



Establishment of Application Guidance for OTC non-Kampo Crude Drug Extract Products in Japan

Layla Somekawa¹, Hikoichiro Maegawa², Shinsuke Tsukada³, Takatoshi Nakamura^{1,4}

ABSTRACT

Currently, there are no standardized regulatory systems for herbal medicinal products worldwide. Communication and sharing of knowledge between different regulatory systems will lead to mutual understanding and might help identify topics which deserve further discussion in the establishment of common standards. Regulatory information on traditional herbal medicinal products in Japan is updated by the establishment of Application Guidance for over-the-counter non-Kampo Crude Drug Extract Products. We would like to report on updated regulatory information on the new Application Guidance. Methods for comparison of Crude Drug Extract formulation and standard decoction and criteria for application and the key points to consider for each criterion are indicated in the guidance. Establishment of the guidance contributes to improvements in public health. We hope that the regulatory information about traditional herbal medicinal products in Japan will be of contribution to tackling the challenging task of regulating traditional herbal products worldwide.

¹Office of OTC/Quasi-drugs, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan, ²Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan, ³Office of New drugs IV, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan, ⁴Division of Pharmacognosy, Phytochemistry and Narcotics, National Institute of Health Sciences, Tokyo, Japan

Address for correspondence:

Hikoichiro Maegawa,
Pharmaceuticals and
Medical Devices Agency,
Japan. E-mail: maegawa-
hikoichiro@pmda.go.jp

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INTRODUCTION

Herbal medicinal products have been used worldwide. Currently, there are no internationally standardized regulatory systems for them. A convergence of the diverse regulatory systems might save resources and lead to an adequate availability of herbal and traditional medicinal products for patients. Communication and sharing of knowledge between different regulatory systems will lead to mutual understanding and might help identify topics which deserve further discussion in the establishment of common standards [1]. Furthermore, regulatory information on herbal medicinal products will help to identify what kind of research is needed for evidence-based herbal medicine use [2]. Summary information for regulation of herbal medicinal products in Japan has been published [3]. Regulatory information on traditional herbal medicinal products in Japan is updated

by the establishment of Application Guidance for over-the-counter (OTC) non-Kampo Crude Drug Extract Products. We describe updated regulatory information on the new Application Guidance.

Traditional herbal medicines in Japan are crude drug products derived from the natural products. They have been used as medicine or as medicinal materials since ancient times and have contributed to public health.

According to the Ministry of Health, Labour and Welfare's (MHLW's) Annual Report on Statistics of Production by Pharmaceutical Industry in 2014 [4], the total amount of pharmaceutical production in Japan is about 6589.8 billion yen worth. A number of traditional medicines produced take up about 2.2% of total pharmaceuticals production in Japan. The amounts

of ethical and OTC Kampo formulations take up about 92.6% in traditional medicines. Others are that of non-Kampo crude drug products. Traditional herbal medicine industry is worth about 158.1 billion yen [5]. Non-Kampo crude drug products production is twice that of antihistamines (about 5.1 billion yen).

Traditional herbal medicines in Japan are classified into two categories, which are Kampo products and non-Kampo crude drug products. Kampo products are formulated based on Kampo medicine principles, whereas non-Kampo crude drug products contain single or multiple crude drugs, their formulations do not follow Kampo medicine principle but folk medicines [6]. Kampo products include ethical Kampo formulations and OTC Kampo formulations. Ethical Kampo formulation is listed in the National Health Insurance (NHI) price list and obtained through a doctor's prescription with NHI reimbursement. Non-Kampo crude drug products can also have ethical status and OTC status. Ethical non-Kampo crude drug products contain single crude drug products and are also listed in NHI Price List. However, most non-Kampo crude drug products are OTC crude drug products [3].

Non-Kampo crude drug products have been publicly used throughout history, are still used as folk medicines today. Having been excavated from ruins of the Jomon period (11,000-300 B.C.), *Phellodendron* Bark is said to be the oldest crude drug in Japan [7]. "*Daranisuke*," is said to be a medicine dispensed free by Japanese Buddhist monk Kukai (774-835), contains *phellodendron* bark and is still used as a gastrointestinal medicine now [7,8]. The benefits of OTC drugs include convenience to patients, better self-management of minor illness, and a reduction in governmental medical costs [9]. In Japan, governmental medical costs are increasing due to mainly aging the population; therefore, non-Kampo crude drug products will have a significant role in self-medication.

