Manufacturing Process for the Prescriptions of Kampo Medicine

The large majority of Kampo Medicines manufactured by Japanese pharmaceutical companies are extract preparations (history of which has been previously described). There are over fifteen pharmaceutical companies in Japan who are manufacturing Kampo Medicine extracts with government approval. Their manufacturing is governed by the regulations of the Pharmaceutical Affairs Law, and strictly controlled by other government regulations, including GMP (Good Manufacturing Practice). The GMP for pharmaceutical products include (1) reduction of human errors to a minimum, (2) prevention of contamination of the drugs or deceasing quality, and (3) establishment of a system to guarantee high quality. As a result, products are assured of quality and safety at the highest level.

I. Quality Standards for Crude Drugs Used as Raw Material

Of all the crude drugs used as raw material for Kampo Medicine, about 200 major drugs (herbal medicines) are listed in the Japanese Pharmacopoeia (JP), which imposes quality standards on them. The quality standards provide detailed requirements for identifying the names of the original plant species (or original animal species or mineral for crude drugs derived from animals or minerals), parts used for medicinal purposes (e.g. roots, stems, leaves, flowers or fruits), preparation methods, methods of purity test and other physical/chemical tests for the purpose of quality evaluation, as well as the test methods for the presence of microbes.

Of all the crude drugs not listed in the JP, the ones in frequent use are published in the Japanese Herbal Medicine Codex (1989) which provides quality standards established by a research team organized by the government. Pharmaceutical companies must use crude drugs which comply with these quality standards as their raw material. Some crude drugs do not have official specifications such as those above. When this is the case, pharmaceutical companies develop their own specifications so as to ensure quality of their products.

At present, of the crude drugs listed in the Japanese Herbal Medicine Codex, widely used ones are in the process of being incorporated into the JP with upgraded quality standards.

II. Quality Control of Extracts

Extracts are manufactured in the following processes: First, liquid extract is made by processing cut crude drugs mixed according to a prescribed composition in hot water (separation of effluent and residual). Residues from the crude drugs are removed from the liquid extract. After the liquid is concentrated under reduced pressure, it is spray-dried into a powdered form. Next, the appropriate measures of the powdered extract and fillers (preparation materials) are mixed together to form a raw material for preparation. It is then processed into the form of granules or tablets, and filled and packaged as a finished product. As the Kampo Medicine extracts are highly hygroscopic, pharmaceutically advanced techniques are used to protect finished products from moisture. (For outline, see diagrams in pages 54-55.)

Initially, the quality of Kampo Medicine extracts released to market varied due to differences in manufacturing methods used by pharmaceutical companies. Consequently, the government issued an administrative guidance (notice) in 1985 in an attempt to ensure better quality and uniformity of these products. Generally, the administrative guidance (notice) prescribes that standard decoction must be prepared for each prescription with the prescribed method; that two or more indicator constituents ("Indicators") must be selected and quantified for the purpose of ensuring the equivalence between the final product and standard decoction; and that the amount of the "Indicators" contained in a daily dose must be 70% or more of the amount contained in the standard decoction.

Kanebo Pharmaceutical, Ltd. which agreed to an interview, is staunchly committed to quality. A consistent quality control system has been employed from the supply of crude drugs through to the finished products in order to ensure that the Kampo Medicine extracts for clinical use produced by Kanebo are equivalent in potency to the standard decoction. For this purpose, Kanebo uses several technical means to extract various constituents efficiently from crude drugs, and provide a stable supply of quality products.

The following example is provided.

(1) Obtaining crude drugs of predictable quality

① The quality of herbal medicines is influenced by the growing region and climate, so herbal medicines of predictable quality can be obtained by designating the area where each medicine is grown.

② To avoid deterioration in quality and bacterial contamination during the storage of herbal medicines, thermostatically controlled storage is used, and cut herbal medicines are stored at a low temperature.

③ A system has been established so that any problems with the quality of finished products can be traced back to a specific growing area.

(2) Management of the extraction process

The individual steps of the various processes from the extraction during the manufacture in the factory over separation of solids from liquids and concentration to the drying of the extract powder are conducted in extremely large-scale equipment. Neglecting quality control during any of these processes could have marked effects on the quality of these traditional formulas. The items listed below are carefully observed during the manufacturing process. Moreover, all processes are controlled via computer using an automatic control system.

