Leading Company for Contract Production of Sterile Products

Toyama 2nd Plant of Fuji Yakuhin Co., Ltd.

(750, Itakura, Fuchu-machi, Toyama City, Toyama Prefecture)

An Outstanding Company in Terms of Consistent and Detailed Services in Processes Ranging from Clinical Testing of Sterile Products through to Sales


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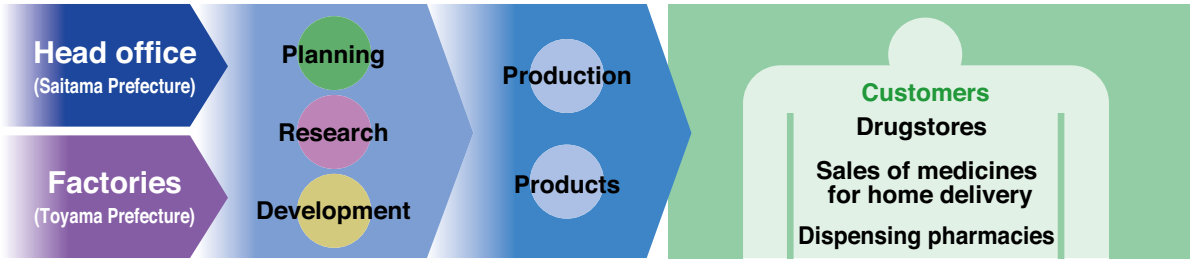
The system of oki-gusuri (sales of medicines direct to the home) started 300 or more years ago in Toyama Prefecture. Fuji Yakuhin Co., Ltd. was founded in 1930 and served as the start for traditional sales of medicines for home delivery as a corporate business in Toyama Prefecture. This company, which established a consistent system from research and development through to production and sales, is a complex pharmaceutical company that also holds the top share in the industry of home delivery medicine sales. Fuji Yakuhin Co., Ltd. has established base offices for sales of home delivery medicines in major cities throughout Japan from Hokkaido to Okinawa and now more than 3.5 million households are using this service. The company established a medical pharmaceutical division in 1995 and has expanded its sales business in the Kanto region mainly in Saitama Prefecture by using various strategies including the starting of a drugstore called “SEIMS.”

We visited the Toyama 2nd Plant which now utilizes the ULVAC Freeze-drying equipment for an interview and tour of the factory’s facilities.



Factory Specializing in Production of Medical Injection Fluids
Ideal Production Environment Utilizing an Ozone Microbiological Control System

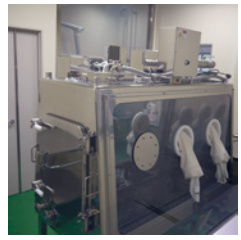
Fuji Yakuhin Co., Ltd. was founded in 1930 and was established in April 1954 as Takayanagi Pharmaceutical Ltd. in Omiya City (current Saitama City), Saitama Prefecture, which was one of the places the company had visited for sales. The company subsequently opened a business office in Maebashi City, Gunma Prefecture, in October 1963. In February 1986, the company constructed a pharmaceutical manufacturing factory and started its production in Fuchu-machi in Toyama City, Toyama Prefecture. The factory is located in nearly the center of the Toyama plain commanding a view of the Tateyama Mountain Range. At present, the main business of the company consists of the following five components: sales of medicines for home delivery; drugstores; dispensing pharmacies; production of pharmaceuticals; and research and development of medical pharmaceuticals. In March of FY 2013, the company declared approximately 289.4 billion yen in total sales for the group and 11.7 billion yen as ordinary profits.

The Toyama Plant produces pharmaceuticals for medical and general use. The pharmaceuticals take various forms, such as tablets, capsules, granules, eye droppers, and ointments. The Toyama 2nd Plant operates a medical pharmaceutical manufacturing factory that produces injection fluids and medical pharmaceuticals and conducts contract studies of these medicines.

We visited the Toyama 2nd Plant. The factory started operation in 1992 specializing in production of medical injection fluids. It occupies an area of 29,000 m^2, and approximately 150 employees work there. In 2004, the factory introduced an ozone microbiological control system, the world's first system developed for microbiological control, into its clean room. With the aid of this system, the factory produces sterile products such as pharmaceuticals in ampoules and vials and freeze-dried formulation and carries out their formulation design and stability tests under contract.

The factory is capable of producing approximately eight million ampoules on its ampoule production line and approximately 14 million units per year on its freeze-dried formulation line.

An ozone microbiological control system is a sterilization system using ozone (O_3) which is a safe gas. An ozone microbiological control system consists of an ozone generating unit and an ozone decomposing unit installed in the air conditioning system of the production room. This sterilization system operates automatically to conduct the processes of fumigation, decomposition, and normal air conditioning in that order and thereby control the production environment essential for preparation of sterile fluids.



