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CHUGAI PHARMACEUTICAL CO., LTD.

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

February 26, 2025

Event Summary

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[Venue Size]	
[Participants]	
[Number of Speakers]	4

Shinya Takuma	Vice President, Head of Manufacturing Technology Division
Dr. Kenji Maeda	Head of API Process Development Department
Kaichiro Koyama	Head of Fujieda Plant
Kae Miyata	Head of Corporate Communications Department

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	Hiroyuki Matsubara	Nomura Securities
	Hiroshi Wada	SMBC Nikko Securities
	Shinichiro Muraoka	Morgan Stanley MUFG Securities

Kazuaki Hashiguchi	Daiwa Securities
Koichi Mamegano	BofA Securities

*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A or whose questions were read by moderator/company representatives.

Presentation

Miyata: Hello, everyone. Thank you very much for coming to today's tour at Fujieda Plant FJ3 of CHUGAI PHARMACEUTICAL CO., LTD. I am the moderator, Miyata from the Corporate Communications Deptartment. Thank you very much for your cooperation.

FJ3, Fujieda plant, is the manufacturing building for synthetic APIs of small- and mid-size molecule. Construction was completed in November 2024. Operations is planning to commence in March of this year. Today, we will open its doors for the press, investors and analysts for the first time.

Mr. Shinya Takuma, Vice President and the Head of Manufacturing Technology Division of CHUGAI PHARMACEUTICAL. Dr. Kenji Maeda, the Head of API Process Development Department of CHUGAI PHARMACEUTICAL will explain the manufacturing technology of mid-size molecule APIs. Finally, Mr. Kaichiro Koyama, the Head of Fujieda plant of Chugai Pharma Manufacturing will talk about the plant.

Followed by the Q&A session, we will invite you to a tour of the FJ3. The tour will take approximately 120 minutes, including transportation, to visit the three main sites. We will divide you into four group and our staff will guide you. Please wear a white coat and an intercom during the tour. Afterwards, we will return here again for a Q&A session and then dismissal. Please note that the tour will be recorded for internal purposes. Thank you very much for your understanding.

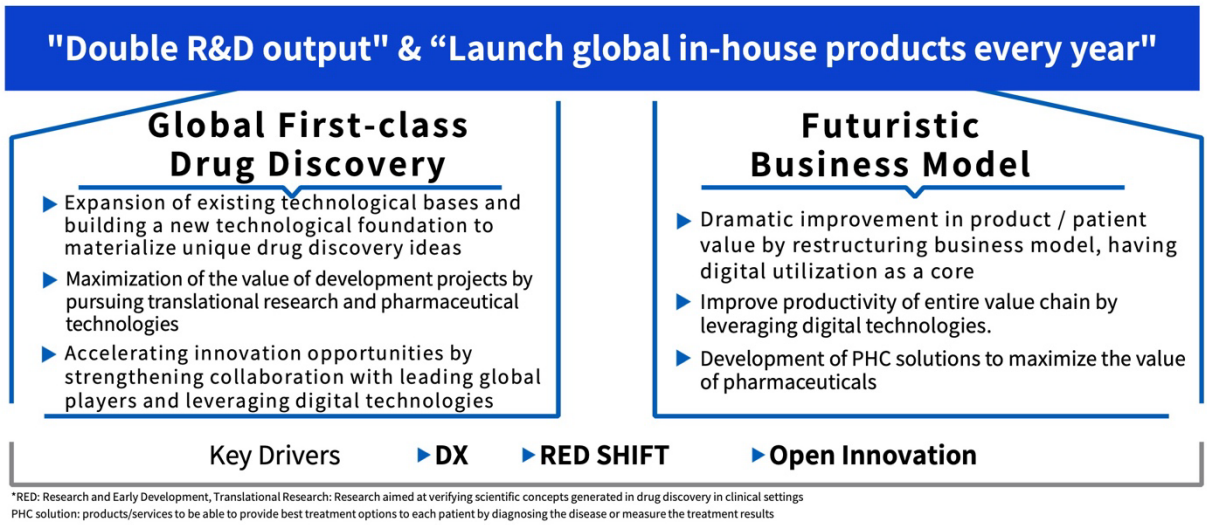
Now, Mr. Takuma, please begin.

Takuma: My name is Takuma, and I am the Head of the Manufacturing Technology Division at CHUGAI PHARMACEUTICAL. Thank you for taking time out of your busy schedule today to visit FJ3, which was completed last year. First of all, I would like to talk about the significance of the establishment of the small and mid-size molecule production system, including this FJ3, in TOP I 2030.

On March 10 next month, CHUGAI PHARMACEUTICAL will celebrate its 100th anniversary. In 1925, two years after the Great Kanto Earthquake, CHUGAI's founder, Juzo Ueno, established the Company with a vision to create medicines that benefit the world, a vision that has been carried forward through the years.

We have embraced bold new challenges in drug discovery technologies, including small molecules, biopharmaceuticals, antibodies, and mid-size molecules. By establishing technology-driven drug discovery, we have developed and launched innovative new drugs. For the next 100 years, we will continue to contribute to healthcare and human health around the world for patients.

Two Pillars of TOP I 2030



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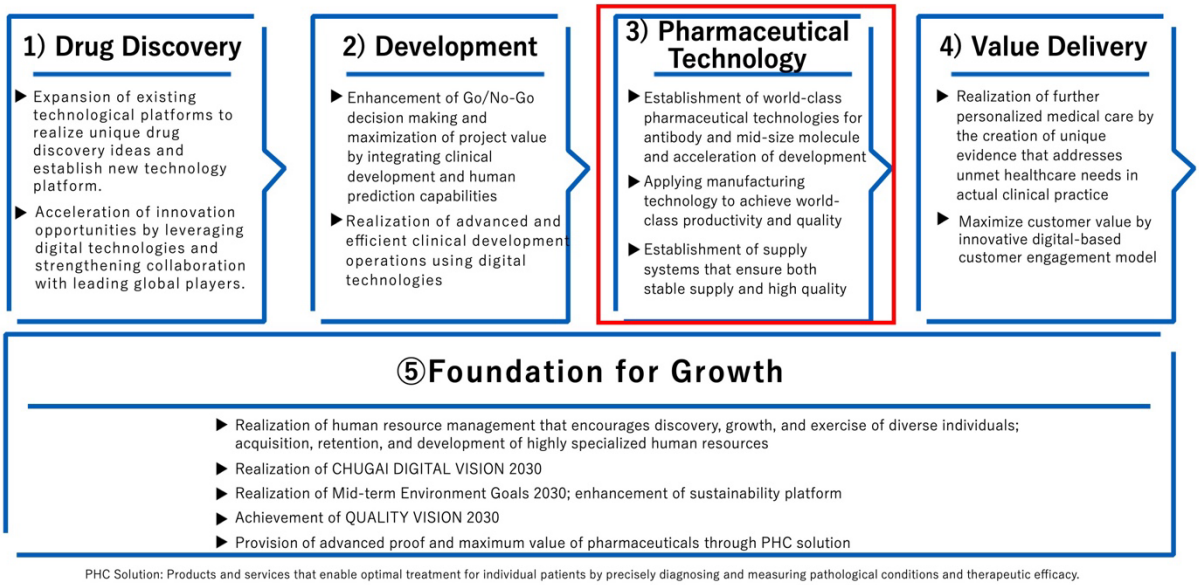
As we have already announced, TOP I 2030 is built on two pillars. One is achieving global first-class drug discovery, and the other one is developing a futuristic business model. It aims to meet the ambitious goals of doubling R&D output and launching global in house products every year. The three key drivers for this will be DX, RED SHIFT, and open innovation.

Summary of Five Reforms



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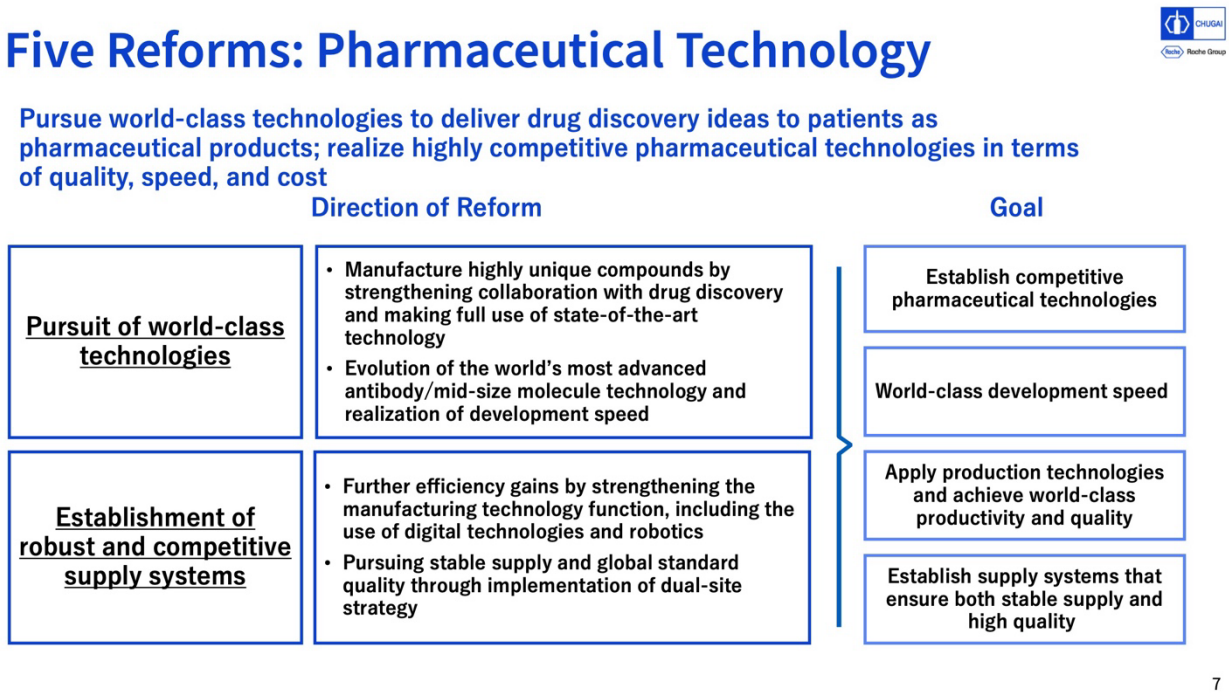
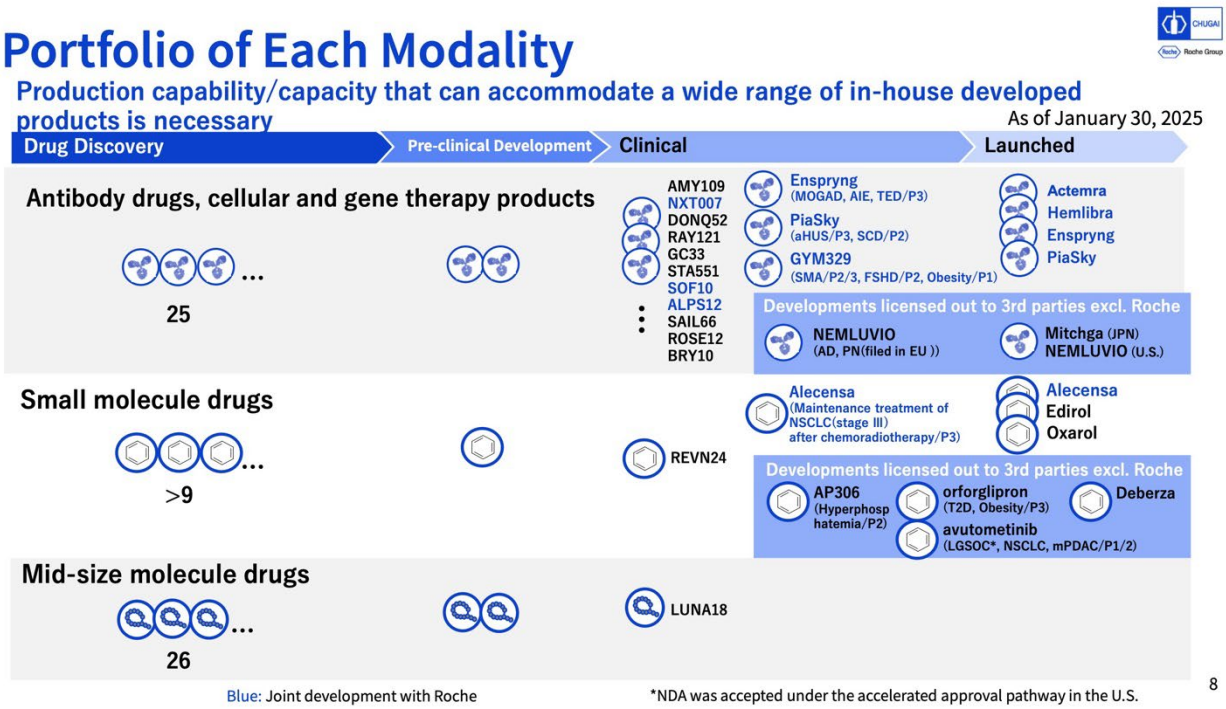
To realize TOP I 2030, we are implementing reforms in the five areas, drug discovery, development, pharmaceutical technology, value delivery, and foundation for growth that supports these areas. And we are involved in pharmaceutical function.



