Feature:

“The Best of Nature and Science”– Tsumura’s Value Creation Capability

Guided by its Corporate Value, “The Best of Nature and Science,” the Tsumura Group has grown as a leading company in prescription Kampo formulations through its pursuit of safety, efficacy, and consistency in its pharmaceutical products, based on scientific evidence. Trust and a performance record built up on the medical front line, along with research driven by advanced technologies, are the sources of Tsumura’s competitive advantage, and its unique value creation capability.

Pursuit of Safety

Quality of Kampo Products Begins from the Growing Fields

The Tsumura Group insists on the safety of raw material crude drugs and applies rigorous quality management as a manufacturer of Kampo and traditional Chinese medicines using crude drugs from plants and minerals found in nature.

Around 90% of the Group’s raw material crude drugs are procured from China. However, we do not purchase crude drugs from crude-drug markets throughout China. This is because the crude drugs that circulate in the markets are incredibly challenging to trace with regard to where and by what methods they were cultivated and processed. Based on our policy that the quality of Kampo products begins from the growing fields, we spent many months establishing a system for directly purchasing crude drugs from production areas. Furthermore, we referred to Good Agricultural Practices to ensure management of agricultural production processes for constant improvement, and built our own Tsumura GACP with additional training, audit, and certification systems.

Under the Tsumura GACP, processes from planting to cultivation methods, use of agrochemicals and fertilizers, harvesting, and processing are all determined by Tsumura GACP Guidelines based on our proprietary quality management standard, the Tsumura GACP Guidelines. We enter contracts with production groups that have acquired the Tsumura GACP Certification and purchase raw material crude drugs from them. This leads to stable income for producers and sustainable agricultural management.

In addition, we have built a crude drug traceability system that enables us to trace information such as which fertilizers or agrochemicals are used, and the cultivation history. Not only does this make it possible to take upstream safety measures against foreign contaminants such as agrochemical residues or microorganisms, but it also means that we can trace and check all processes up to delivery to the medical institutions by matching the history information for the Kampo formulation manufacturing process and logistics steps.

Raw material crude drugs procured through contract producers across China are concentrated mainly at SHENZHEN TSUMURA MEDICINE and CHINA MEDICO CORPORATION. The raw material crude drugs are tested for safety, such as agrochemical residues, microorganisms, and heavy metals, and undergo physical and chemical testing to remove any foreign objects and defective products. Only raw material crude drugs that clear quality standards are supplied to each plant, where they are manufactured into Kampo formulations.

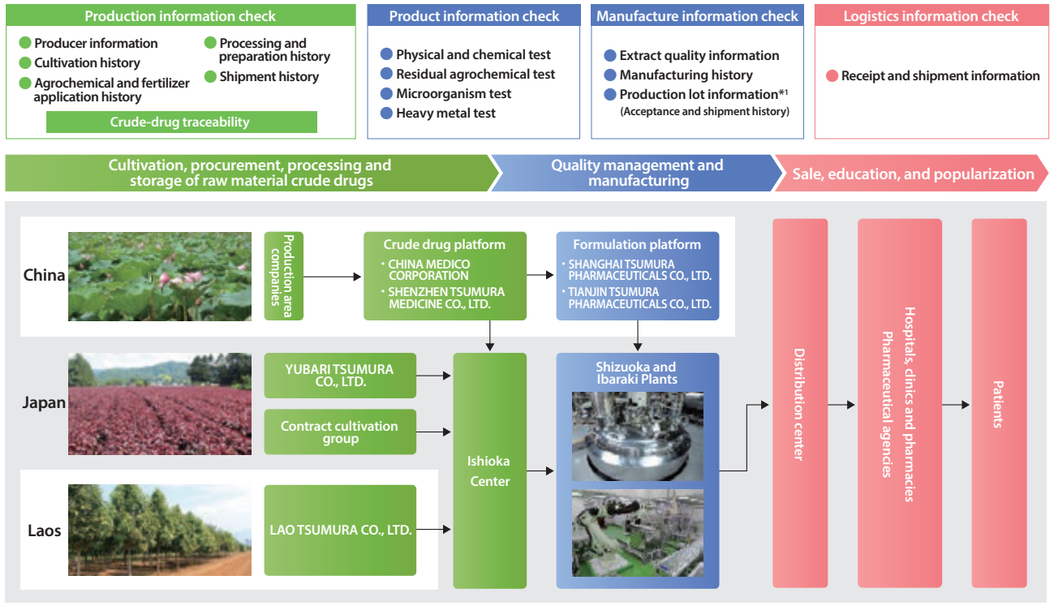
Moreover, the Group manages its own fields where it can provide cultivation instruction directly, and it is expanding the ratio of such fields. In this way, we are working to strengthen the raw material crude drug quality assurance system and stabilize prices.

