Review 述评

提高中草药随机对照试验的质量 Ⅲ:中草药的质量控制

梁士贤[1],卞兆祥[1],David MOHER[2],Simon DAGENAIS[2],李幼平[3],刘 良[1],吴泰相[3],缪江霞[4]
(1.香港浸会大学中医药学院,香港;2.加拿大东安大略省研究所儿童医院,加拿大 渥太华;3.四川大学华西医院中国循证医学中心,四川 成都 610041;4.香港中文大学中医学院,香港)

[摘要] 目的:通过对中草药临床随机对照试验中有关中草药质量控制的方法进行分析评价,探讨如何实施中草药临床试验的药物质量控制。方法:文献检索 2005 年 7 月前发表于 Cochrane 图书馆的中草药系统评价共 11 篇,包含 167 个中草药临床随机对照试验,实证分析中草药临床试验中有关中草药质量控制的方法。结果:在纳入分析的 167 个中草药临床随机对照试验中,所采用的中草药制剂类型共有 11 种,其中只有 1 个临床随机对照试验提及中药的质量控制方法。结论:在中草药临床随机对照试验过程中,中草药的质量控制是一个非常薄弱的环节。建议:在中草药临床随机对照试验过程中,必须提高中草药的质量控制意识及建立中草药质量控制的技术平台,整合包括中药材生产质量管理规范(Good Agricultural Practice, GAP)、药物生产质量管理规范(Good Manufacturing Practice, GMP)、药物临床试验质量管理规范(Good Clinical Practice, GCP)以及中药指纹图谱等技术,建立系统控制临床试验药物的质量控制体系。

[关键词] 随机对照试验; 中草药; 质量控制
[中图分类号] R-3 [文献标识码] A [文章编号] 1672-1977(2006)03-0225-08

Improving the quality of randomized controlled trials in Chinese herbal medicine, part Ⅲ: quality control of Chinese herbal medicine used in randomized controlled trials

Kelvin S.Y. LEUNG[1], Zhao-Xiang BIAN[1], David MOHER[2], Simon DAGENAIS[2], You-Ping LI[3], Liang LIU[4], Tai-Xiang WU[3], Jiang-Xia MIAO[4]
(1. School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, China; 2. Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada; 3. Department of Clinical Epidemiology, Chinese Evidence-Based Medicine Centre, West China Hospital, Sichuan University, Chengdu, Sichuan Province 610041, China; 4. School of Chinese Medicine, Chinese University of Hong Kong, Hong Kong SAR, China)

ABSTRACT Objective: To discuss quality control of Chinese herbal medicine (CHM) in randomized controlled trials (RCTs), and to provide suggestions for improving this aspect in future clinical study in this therapeutic area. Methods: A search of the Cochrane Library was conducted to identify RCTs of CHM. Quality control information reported in those RCTs was then assessed independently. Results: The search yielded a total of 167 RCTs of CHM for a variety of conditions. A total of 11 CHM preparations were used in those RCTs. Only one trial discussed quality control of the CHM interventions used. Issues affecting the safety and efficacy of CHM products used in RCTs were discussed including standardization of raw herbal materials, processing methods, screening for product contamination, and effects of combination products. Conclusion: The overall quality of reporting of RCTs of CHM was poor, reflecting the need for improvements in reporting future clinical trials in this area. Recommendations: To improve quality control of CHM used in RCTs in future, we recommend developing and implementing guidelines such as Good Agricultural Practice (GAP) for Chinese

Correspondence to: Zhao-Xiang BIAN, PhD, Associate Professor. E-mail: bzxiang@hkbu.edu.hk

crude drugs, and current Good Manufacturing Practice (GMP) specific to CHM products . Chemical analyses of individual herbs of CHM and combination products are also recommended to provide reference standards for quality control .

KEY WORDS randomized controlled trial; Chinese herbal medicine; quality control

Zhong Xi Yi Jie He Xue Bao/ J Chin Integr Med, 2006, 4(3): 225-232 www .jcimjournal .com

1 INTRODUCTION

In this third part of our four-part series on assessing the methodological quality of randomized controlled trials (RCTs) in Chinese herbal medicine (CHM), we discuss the issue of quality control of CHM .

The primary purpose of RCTs is to investigate the efficacy and safety of specific interventions to improve health care . To achieve this aim, RCTs must adhere to several basic principles, one of which is to ensure consistency in the intervention being studied . Thus all participants in one treatment arm of the trial should be given exactly the same intervention in terms of product identity, purity, dosage, formulation, route of administration, treatment frequency, treatment duration, etc . In order to standardize these elements of the intervention, quality control must be performed on the CHM product used in the trial . Without quality control, investigators cannot affirm that the intervention was the same within each treatment arm, threatening both the internal and external validity of the trial . Failure to perform quality control on the CHM product examined in a RCT also makes it difficult for clinicians to emulate the interventions used in a trial reporting positive clinical results . Other researchers wishing to repeat the results of a trial may be unable to do so if quality control of the CHM product was not performed and reported .

An additional concern regarding quality control of the interventions used in RCTs of CHM is that of participant safety . Numerous studies have now identified toxic substances in CHM and other herbal products, including the presence of heavy metals, herbicides, pesticides, microorganisms, mycotoxins, insects, pharmaceuticals, and other undeclared herbal constituents[1,2] . Although the effects of these products on the efficacy and safety of CHM interventions are unknown, quality control is essential for detecting their presence prior to administration in RCTs .

