Letter to the editor: Comment on the Regulations of the Simplified Registration and Approval Management for Compound Recipe of Classical Prescription of Traditional Chinese Medicine

To the Editor:

On Oct 9, 2017, China Food and Drug Administration announced1 the Regulations of the Simplified Registration and Approval Management for Compound Recipe of Classical Prescription of Traditional Chinese Medicine ( Exposure Draft) which has been stirring up intense debate in the West. The article China to Roll Back Regulations for Traditional Medicine Despite Safety Concerns lately published on Nature2 has raised worldwide attention by stressing its worries over the safety issue of traditional Chinese herbal medicines. However, we noticed that classic Chinese herbal formulations with long-term traditional use are not yet well known to the Western world. Hereby we intend to elaborate on a clearer picture of classic Chinese herbal formulations and to offer a better understanding to the western researchers.

In our study, the classic Chinese herbal formulations only refer to those quoted from the ancient Chinese medical classics prior to 1911 which have conformed with the same stringent examination, regulation model, and approval standards as other medications in China since the implementation of “Provisions for Drug Registration” in 1985. In 2016, the China Food and Drug Administration (CFDA) approved only two types of new classic Chinese formulations, yet hundreds of chemical and biological drugs. Effects of classic Chinese herbal formulations, though being proved by hundreds of years’ clinical application, have to over and over again go through time-consuming and costly lab tests. It is the indiscriminate regulation that slows down the development of classic Chinese herbal formulations. In fact, the traditional herbal medicines and modern biochemical drugs differ both in pharmacology and in applications history. Therefore we suggest that the current regulation policy for chemical drugs should not be applied to Chinese herbal medicines without any adjustment. Based on this characteristic, CFDA plans to adopt a simplified registration and approval management. This is beneficial to speed up the launch of new drugs of Chinese herbal medicines, reduce the research and development cost, ease the burden of medical care, achieve WHO’s accessibility and affordability on traditional drugs and promote the goal for TCM to serve human health3.

1. Minimizing clinical trials is an internationally customary regulation for traditional herbal medicines

The registration and regulation of traditional herbal medicines are different from chemical drugs in many countries. The efficacy of traditional herbal medicines is mainly proved by long-standing clinical use in mass population and thus a simplified registration procedure for herbal medicines is internationally accepted. The European Union Herbal Medicines Directive7 notes that with long-term traditional application, it is necessary to provide a specially simplified registration procedure for herbal medical products. The Action Plan for Herbal Medicines (2010–2011) published by European Medical Agency (EMA) on June 11, 20107 presented that recommendations on extending the scope of simplified registration procedures have been made to European Parliament. If this proposal is adopted, the simplified registration procedure will be extended to other traditional products, including those drugs of animal origins. The Ministry of Health and Welfare, Japan3,5 approved 210 classical prescriptions of Kampo medicines without clinical trials produced by Japanese enterprises. The Ministry of Health, Korea stipulated that pharmaceutical factories could produce 11 recipes from its medical classics without clinical trials. In the U.S.A., herbal medicinal products8 have been classified as dietary supplements and are widely sold in market with no need for clinical trials (See Table 1 for details). With an application history of hundreds and even thousands of years, herbal medicine efficacy and safety have been supported by long-term clinical practice. Considering above situation and experiences, China plans to adopt a simplified registration approach to classic Chinese herbal formulations, which is in conformity with international acknowledgment.

2. Non-clinical safety and quality control studies are still required

The research and development process for new classic Chinese herbal formulations differs from that of chemical drugs and biological drugs. No chemical or biological drug is supposed to be applied to clinical use before it is approved by tests in lab, concerning the efficacy and safety issues. Yet the Chinese herbal medicines, especially the classic Chinese herbal formulations with

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| Item                          | Japanese Kampo                                                                 | Herbal medicine in European Union                          | The USA                                      | OTC drugs                                      | Chinese classic formulations                      |
|------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------|-----------------------------------------------|---------------------------------------------------|
| Relevant laws and regulations| Acknowledged Benchmark for General Kampo Preparation, 1974; Treatment on Medical Kampo Preparation, 1980 | DIRECTIVE 2001/83/EC, Directive 2004/24/EC                  | Dietary Supplement Health and Education Act of 1994 | Botanical Drug Development, Guidance for Industry, 2016 | Registration and management of TCM, 2007; Supplementary Regulations on the Registration and management of TCM, 2008 |
| Source of products           | Classical herbal formulations included in 1974 quoted from ancient medical classics such as “Treatise on Cold Pathogenic and Miscellaneous Diseases”, etc. | Tradition herbal medicine                                  | Herbal medicine or dietary supplement        | The drugs listed in OTC Monographs              | The classic Chinese formulations are quoted from the ancient Chinese medical classics prior to 1911 |
| Product requirements         | In principle, the product shall not contain toxic or rank toxic drugs.          | Those with a traditional usage for over 30 years and literature proof or expert evidence, including those with a traditional usage for over 15 years in European Union countries. | Do not claim to be able to diagnose, treat, or prevent disease | The drugs conform to OTC monograph              | The product shall not contain toxic materia medica or ingredients, and the scope of application does not include emergencies, infectious diseases, pregnant women or infants. |
| Pharmaceutical research      | Data of standard decoction, preparation, quality, etc.                         | Physical, biological, and microbiological tests are required, the quality conforms to the standards of the European pharmacopoeia | Not required                                 | The drugs conform to OTC monograph              | Data of standard decoction, preparation research, and quality studies, etc. |
| Toxicological research       | Not required                                                                  | Generally not required                                      | Not required                                 | Not required                                   | Non-clinical safety evaluations are required       |
| Clinical research Approval    | Not required Registration                                                      | Not required                                               | Not required No need for examination and approval | Not required No need for examination approval | Not required Registration                         |