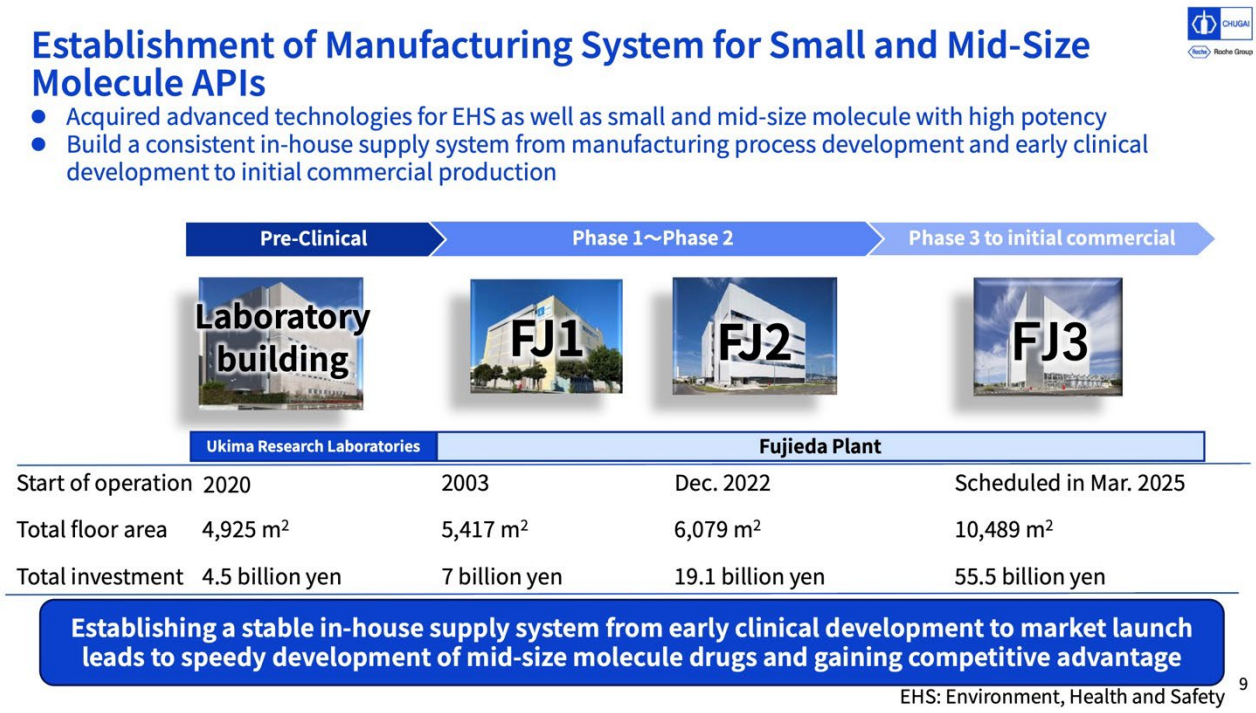
The pharmaceutical technology function has become increasingly vital in transforming CHUGAI's original drug discovery ideas into pharmaceutical products. As shown in the upper stage, we must first develop user-friendly formulations and dosage forms, along with robust and efficient production processes. Our goal is to achieve world-class development speed through competitive pharmaceutical technologies.

As show in the lower stage, production, we aim to enhance competitiveness across quality, speed, and cost which are factors that often can be trade-offs. By leveraging digital technology, robotics, and our dual-site strategy, we strive to optimize all aspects of manufacturing.



Currently, CHUGAI PHARMACEUTICAL has a large number of products discovered in-house, projects under development in clinical trials, and projects in the research stage. This chart shows the portfolio of antibodies at the top, small molecule drugs in the middle, and mid-size molecule drugs, which are expected to be a new modality, at the bottom.

There are products and projects that we license out not only to Roche but also to third parties. In the mid-size molecules, LUNA18 is in clinical trials, followed by two projects in preclinical development and 26projects in drug discovery.



These plants will be responsible for the production of APIs for this abundance of small and mid-size molecules, especially those compounds that have highpotency.

The Fujieda plant consists of FJ1, FJ2, and FJ3 facilities. By adding FJ3, the largest production facility investment to date at JPY55.5 billion, to FJ2, which began operations in 2022 with a JPY19.1 billion investment, these facilities enable us to provide an integrated in-house production system from development to early commercial manufacturing and adapt flexibly to changing development schedules, accelerate development timelines, and gain hands-on experience in production processes, including troubleshooting.

We believe that this will be the future strength of CHUGAI, and we are confident that it will make a significant contribution to the commercialization of the portfolio we mentioned earlier, and ultimately to realize TOP I 2030. That concludes my explanation. Thank you very much.

Miyata: Next, Dr. Maeda will introduce the pharmaceutical technology for mid-size molecule APIs.

Pharmaceutical Technology for Mid-Size Molecule APIs

February 26, 2025

CHUGAI PHARMACEUTICAL CO., LTD.

API Process Development Dept., Pharmaceutical Technology Div.

Dr. Kenji Maeda

Maeda: My name is Maeda from the API Process Development Department. I am involved in API process development at our Ukima Research Laboratory. Today I will explain about the pharmaceutical and manufacturing technologies of mid-size molecule APIs.

Agenda

01 **Drug Discovery Modality Strategy**

02 **What Are Small and Mid-Size Molecules?**

03 **Method and Issues of Synthesizing Mid-Size Molecules**

04 **Chugai's Peptide Synthesis Technology**

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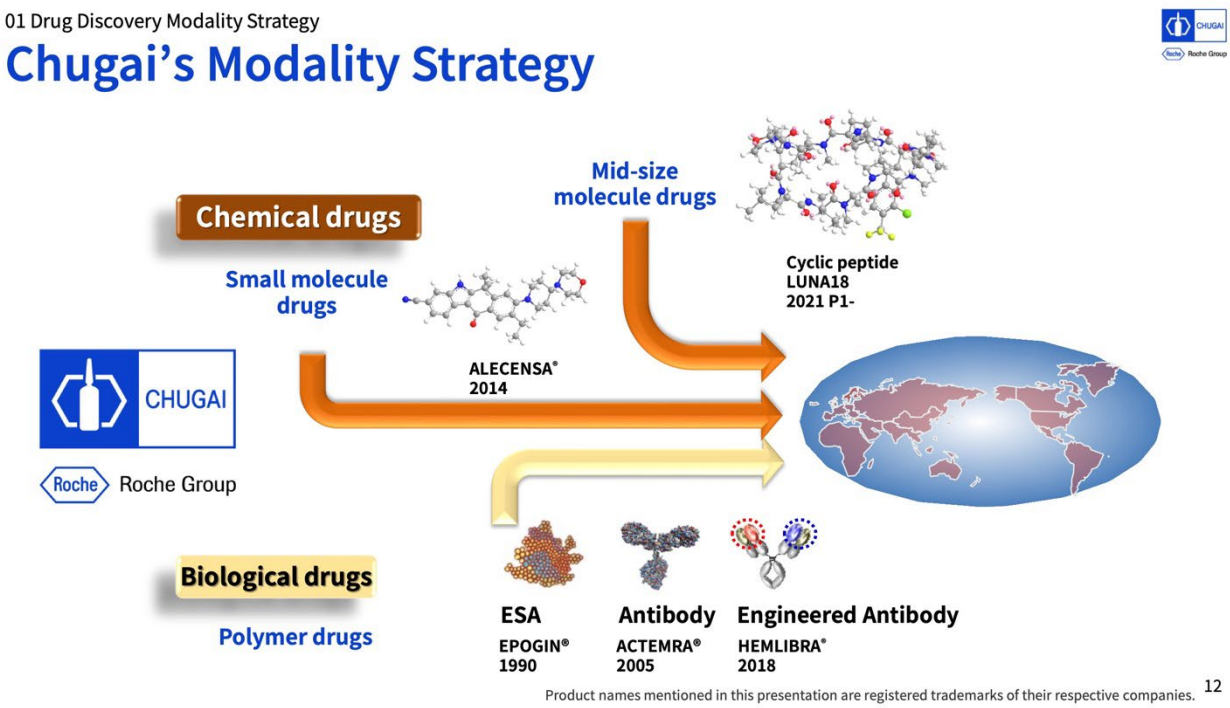
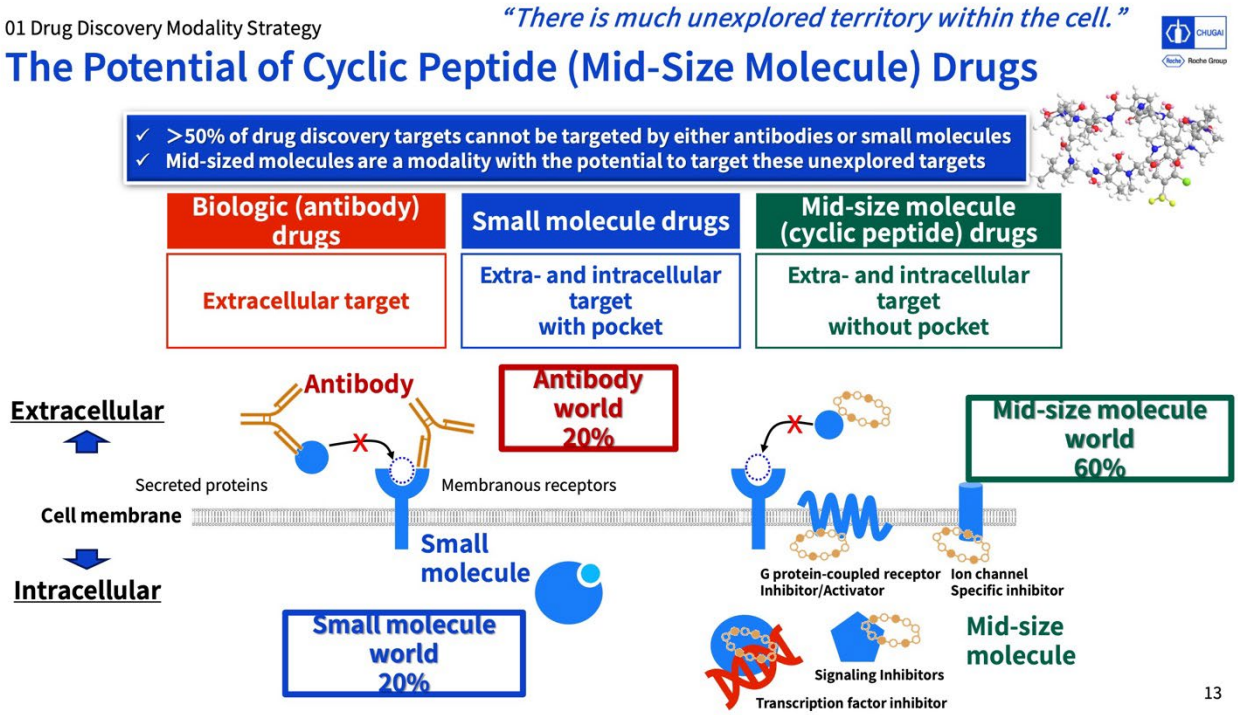
Here is today's agenda. In the first half of the presentation, I will give an overview of our modality strategy and overall explanation of small and mid-size molecules. In the second half, I will explain the challenges of synthesizing mid-size molecules and our synthesis technology.

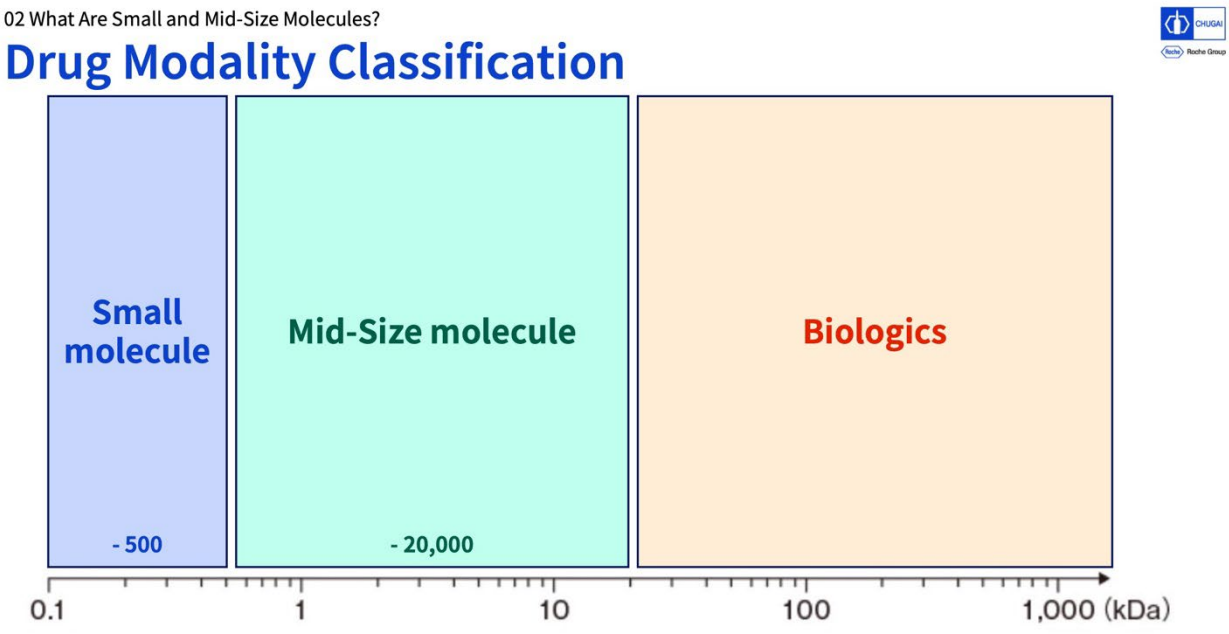


First, our drug discovery and modality strategy. In addition to the small molecule drugs that we have focused on since our drug discovery, we entered the biopharmaceutical business in the 1980s. Since then, we have successively launched innovative drugs. We have recently begun to take on the challenge of mid-size molecular medicine. This is our first mid-size molecule clinical development medicine, as Mr. Takuma mentioned earlier.