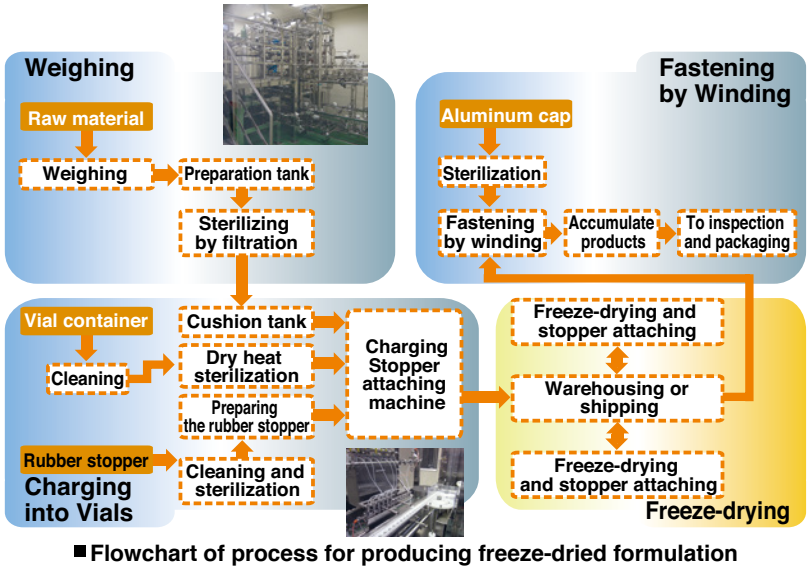
Weighing facility

Injection fluid production facility

Air conditioning facilities of the factory are under integrated control in the central monitoring room so the work environment can be thoroughly controlled by constantly monitoring the air cleanliness in the clean room. In addition, the production capacity of the facility for producing water for injection has been improved, and this water produced at the facility is also used to clean the containers and facilities that come in direct contact with medical solutions.

Pursuit of Quality and Pproduction Efficiency in Freeze-dried Formulation

Fuji Yakuhin Co., Ltd. has commenced use of the ULVAC's DFB series Freeze-drying. The production process for freeze-dried formulation proceeds under a production control system in the following order: raw materials are weighed by a predetermined method; a medical solution is prepared by a predetermined method; the prepared solution is put through sterilization by filtration and transferred into a tank. The following steps are then implemented. Namely, a vial container is cleaned with water for injection with the aid of ultrasonic waves; a rubber stopper is prepared by a sterilized rubber stopper prepping system, the medical solution is charged into the vial container with the aid of the mass flowmeter of a "mass flow measurement system." Charged vials are then transferred with a conveyer and automatically arranged in lines on shelves in a freeze-drying warehouse where they are put through a freeze-drying process. After this process, the vials are automatically taken out of the warehouse and put through fastening by winding



■ Flowchart of process for producing freeze-dried formulation

ULVAC's Freeze-drying equipment
Upper photograph: Partial view of sterile room for automatic warehousing and shipping section
Lower photograph: Partial view of machine room section

on a conveyer. Finally, the vials are inspected and those vials that have passed the inspection are packaged as products.

Most of these processes are conducted at Grade-A level which is the highest air cleanliness level. Grade-A level areas are in aseptic manipulation areas and classified as high priority areas. The air cleanliness of all areas including aseptic areas is classified into Grade A through Grade D. According to the definition of air cleanliness at Grade A, the number of 0.5-μm or larger drifting particulates contained in 1 cubic meter of air must not exceed 3,520 either during or outside of the job operation.

This air cleanliness is equivalent to Class 5 of the ISO and Class 100 of the U.S. standards; this means that Grade A is equivalent to the level of bioclean rooms in hospitals.