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its longstanding popular use, have already established a solid foundation for their reputations.

However, stringent stipulations are still applied to the registration scope of classical prescription of Chinese herbs. It specifies that only those recipes for traditional Chinese herbal medicines listed in the “Ancient Classical Prescription List” can be adopted to prescription. After thorough consideration only one hundred classical herbal formulations are to be included initially, all these were screened with rigorous criteria. The purpose is to make sure that those selected classic Chinese herbal formulations do not contain any known toxic materia medica or ingredients.

In addition, there is a strict requirement for the safety of classic Chinese herbal formulations. Despite its long-standing massive use, systematical and profound non-clinical safety studies are expected for every classical formulation. Currently, the safety protocol for newly developed classic Chinese formulations conforms to the GLP standard. The conventional contents and technical requirements for the safety evaluation are the same as those for chemical drugs.

3. Chinese herbal medicines with a longstanding traditional use act relatively safer in the clinic

Chinese herbal medical products are widely used in the clinic. The reported adverse reaction of traditional Chinese herbal medicines accounts for only 17.3% of the total adverse drug reaction, whereas that of chemical drugs accounts for more than 81%

Generally, Chinese herbal medicine presents to be safer than chemical drugs. The adverse effect of aristolochic acids has drawn attention to the entire TCM field. The toxicological tests of Chinese herbal medicine are strongly encouraged by Chinese government and many of them are already being undertaken. In the past decades, Chinese government has been supporting the researches on the toxicology of both single Chinese herbs and TCM patent prescriptions. The mechanism of how Chinese herbs function in human body was unveiled and a systematic structure of the toxicology and pharmacology attributes of both individual Chinese herbs and herbal prescription compounds have already been built up.

Chinese herbal pharmacology is a fundamental carrier of Chinese culture and civilization. The economic entity of health industry, which took TCM as its core, has achieved a market share of nearly USD 3000 billion annually. TCM is an inseparable chain in Chinese medical security scheme and the world medical reform calls for "China Program". Marveled at the discovery of artemisinin, the world has been expecting more from TCM.

References

1 China Food and Drug Administration. The Regulations of the Simplified Registration and Approval Management for Compound Recipe of Classical Prescription of Traditional Chinese Medicine (Exposure Draft) [EB/OL]. October 9, 2017. Available from: (http://www.sda.gov.cn/WS01/CL0778/178324.html).
2 David C. China to roll back regulations for traditional medicine despite safety concerns. Nature 2017;551:552–3.
3 World Health Organization. WHO Traditional Medicine Strategy: 2014–2023. December 2013. Available from: (http://www.who.int/medicines/publications/traditional/trm_strategy14_23/en/).
4 Official Journal of the European Union. Directive 2004/24/EC of the European Parliament and of the Council [EB/OL]. April 30, 2004. Available from: (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2004_24/dir_2004_24_en.pdf).
5 European Medical Agency. Action Plan for Herbal Medicines 2010–2011 [EB/OL]. [2014-08-08]. June 11, 2010. Available from: (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/06/WC500093179.Pdf).
6 Maegawa Hikoichiro, Nakamura Takatoshi, Saito Kazuyuki. Regulation of traditional herbal medicine products in Japan. J Ethnopharmacol 2014;158:511–5.
7 The Japan Pharmaceutical Manufacturers Association (JPMA). Pharmaceutical Administration and Regulations in Japan 2015 [EB/OL]. July 13, 2015. Available from: (http://www.jpma.or.jp/english/parj/whole.html).
8 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Botanical Drug Development Guidance for Industry. December 2016. Available from: (https://www.fda.gov/downloads/drugs/guidancocomplianceinformation/guidances/ucm458484.pdf).
9 China Food and Drug Administration. Annual Report of National Adverse Reaction Monitoring between year 2013–2015 in China [EB/OL]. 2015. Available from: (http://sfda.gov.cn).

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