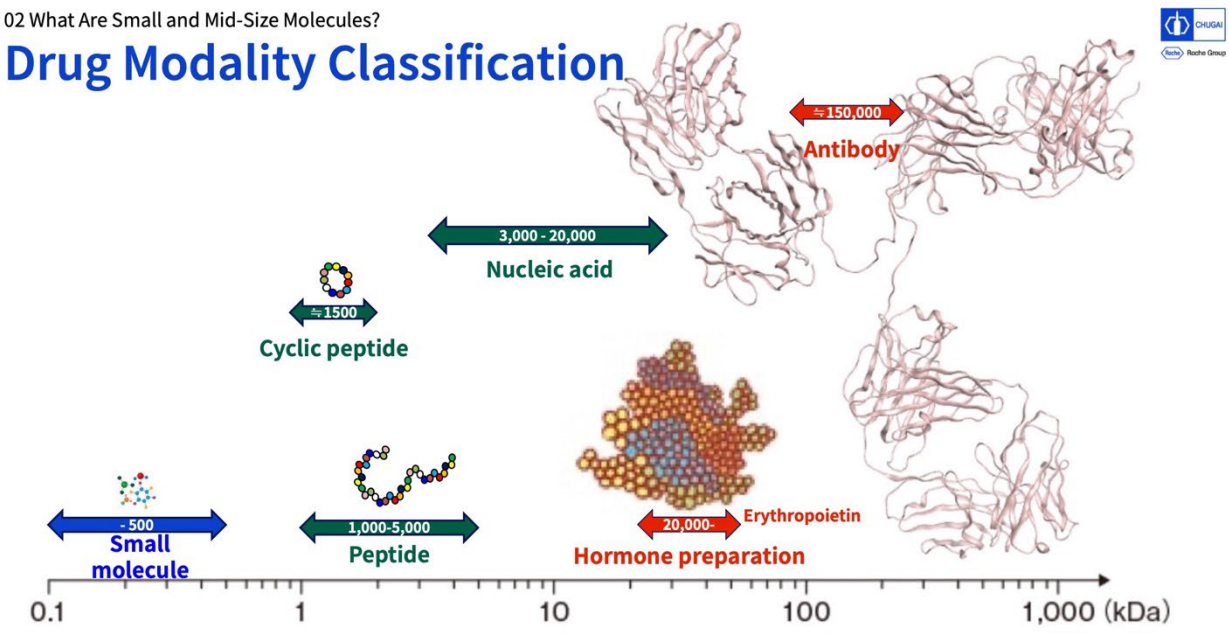


I will explain about drug discovery targets. First of all, the image shows the intracellular and extracellular targets and proteins of the cell membrane. First, antibodies target extracellular proteins such as secreted proteins. They account for 20% of the total. Next is small molecules, which are inside and outside the cell, but it requires molecular pockets as in the image. Therefore, it accounts for about 20% of the total.

On the other hand, for the mid-size molecules, it can target molecules outside and inside target the cell that small molecules cannot reach. Then, the mid-size molecules can aim at roughly 60%. This means that over 50% of previously untargeted molecules are still inside cells. As shown here, I believe there are still many unexplored areas within cells.

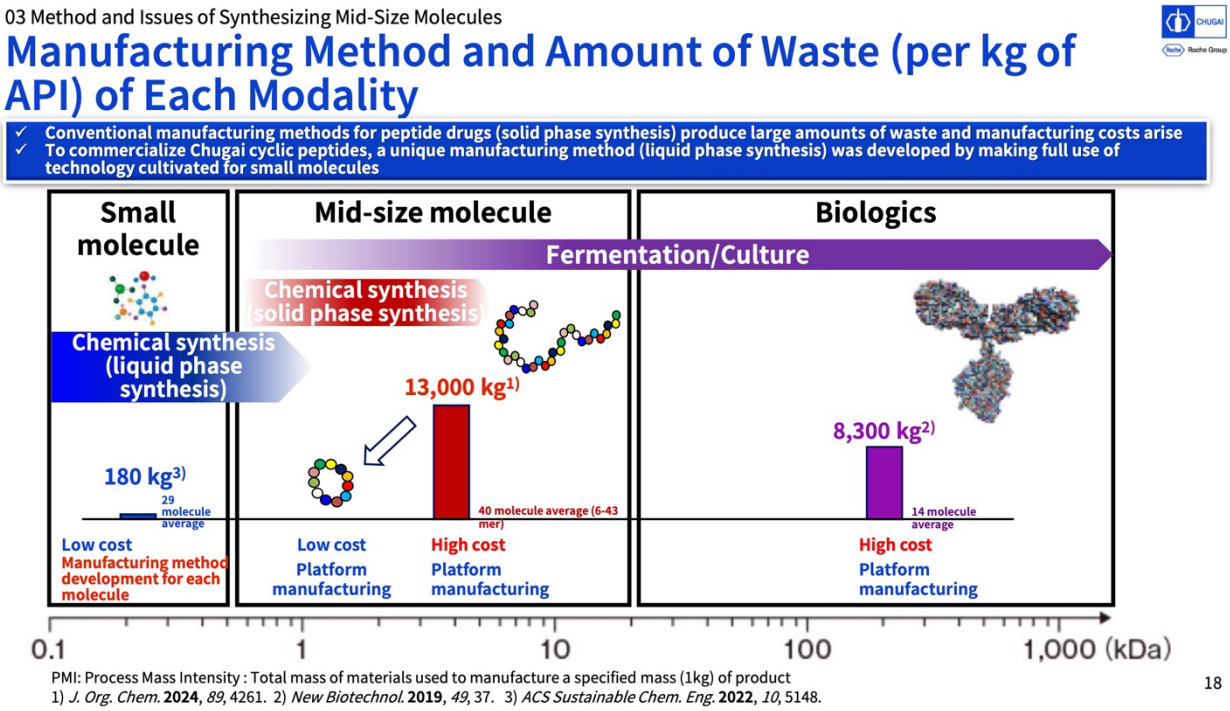


Next, I will give an overview of small and mid-size molecules. The horizontal axis represents the logarithm of mass. There is no fixed definition of small, mid-size, and biologics, but small molecules are roughly up to 500, mid-size molecules are roughly 20,000 daltons, and anything above that is often classified as a biologics.



Each modality is plotted separately. First, 500 for the small molecular. The next is mid-size molecules. Roughly 1,000 to 5,000 for peptide drugs. Our cyclic peptides are about 1,500 of them. Oligonucleic acid can be up to 20,000 daltons for the larger ones. Above that becomes the field of protein. Hormone preparations are more than 20,000 daltons, and antibody drugs, which we are also engaged in, are about 150,000 daltons. This figure

plots the approximate size. Antibodies are 300 times larger than small molecules, and mid-size molecules are 3 times larger than small molecules.



Next, I will briefly explain the methods and challenges involved in the synthesizing mid-size molecules. I will explain the manufacturing process and challenges. First, small and mid-size molecules with a molecular weight of up to 1,000 are chemically synthesized using liquid phase synthesis, similar to conventional flask-based methods.

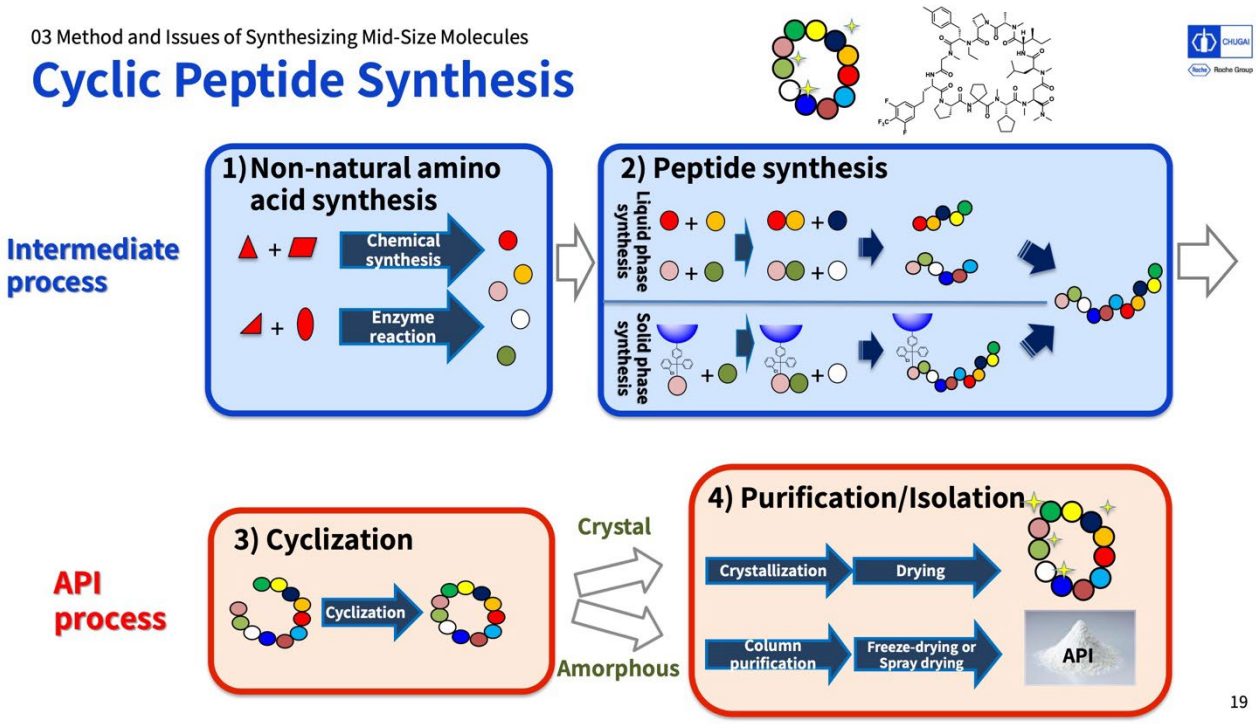
When the molecular weight exceeds 1,000, liquid phase synthesis becomes challenging, so solid phase synthesis is generally used. In this method, a resin serves as a support, and amino acids are sequentially attached to it. Beyond that, cultivation and fermentation are used in the manufacturing process. We produce antibodies by genetically modifying cells to generate them.

As the molecular weight increases, the amount of waste becomes a challenge. This can be described as a cost. This is based solely on literature information and represents the average of the data reported in the literature. This is the figure how much waste is produced to make one kilogram of API.

First, it is averaging 180 kilograms for the small molecules. With the antibodies we are working with, the average is 8,300 kilograms. The mid-size molecule is more than the antibody, 13,000 kilograms of waste. This amount of waste is produced to make 1 kilograms of API.

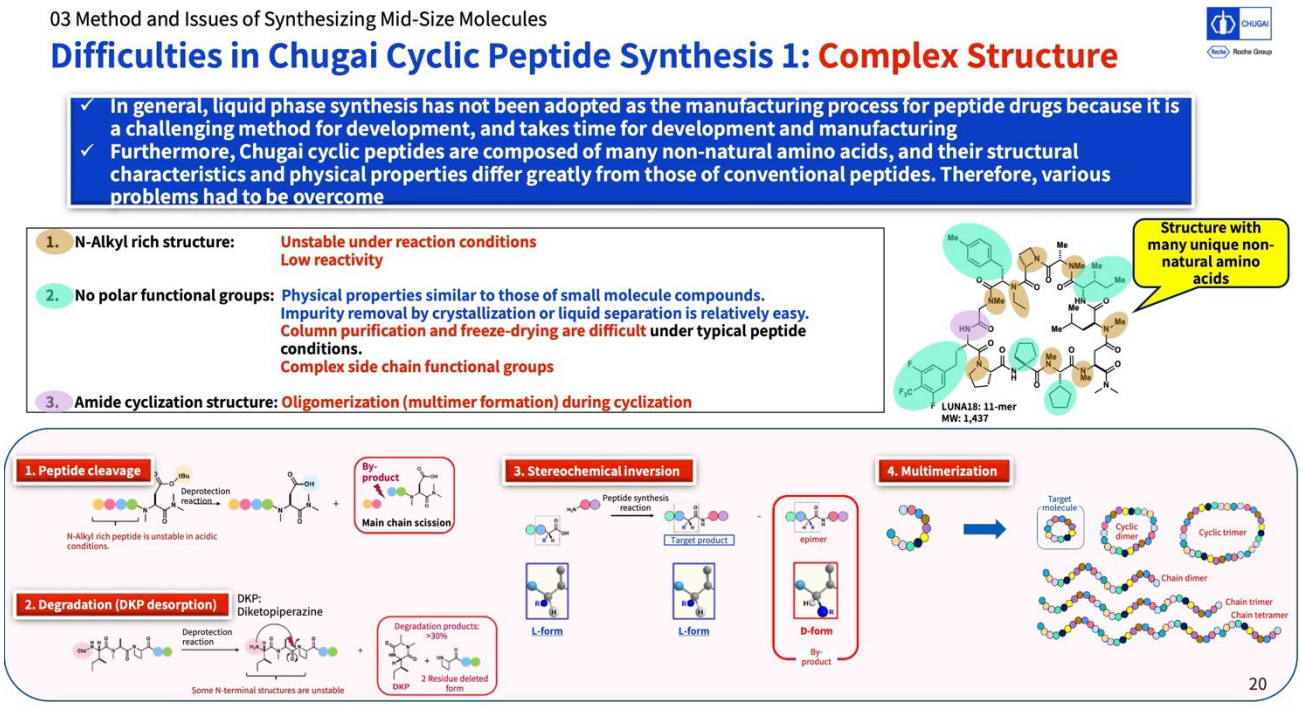
The manufacturing process characteristics of each modality are described below. For small molecules, they are low-cost. However, we have to develop each process one by one, and that is a bottleneck. Although polymers and mid-size molecules are costly, their development progresses relatively quickly because a platform manufacturing method has been partially established.