In our quality testing, we conduct tests prescribed in the Japanese Pharmacopoeia, as well as testing for residual agrochemicals, microorganisms, mold toxins, and elemental impurities under our own in-house specifications and our own standards. We are also working to ensure safety by developing proprietary technologies for analyzing crude drugs and Kampo extract powder and granules that contain multiple and diverse components.

Crude drug varieties used in the Japan business

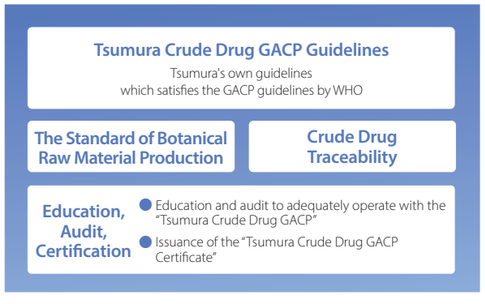
Plant-based 110　Animal-based 5　Mineral-based 4

Tsumura Traceability System

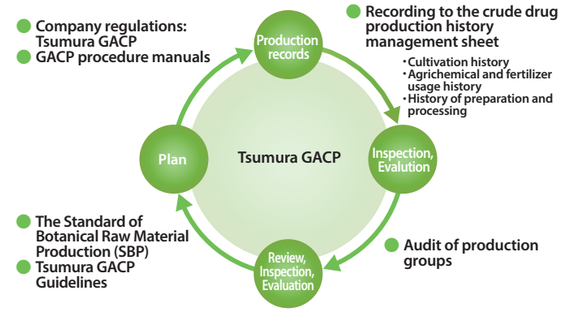


*1 Groups of products made under the same conditions are referred to as a lot. The smallest unit of information when producing products is referred to as production lot information.

Tsumura GACP Guidelines



PDCA Cycle in the GACP



Proof of Efficacy

Promoting Knowledge of the Efficacy of Kampo Medicines with "Drug-fostering" through the Building of Evidence

Kampo medicines are pharmaceutical products with multiple components derived from natural substances. Due to this characteristic, it has been considered difficult to show their efficacy and safety scientifically. To establish a position for Kampo formulations as a treatment option, it is necessary to prove the efficacy and safety of Kampo formulations in the field of Western medicine. We have therefore been engaged in basic and clinical research, and in building evidence.

Since fiscal 2004, we have focused our resources on drug-fostering research. Drug-fostering research is a program for accumulating basic and clinical data to establish evidence for diseases in areas of high medical need that have been resistant to new Western drugs and for which prescription Kampo formulations have demonstrated special efficacy. The program started with three formulations—Daikenchuto, Yokukansan, and Rikkunshito—with the subsequent addition of two more. These drug-fostering program formulations are contributing to expansion of the Kampo market as growth drivers for the Tsumura Group. In fiscal 2016, we established "Growing" formulations as new strategic formulations to follow the five drug-fostering program formulations. Focusing on the areas of geriatric health, cancer (supportive care*2), and women's health, we have been working to gain write-ups for these formulations in medical treatment guidelines.*3 We are promoting the formation of packages for drug-fostering program formulations and "Growing" formulations. The packages include five items: evidence from clinical studies,*4 elucidation of action mechanisms, study on frequency of side effects, pharmacokinetics (ADME*5), and database research (health economics, etc.). The results of successful evidence accumulation include a more than two-fold increase in the number of write-ups in treatment guidelines over the past 10 years.

