



**Good Practice in Traditional Chinese Medicine Research in
the Post-genomic Era**

GP-TCM

223154

D7.5

Publication of agreed guidelines on R&D

Joint Month 24/30 Report

Document description	
Name of document	Publication of agreed guidelines on R&D (Joint Month 24/30 Report)
Abstract	This joint Month 24/30 Report summarises the work carried out since Month 18. In addition to reviewing and projecting future development of global regulations of Chinese herbal products in the EU and China, we have extended the exercise to include other countries/regions: Africa, Australia, Brazil, Canada, Japan, Russia, South Korea, Taiwan and the United States. New experts in these regions were recruited. Despite complexity and difficulties in translating their local documents (in a variety of languages) into English, we were able to collate data and draw comparison of these regulations. Case studies are also presented to illustrate the problems involved in registering TCM products in different regions worldwide. A manuscript " <i>Future development of global regulations of Chinese herbal products</i> " was submitted to the Journal of Ethnopharmacology on 18 th December 2011, respectively. On 10 th February 2012, it was accepted for publication.
Document identifier	D7.5 (Month 24/30)
Document class	Deliverable
Version	1.1
Author(s)	Tai-Ping Fan, Greer Deal, Hoi-Lun Koo, Daryl Rees, He Sun, Shaw Chen, Jin-Hui Dou, Valery Makarov, Olga Pozharitskaya, Alexander Shikov, Yeong Shik Kim, Yi-Tsau Huang, Yuan Shiun Chang, William Jia, Alberto Dias, Vivian Chi-woon Wong, Kelvin Chan
Date of creation	22/5/2011
Date of last modification	20/04/2012
Status	Final
Destination	European Commission
WP number	WP7



DISCLAIMER

THE AUTHORS AND EDITORS OF THIS GP-TCM WORKPACKAGE DELIVERABLE ARE ENGAGED IN CREATING ACCURATE AND UP TO DATE CONTENT REFLECTING RELIABLE RESEARCH EVIDENCE, GUIDANCE AND BEST PRACTICE IN TCM RESEARCH AND DEVELOPMENT. THEY ARE FREE FROM ANY COMMERCIAL CONFLICTS OF INTEREST. REFERENCE HEREIN TO ANY SPECIFIC COMMERCIAL PRODUCT, PROCESS OR SERVICE, WHETHER BY TRADE NAME, TRADE MARK, MANUFACTURER OR OTHERWISE DOES NOT IMPLY ITS ENDORSEMENT, RECOMMENDATION OR FAVOURING BY THE MEMBERS OF GP-TCM, AND IS NOT HEREBY ENDORSED, RECOMMENDED OR FAVOURED BY GP-TCM AS AN ORGANISATION. THE EXAMPLES OF TCM-DERIVED PRODUCTS QUOTED ARE SOLELY INTENDED AS CASE-STUDIES OF SUCCESSFUL REGISTRATION OF HERBALS, THEIR PARTICULAR ROUTE TO MARKET AND LESSONS LEARNT TO DATE.



TABLE OF CONTENTS

1	INTRODUCTION	5
2	THE 2 ND ANNUAL GP-TCM MEETING IN BRAGA, PORTUGAL (21-23 JULY 2011).....	6
3	GP-TCM (WP1-WP3-WP7-WP10) JOINT WORKSHOP on “Quality control of CMM from a regulatory & toxicological Perspective” in Strasbourg, France on 29 Sept 2011	9
4	OUTCOME: 1 ST WP7 MANUSCRIPT PUBLISHED IN <i>THE JOURNAL OF ETHNOPHARMACOLOGY</i> <i>Future development of global regulations of Chinese herbal products</i>	10

1 INTRODUCTION

Since the outset, it has been the plan for WP7 to focus on two objectives of the GP-TCM Consortium and to publish our findings at the end of the project for global dissemination:

- To establish a collaborative network (consortium) that discusses the problems and solutions in developing Chinese herbal medicines (CHM) as drugs that meet the market-entry standard and requirement of the European Union and China.
- Special emphasis will be given to application of emerging functional genomics technology in this specific area.

With the approval of the Coordinating Office, WP7 underwent extensive re-structuring over the first 18 months, so as to clearly re-assess its objectives and recruit appropriate members to execute agreed action plans. There was an urgent need for a universal regulatory framework for complex herbal mixtures. Without such a framework in place, major research proposals involving both academia and industry cannot be put forward as their commercial impact would be undermined. WP7 members agreed that their priority should be to support the development of harmonised guidelines for the regulation of botanicals as follows:

Objective (1) – Regulations:

To establish a collaborative network towards formulating an easy-to-follow statement on the various regulatory frameworks for botanicals, emphasising the synergies and highlighting the differences, in order to contribute to the long-term goal of global harmonisation.

