How to receive regulatory approval in Japan for Western Herbal Medicinal Products (WHMP)

古くから医療につかわれてきた西洋ハーブ。
いまも信頼される「医薬品」として利用されています。

Kenny Kuchta, Bonn, the 24th of July 2015
Western Herbal Medicinal Products (WHMP)

• Presently, there is no official definition of the term “western herbs”.
• Connotations that come to mind for most Japanese people are vague concepts like “healthy European herbal teas”.
• Only experts understand it as a technical term for “plants and plant-derived products that are used as pharmaceutical products and luxury goods in Europe and America”.
• The term was coined in Japan to describe the ethnopharmacological use of medicinal plants in the West from a Japanese perspective.
• From “Rational Phytotherapy” to “Traditional Use”.
• Analogue to terms like “Oriental Medicine” in the West.

→ This means it can only be understood from the perspective of traditional Japanese Kampo medicine!
What is Kampo?

• Traditional Japanese academic medicine
• Derived from the introduction of TCM books to Japan between ca. 500 and 900 AD
• Subsequently independent and divergent cultural evolution with European influences and independent developments
• More than 80 % of the plants are identical to TCM

**Differences to TCM:**
Standardised prescriptions instead of free combination, different drug quality, finer cut, less drug used, different decoction process, vastly different diagnostics, many ready made drug combination extracts (Ekisu), integrated in the standard medicine systems, only western style trained doctors may study Kampo additionally, . . .
Kakkonto (葛根湯)

- **Composition:**
  Pueraria lobata root (葛根, kakkon) 8.0 g, Ephedra sinica aerial parts (麻黄, mao) 4.0 g, Ziziphus zizyphus fruits (大棗, taiso) 4.0 g, Cinnamomum cassia bark (桂皮, keihi) 3.0 g, Paeonia lactiflora root (芍薬, shakuyaku) 3.0 g, Glycyrrhiza uralensis root (甘草, kanzo) 2.0 g, dried Zingiber officinale root (乾姜, kankyo) 1.0 g

- **Indications:**
  1) Common cold, Influenza; 2) Stiffness in the neck; 3) Sinusitis, Otitis media, Conjunctivitis; 4) Neuralgia of the trigeminal nerve; . . .

- **Remark:**
  The most common medication against the common cold!
Kampo: From Ban to Renaissance

• 1880: The Meiji Emperor commands the forced westernisation of all areas of society. All medicines that are not in accordance with accepted practice in Europe lose their status as medicines. All doctors who have not studied at a Western style university (opened since the 1860s) lose their approbation.

• In the following decades Kampo is kept alive by engaged doctors and pharmacists as well as interested lay men.

• 1960s: Health boom after the war. For the first time, chronic diseases more pressing than infectious ones.

→ Re-Legalisation Law: Kampo prescriptions with proven safety and minimal prove of efficacy are again accepted if they had originally been medicines before 1880. They can enter the National Health Insurance.

• 2015: More than 160 Kampo prescriptions are in the Insurance!
Approval of OTC Drugs in Japan (old law)

- For regulatory approval of **any drug other than traditional Japanese Kampo preparations**, a variety of data concerning its specifications, stability, toxicity, and clinical trial results are required.

- Further, for ensuring their safety, the class of OTC drugs has been subdivided in categories according to their type of active ingredient, route of administration, dosage form, dose, etc. and different sets of data can be necessary for approval depending on the category. “About the approval of pharmaceutical products” (doc. No. 0331015 on pharmaceuticals and food, 31st of March 2005) and “About the approval of OTC drugs” (doc. No. 1020001 on pharmaceuticals and food, 20th of October 2008).

- Because “Western Herbs” are “pharmaceuticals including OTC drugs containing an active ingredient that is used **for the first time**” [in Japan], they fall into the **toughest category**, namely “drugs with novel effective ingredients”.

→ These hurdles could not be overcome by even a single Western Herbal Medicinal Product up to now!
Approval of OTC Drugs in Japan (new law)

• General Drug Approval Review Committee (2002): “Concerning so-called “Western Herbs” that are used as drugs outside of Japan and for which it seems reasonable to assume that they contain active pharmaceutical constituents that are responsible for their pharmacological effects, the Japanese regulatory authorities should consider the way how these products are treated in their native countries when deciding how they are to be handled in Japan.”

• As the application category “Pharmaceutical products containing a new effective ingredient” remains unchanged, the new drug has to provide results from a clinical trial when submitted for approval.

• However, now all data that have been handed in to the EU regulators can be reused with the Japanese authorities! All statistical requirements have been reduced to EU level. (Under the old laws, a new study, preferably in Japan, was required!)
Approval of OTC Drugs in Japan (new law)

• For example, if a “Western Herbal Medicinal Product” has already received approval from a Western regulatory authority [→ “well established use”] after the results of an objective and comparable clinical trial were submitted there (this means with efficacy, dosage, and drug quality equivalent with the standards expected for a study performed for OTC drug approval in Japan herself), or if there is a precise and objective clinical trial the results of which are published in a reliable international scientific journal, it is now possible to receive OTC drug authorization in Japan on the basis of these documents.

• Subsequently, only drug safety has to be documented with a clinical observation in Japanese patients.
Possibility for Cooperation

• As “Western Herbal Medicinal Products”, which are marketed in the EU as OTC drugs, had to undergo the abovementioned “comparable clinical trials” anyway due to the similarity between EU and Japanese quality standards, an increasing number of Japanese plant drug producing companies considers to cooperate with European companies to introduce “Western Herbal” OTC drugs to Japan.

• This is also the way how regulatory approval for the initially mentioned Antistax® and Prefemin® was achieved.
Motivation for the new law: Bad Herbal Supplements!

- Within the range of products called “Western Herbs”, the percentage of products that have been tested by strong clinical trials is very low.
- Not all “Western Herbs” can be accepted as OTC drugs and many will continue to circulate as “health foods” for the foreseeable future.
- Due to the high interest of the Japanese populace in “Western Herbs” regulator had previously tried to get around a change in herbal drug regulations by being extremely lax on these supplements.
- There are several studies on the quality of “Western Herbal Medicinal Products” that are sold as health foods in Japan, especially for the plant drugs *Cimicifuga racemosa* (L.) Nutt. (syn.: *Actaea racemosa* L.) roots, *Vitex agnus-castus* L. fruits, and *Ginkgo biloba* L. leaves.
- In all cases, supplements that are not registered drugs in the EU are of extremely low quality; if not outright counterfeit!
- Internet orders from the US are especially bad!
Closing Remarks

• Some "Western Herbs" have been included in the “List of Non-Medicines” during the demarcation of food vs. drug plants so that even if some companies were able to get a respective product registered as a OTC drug in Japan and thus to advertise for this product with medicinal indications, they could not receive a legal standing against another company that might distribute an almost identical product as a health food.

• There are a lot of health foods that do comply by the quality standards for medicinal drugs and their lower price may also have its merits, but it is a fact that a certain and not minor part of health foods have severe quality deficits.

• We are therefore convinced that it is good news for the Japanese people when now “Western Herbal Medicinal Products” that are registered drugs in the EU can be registered as OTC drugs in Japan!
Thank you for your kind attention!

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