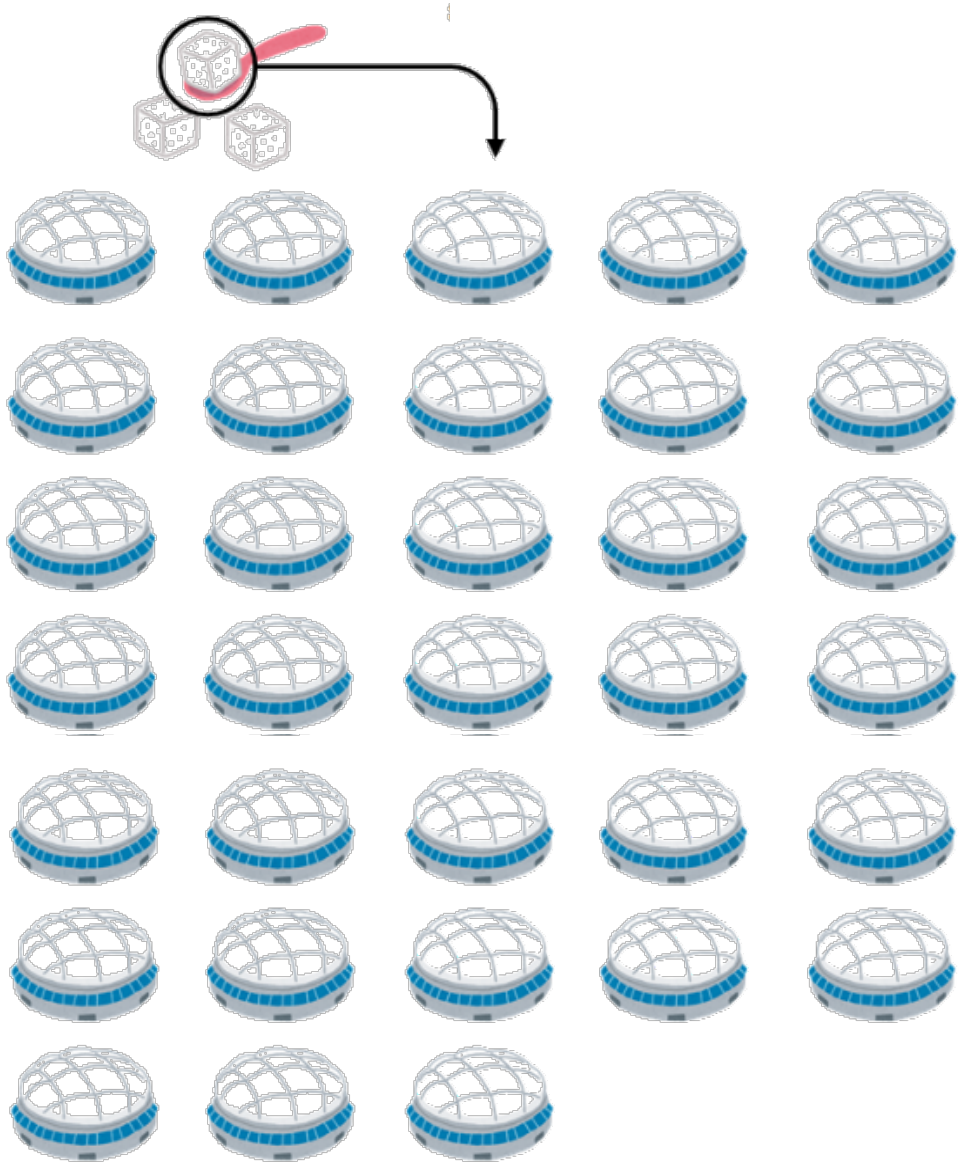


Containment level

0.03

μg/m³ or less

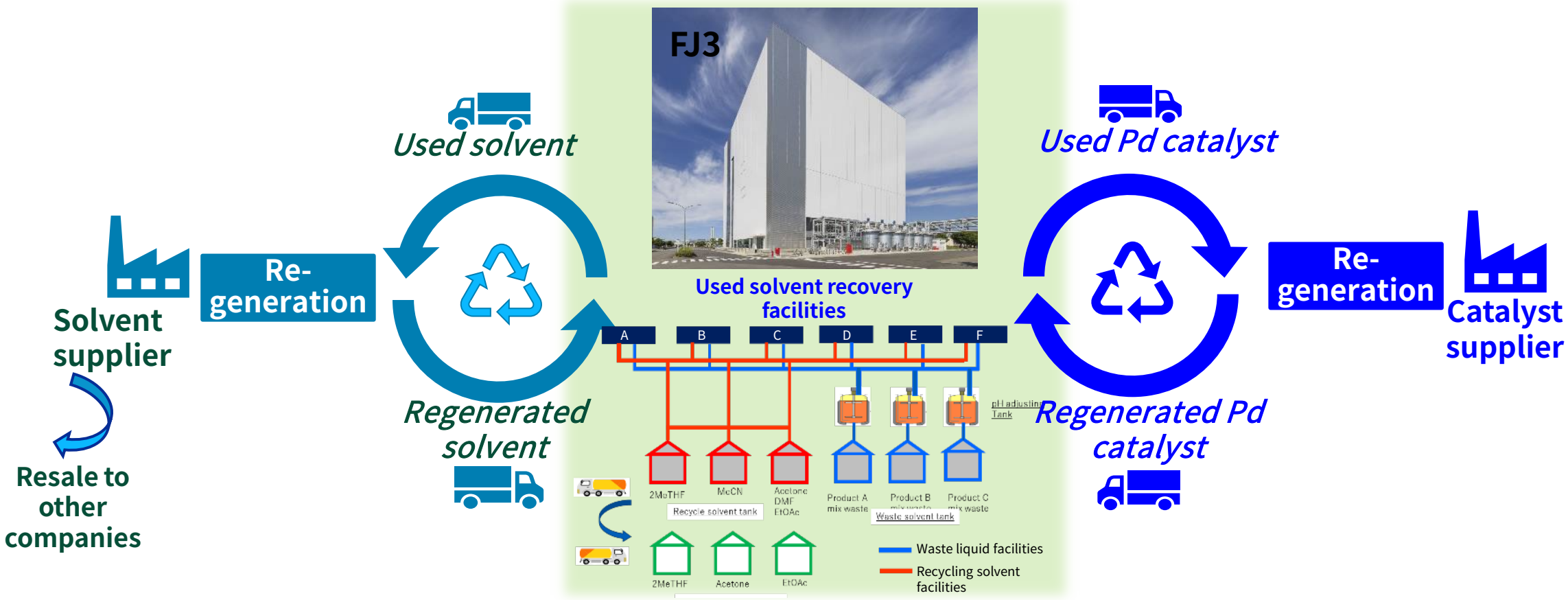
Isolator



The concentration of a single sugar cube dispersed in a volume equivalent to 33 Tokyo Domes

Environmental Considerations (Recycle)

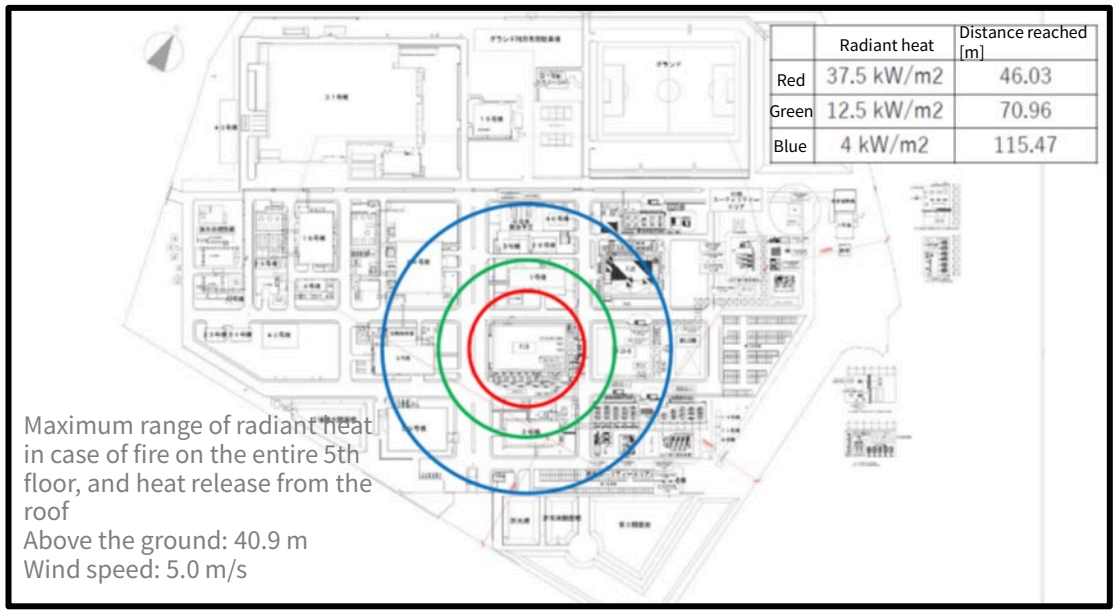
- Aiming to minimize waste by constructing recovery facilities for organic solvents and palladium (Pd) catalysts used for manufacturing, and building a system for their regeneration and reuse



Safety/Facility Design that Thoroughly Supports Safety

- Facility measures to avoid effects on the outside environment even in worst case scenarios
- In addition to various Japanese regulations, aligned with Roche's safety and environmental concepts

(Example) Simulation of radiant heat diffusion during a fire



■ Worst case analysis
✓ Explosion simulation
✓ Gas diffusion simulation
✓ Fire simulation

■ Environmental safety: Regulations and concepts
✓ Firefighting, high pressure gas safety, etc.
✓ SHE (Safety, Health and Environment) Concept
✓ Energy Review

■ Measures
✓ Explosion: Introduction of explosion-release shaft
✓ Fire: Radiant heat blocked by fire extinguishing foam
✓ Gas diffusion: Containment by foam dispersion

Avoid effects off-site

Contacts

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INNOVATION BEYOND IMAGINATION

CHUGAI PHARMACEUTICAL

Roche A member of the Roche group