Now the mid-size molecules we are challenging on. We are challenging the mid-size molecules by applying our technology from our small molecule development to reduce costs and by establishing a platform to solve this issue.



Next, I will briefly explain how we make our cyclic peptides. The process consists of four steps in total. First, non-natural amino acids are synthesized. Our products contain many non-natural amino acids, other than natural amino acids, so we need to start with these first.

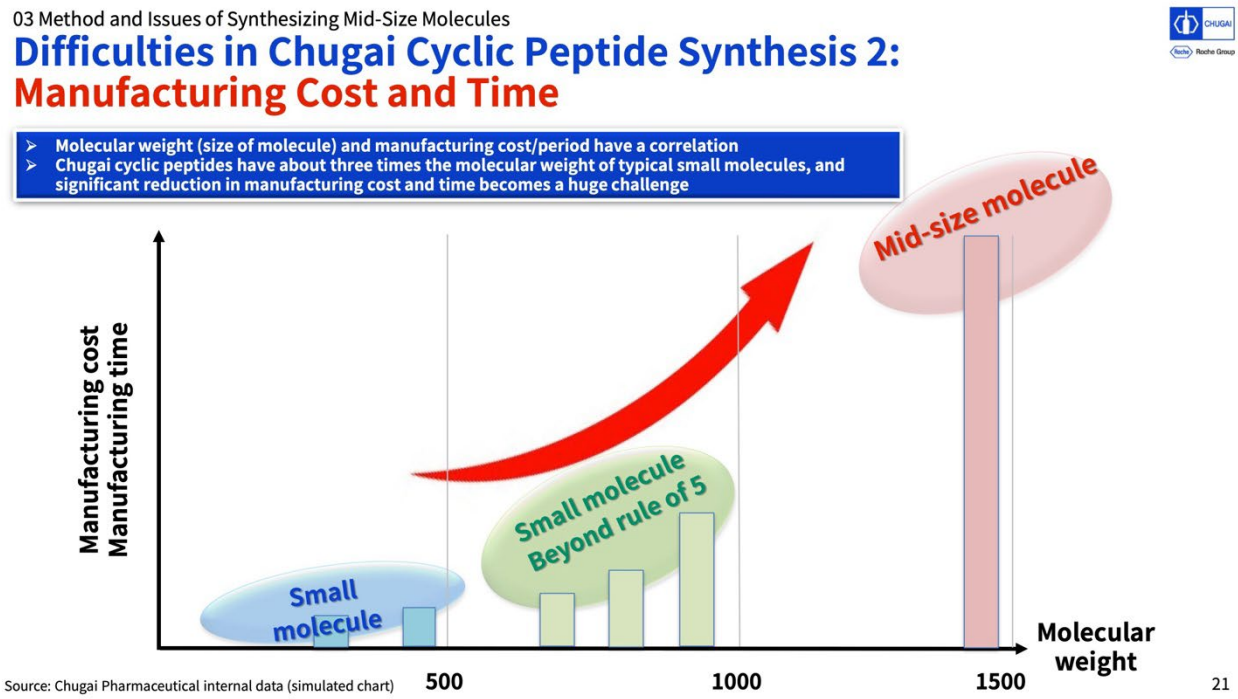
Next, as mentioned earlier, peptides are synthesized by liquid phase synthesis or solid phase synthesis. Our cyclic peptide has 11 amino acids, so we synthesize 11 amino acids here. Next, cyclization. We have challenges here as well, but I will explain them later. Next, the drug ingredient is isolated through crystallization or column purification, depending on its physical properties. This is the standard method for synthesizing our cyclic peptides.



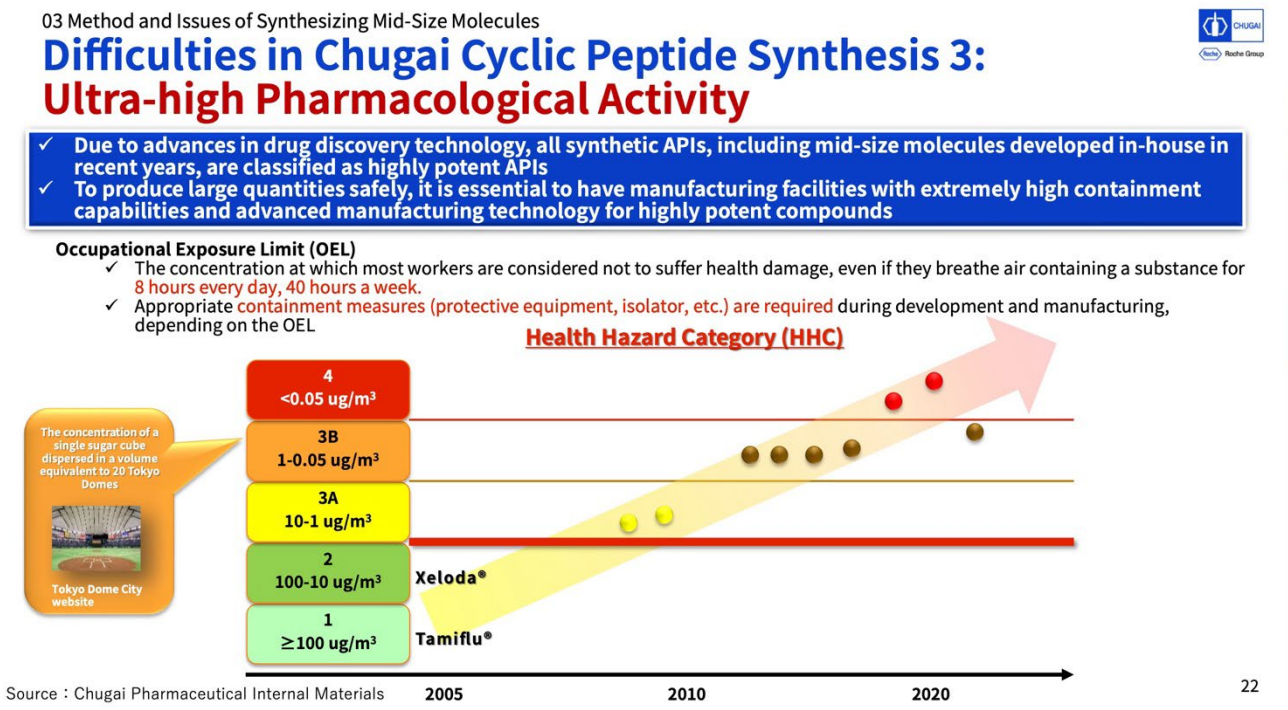
In the next three slides, I will explain the challenges of cyclic peptide synthesis. The first point is the complexity of the structure. To begin with, as mentioned earlier, liquid phase synthesis is generally difficult to develop, so it has not been widely used for manufacturing peptide drugs. Additionally, as shown here, our cyclic peptides contain a large number of non-natural amino acids.

Moreover, due to their structural characteristics, their physical properties differ significantly from conventional peptides, presenting many challenges that we had to overcome, which we mentioned earlier as well.

The below is one of examples. I won't go into details, but peptide cleavage and degradation, and also stereo inversion, which is a common challenge in peptide synthesis. Furthermore, since our peptides are cyclic, we must address issues such as multimerization and oligomerization during the cyclization process, solving them one by one.

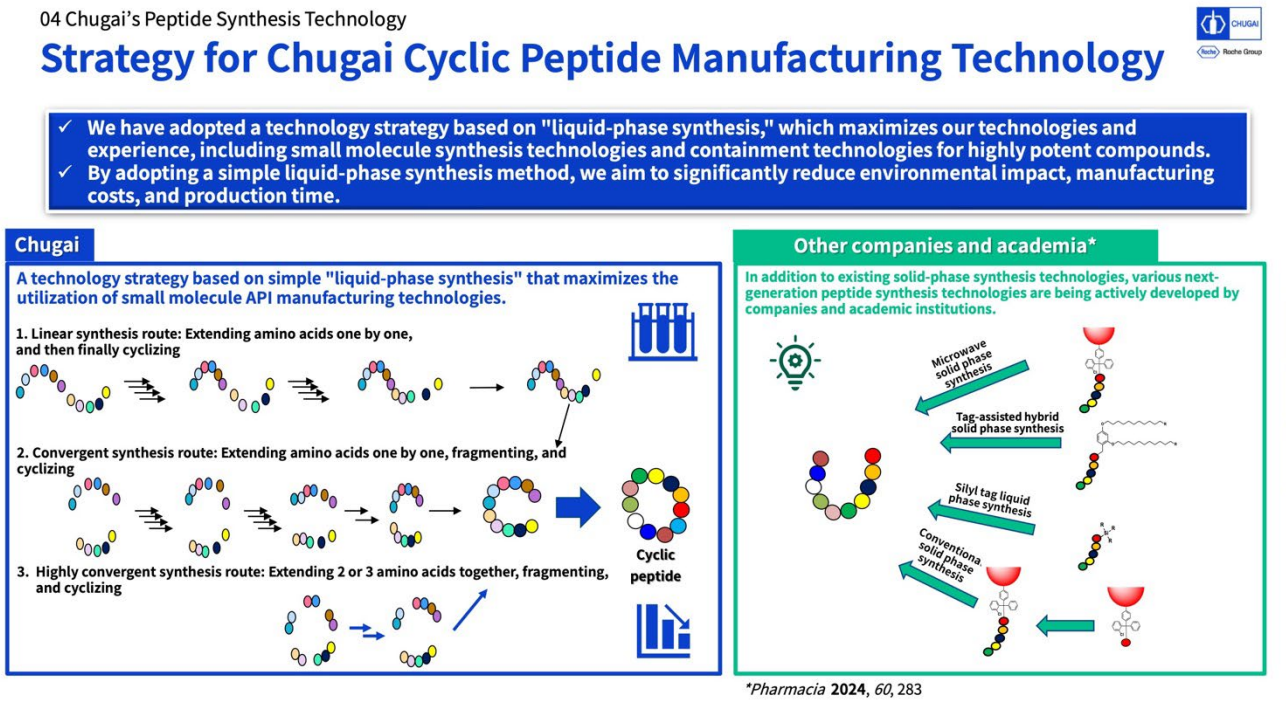


Next, I will explain manufacturing cost and time. This is just a diagram from our simulation, but the molecular weight and the size of the molecule, and the manufacturing time and cost are roughly correlated. Therefore, for small molecules up to 500, small molecules above 500, and mid-size molecules, which we are focusing on this time, manufacturing cost and time are generally correlated in this way. In our process, the bottleneck is that the molecular weight is three times that of small molecules, making reducing manufacturing cost and time a major challenge.



Finally, the pharmacological activity. The horizontal axis shows age, and the vertical axis shows the intensity of activity. The figure shows that the pharmacological activity becomes stronger as moving upward. As you can see, this plot shows the activity of our own products, and in recent years, all of them have exhibited higher activity. I forgot to mention that we classify the activity above the red line as high.