① Measures to increase the dissolution rate of insoluble ingredients:
Saponins such as Bupleurum saponins, Ginseng saponins etc. are important ingredients and are insoluble. The surface structure of Ephedra herb is so tight that it prevents the penetration of water and this makes it difficult to dissolve ephedrine, a major ingredient. To promote the efficient dissolution of these ingredients, the particle sizes of these herbal medicines are adjusted appropriately.

② Measures to reduce the degradation of heat labile ingredients:
Sennosides of Rhubarb are pharmacologically active ingredients of a crude drug, and are representative heat labile substances. The sennoside content of a extract is dependent on the amount dissolved from Rhubarb and the extent of degradation. When heated at 100℃ for 1 hour, most sennoside is degraded and the cathartic effect is markedly decreased. To constantly maintain the sennoside content, extraction of Rhubarb is performed in a short time during the latter half of the extraction process.

③ Measures to prevent enzymatic reaction:
It has been reported that herbal medicines contain enzymes that degrade various ingredients. Baicalin is a major ingredient of Scutellaria root that is degraded by baicalinase to baicalein, while amygdalin (a major ingredient of Peach kernel and Apricot kernel) is degraded by emulsin. Generally, the optimum temperature range for enzyme activity is 35-40℃. Heating time is shortened in order to prevent enzymatic reaction.

④ Measures to preserve volatile ingredients:
Volatile ingredients, cinnamaldehyde in Cinnamon bark, paeonol in Tree peony bark, ligustilide in Szechwan lovage rhizoma etc., can diffuse out more during the graduation process. To maintain these ingredients in the finished product at the specified level, the effluent after extraction process is controlled below 60℃ at temperature and between quadruple to octuple in a graduation rate.

(3) Control of the manufacturing processes of extracts (final products)

The obtained extract powders are precisely weighed and then mixed with filling material before they are further processed into granules or tablets. The manufactured granules or tablets are then packed in aluminum foils (SP package) or else placed in containers. After that they are further wrapped and packed in boxes for shipment. In the factory, completely computerized production control systems have been introduced. Under this system, all the information pertaining to the manufacturing process, from the receptance of stocks to the shipment of the final products is completely controlled.

① After storing the various extract powders serving as crude materials for the products and filling materials in a warehouse with automatic temperature control, the production control system releases upon instruction from the warehouse only those materials passing quality tests from the warehouse into the production process.

② Weighing of prescription crude materials is conducted as an interactive process with the computer and all weighing results are stored in the computer.

③ After the extract powders and the filling materials are mixed during the manufacture of fine granular products, the system automatically manufactures the relevant granules.

④ Moreover, during the manufacture of tablets, a tablet, press observation device, tablet weighing device, a metal detector, and a transport device work in unison allowing unmanned operation.

⑤ All the steps involved in packaging or filling in containers of the granules or tablets obtained in above described steps (2), (3) and (4) are performed in a clean area.

⑥ Sensors are installed to detect whether the individual packages are properly packaged during the packaging process, controlling the entire system in such a way to prevent the necessity for replacements due to defective packages or products.

⑦ Products packaged on the individual lines are then transported by the automatic transfer system to the automated warehouse.

⑧ Untested products or non-standard products are locked out by the manufacturing control system and managed in a way that prevents them from being handled or shipped.

III. Prevention of Pesticide and Microbial Contaminations

Pesticides have low solubility in water, instability in heat, and are evaporative. Some residual pesticides may be found in a crude drug used as material. Less than one-tenth of the amount will be transferred to the heat-processed extract. The amount of the residue will be reduced below the detection limit in the final product, meeting the safety standard. Yet, with its strong commitment to quality and safety, Kanebo carries out a strict inspection of every batch of crude drugs it receives by measuring residual amounts of several types of organochlorine, organophosphorus and pyrethroid pesticides.