Non-Kampo crude drug products are extracts, pieces, or powders made from naturally derived medicines. Some of the non-Kampo crude drug products are prepared by concentrating the infusion of a crude drug, which is mainly used as a decoction. The decoction is a method to extract soluble components including pharmaceutically active ingredients from crude drugs by boiling. There are various methods used for formulating decoctions into granules, one of which is the spray-drying method. There have been demands for these granule formulations due to the relative ease of storage and administration to patients.

Currently, Kampo products and crude drug products used since ancient times in Japan have contributed to the prevention of diseases and maintenance of health, but in recent years due to changing prevalence of an increase in lifestyle diseases, neurological diseases, and the aging population, new crude drug products with new active ingredients or new indication are expected to get approval. However, when applying for new crude drug products with new active ingredients or new indications, it is necessary to show the efficacy and safety of the products through clinical trials.

As for Kampo products, "approval standards for OTC Kampo products" were established [10-13]. Under the approval

standards, it is unnecessary to attach clinical trial data. However, as for crude drug products used as medicines, there are only the internal assignments on the review for crude drugs that is "the guide book of the application for drugs listed in The Japanese Pharmacopoeia (JP)" [14]. Over 200 crude drugs have been listed in JP17. Kampo products are approved as OTC drugs based on the approval standards. However, most single crude drugs are raw materials for Kampo products. They are not approved as medicines except for 30 pieced and powdered crude drugs. One of the reasons is because there is no Application Guidance for crude drug products [15].

In 2002, an interim report by the Investigative Committee for Review Rationalization of OTC Drugs proposed that non-Kampo crude drug products should be utilized because they have contributed to public health. Non-Kampo crude drug products should be used effectively, and that the establishment of approval standards for OTC non-Kampo crude drug products based on changing prevalence should be done in the future [16].

DEVELOPMENT OF APPLICATION GUIDANCE FOR OTC NON-KAMPO CRUDE DRUG EXTRACT PRODUCTS

In response to the above proposal, a research group; MHLW Research Project for Crude Drug Products, was established from 2010 [15]. The group involved academics, representatives from pharmaceutical regulatory agencies, and industrial researchers specializing in the herbal medicine field. The project meetings were held 3 times a year. The group discussed the following agenda items to establish Application Guidance for OTC non-Kampo Crude Drug Extract Products.

- Considering crude drug candidates for listing in draft of Application Guidance for OTC non-Kampo Crude Drug Extract Products with reference to "The guide book of the application for drugs listed in JP" [14]
- Confirming scientific efficacy and safety evidence of each crude drug candidates listed in the draft
- Based on the evidence information, considering additions of new indications or changing indications of crude drugs listed in "The guide book of the application for drugs listed in JP" [14]
- Selection of marker compounds for quality control of Crude Drug Extracts based on pharmacopoeia of various countries and examination of its identification and assay methods
- Establishment of quality equivalence guidelines between Crude Drug Extracts and decoctions or powder of crude drugs for its quality control.

The drafts were posted on MHLW website for public review and comments.

Study of Efficacy and Safety Evidence for Listing Crude Drug Candidates

"The Core Evidence" defined by the research group must satisfy both: (1) Clinical research (randomized controlled trial (RCT),

other than RCT, survey research, and case report) and (2) a single crude drug products under clinical research. If the evidence does not satisfy both (1) and (2), it was treated as “The Support Evidence”. Based on “Consolidated Standards of Reporting Trials (CONSORT) Statement” [17] and “CONSORT of Herbal Intervention” [18], “The Core Evidence” was examined. Evidence level was assessed with reference to Agency for Health Care Policy and Research classification of evidence level [19], Jadad score [20], and the revised risk assessment of bias in The Cochrane Collaboration [21].

Study of Quality Standard for Listing Crude Drug Candidates

Quality control criteria regarding crude drugs, powdered crude drugs, and Crude Drug Extract were examined with reference to the European Medicines Agency guidelines on herbal medicinal products [22-25] and the US Food and Drug Administration Botanical Drug Development Guidance for Industry [26] and quality control criteria under consideration for listing in Japanese draft guidance were examined.

Marker compounds for quality control of crude drugs and its identification and assay methods were examined with reference to JP, Pharmacopoeia of The People’s Republic of China, United States Pharmacopeia, European Pharmacopoeia, British Pharmacopoeia, and Hong Kong Chinese Medica Standards.