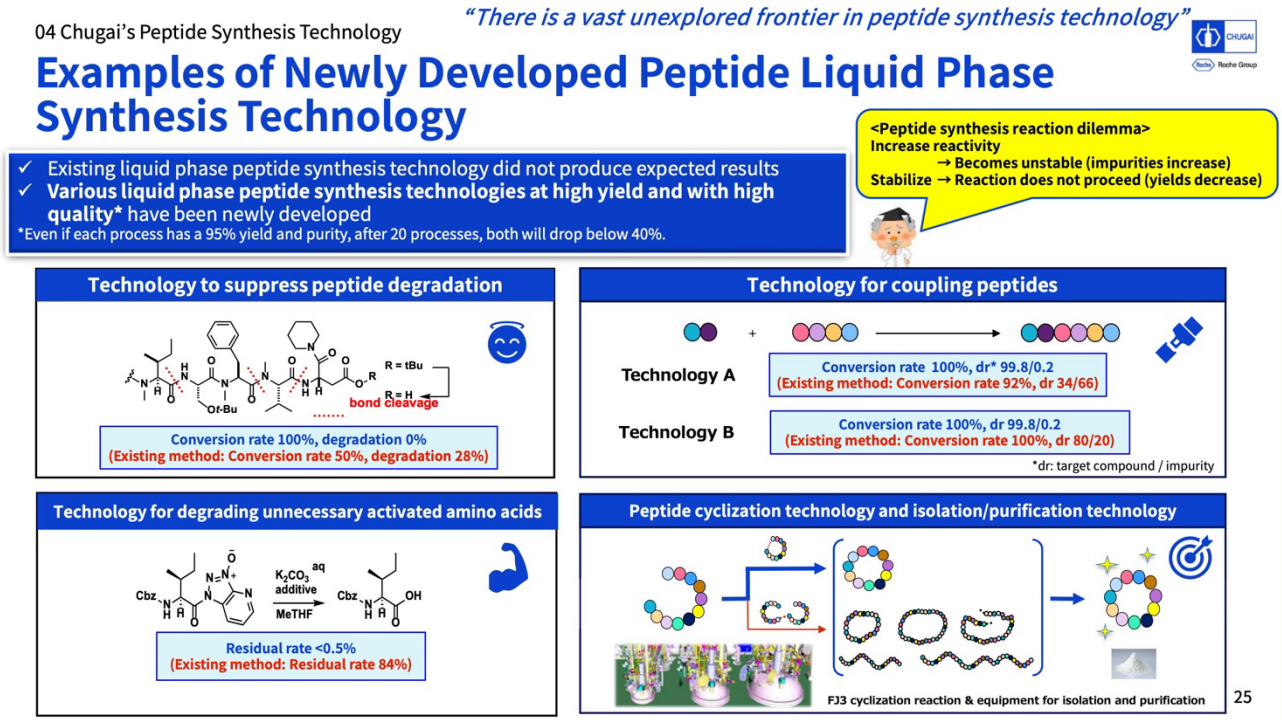
Products lanuched all recent years are highly active. In addition, we are also seeing products in near maximum and strongest activity levels. So, we will develop, manufacture, and supply such products safely and in large quantities. This kind of technology is very difficult, and this was also a major challenge for us.



Lastly, I will explain our peptide synthesis technology. There have been a variety of peptide drugs developed in the past, but the development of peptide drugs has become even more active in recent years. In this context, many next-generation peptide synthesis technologies are emerging from various companies and academia.

Our synthesis strategy is to maximize the use of our small molecule technology, which have been already accumulated, as described here. Our manufacturing strategy is to adopt a simpler liquid phase synthesis method.

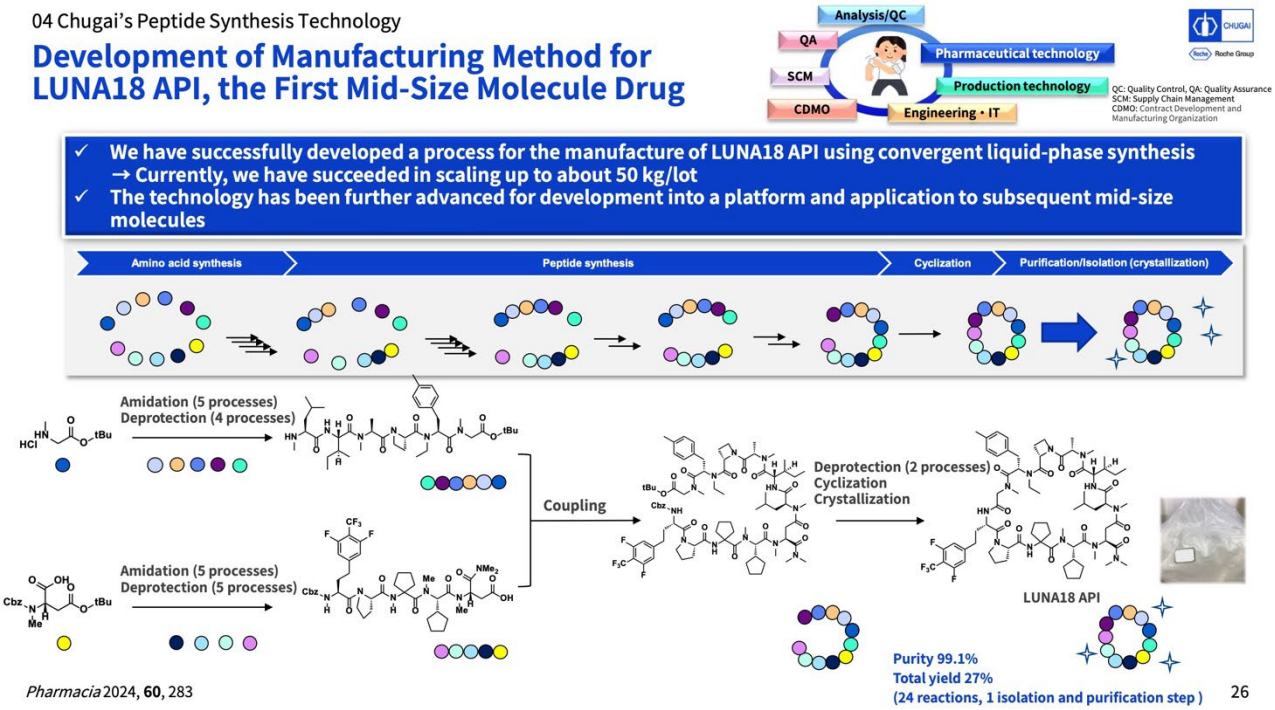
This simple liquid phase synthesis method is a crucial point. By adopting this approach, we can design synthetic routes with great flexibility. The manufacturing route can be designed as a straight-line process, a two-line process, or a multi-line process. We believe we can design a synthetic pathway based on the technological strategy of utilizing this simple liquid phase synthesis method. Through this synthetic route, we aim to significantly reduce the environmental impact, manufacturing costs, and time, as mentioned earlier.



This is examples of synthesis technologies that we have developed so far. Although we had known this from the beginning, we tried existing peptide synthesis techniques, but they did not produce the expected results. First of all, there is the dilemma of peptide synthesis, as is the case with ordinary synthesis. The more you want to increase activity and reactivity, the more impurities you will find. On the other hand, if you try to stabilize the reaction, the reaction will not proceed and the yield will not increase.

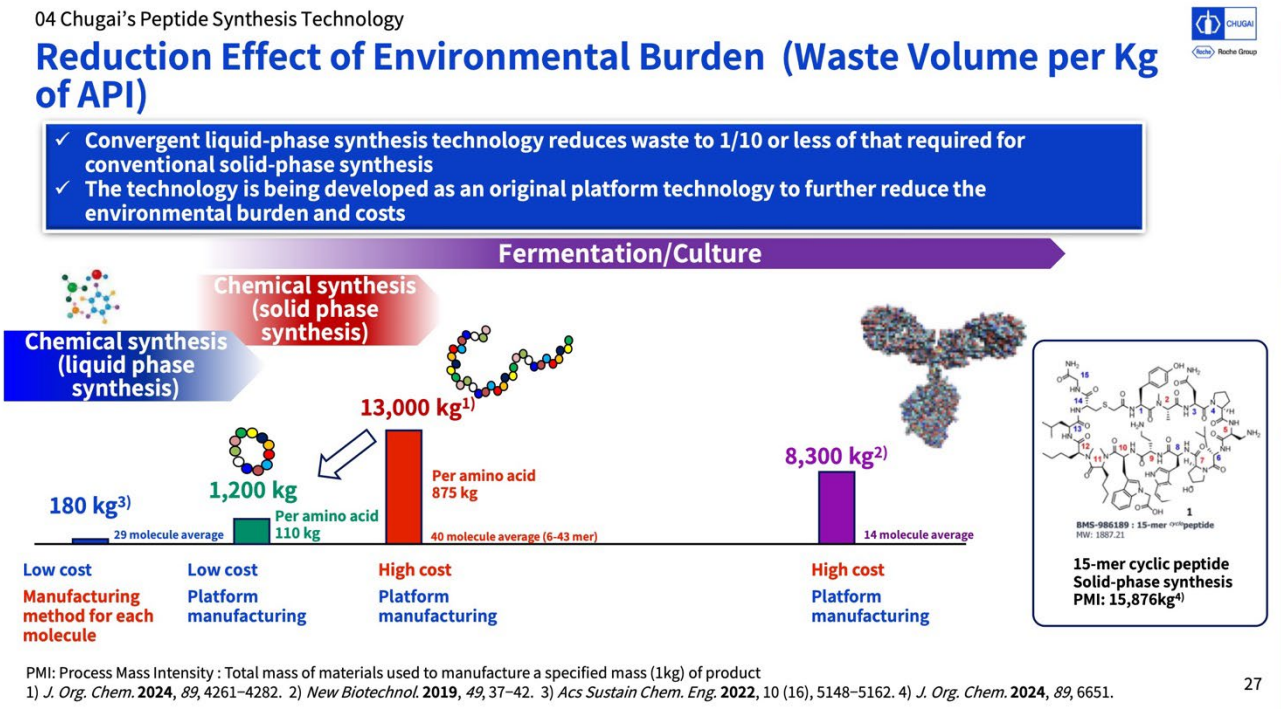
For the mid-size molecules compound and cyclic peptides, the synthetic pathway is very long. Even if each step proceeds at 95% yield, as shown here, the overall yield drops to less than 40% after 20 steps. So, 95% is still not enough. Therefore, it is essential to refine each synthesis technique step by step.

Shown below is the synthesis technology that we have developed so far. Technology that inhibits degradation, or conversely, degrades unnecessary actives. Then there is the technology of coupling or bonding peptides together. Finally, as I mentioned earlier, the cyclization technology. We are now developing such things.



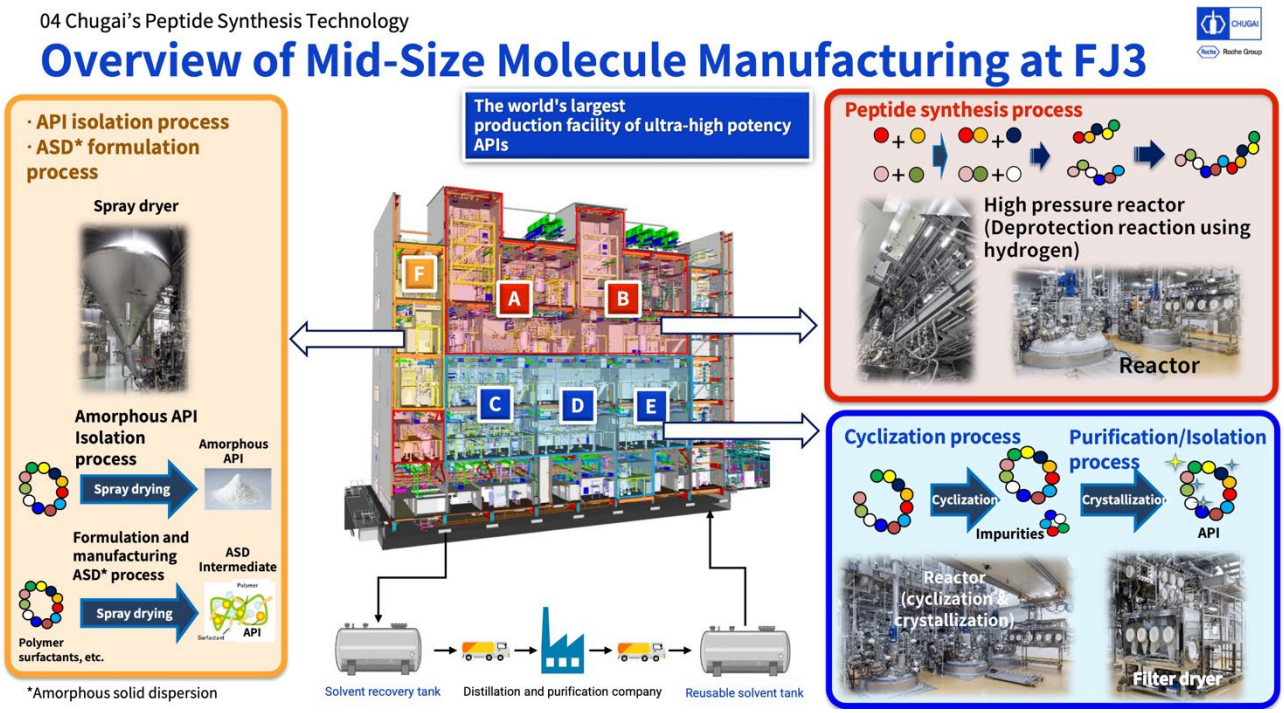
I would like to explain the manufacturing process of API for ourfirst mid-size molecule drug, LUNA18, which was done using the technology I have just described. As shown here, we have succeeded in developing a manufacturing process for LUNA18 API using a simple liquid-phase synthesis method. Although it is a small picture, this is the actual API. Thus, we have been able to obtain a high quality API.

We are currently improving this process and have succeeded in scaling up to 50 kilograms per batch. This technology was realized not only through our pharmaceutical expertise but also through the collaboration of various functions within our group and the support of CDMO. We are further enhancing this technology and developing it into a platform. As Mr. Takuma mentioned earlier, we are also applying it to our next-generation mid-size molecule portfolio.



Let me explain the reduction effect of environmental burden that I mentioned earlier. The production of LUNA18 API resulted in a waste volume of 1,200 kilograms per kilogram. We believe that these 1,200 kilograms is less than one-tenth of the amount compared to typical solid-phase synthesis and considerably lower than that of compounds with similar structures.

As you can see, there is still much development work to be done. However, we are advancing by addressing major issues in order through low-cost platform development.