Objective (2) – Use of “Omics”:

To review the use of “Omics” in the regulation of drugs and its implication on the R&D of complex herbal products

This joint Month 24/30 Report summarises the work carried out since Month 18. In addition to developing future projects and reviewing the regulation of Chinese herbal products in the EU and China, we have extended the project to include other countries/regions to make the project as truly global as possible. Thus, new experts on Africa, Australia, Brazil, Canada, Japan, Russia, South Korea, Taiwan and the United States were recruited. Despite the complexity and difficulties in translating local documents (in a variety of languages) into English, we were able to collate data and draw comparison of these regulations. Case studies are also presented to illustrate the problems involved in registering TCM products in different regions worldwide.

During the course of developing this deliverable, the following experts were recruited to cover Africa, Australia, Brazil, Japan, Russia, South Korea and Taiwan and the United States:

Country/Region	Name	Institute
Africa	Pierre Duez	L'Université Libre de Bruxelles (ULB), Belgium
Australia	Kelvin Chan	University of Western Sydney & The University of Sydney
Brazil	Alberto Dias	CITAB-UM, Dep. Biologia, Universidade do Minho, Portugal
Canada	William Jia	University of British Columbia, Canada
Japan	Zhong-zhen Zhao	Hong Kong Baptist University School of Chinese Medicine, Hong Kong

Russia	Valery Makarov Olga Pozharitskaya Alexander Shikov	Saint-Petersburg Institute of Pharmacy, Russia
South Korea	Yeong Shik Kim	College of Pharmacy/Natural Products Research Institute, South Korea
Taiwan	Yi-Tsau Huang	National Research Institute of Chinese Medicine, Taiwan
Taiwan	Yuan Shiun Chang	China Medical University, Taiwan
United States	Shaw Chen Jinhui Dou	U.S. Food and Drug Administration, USA

Email exchanges and Skype teleconferences were instrumental to establish a team to take on this task.

In addition, a new task force was established to examine how emerging functional genomics technology can be applied to the R&D of TCM. (see D7.6 for details).

The team consists of:

- Olavi Pelkonen (University of Oulu, Finland)
- Markku Pasanen (University of Eastern Finland, Finland)
- John C. Lindon (Imperial College London, UK)
- Kelvin Chan (The University of Sydney and University of Western Sydney)
- Liping Zhao (Shanghai Jiao Tong University, China)
- Greer Deal (Global Regulatory Services, UK)
- Qihe Xu (King's College London, UK)
- Tai-Ping Fan (University of Cambridge, UK)

2 The 2nd Annual GP-TCM Meeting in Braga, Portugal (21-23 July 2011)

Below is a summary of what had been discussed. Readers who are interested in the full report of this meeting are directed to view the D10.4 report (the full name is "Quarterly Management and Science Meetings online or face-to-face") for full meeting details (which can only be accessed by the EC members).

2.1 WP objectives

To:

- establish a collaborative network towards formulating an easy-to-follow statement on the various regulatory frameworks, we will emphasise the synergies and highlight the differences with the aim of helping to establish a universal harmonised regulatory framework for botanicals;
- discuss the problems and solutions in developing Chinese *materia medica* as proprietary Chinese herbal medicines that meet the market-entry standard;
- place emphasis on the application of emerging functional genomics technology in this specific area;
- interface with regulatory agencies in the European Union (EMA = European Medicines Agency) and China (SFDA = State Food and Drug Administration);

- undertake analysis of the Botanical Guidelines in the United States (FDA = Food and Drug Administration) and equivalent guidelines in Australia (TGA = Therapeutic Goods Administration), Canada (NHPD = Natural Health Products Directorate) and other territories (e.g. SE Asia, India, Russia, Africa and South America);
- propose a universal harmonised registration strategy;
- search the literature beyond herbal products and summarise what has been reported on the application of “omics” in regulation of any drugs and then discuss its implications on regulation of complex herbal products (CHP) and Chinese herbal medicine (CHM).