ESTABLISHMENT OF APPLICATION GUIDANCE FOR OTC NON-KAMPO CRUDE DRUG EXTRACT PRODUCTS

In Japan, “Application Guidance for OTC non-Kampo Crude Drug Extract Products” was published in 2015 [27].

Methods for comparison of Crude Drug Extract formulations and standard decoction and criteria for application and the key points to consider for each criteria are indicated in the guidance.

Crude drugs listed as reference information on the guidance are bearberry leaf, powdered phellodendron bark, coptis rhizome, powdered coptis rhizome, polygala root, Prunella spike, Glycyrrhiza, powdered Glycyrrhiza, powdered Platycodon root, catalpa fruit, powdered cinnamon bark, cassia seed, powdered gentian, geranium herb, powdered geranium herb, safflower, red ginseng, condurango fluidextract, saffron, smilax rhizome, powdered gardenia fruit, plantago herb, Houlttuynia herb, swertia herb, Mulberry Bark, ginseng, belladonna extract, Sinomenium stem and rhizome, akebia stem, bear bile, coix seed, powdered coix seed, and powdered Japanese gentian. All crude drugs listed as reference information on the guidance are listed in JP17.

Methods for Comparison of Crude Drug Extract Formulation and Standard Decoction

The data to be submitted for OTC non-Kampo Crude Drug Extract Products applications should be based on the guideline on data requirements for ethical Kampo formulation [28].

A crude drug which is thought to have standard quality should be used. Data should be provided on at least three batches of the crude drug. Each batch must be subjected to testing at least 3 times.

A standard decoction made in accordance with the guidance is required for evaluation. Marker compounds for quality control of standard decoction must be evaluated. Data should be provided on at least three batches of the standard decoction. Each batch must be subjected to testing at least 3 times.

The quality of OTC non-Kampo Crude Drug Extract must be comparable with that of standard decoctions made from a crude drug. To assure the quality of OTC non-Kampo products, the guidance indicates data requirements for approval as OTC non-Kampo Crude Drug Extract Products. In the guidance, comparison of OTC non-Kampo Crude Drug Extract and a standard decoction is required for the application. The reason why is to evaluate whether appropriate marker compounds’ contents for quality control of OTC non-Kampo Crude Drug Extract are comparable with that of standard decoctions or not. Data should be provided on at least three batches of the drug products. Each batch must be subjected to testing at least 3 times.

The criteria for the comparison between the standard decoction and OTC non-Kampo Crude Drug Extract are in accordance with guideline on data requirements for ethical Kampo formulation [28]. The outline of the criteria is shown below.

- Assay of marker compounds for quality control of a crude drug should be established.
- The standard of marker compounds’ contents for quality control is acceptable if not less than 70% of the lower limit of standard decoction in a daily dose, not less than the lower limit is desirable.
- The standard of marker compounds’ contents for quality control is acceptable within $\pm 50\%$, within $\pm 30\%$ is desirable.

Criteria for Application and the Key Points to Consider for Each Criteria

The outline of each criterion for application indicate the following;

- Preparation methods for non-Kampo Crude Drug Extract formulation should indicate the following;
 - Fineness of crude drug powder
 - Amount and kind of extraction solvent
 - Extraction condition such as temperature, time, and number of times
 - Method of solid-liquid separation
 - Method of concentration
 - Method of drying
 - Percentage yield.
- Standards and test methods of non-Kampo Crude Drug Extract formulation should indicate the following;
 - Description of its color, form, smell, and taste should be indicated.
 - Identification should be specific for a crude drug such as thin-layer chromatography.
 - Establishment of impurity test of heavy metals, arsenic, and pesticide residue is the case-based considering characteristics of crude drugs.

- Loss on drying and total ash should be established. For loss on drying, standards should be determined to avoid problems in distribution and storage. For total ash, in the case of crude drugs of which root is mainly used such as Ginseng and Red Ginseng, as narrow root tends to show higher values, the standard of upper limit should be established. In the case of crude drugs of which leaves are mainly used, lower leaves content leads to lower total ash. It is actually non-indicative since leaves are the desired part of the ingredients. Standard of lower limit should be established.
- Acid-insoluble ash may need to be considered. For testing of soil content of crude drugs, the test of acid-insoluble ash is used. The standard amount of acid-insoluble ash for each crude drug is material based. This test may not always necessary for extracts. For example, some extracts are made with the use of filtration process. If the filtration produces extractions with no detectable soils, then the standard of the acid-insoluble ash is unnecessary.
- Assay of marker compounds for the quality control of a crude drug should be established based on JP. If the

assay is difficult to establish, extract content should be established alternatively.