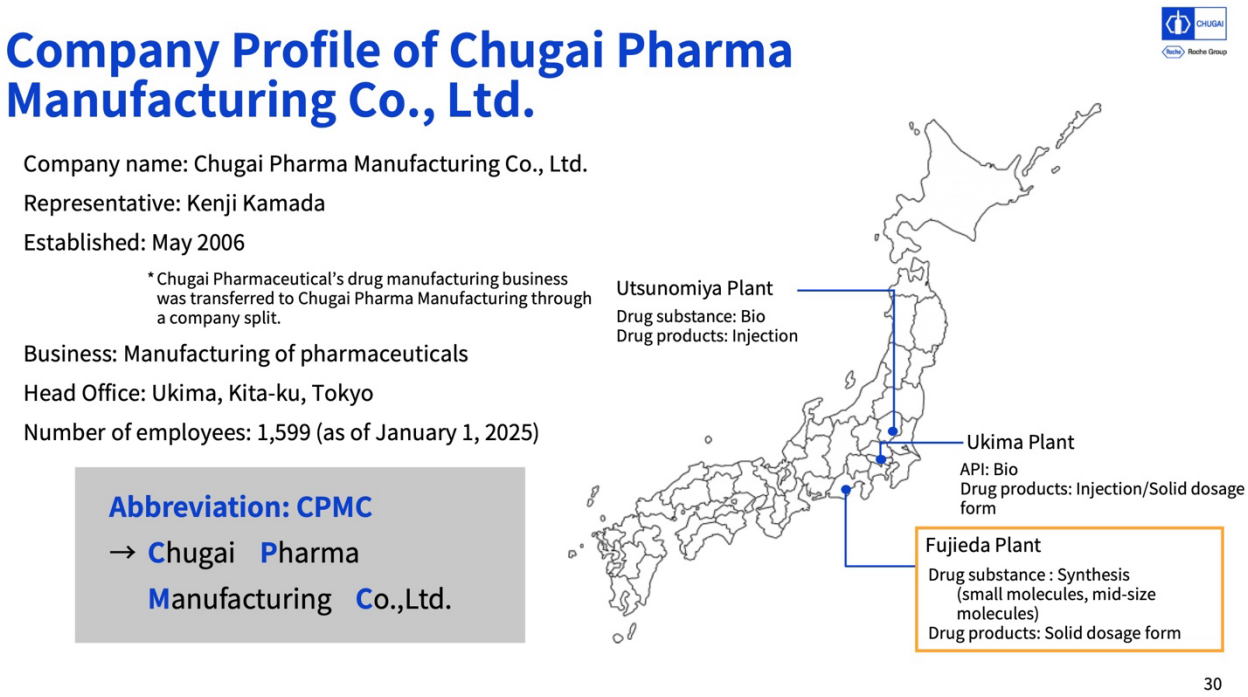


Lastly, I would like to give you an overview of the mid-size molecule production plant, FJ3, which is today's tour. This is a cross-sectional view. The upper floor is for peptide synthesis, and the lower floors, C, D, and E areas, are for cyclization and API control. In addition, in the F-area, spray dryers can be used to isolate API crystals or to produce solid or dispersed formulations of drug product intermediates.

Since this production facility consumes a large amount of solvent for both production and cleaning, it is equipped with tanks for collecting used solvent and for recycling and reusing solvent. This facilitates the solvent recycling function. Thus, FJ3 is the world's largest production facility for ultra-high potency APIs.

That is all from me.

Miyata: Next, Mr. Koyama will introduce about the Fujieda Plant.



Koyama: My name is Koyama, the Head of the Fujieda Plant. Thank you very much for coming to the Fujieda Plant today. I will give a presentation about the Fujieda Plant of Chugai Pharma Manufacturing for about 10 minutes.

First of all, this is our company profile. The representative is Kenji Kamada. The Company was established in May 2006. We are a subsidiary of the CHUGAI Group specializing in production. We manufacture pharmaceutical products, and our head office is located in Ukima, Kita-ku, Tokyo. We have three plants. From the north, Utsunomiya, Ukima, and Fujieda plants.

The Utsunomiya and Ukima plants are core facilities for biopharmaceutical production. On the other hand, the Fujieda plant is the core facility for small and mid-size molecule products.

Overview of Fujieda Plant

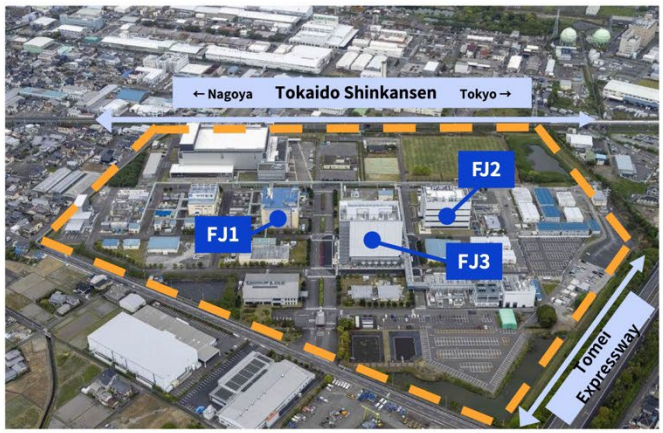
- Responsible for the production of APIs, which are the active ingredients of drugs, and the production of oral solid dosage forms, which involves forming raw materials into capsules or tablets and packaging them
- In addition, it will be the center of the production of mid-size molecule drugs, which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



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This is an overview of the Fujieda Plant. The plant is 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. The Fujieda Plant will become the center of production for mid-size molecule drugs. Mid-size molecule drugs are expected to be the next pillar for the Chugai Group, following small molecule drugs and antibodies.

It is located in Fujieda City, Shizuoka Prefecture, where you are in now. Operations began in 1971. The site area is 216,804 square meters. It is a repetition, but our business activities include production of APIs, manufacturing of solid formulations, packaging of pharmaceuticals, manufacturing of APIs for clinical studies.

The main lineup of manufacturing building for APIs includes FJ1, FJ2, and FJ3, as Mr. Takuma and Dr. Maeda mentioned earlier. You are all now in a conference room of so-called the administrative office Building.

The Tokaido Shinkansen runs northward from here. And the Tomei Expressway runs on the other side. FJ1, FJ2, and FJ3 are currently mapped in the center, with the administrative office building within the area outlined by the dotted line.

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.)

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Here is an overview of FJ3. As I have mentioned several times, the FJ3 aims to address the manufacturing functions of small and mid-size molecule drugs with high potency, covering APIs for early-stage clinical trials and early commercial production after launch.

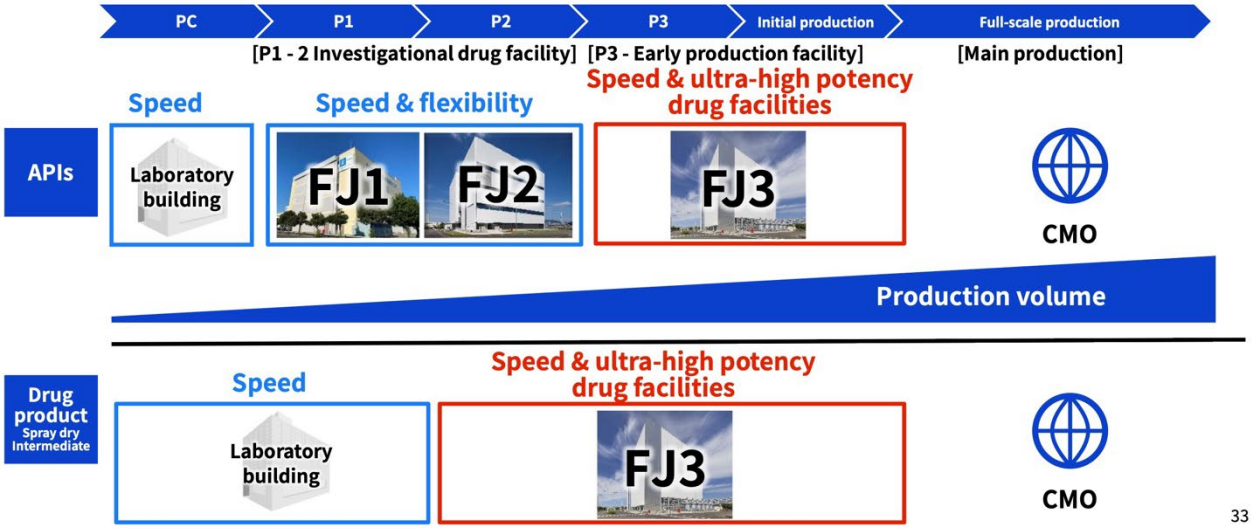
By adding FJ3 to the existing manufacturing buildings, FJ1 and FJ2, we will gain the capability to consistently supply APIs throughout early clinical development to early commercial production. JPY55.5 billion was invested. The building area is 2,205 square meters, and the total floor area is 10,489 square meters. It is a steel-framed five-story building, as is commonly known.

Its characteristics are world-class high potency containment technology. We have also implemented environmental considerations, such as non-fluorocarbon design, energy conservation, reducing CO_2 emissions, and consideration for waste, as Dr. Maeda mentioned.

From a safety perspective, since the plant is a chemical facility, it is designed to prevent explosions. Additionally, it features a seismic isolation structure to protect against natural disasters, including earthquakes.

Role and Positioning of FJ3

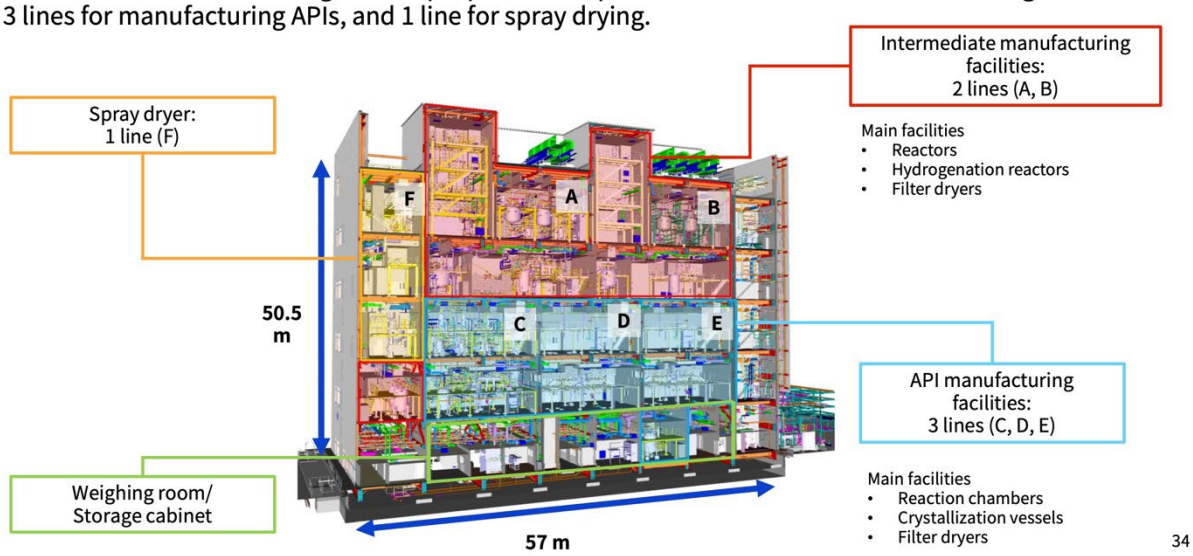
- FJ3 is responsible for the large-scale manufacturing of APIs and formulations for late-stage development and early commercial production of small- and mid-size molecule drugs



The role and positioning of FJ3. This was already touched, but I will repeat it again. First of all, let me explain this image. The upper line shows the clinical development timeline. From preclinical to Phase I, Phase II, Phase III, initial production, and full production. What this means that the production volume will gradually increase. As for FJ3, it will be responsible for initial production from the late clinical stage, just like Phase III here.

FJ3 Layout

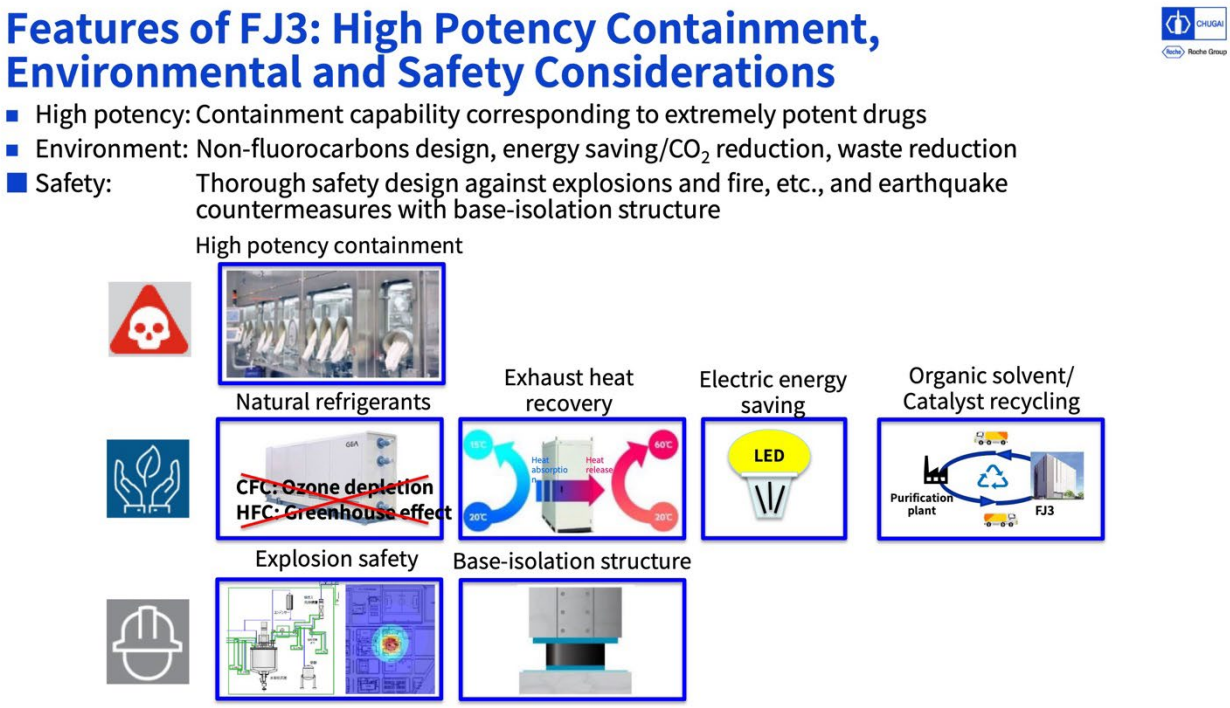
- Simultaneous manufacturing of multiple products is possible with 2 lines for manufacturing intermediates, 3 lines for manufacturing APIs, and 1 line for spray drying.