2.2 WP7 activities

- Agreed to use Dantonic[®] (for human angina; Tasly Pharmaceuticals, China) and Phytopica[®] (for canine skin health; Phytopharm, UK) as case studies for regulatory issues; and two new formulae: PHY906 (for cancer chemotherapy; Yale University and Phytoceutica Inc) and *Fuzhen Huayu* (for liver fibrosis; Shanghai University of TCM) as examples of ‘omics in the regulation of drugs and the R&D of complex herbal products.
- Where specific CHM products are named in WP7 reports, it was agreed to include a disclaimer to make it clear that WP7 is not endorsing these or indeed any other products.
- Held three teleconferences (23rd December 2010, 25th March 2011 and 26th May 2011) to focus on additional WP7 deliverables.
- Discussed the implementation and enforcement of EU Herbal Directive 2004/24/EC on 1st May 2011.
- Contacted the UK Register of Chinese Herbal Medicine to discuss the impact of the UK Department of Health announcement on regulation of herbal practitioners in 2012.
- Dialogues with regulatory bodies in Europe, UK, United States, Canada and Australia: European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA), US Food & Drug Administration (FDA), Natural Health Products Directorate (NHPD) and Therapeutic Goods Administration (TGA), respectively.
- Agreed to initiate contacts with regulatory bodies in other countries/territories: China, India, Russia, Middle East, Africa and South America.
- Took active part in rewriting and resubmitting FP7 Marie Curie Initial Training Network Application: “*Training EU Scientists Towards Good Practice in Complex Herbal Product Research (TEST-GP)*”.
- Mr. Alan Koo and his colleagues at Pfizer Corporation Hong Kong have been working with Greer Deal, Kelvin Chan and Tai-Ping Fan to produce regulatory flowcharts and a comparative table in March 2011. These comprehensive data will be refined and form the basis of a review in the Special Issue of Journal of Ethnopharmacology.
- Submitted abstract on WP7’s first review “Global regulation of Chinese herbal medicines” to Dr. Qihe Xu, Guest Editor of the GP-TCM Special Issue of Journal of Ethnopharmacology.
- To fully address functional genomics aspects of WP7, Prof. Olavi Pelkonen was invited to lead the development of WP7’s second review on “Omics” in regulation of drugs and its implication on the R&D of complex herbal products.
- WP7 members organised and/or lectured in the following meetings: (1) Focused Conference: *Natural Products: Past and Future?* in the 16th IUPHAR World Congress on Basic & Clinical Pharmacology (Copenhagen; 17-23 July, 2010); (2) “Potent Substances: on the Boundaries of Food and Medicine” Symposium at Wellcome Trust



Centre for the History of Medicine at UCL (13-15 September, 2010); (3) the 3rd International Conference & Exposition on the Modernisation of Traditional Chinese Medicine in Chengdu, China (25-26 Nov., 2010); (4) Botanicals/Natural Products Stream at Genesis 2010 in London (9 Dec., 2010).

- Publication of article re GP-TCM in TOPRA's (The Organisation for Professionals in Regulatory Affairs) professional journal *Regulatory Rapporteur*, Vol 8, No 5, May 2011.
- Prepared 18-month reports of WP7 in November 2010.

2.3 WP7 plans for the final year:

- Joint Workshop for WP1, WP3 and WP7 with EDQM-TCM Working Group in Strasbourg on 29th September 2011.
- Close interactions with WP1, WP2, WP3, WP4, WP5 and WP6 to answer the WP7 central questions on D7.4, D7.5 and D7.6.
- Improve and complete flowcharts on (1) EU Traditional Herbal Medicine Products Marketing Authorisation; (2) Master flowchart of natural products in Europe; (3) Simplified registration procedure for traditional herbal medicinal products in EU with reference to Directive 2004/24/EC.
- Gather regulatory information from India, SE Asia, Russia, Africa and South America, to produce a comprehensive database.
- Draft, improve and submit two reviews for the GP-TCM Special Issue of Journal of Ethnopharmacology:
 - **Review 1:** "Global regulation of Chinese herbal medicines" [led by Dr. Tai-Ping Fan] to be submitted to the Coordinating Office in October 2011, **as part of D.7.5 and D7.7.**
 - **Review 2:** "Omics in regulation of drugs and its implication on the R&D of complex herbal products" [led by Prof. Olavi Pelkonen] to be submitted to the Coordinating Office in October 2011 – **this will form part of D.7.6 and D7.7.**

3 GP-TCM (WP1-WP3-WP7-WP10) Joint Workshop on “Quality control of CMM from a regulatory & toxicological Perspective” in Strasbourg, 29th Sept 2011

The attendees of the workshop were from WP1, WP3, WP7 and WP10, as well as experts from European Directorate for Quality Medicines & Healthcare (EDQM). The EDQM experts attended the meeting in their personal capacities and acted exclusively outside the scope of their official positions at EDQM. WP7 was represented by Kelvin Chan (Australia), Tai-Ping Fan (UK) and Alan Koo (Hong Kong).

Below is a summary of what had been discussed. Readers who are interested in the full report of this meeting are directed to view the D10.4 report (the full name is “Quarterly Management and Science Meetings online or face-to-face”) for full meeting details (which can only be accessed by the EC members).