*2 Treatment to reduce the symptoms arising from the cancer itself or from the side effects caused by the cancer treatment, etc.
*3 A compendium of diagnoses and standard guidance on treatment for each illness, describing the best tests and treatment methods, etc., based on evidence.
*4 Data from meta-analysis (integration of multiple study results for analysis from a higher perspective) and randomized comparison trials (RCTs)
*5 Absorption, Distribution, Metabolism, Excretion. Looking at how a drug acts within the body after being taken.

Status of Evidence-building

As of end of March 2023

	No.	Formulation name	Integrated analysis	RCT	Mechanism of action	Study on frequency of side effects	Pharmacokinetics (ADME)	Database research (health economics, etc.)
Drug-fostering program formulations	100	Daikenchuto	4	36	○	○	○	○
	54	Yokukansan	4	18	○	○	○	○
	43	Rikkunshito	2	26	○	○	○	—
	107	Goshajinkigan	2	15	○	—	○	—
	14	Hangeshashinto	1	10	○	—	—	○
Growing formulation	17	Goreisan	1	11	○	—	—	○
	24	Kamishoyosan	—	7	○	—	—	—
	41	Hochuekkito	—	17	○	In progress	—	—
	108	Ninjin'yoeito	—	2	○	—	—	—
	137	Kamikihito	—	0	○	—	—	—

Notes: 1 ○ indicates the existence of a relevant academic paper, etc.
2 Numbers of statistical analysis and RCT papers are collated from 2000 to January 2023

Contribution to Solving Social Issues through the Expansion of Standard Treatments

Tsumura is working to build evidence through both basic and clinical research. Taking Daikenchuto as an example, in basic research we worked to elucidate the pharmacological effects, such as promoting intestinal motility, increasing intestinal blood flow, and anti-inflammatory effects, as well as the mechanism of action. In clinical research, we examined the pharmacokinetics and frequency of side effects. In addition, we conducted a double-blind randomized comparison trial (DB-RCT) and meta-analysis on the effect on post-operative gastrointestinal function and symptoms to prove its efficacy, resulting in the write-up of Daikenchuto in treatment guidelines for several conditions.

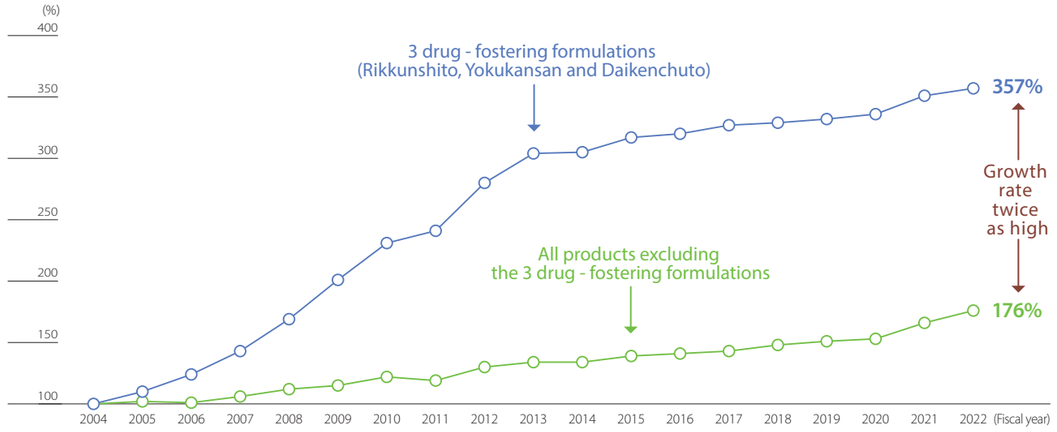
The establishment of such evidence has led to new write-ups and increased recommendation levels in treatment guidelines. Ultimately, we will expand the use of Kampo formulations as standard treatments.*6 Through the Company's research activities, it has established a foundation for recognition of Kampo formulations as standard treatments by physicians, to a degree. This foundation includes qualitative and quantitative improvement in write-ups in treatment guidelines and inclusion of Kampo training-related content in the education models and core curricula for disciplines including medicine, dentistry, pharmacology, and nursing.