- Dosage, dosage interval, and route of administration must be in accordance with the guidance and application guideline for ethical Kampo formulation [29].
- Indication for the non-Kampo Crude Drug Extract Products must be in accordance with this guidance.

The Application Guidance for OTC non-Kampo Crude Drug Extract Products covers acceptable crude-drug component, dosage and administration, and indication for each crude drug. Currently, 33 crude-drug components are listed. This includes non-Kampo Crude Drug Extract Products which have been in use for many centuries; no pre-clinical and clinical data is necessary under the Application Guidance. The data requirements for OTC non-Kampo Crude Drug Extract Products application under the Application Guidance are indicated in Table 1. For new non-Kampo crude drug products with new active ingredients to get approval with ethical status, almost all data stated in Table 1 are required.

Table 1: Summary of the data requirements for non-Kampo crude drug products in Japan

Contents of the data submitted for application	OTC non-Kampo crude drug products under the Application Guidance	OTC Kampo products under the approval standards	New non-Kampo crude drug products for obtaining ethical status ²
A. Origin or background of discovery, conditions of use in foreign countries			
1. Origin or background of discovery	×	×	○
2. Conditions of use in foreign countries	×	×	○
3. The therapeutic group, comparisons with other drugs, and related information	○	○	○
B. Manufacturing methods, standards, and test methods			
1. Chemical structure, physicochemical properties, and related information	×	×	○
2. Manufacturing methods	×	×	○
3. Standards and test methods	○	○	○
C. Stability			
1. Long-term storage tests	△	△	○
2. Tests under severe conditions	×	×	○
3. Accelerated tests	△ ¹	△ ¹	○
D. Pharmacological action			
1. Primary pharmacodynamics	×	×	○
2. Secondary pharmacodynamics, Safety pharmacology	×	×	○
3. Other pharmacological action	×	×	△
E. Absorption, distribution, metabolism, and excretion			
1. Absorption	×	×	○
2. Distribution	×	×	○
3. Metabolism	×	×	○
4. Excretion	×	×	○
5. Bioequivalency	×	×	×
6. Other ADME	×	×	△
F. Acute, subacute, and chronic toxicity, teratogenicity, and another type of toxicity			
1. Single-dose toxicity	×	×	○
2. Repeated-dose toxicity	×	×	○
3. Genotoxicity	×	×	○
4. Carcinogenicity	×	×	△
5. Reproductive toxicity	×	×	○
6. Local irritation	×	×	△
7. Other toxicity	×	×	△
G. Clinical studies			
1. Clinical trial results	×	×	○

In principle, ○ means that the indicated data are required. × means that the indicated data are not required. △ indicate the necessity of the indicated data is case based. ¹If a drug of which stability for 3 years cannot be estimated from accelerated test, long-term storage test is required. ²In the case of products with new active ingredients. OTC: Over-the-counter

However, in the case of OTC non-Kampo Crude Drug Extract Products application under the Application Guidance, A.3. (Therapeutic group, comparison with other drugs, and related information), B.3. (Standards and test methods), and C.3. (Accelerated tests) are required.

In regards to reviews, Pharmaceuticals and Medical Devices Agency (PMDA), which is the Japanese regulatory agency working together with MHLW, must confirm that active ingredients, contents, dosage and administration, and indication, all comply with the Application Guidance. Furthermore, the standards and test methods used must be appropriate to ensure product quality. In the review, there were cases where main issues were whether the marker compounds for quality control were appropriate for the quality standards or not.

DISCUSSION

It seems important to establish Application Guidance for crude drugs and to utilize crude drugs as medicines. In Japan, the main traditional herbal medicines, Kampo medicines, are considered as medicines. Regulation of Kampo medicines is well established. Therefore, we provide Kampo medicines with high quality, which contributes to improvements in public health. As some of the Western herbs have been listed under non-pharmaceuticals [30], these products are sold as a dietary supplement without review. Because the quality of herbal products sold as foods is unclear and does not provide appropriate information, regulatory guidelines for Western herbal products having efficacy and safety as medicines were established. Based on guidance of Western traditional herbal medicines application as OTC drugs [31], Western traditional herbal medicines could be approved as OTC drugs in Japan. By establishing the guidance, strictly informative labels including indication, dosage, and administration, precautions are enforced. We are able to control the safety of Western herbal products through pharmacovigilance. The pharmacovigilance facilitates proper use of them. The quality of Western herbal products gets assured by standards, self-imposed Good Agricultural and Collection Practices [32], and Good Manufacturing Practice. Overall, it is important for us to evaluate and regulate traditional herbal medicines to use them therapeutically.

