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Short Review

A Short Review on "Traditional Use and Safety Evaluation of Combination Traditional Chinese Medicine in European Registration: with XiaoYao Tablets as an Example"

Qiong Wang[1,2#], Shenghan Gao[2#], Yi He[2], Wei Sun[2], Jingwen Cui[3], Yongfa Chen[1*] and Shunnan Zhang[2*]

[1]School of International Pharmaceutical Business, China Pharmaceutical University, Nanjing, PR China

[2]State Key Laboratory of Core Technology in Innovative Chinese Medicine, Tasly Pharmaceutical Group Co., Ltd., Tianjin, PR China

[3]Tasly Healthcare Deutschland GmbH, Bahnhofstraße, Hannover, Germany

[#]Co-first author

Mental health disorders are common, undertreated and under-resourced. Depressive disorder, which is at the top of the list, has already become a major public health problem. Additionally, the COVID-19 pandemic has led to increased and widespread social concern about such disorders as it has intensified the short- and long-term stresses on the population. It is estimated that during the first year of the pandemic, the number of people suffering from mental disorders around the world surged to approximately one billion [1]. Traditional Chinese Medicine (TCM) has long experience in the treatment of depressive disorders, and a growing body of research suggests that TCM has significant therapeutic effects in the treatment of pandemic and mental health disorders [2-4].

Depressive disorder, known as "Yu Syndrome" in TCM, is mainly caused by spleen dysfunction, liver dysfunction, and a yin-yang imbalance of zang-fu qi and blood. The Xiaoyao formula has long been used to soothe the liver, fortify the spleen, nourish the blood, and relieve depressive disorders. It has been recorded in the Song Dynasty since 1151 and has been included in successive editions of the Chinese Pharmacopoeia since 1963. On August 23, 2021, the Netherlands Medicines Evaluation Board approved XiaoYao Tablets, developed based on the time-proven TCM Xiaoyao formula, as a Traditional Herbal Medicinal Product (THMP) to relieve the symptoms of mental stress and exhaustion, such as low mood and reduced appetite [5].

The European Union (EU) developed a simplified registration procedure (traditional use registration, TUR) in 2004 to encourage the free movement and harmonization of herbal medicinal products. However, only a small number of non-European traditional herbal products, including just five TCM products, have been successfully registered as THMP in the EU. XiaoYao Tablets is the first and only successfully registered combination THMP from China. Therefore, in the article, we summarized and analyzed the regulatory and application status of THMP in the EU, identified that the justifications of the traditional use and safety evaluation are two challenges impeding combination TCM registration in the EU, and proposed solutions based on the registration experience of XiaoYao Tablets.

Firstly, the applicant should provide several sources and types of traditional use evidence, such as EU lists/monograph, pharmacopoeias, official reports, expert evidence, or bibliographical, to prove that the proposed product has a medicinal use period of at least 30 years (15 years within the EU). At the same time, the applicant should also justify that the indication, active ingredients, strength, posology, and administration route of the proposed product are consistent with its traditional use. It is worth noting that the indication of the proposed product should meet the requirements of self-treatment and needs to be transformed from traditional words into modern medical terminology. For TCM products, the transformation could begin with TCM principle and pharmacopoeia, then analyze the relationship between the formula and the indication through a literature review; occasionally, efficacy and pharmacological studies are required to demonstrate the suitability of the intended indication.

Secondly, it is recommended to comprehensively evaluate the safety of the proposed THMP in terms of the combination herbal medicinal product, herbal substances, and drug interactions. While long-term human experience is used to demonstrate the clinical safety of combination TCM products, explaining the pharmacological effect of the product using TCM principle is also an important step in proving clinical safety. The bibliography of clinical practices and meta-analysis of proposed indications, can be used to evaluate the indication, usage, and adverse reactions of THMP. Meanwhile, the usage and dosage of the constituents in the whole formula need to be carefully justified. Retrievable reports or documents on the safety of herbal substances should be cited in the application dossier, and the herbal substances should be analyzed from the perspective of dosage and usage period to prove that the proposed product has no safety concerns. In addition, drug interactions are also an important aspect of the THMP safety evaluation. It is important to clarify human

***Corresponding authors:** Yongfa Chen, School of International Pharmaceutical Business, China Pharmaceutical University, China, Tel: +86 2586185038; E-mail: cyf990@163.com

Shunnan Zhang, State Key Laboratory of Core Technology in Innovative Chinese Medicine, Tasly Pharmaceutical Group Co., Ltd., China, Tel: +86 2226736870; E-mail: zsn@tasly.com

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clinically related interactions and investigate the potential interactions, including theoretical analysis of pharmacodynamics and *in vitro* studies of enzyme inhibitory potential.

Based on the discussion of the approved XiaoYao Tablets, we developed a safety evolution pathway for combination TCMs, in which traditional use evidence and modern evaluation techniques can be combined to justify the product's safety under the proposed indication. The safety of traditional use can be demonstrated by sales evidence, practitioner evidence (doctor's declarations), and bibliographic materials (literatures and EU monograph). In terms of modern technology, safety can be supplemented by toxicology evaluation (such as genotoxicity test), pharmacology evaluation (mechanisms of action, enzyme inhibition/induction tests), and clinical evaluation (such as clinical assessment). On the basis of clinical safety control, an effective quality control strategy is also crucial for the products' safety. In terms of safety evaluation, based on long-term application history and non-clinical, clinical and quality control research data, the comprehensive analysis demonstrates that XiaoYao Tablets fully meets the safety requirements for EU TUR registration.

In conclusion, the recommendations made in our article may be helpful for the development of TCMs in the EU market, taking into account the challenges TCMs encounter as medical products in the EU, such as cultural differences and marketing barriers. In the first place, cooperation between domestic enterprises may enhance TCM research and promote the registration of classic TCM products in the EU. Furthermore, it is proposed that the EU authority could enact and revise more guidelines for THMP, particularly for non-European traditional herbal products, to encourage and help herbal product registration. Finally, we urge the regulatory authorities of China and the EU to strengthen communication and cooperation in the field of TCM, as well as to provide practical policy support for in-depth cooperation among enterprises, so that more and more safe, effective, and high-quality TCM can bring more benefits to public health in the EU.

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