In addition, since Kampo medicine enhances people's inherent natural healing ability and promotes improvement of symptoms, it is considered a "personalized medicine" that treats both mental and physical aspects together. Aiming to realize a society where everybody can receive optimal Kampo treatment, we will increase our efforts to develop a Kampo medical exam support system using DX and AI technology, clearly identifying the responders to Kampo formulations (cohorts that show efficacy, "patterns" for Kampo), and establishing objectivity for Kampo medical exams.

*6 Optimal treatment methods recommended to most patients, with efficacy and safety confirmed based on evidence.

➡For details, see page 51 "Strategic Challenge 2".

Impact of Drug-fostering Research on Sales of Prescription Kampo Formulations
(rate of sales growth compared to fiscal 2004, when drug-fostering was started)



Innovation of Consistency

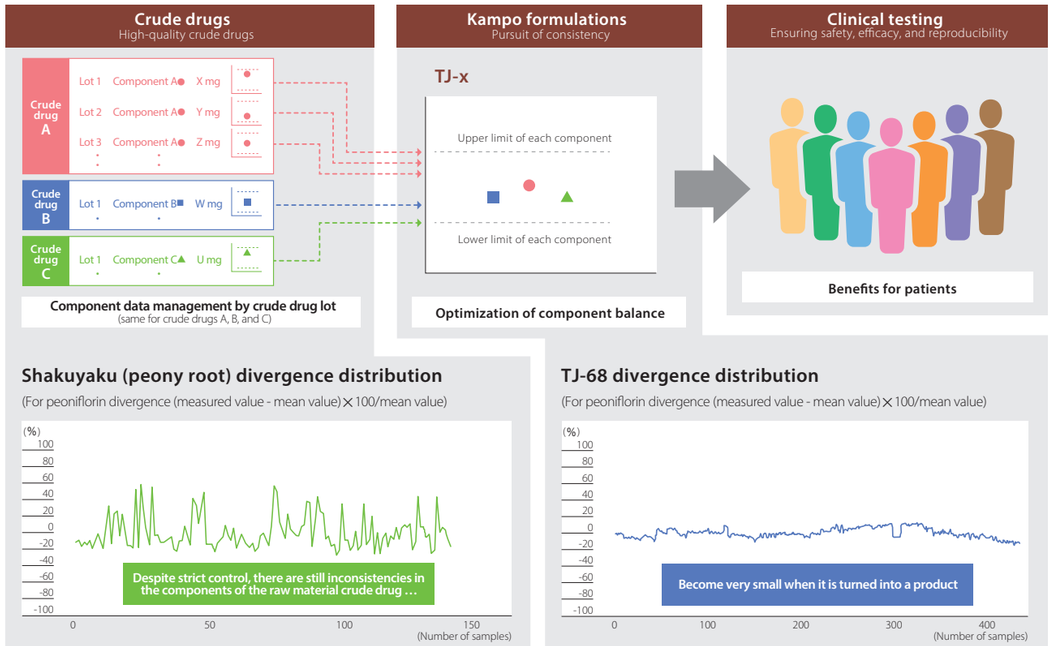
Consistency Across the Entire Kampo Value Chain

Since crude drugs are natural substances, the component content varies depending on factors such as production area, cultivation environment, and processing and storage conditions. However, they must achieve clinical reproducibility in order to become pharmaceutical products, and this is ensured by stable quality of crude drugs and the technology and expertise to create consistent Kampo products in the formulation process.