Since crude drugs and crude drug products have been used as folk medicines and have contributed to public health, it is important to use crude drugs and crude drug products effectively. However, a number of approved crude drug products are much lower than that of Kampo products since there is no Application Guidance for crude drugs. In the early 1970s, "The Internal Assignments on the Review for Approval of OTC Kampo Products," known as "210 OTC Kampo Formulae," was published by the Ministry of Health and Welfare. In 2008, "210 OTC Kampo Formulae" was revised and presented as "the approval standards for OTC Kampo products" [3]. On the other hand, for non-Kampo crude drug products, the internal assignments on the review for crude drugs that is "The guide book of the application for drugs listed in JP" had been left as they were for a long time. There was no description on the handling of Crude Drug Extracts in the guide book. Crude drugs under the approval standards will not need to show clinical trial data. However, crude drugs not under the standards must

show non-clinical study data and clinical trial data depending on the novelty of the application. Therefore, the Application Guidance for OTC non-Kampo Crude Drug Extract Products was published to make use of non-Kampo crude drug products as medicines effectively. After the establishment of the guidance, under the Application Guidance, non-Kampo crude drug products applications do not require clinical trial data the same as OTC Kampo products under the approval standards [Table 1].

New indications of non-Kampo crude drug products for symptoms in the elderly, such as support for diabetes and forgetfulness, was added in this guidance. However, regarding Japanese traditional herbal medicinal products, there are not many papers on their efficacy or effectiveness, and the verification of their efficacy by data is still insufficient. For example, there are no papers on clinical trials using Mulberry Bark, which is listed in the guidance, but there are papers on pharmacological studies. Since Mulberry Leaves contain the active ingredient 1-deoxynojirimycin also contained in Mulberry Bark and original plant source of Mulberry Leaves is the same as Mulberry Bark, papers on clinical trials using Mulberry Leaves were examined for the efficacy of Mulberry Bark [15]. Therefore, it is necessary to continuously examine papers on crude drugs listed and unlisted in the guidance in the future.

In this guidance, non-Kampo Crude Drug Extract Products can be approved as OTC drugs by confirming the equivalence of marker compounds' contents for quality control of the standard decoction and that of the Crude Drug Extract. However, only 11 crude drugs out of the 33 crude drugs listed in the guidance have established assay of marker compounds for quality control in JP17. Although the research group proposed assay of marker compounds for quality control for 16 crude drugs out of the 22 crude drugs without established assays in JP17 [33,34], there are still crude drugs with no established assay methods. The future challenge is to establish officially for all the crude drugs listed in the guidance.

For better utilization of crude drugs as medicines, Application Guidance for non-Kampo OTC Crude Drug Extract Products was established. Efficacy, safety, and quality based on scientific evidence are required for the approval of traditional herbal medicinal products. Previously available data regarding traditional herbal medicinal products should not be ignored and should be utilized for making Application Guidance for herbal medicines. The data and pharmacopoeias of each country were examined to list crude drugs in the guidance from the viewpoint of ensuring efficacy, safety, and quality. If science-driven regulation of herbal products is facilitated, traditional herbal medicinal products will contribute to improvements in public health worldwide.

CONCLUSION

Establishment of Application Guidance for OTC non-Kampo Crude Drug Extract Products will help manufactures develop new Crude Drug Extract Products in Japan, as data requirements for the application are clear. We have expectations about new crude drugs and new indications will be listed in the guidance based on new evidence from clinical trials in the future.

In conclusion, the establishment of Application Guidance for OTC non-Kampo Crude Drug Extract Products contributes to improvements in public health following the development of new crude drug products of which efficacy, safety, and quality are ensured. These products can be used for self-medication. We hope that the regulatory information about traditional herbal medicinal products in Japan will be of contribution to tackling the challenging task of regulating traditional herbal products worldwide.

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