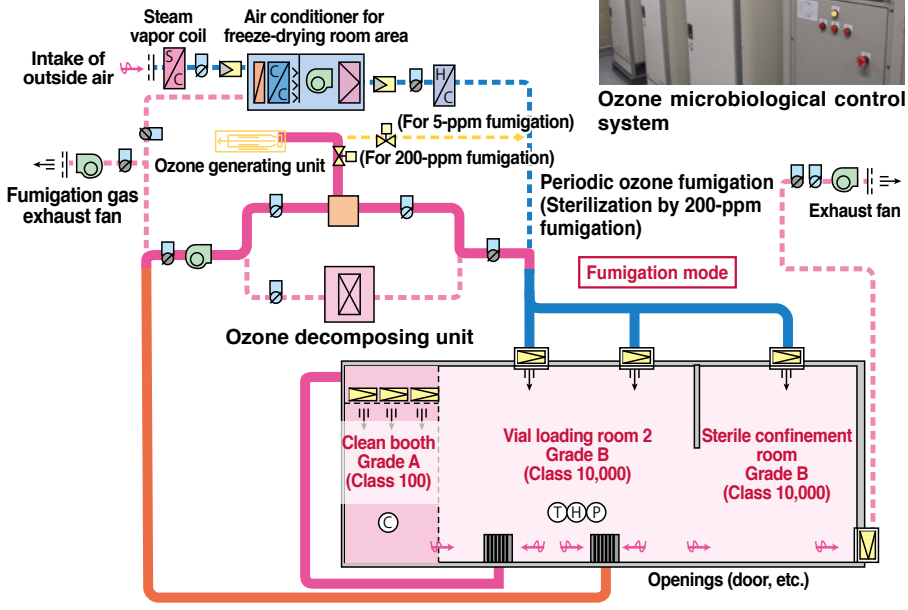
Quality Control Compliance with GMP

An even stricter control system will be established to support PIC/S.

Fuji Yakuhin Ltd. produces pharmaceuticals in clean zones whose environments are controlled as needed to comply with GMP, which is the world's strictest standard in this field. GMP is an abbreviation for Good Manufacturing Practice and is international standard for production of pharmaceuticals and quality control in production. The WHO (World Health Organization) passed the resolution for establishing the standards in 1968 and recommended that its member countries adopt these standards. In Japan, the Minister of Health, Labour and Welfare specifies standards in compliance with the Pharmaceutical Affairs Act.

Progress is being made towards consensus through agreements on inspection and establishing cooperative schemes for inspection in order to implement a worldwide uniform operation of PIC/S (a system for quality control of pharmaceuticals) and GMP standards. So starting usage of facilities and systems that support this trend will enhance management and consequently allow smooth progress in contract production for Japan's domestic and overseas customers. PIC/S is a collective name for the pharmaceutical inspection convention (PIC) and pharmaceutical inspection co-operation scheme (PICS) which are two cooperative organizations for GMP among governments and inspection organizations. PIC/S was established in Europe in 1970 and consists of organizations in approximately 40 countries at present. The member organizations are mainly in EU member countries and also include the U.S. FDA. This situation suggests that PIC/S is well on its way to becoming a global standard. Against this backdrop, Japan has also applied for membership in PIC/S and its application is currently undergoing an examination process (December 2013).

Ozone microbiological control system



■Structural outline of ozone air-conditioning system

Q&A exchange with the factory manager

We also make strong efforts in handing down techniques to our junior staff members for the future.

Mr. Sanae Tatara
General Manager of Toyama 2nd Plant, Fuji Yakuhin Co.Ltd.

—What advantages does Fuji Yakuhin offer?

Tatara: I think that we have the following three advantages. First, we have technical strength in sterile fluid preparation. Second, we are capable of contract production that satisfies the needs of our customers in detail. Large pharmaceutical manufacturers cannot currently provide this same type of service. Finally, we can provide a wide range of services from clinical testing to production and have successfully achieved standardized systems from production through sales when handling our products.

—By what are the main features of the Toyama 2nd Plant?

Tatara: We have the Toyama Factory and Toyama 2nd Plant. The Toyama 2nd Plant specializes in production of injection fluids. Many of the staff members working at the Toyama 2nd Plant are young with an average age of 33. There are strictly defined behavioral standards and all members are serious about performing their tasks in accordance with pre-established procedures. After work, however, they are all spirited and happy. The most striking feature of the Toyama 2nd Plant is the fact that its production is controlled by an ozone microbiological control system.

—Are there any future issues?

Tatara: We need to advance into overseas markets in order to expand. We have a large share of the domestic market in the sales of medicines for household delivery. We have also opened drugstores in Shanghai and are planning to expand the drugstore business elsewhere. We highly expect that positively supporting PIC/S will allow us to smoothly handle contract production for overseas export products. To make this happen, we have to increase our investment in plants and equipment. We must also put our energy increasingly into educating the younger generation. As part of this education, we will hand down techniques from veteran workers to younger staff members.

—Do you have any opinions on the ULVAC's Freeze-drying equipment?

Tatara: We have been using your Freeze-drying experimentally. We also make use of the loading system which you developed first and ahead of other companies. Your technical capabilities and quick support services are always helpful to us. Pharmaceutical production tends to depend significantly on the technical capabilities of facility manufacturers. So we hope that you will become even more highly aware of the fact that pharmaceutical manufacturers use production facilities in aseptic conditions such as in Grades A and B.

—I am looking forward to our continued business relationship. Thank you very much for your time today.