Such consistency has been considered difficult to achieve in the finished Kampo formulation products, because even if they are grown from seeds or seedlings from the same origin, crude drugs may vary in their shape or component content due to factors including growing environment, such as soil or climate, harvest timing, and storage conditions. The Tsumura Group has built the Kampo value chain, a proprietary supply chain that manages business activities consistently from upstream to downstream. To achieve consistency, it is vital to pursue quality throughout the entire Kampo value chain. In the upstream process of crude drug cultivation, we control variation in raw material crude drugs by providing guidance on cultivation and processing methods and using only crude drugs that meet Tsumura's quality standards. The component balance of the crude drugs can be further optimized in the formulation process by analyzing and managing the component content data for each lot, then prescribing the ratio of the crude drug lots to be used in the preparation. In the formulation process, to minimize changes to the components of the extract, we have developed a proprietary manufacturing line and we control the system for each formulation to achieve consistency in our final Kampo formulation products.

These activities are truly the practical embodiment of our Corporate Value, "The Best of Nature and Science," and we will continue to hone our strengths in safety, efficacy, and consistency, aiming to contribute to the solution of social issues through business, such as protection of human health, preservation of the global environment, and revitalization of local communities.

Consistency and Clinical Reproducibility of Kampo Medicines



Future Development

Development of Business in China Leveraging the Tsumura Group's Strengths

In Japan, the portion of the population aged 65 and over surpassed that aged under 14 in 1997, and the country is now known as the fastest aging country in the world. However, population aging is advancing globally, and the portion of the population aged 65 and over (aging ratio) is expected to increase rapidly over the next 40 years.

China is also experiencing a falling birthrate and aging population. The Tsumura Group has defined its vision for the China business as contributing to the health of the citizens of China through its accumulated technology and experience, and is steadily putting it into action.

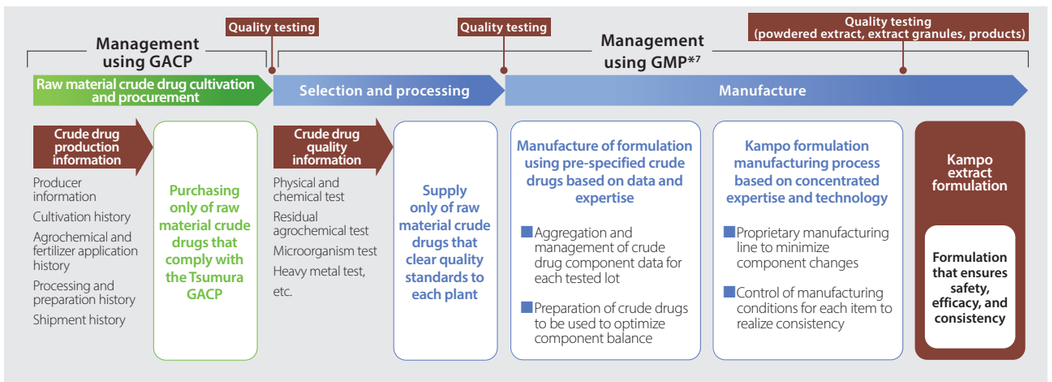
The Healthy China 2030 initiative promoted by the Chinese government places importance on both modern medicine and Chinese medicine. It promotes the development of rules regarding traditional Chinese medicine production and also encourages expanding the scale of production. Within traditional Chinese medicines also, the key to the development of traditional Chinese medicinal products is standardization, and the Chinese government views the standardization of traditional Chinese medicinal products as a priority issue. The Tsumura Group seeks to achieve the standardization of traditional Chinese medicinal products and contribute to the development of the Chinese medicine industry. We will do this by using our technologies and expertise related to safety, efficacy, and consistency, which have been honed in the Kampo business.

In addition, with regard to the sale of raw material crude drugs and drug pieces, we will contribute to the citizens of China and healthcare by supplying high-value-added services using high-quality crude drugs.

We aim to continue striving to be a corporate group that contributes to the well-being of people, societies, and the environment globally by working to create shared value with all stakeholders involved in our value chain, and to popularize pharmaceutical products derived from natural substances.

➡For details, see page 53 "Strategic Challenge 3".

Process for Managing Consistency



*7 Good Manufacturing Practice. A Ministry of Health, Labour and Welfare ordinance that sets out permission requirements for the manufacturing of pharmaceutical products and quasi-pharmaceutical products, as well as requirements for obtaining marketing authorization, with manufacturing management and quality control standards for pharmaceutical products and quasi-pharmaceutical products.