As crude drugs are natural products, the presence of some bacteria and fungus is unavoidable. The JP prescribes the baseline limit for presence of microbes in crude drugs and preparations made with crude drugs. Although almost all microbes are eliminated by heat during the extraction process, Kanebo employs a brief sterilization of graduated fluid and carries out an inspection for microbes in the final stage of the production to ensure the safety of its product. The company ships only products for which inspection has confirmed the microbial count to be below the baseline limit.

Although monographs of crude drugs may indicate their use in the form of pill or powder, they convert the amount specified in the monograph to water-extracted equivalent for its extract products. This in itself is irrelevant to the efficacy of our drugs, but it is significant in terms of the elimination of toxic elements such as microbial contamination.

IV. Environmental Protection

The factory of Kanebo, which we visited, met the standards of the ISO 14001: Environmental Management System.

The original text records the use of pills and powdered drugs. For our extracts we convert the amounts given in the original texts into the amount of aqueous extracts, a form which also allows to achieve a uniform distribution. This renders carrying the products easier and serves also the function of excluding contamination with bacteria or other hazardous substances.

Acknowledgements:

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Cutting raw herbal medicines

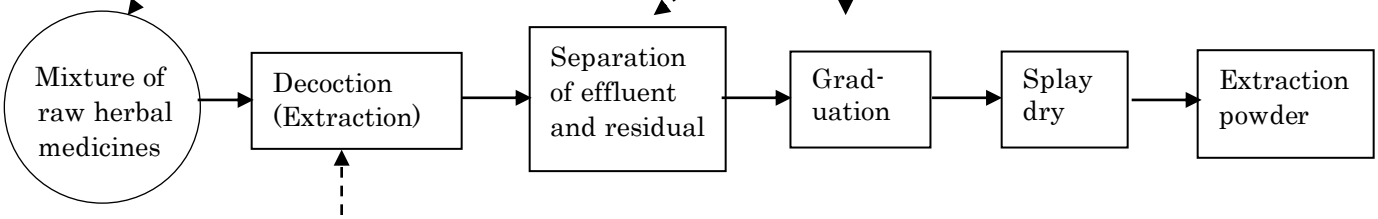
Store cut herbal medicines

Extraction tank

Top of separator of solid and liquid

To promote the efficient dissolution of insoluble ingredients, the particle sizes of herbal medicines are adjusted appropriately.

To maintain volatile ingredients in the finished product at the specified level, the effluent after extraction process is controlled below 60℃ at temperature and lowered in a graduation rate.



1) To maintain the sennoside content, extraction of Rhubarb is performed in a short time during the latter half of the extraction process.
2) Heating time may be shortened in order to prevent enzymatic reaction.

Residua/disposal after solid/liquid separation

Instant fungus reduction machine

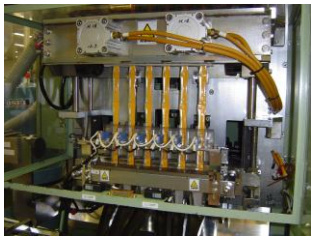
Hot-air generator for drying

Central control room

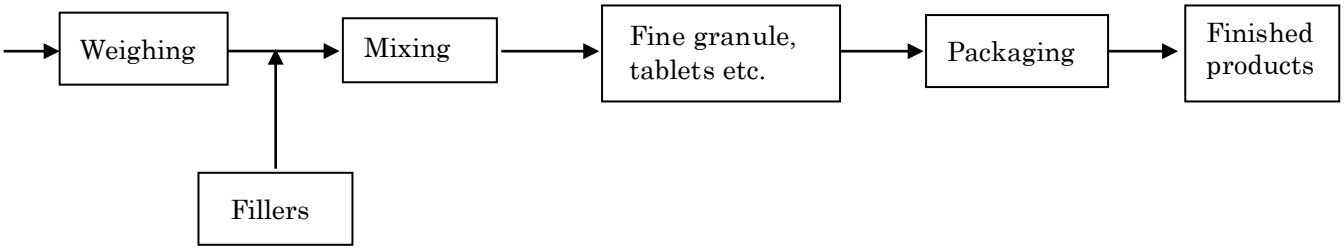
Weighing

Mixing

Granulating tablets



SP packaging



Automatic Transfer System

Automated Warehouse