This is the layout. Dr. Maeda previously explained each area from a process perspective. Now, I would like to briefly outline the functions of the facilities and their lineup. First, there are two intermediate manufacturing lines in total, which produce compounds before they become APIs. Named A and B, respectively. The main facilities include reactors, special devices called hydrogenation reactors and filter dryers. These devices are installed.

This is the area where the final bulk drug or APIs are completed. There are three lines in total. The main facilities include reaction chambers, crystallization vessels and filter dryers. A dryer called a spray dryer is installed in the west of the building. The bottom is storage cabinets for raw materials and the weighing room.

The size of the building is 57 meters and the height is 50.5 meters, which, according to the architectural project members, is just about the same volume as the Great Buddha statue in Nara.

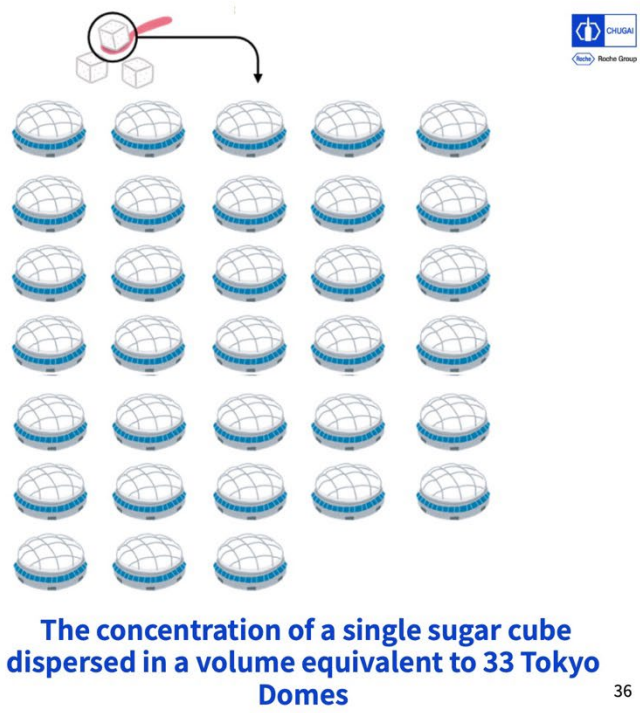


I created a couple of pages of documents to provide an in-depth look at the characteristics of each. This shows three features of FJ3. The first will be high potency containment, then, environmental considerations, and safety considerations. First, regarding high potency, please refer to this diagram as well. Our facility is equipped with containment capabilities to handle highly potent pharmacological activity. Here, this photo shows an isolator, a containment device designed for this purpose. I will show you it during the tour later.

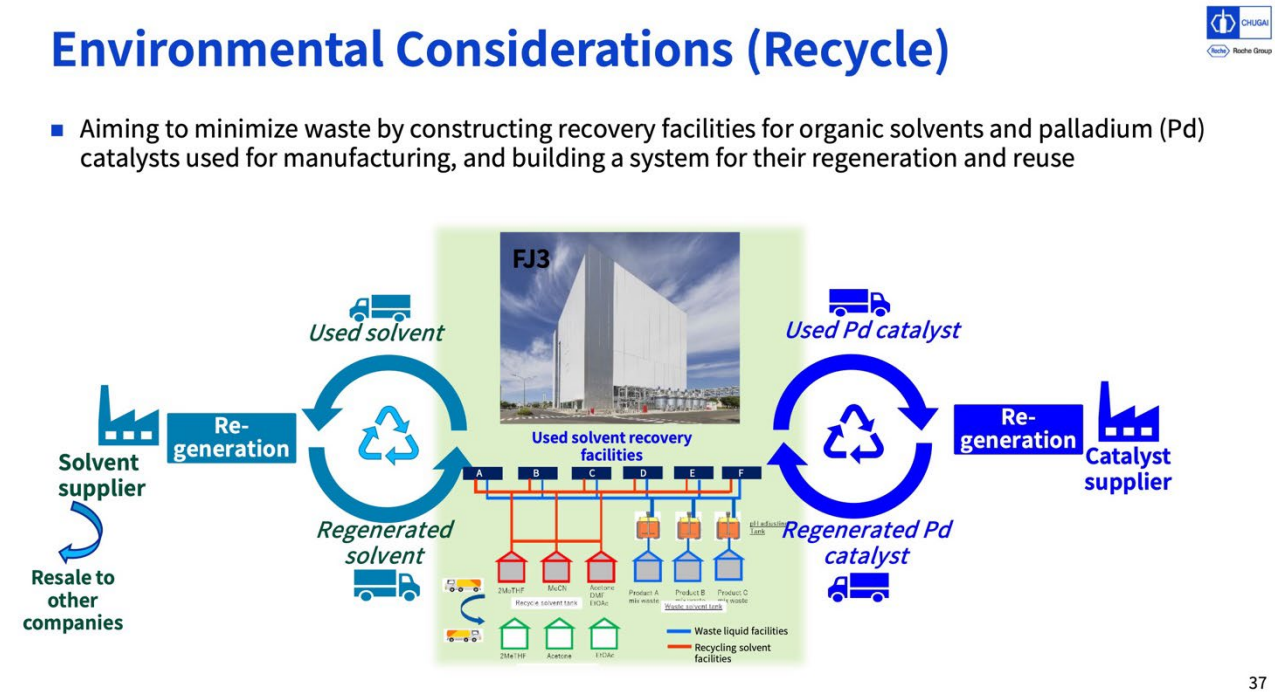
As for environmental considerations, we use natural refrigerants, aligning with globally required environmental initiatives. We also provide exhaust heat recovery to make better use of the generated heat. We are also actively adopting LEDs, which is small power but have a great impact when used collectively

As Dr. Maeda mentioned earlier, we have reduced waste to address challenges. To further minimize waste, we will actively promote the recycling of organic solvents and catalysts used in the hydrogen reduction reaction.

As for safety, explosion safety. I will briefly explain this in the next slide. We are simulating the impact on the neighborhood and solidifying it with hardware. This building is constructed with a seismic isolation structure to resist natural disasters.



When we often talk about containment, it is difficult to visualize with just these numbers. So, here we show it as a picture. The containment level of 0.03 micrograms per cubic meter or less is equivalent to the concentration of a sugar cube evenly distributed over a volume of 33 Tokyo Domes. This stringent control is implemented to ensure worker safety and minimize environmental impact.

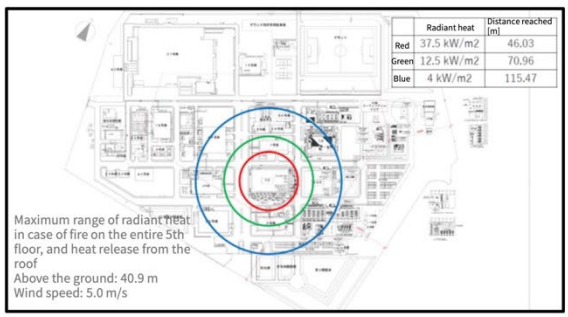


Also, recycling. This was already touched, but I will repeat it again. This shows that the solvent used in the process is distilled and reused in the next step and the palladium catalyst is recycled and used again.

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

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This will be the last page of my presentation. Facility design with thorough safety measures. We run various worst-case simulations and, of course, implement countermeasures in compliance with laws and regulations. In fact, we have taken measures to prevent explosions and fires. We have also implemented gas diffusion control measures within the building, designing it to minimize offsite impacts as much as possible.

This is a simulation of radiant heat diffusion. The blue area represents a level with almost no effect on the human body. We minimize the impact on the surrounding neighborhood by implementing protective measures within the site.

That is all for my presentation. Thank you very much.

Question & Answer

Miyata [M]: We will now take your questions. Please note that a transcript of the Question and Answer session, along with the presentation, will be posted on our website at a later date.

Sogi [Q]: My name is Sogi from Sanford C. Bernstein. In the section on the role and positioning of FJ3, it says that this FJ3 will cover from Phase III to initial production, and after that it will go to CMO. I understand that FJ3 is an outstanding facility that fully utilizes the latest technology. However, can we assume that production from this plant will be smoothly transferred to a CMO? It seems FJ3 is a very special plant to me.

Takuma [A]: In general, we have a dual-site strategy, where one site is used for the initial market launch, and a second site is prepared within five years after the market launch to ensure a stable supply in the event of an emergency.

Regarding FJ3, we are currently using the cutting-edge technology, as we mentioned earlier, so there is a high possibility that we will not be able to find a CMO right now. However, we will cooperate with CMOs and find a CMO within five years after launch. However, this does not mean we will stop manufacturing at FJ3. Instead, we aim to ensure a stable supply through a dual manufacturing approach.

Sogi [Q]: One more thing, you have invested in FJ3 quite a bit, and you consider it as an investment in the mid-size molecules manufacturing. Of course, I am fully aware that you have to make an upfront investment, but we have yet to see data from the first clinical asset for a mid-size molecule, in Phase I.

If mid-size molecule development does not succeed and there is still no guarantee that it will, is there a Plan B for FJ3? Given that FJ3 is highly specialized for mid-size molecules, what alternative use is planned if mid-size molecule production does not move forward for some reason?

Maeda [A]: First of all, the FJ3's role is, of course, to produce mid-size molecules. However, we can also produce small molecules in the plant. Therefore, we can produce both small molecules and mid-size molecules. I don't believe that will be the case, but even if mid-size molecule production is delayed, we can still utilize the plant for small molecules.

Miyata [M]: As our presentation has run over time, I would like to conclude the Q&A session with the next person and then move on to the tour.

Yamaguchi [Q]: My name is Yamaguchi from Citi. I know you have presented a lot about manufacturing costs and timeframes through the images. Of course, we do not have insight into gross margins before the product launches, but I believe small molecules have been produced at a much lower cost.

Regarding the gross margin of antibodies, I believe it was originally started from around 70%. However, I still am unsure about the cost for the mid-size molecules at 1,500. Can you tell us if you're seeing a trend where costs can be kept to several times that of small molecules?. Or perhaps a fraction of the cost compared to large molecules? Please elaborate on this point.

Maeda [A]: I can't give you specific figures because they are not disclosed. What we can explain is that the size of the molecule roughly correlates with the cost, as shown here. Not proportional. Correlation. Therefore, we would like to do our best to keep costs lower than the difference in molecular weight, but, in general, there is correlation in this matter.

Yamaguchi [Q]: I would like to add one more. You have managed to complete LUNA18. There may be some improvements in the future, to some extent, but has the cost of LUNA18 come down to a level where it can generate a proper gross profit if it were a standard anticancer drug targeting RAS? Is this still in progress?

Maeda[A]: That is also difficult to answer, but the business potential is not going to be negative.

Miyata [M]: I apologize for the short Question & Answer session. We will have time for a Question & Answer session at the end of the tour. Questions are welcome at the time.

Miyata [M]: Now, we will take questions for about 25 minutes.

Wakao [Q]: My name is Wakao from JPMorgan. Thank you for showing various process. I would like to know about page 26 of the slide. The reaction process you showed seemed the same as that of small molecules, and there may not be significant differences in the reaction process itself or the facilities used. However, what you have described here focuses on further technological advancements and platform development. From what I have observed, there are quite a few process steps, which seem to require a quite bit of manpower. How do you plan to streamline this into a platform?

Additionally, for LUNA18, the current production scale is 50 kilograms per lot. It would be helpful to understand what scale you are aiming for in the future.

Maeda [A]: See page 24. As for further technological development, in the case of LUNA18, this is the second manufacturing method or platform here. It still allows us to improve efficiency. What we are aiming for now is the third stage, which involves greater multi-fragmentation. We only do the final assembly. If we achieve this, we can significantly reduce manufacturing time and cost, and it will be our next step.

Wakao [Q]: To extend two or three amino acids together, do you establish some kind of technical way to do so to start with? Do you make two or three in advance and keep them ready for production?

Maeda [A]: First of all, it is difficult to attach two or three pieces together. So, we will create a technology. Talking about pre-made units, we can likely procure two or three from an outside source instead of making them ourselves. This would considerably shorten the number of processes for the part we do.

Wakao [Q]: You are at 50 kilo per lot now. How much further do you expect this to scale in the future?