3.1 Introduction & brief progress of WP7 by Tai-Ping Fan

- Tai-Ping Fan presented the work of WP7 which can be divided into 2 parts. The first part is the regulatory issues of TCM products in different countries including major countries/regions like EU, China, the US, Canada and Australia as well as countries that have not been mentioned by any previous reviews such as Brazil and some African countries. The second part is about how “Omics” technology can be applied for product registration in the future. Due to the time constraint, this issue had not been discussed in detail.
- It was updated that Greer Deal has been in touch with the MHRA and EMA and has been evaluating regulatory issues in the UK and EU.
- Alan Koo had a meeting with Prof. Guo De-an and Prof. Qian Zhongzhi in Shanghai and Beijing respectively to discuss the regulatory issues under China SFDA. A section on SFDA regulations on TCM is being developed.
- Tai-Ping Fan also reported that other sections of the review will be contributed by experts of the respective countries.
- Rudi Bauer suggested that the team may make reference to the article written by Prof. Dobos on the *Complementary Therapies in Medicine* in 2005. This article has been downloaded by Alan Koo and he will make reference to the sections related to regulatory issues of Chinese medicine.

3.2 Rounding up Session

- Tai-Ping Fan presented the case study of Dantonix and its registration categories in different countries in the world.
- Medical device under the EU regulations has been highlighted to be important to the JEP review.
- The key requirements of traditional herbal medicines, such as soft claims, are an area of interest.
- WP7 has engaged various members in writing and/or reviewing the regulatory section of the JEP review in their respective countries or regions. Details are as follows:
 - US: Jinhui Dou and Shaw Chen
 - China: Alan Koo, De-An Guo, Zhongzhi Qian
 - EU: Greer Deal, Tai-Ping Fan
 - Australia: Sam Wong, Kelvin Chan
 - Canada: William Jia
 - Africa: Pierre Duez
 - Brazil: Albert Dias
 - Japan: Zhao Zhongzhen
 - Korea: Yeong Shik Kim
 - Russia: Alexander Shikov



4 OUTCOME: 1ST WP7 MANUSCRIPT PUBLISHED IN JOURNAL OF ETHNOPHARMACOLOGY

Future development of global regulations of Chinese herbal products

As part of D.7.5 and D7.7, we submitted this manuscript on 18th December 2011. Following revisions, it was accepted for publication on 10th February 2012; and appeared online on 22nd March 2012. The paper version will be disseminated at the GP-TCM Final Conference and GP-TCM Congress. It can be cited as follows: [Future development of global regulations of Chinese herbal products](http://www.sciencedirect.com/science/article/pii/S0378874112001134), Fan TP, Deal G, Koo HL, Rees D, Sun H, Chen S, Dou JH, Makarov VG, Pozharitskaya ON, Shikov AN, Kim YS, Huang YT, Chang YS, Jia W, Dias A, Wong VC, Chan K. **J Ethnopharmacol.** 2012 140(3):568-86. This article is open access: <http://www.sciencedirect.com/science/article/pii/S0378874112001134>

The abstract of this manuscript is given below.

Abstract

Background and aim: GP-TCM is the first EU-funded Coordination Action consortium dedicated to traditional Chinese medicine (TCM) research. One of the key deliverables of the Work-Package 7 in GP-TCM was to investigate information of the existing requirements for registration of TCM products listed by global regulatory bodies. The paper aims to collate data and draw comparison of these regulations. Case studies are also presented to illustrate the problems involved in registering TCM products in different regions worldwide.

Materials and methods: A collaborative network task force was established during the early stage of the GP-TCM project and operated through e-mail exchanges, teleconferences and focused discussions at annual meetings. The task force involved coordinators, academics who are actively involved with R&D of Chinese herbal medicines, experts on monographic standards of Chinese materia medica, representatives from regulatory agencies, experts from industries in marketing Chinese medicines/ herbal medicines and natural products. The co-ordinators took turns to chair teleconferences, led discussions on specific issues at AGM discussion sessions, at joint workshops with other work-packages such as WP1 (quality issues), WP3 (toxicology issues) and WP6 (clinical trial issues). Collectively the authors were responsible for collating discussion outcomes and updating written information.

Results: A *global overview of regulations on herbal registration* has been compiled during the three years of the consortium. The regulatory requirements for registration of herbal products in the EU and China were compared, and this is extended to other regions/countries: Africa, Australia, Brazil, Canada, Japan, Russia, South Korea, Taiwan, and the United States. A wide variation of the regulations for the categories of herbal products exists: food (Functional Food, Novel Foods, dietary food for special medical purpose, food supplement); cosmetic, traditional herbal medicine products; herbal medicines for human use and veterinary use.

Conclusion: The regulatory issues for registration of herbal products are complicated among the countries and regions worldwide. The information summarized in the text is for reference only. Before taking any regulatory action, readers are advised to consult current official legislation and guidance and/or to seek appropriate professional advice. The lessons learnt from global regulation of TCM will provide valuable insights for regulation of other traditional medicine such as Ayurveda and Unani medicine, as well as other forms of indigenous medicine. The WHO is well placed to co-ordinate a consultation process with the aim of putting forward suggestions for harmonization to key regulatory agencies etc.