Maeda[A]: I will not disclose that.

Matsubara [Q]: My name is Matsubara from Nomura Securities. I believe that with technology innovation, the yield part can be improved. Do you have a current idea of what percentage of yield your company should be aiming for? I would also like to know the target percentage for LUNA when it is ready for manufacturing and market release. I would appreciate your comment to this question as well.

Maeda [A]: Our goal is 100%, but that is theoretically difficult. So, we are aiming for an average of at least 98% or 99% for each. There are key metrics for yield, which are isolated yield and conversion rate. We aim at 100% for conversion rate. However, when it comes to the stage of actual isolation, there is some loss, so that will be a little lower. Our goal is to achieve a 100% conversion rate.

Matsubara [Q]: How much is the profit margin?

Maeda [A]: I will not disclose the profit margin, but the higher it is, of course, the more advantageous it is.

Wada [Q]: My name is Wada, SMBC Nikko Securities. I would like to ask you about the superiority and uniqueness of peptide synthesis. Page 12. I think there is a hybrid synthesis method for the tag-assisted or AJIPHASE by Ajinomoto.

The challenge with liquid-phase synthesis lies in the need for purification at each step. I see hybrid synthesis is being improved by allowing movement between liquid and solid phases to optimize the process. Looking at your company's synthesis process, it seems that you crystallize the product to solidify it, then wash it out and reconnect it. Is my understanding correct? Also, what specific challenges do you have in liquid-phase synthesis, and in which areas?

Maeda [A]: First of all, since our technology differs from that of other companies, a direct comparison is not possible. However, as I mentioned in my presentation, our approach is to simplify. Let's say, if other companies do for a tag, or the second from the top, it will lose the flexibility of the route. Our ideal approach is to refine at the final stage through an end-to-end process, rather than isolating intermediates along the way. That is the most efficient way.

LUNA18, which I explained earlier, is purified only once. So, it is the most efficient production method. However, it does not mean that we avoid purification entirely. Rather, we combine purification with methods other than isolation. That is where our technology lies.

Wada [Q]: So, whether it's liquid-liquid separation or crystallization, you are generally using the technology employed in the production of small molecules. The simple refining process is one of the strengths of your company.

Maeda [A]: Yes, we can use simple purification methods. That's one of our strengths.

Muraoka [Q]: My name is Muraoka from Morgan Stanley MUFG Securities. I have questions about the slide as well. Was it two years ago? At the R&D briefing, you previously mentioned a 24-step process with a 30% yield. However, that may be a general term. Since then, can you describe how much the yield rate improved over the past two years? For example, improvements don't happen easily within just two years or so. Can you comment on this?

Maeda [A]: I don't remember the figures of two years ago, but the latest figures I can show you now are on page 26. It is in small print, and they are 27% total yield for 24 reactions and 1 isolation.

Muraoka [Q]: Then, it seems that the numbers have remained almost the same or even declined slightly, despite some scaling up. If I'm not mistaken, that's what you mean.

Maeda [A]: Yes, that's right. Another thing is that it may fall when isolated, and also in the scale-up process. This 24 steps at 27% is quite high, and 30% is a very high number. So, I wonder if this has reached a plateau.

Muraoka [Q]: At this level, although the drug is still in Phase I, do you feel that, at the plant level, the profitability for future commercialization is nearly secured, considering the improvements that can be made at this point? I wish I could have asked this earlier.

Maeda [A]: Yes, that's right. Now, as I said earlier, the business potential doesn't become negative, and furthermore, we are trying to make it more efficient by fragmenting it a little more. But even with this current manufacturing method, we're at a level where there's no problem.

Muraoka [Q]: Can fragmentation be done on a three to four year basis?

Maeda [A]: We are just working on it.

Muraoka [Q]: I remember that you will try to find suppliers.

Maeda [A]: You can see our supply chain in the upper right corner, and including there, the supply chain is very important for the production of the mid-size molecules. So, we are in the process of building a supply chain, including global procurement of non-natural amino acids, as well as developing manufacturing methods. We are now working to increase the capability of the CHUGAI Group as a whole, including development.

Hashiguchi [Q]: My name is Hashiguchi from Daiwa Securities. On page 24 of the slide, you mentioned that the types of products that can be manufactured differ between the left and right. If your lab wants to manufacture something specific, do you position yourselves as a pharmaceutical facility that can only produce what is on the left, or do you take the stance that you can manufacture most products? Do you instruct the lab to focus on producing only what is on the left? I'm sorry for a basic question, but could you please help me to understand better?

Maeda [A]: As I mentioned earlier, there are some differences between our molecules and those of other companies. First, the tag on the right is designed for dissolution. Other companies' peptides tend to be more hydrophilic at the molecular level. To improve their solubility in organic solvents, they use a tag.

On the other hand, our molecules on the left side are lipophilic in nature, so there is no need to put a soluble tag. That is one of the points. So, the technology is selected according to physical properties there. Basically, the simpler the manufacturing process is, the lower the cost will be.

Hashiguchi [Q]: I understand that each case will require careful consideration, but I believe the current manufacturing methods established by your company can accommodate the products developed by the lab to a certain extent.

Maeda [A]: We have no problem with the current level. From now on, we are at the stage where adding more value, such as further lowering costs, further increasing productivity, and reducing environmental impact.

Yamaguchi [Q]: My name is Yamaguchi from Citi. To begin with, the FJ3 cost JPY55.5 billion, which is more than double the cost of FJ2, while in terms of size it is about two times. Can you briefly explain the biggest cost differences between FJ2 and FJ3? Specifically, what are the differences in terms of which areas incur higher costs?

Koyama [A]: I am Koyama, the manager of the Fujieda Plant. Is your question about the difference between FJ2 and FJ3 in terms of scale?

Yamaguchi [Q]: Beyond just scale, I believe the costs are significantly different. What are the key factors for this difference?

Koyama [A]: There is a clear difference. FJ3 was designed for the late development stage and early commercial production, so various automation technologies were introduced to reduce manpower. As you may have seen today, we are trying to minimize operational costs in non-manufacturing areas wherever possible. At the same time, we focus on tasks that should be handled by people. For example, our investment in facilities like automatic transfer equipment has led to higher overall costs compared to FJ2.

It is a detailed matter, but another factor is the plant require extensive piping in the API production building. As the building scale increases, ancillary facilities naturally expand as well, leading to a difference in investment costs.

Yamaguchi [Q]: When you look at each item, do you think the cost differences are due to size and various automation expenses, rather than generational differences?

Koyama [A]: Yes, you can understand it that way.

Mamegano [Q]: My name is Mamegano from BofA Securities. I would also like to ask about the synthesis. I would like to understand your company's strengths. I am wondering if the liquid phase synthesis method is the key. Earlier, you talked about whether it is lipophilic or hydrophilic. In the case of liquid-phase synthesis, I believe the final step will likely involve producing the API using a spray dryer.

What is the reason that other companies which adopt solid-phase synthesis cannot use this method? Do the original physical properties differ? I would like to understand in which area your company's strength lies.

Maeda [M]: Are you asking whether this liquid-phase process can be done using solid-phase synthesis? Or, whether a solid-phase process can be carried out in the liquid phase?

Mamegano [Q]: I believe other companies use solid-phase synthesis, while your company employs liquid-phase synthesis, which follows the same process as small molecules. Could you explain why other companies must use solid-phase synthesis and why your company can achieve the same process in liquid phase?

Maeda [A]: The easiest way to understand is on page 18. First of all, there is a limit of the liquid phase. As shown here, the range of what can be done in the liquid phase is about 15 or 20 amino acids. Beyond that, it becomes difficult even in the liquid phase, so we do it in the solid phase.

Currently, GLP-1 agonists and similar compounds consist of about 30 to 40 amino acids. At that scale, liquid-phase synthesis becomes challenging to complete in a single process, so we consider splitting the synthesis and using a hybrid approach.

The key factor is the number of amino acids. Since our Chugai-type cyclic peptide consists of 11 amino acids, it was at the very limit of what could be synthesized in the liquid phase. We also struggled with the strategic decision of which approach to take. However, through technological development, we managed to achieve liquid-phase synthesis, so we have now adopted the liquid-phase approach.

Yatsunami [Q]: I am afraid to ask a very basic question and additional question to the previous person, but if we assume, as stated on page 24, that your company's liquid phase manufacturing technology is the simplest and that no other company can replicate it, does that mean you can extend the amino acid chain one by one in a way that only your company can achieve? Or something else. What would be the most impressive aspect for a layperson? I think other companies are doing the liquid phase method itself.

Maeda [A]: On page 20. First is the structure of our cyclic peptide. As I mentioned earlier in my presentation, there are many non-natural amino acids. These non-natural amino acids have alkyl side chains attached to the amino group of the amino acid. What this means is they are very large amino acids. It is very difficult to attach such large amino acids. If reactivity is increased, impurities are formed or stereochemical inversion occurs. Until now, there has been no technology to attach these large amino acids to our structure using liquid-phase synthesis.

That is partially shown on page 25. As I said here, the existing liquid phase technology for peptides did not give the expected results. In fact, it was. It is difficult to attach our large amino acids, so we have to establish our own technology. We developed this technology in-house, starting partially, enabling us to synthesize LUNA18 and other subsequent mid-size molecules using liquid phase synthesis, as written here. This is where the technical differences are greatest.

Yatsunami [Q]: By large, do you mean two or three amino acids stuck together?

Maeda [A]: One amino acid itself is big.

Yatsunami [Q]: One itself is big.

Maeda [A]: GLP-1 and those 40 or so, peptides are natural amino acids, mostly. Therefore, sequential attachment is possible in solid phase synthesis, even with less reactive technologies. However, since our amino acids are non-natural and large, attaching them in the same way is quite challenging. So, we have developed a new technology.

Yatsunami [Q]: Isn't it difficult to extend amino acids?

Maeda [A]: I am talking about the same for extending. So, it is difficult to extend large amino acids and make them into peptides.

Banno [Q]: My name is Banno from Nihon Keizai Shimbun. I apologize if this is a basic question, but I think you mentioned that the process you just showed us is not significantly different between small molecules and the mid-size molecules drug manufacturing. I would like to understand the biggest difference in those two molecules drug manufacturing. Is it the frequency or where is the difference?

Maeda [A]: The biggest difference lies in cyclic peptides and their peptide structure. In this process, amino acids are attached together basically. The primary focus is on condensation reactions. Small molecules come in many different structures. Small molecules exhibit greater structural diversity, involving not only condensation reactions but also various other reaction types.

In this sense, cyclic peptides are structurally simpler. The process mainly consists of repetitive condensation reactions followed by deprotection reactions, which is simple. Small molecules require synthesis and design through a combination of multiple reaction types. That is the difference. However, with this manufacturing facility, both can be feasible. This facility is capable for both.

Banno [Q]: Are you saying that there is no difference in terms of the apparent process? The content of the synthesis may be different, though.

Maeda [A]: Yes, that's right. The contents of synthesis are different, but small molecules are produced through a combination of various reactions. The mid-sized molecules are produced by repetition of similar reactions. That is the difference.

Sogi [Q]: This is unrelated to FJ3, but you use digital, AI and machine learning methods in your research. I would appreciate any insights you have on manufacturing, as I assume it is something currently under consideration.

Takuma [A]: Using AI is becoming a reality in the manufacturing side. The focus is on how quickly we can derive the optimal solution from databases of past issues, such as previous troubles or inspection findings. Of course, we are actively working on leveraging AI in these areas.

Kimura [Q]: My name is Kimura from Nikkei BP. I apologize if this is a very basic question, but on the first page of the Appendix, you have provided the basic data for FJ3. If it were operated continuously for one year, approximately how much API would be manufactured annually? Additionally, in the reaction mass section, you mentioned 28 units, with a maximum capacity of 10,000 liters. Could you provide more details on the number and capacity of the individual reaction mass?

Koyama [A]: The scale is as shown there. As for the manufacturing volume, it varies considerably depending on the contents of the process, so I can't give you an exact figure like how much kilograms per unit and such. We hope you will understand that. Regarding the equipment lineup details, please understand that specifics, such as the number of units for each type of reaction mass, are confidential and not disclosed.

Wada [Q]: I am Wada from SMBC Nikko Securities. I would like to confirm whether you avoid working with molecular weights above 1,500, as indicated on page 16. Some peptides are about 3,000 to 4,000 in size, so I would think that 3,000 or 4,000 would be in the range if you chose extracellular ones. So, I would like to ask you how and why you decided on 1,500.

I think one thing, as you mentioned earlier, is that liquid phase synthesis would be difficult for larger molecules beyond the current size. Since there are other intracellular targets, I assume that the molecular weight only needs to be around that size to enter the cell. I was also wondering about your perspective on screening and related processes. I assume there are some challenges in defining drug-like compounds in this range. Could you provide some background on this?

Maeda [A]: This is about drug discovery, but as you commented at the end, this is the drug-like part. The 1,500 is not a fixed number but rather a result. Therefore, at CHUGAI, we now define drug-like compounds based on the number of amino acids, meaning the molecular weight is determined accordingly.

Miyata [M]: That concludes the tour of CHUGAI's Fujieda plant. If you have any questions that we were unable to answer due to time constraints, please contact the Corporate Communications Department. Thank you very much for taking time out of your busy schedule to attend today.

[END]

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Document Notes

1. *Portions of the document where the audio is unclear are marked with [inaudible].*
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