Challenge exists in integrating quality control with CHM . CHM practitioners typically prescribe CHM products tailored to individual patients and indications . The prescription often contains multiple herbs, each of which may contain several active ingredients (known and unknown) . Such herbal mixtures are often prepared from bulk herbal ingredients by practitioners in their clinics on hand or by patients themselves . A number of preparation forms (e .g . decoction, tablet, powder, granule, etc .) may also be used according to the properties of particular herbal ingredients, indications, or practitioner preference . Few remedies in CHM are standardized or prepared in advance, except the licensed herbal products . Furthermore, different countries and areas have different criteria for registration and approval of herbal products, thus with different quality standards . However, interventions should be standardized for all participants in RCTs . Thus quality control for products used in RCTs should be performed . The primary objective of this study is to assess the current status of quality control in studies of CHM by conducting a focused systematic review of this issue in relevant RCTs . The secondary objective was to provide recommendations for improving this situation in the future .

2 MATERIALS AND METHODS

2 .1 Identification of RCTs of CHM

The search strategy used in this study was reported previously[3] . Briefly, “ Chinese herbal medicine ” was used as a search term in the Cochrane Library, a total of 11 reviews were included in the search, excluding 14 reviews that did not relate to CHM . The 11 reviews reported on a total of 167 RCTs , which were identified and selected for further review . Detailed information about these 11 reviews can be found in part I of this series of articles[3] .

2 .2 Data extraction and analysis

Two observers (Zhao-Xiang Bian and Jiang-Xia Miao) independently reviewed the RCTs to determine the identity, preparation form, and quality control of the CHM interventions reported . Disagreements were resolved by consensus and further review of the articles . Data from the two reviewers

were entered into an Excel file for analysis .

3 RESULTS

In the 167 RCTs reviewed, 11 different preparation forms of CHM products were used . Table 1 gave the definitions of these preparation forms . The preparation forms used in the trials reviewed included: (1) decoction; (2) injection; (3) capsule; (4) oral liquid; (5) pill; (6) tablet; (7) granule; (8) sachet; (9) tea; (10) powder; (11) syrup . The reasons for selecting a particular preparation form of CHM product were rarely discussed in the RCTs reviewed . The most common preparation form for CHM was decoction, and reported in 76 (42 .9%) of 167 RCTs, while the least common preparation form was syrup, used in only one RCT (see Table 2) .

Table 1 Definitions of preparation forms of CHM

Preparation form	Definition
Capsule	Herbs inside hard or soft gelatin envelope
Decoction	Liquid extract made by slowly boiling herbs in water
Granule	Raw herb powder or herb extract compressed into solid form
Injection	Administration of extracted herbs with a needle, usually subcutaneously, intramuscularly, or intravenously
Oral liquid	Herbs soaked in solvent such as alcohol to extract active ingredient(s), then distilled to reduce solvent
Pill	Solid round form of herbs ground into fine powder and mixed with liquid and binding agent such as honey, paste, or flour
Powder	Herbs ground into fine dry powder
Sachet	Dried or powdered herbs prepared in individual bags as a single dose administration, added to water prior to consumption
Syrup	Herbs mixed with thick liquid such as honey, sugar, or glycerin
Tablet	Herbs mixed with excipients and pressed into solid form
Tea	Herbs steeped in hot water

Table 2 Preparation forms of CHM in 167 RCTs

Preparation form of CHM	Trials reported (%)
Decoction	76 (42 .9)
Injection	34 (19 .2)
Capsule	22 (12 .4)
Oral liquid	12 (6 .8)
Pill	8 (4 .5)
Tablet	8 (4 .5)
Granule	6 (3 .4)
Sachet	4 (2 .3)
Tea	3 (1 .7)
Powder	2 (1 .1)
Syrup	1 (0 .6)
Unclear	1 (0 .6)
Total	177 (100)

Note: Multiple preparation forms were used in certain RCTs .

It was surprising to note that none but one of all RCTs reviewed discussed the issue of quality control of the CHM products used in their studies . The main methods used for quality control involve[4]: (1) getting top-grade ingredients from a single supplier of medicinal herbs; (2) preparing herbs with methods described in the *Chinese Pharmacopoeia*; (3) testing heavy metal content and possible microbial contaminants; (4) using thin-layer chromatography to“ fingerprint ”each batch of every constituent, rejecting them if they differ substantially from the reference material; (5) having one drug company prepare the final products . But there were no details or definitions provided about top-grade ingredients and procedures for preparing herbs, which herbs should follow the procedures of the *Chinese Pharmacopoeia*[5] and which ingredients should be targeted for chromatography“ fingerprinting ” . Although 54 of 167 trials mentioned that CHM products were from specific pharmaceutical factories, it was not specified whether quality control was performed by the manufacturer .

4 DISCUSSION

The main findings from this study were that in RCTs of CHM: (1) 11 different preparation forms of CHM were commonly used; (2) none but one of the RCTs mentioned quality control for the CHM interventions used . These findings highlight the need for establishing a quality control system for CHM in RCTs .

4 .1 Why is the quality control of CHM for RCTs necessary

This situation contrasts sharply with pharmaceutical RCTs conducted in countries adhering to guidelines determined by the International Conference on Harmonization (ICH) . These guidelines call for extensive quality control measures in studies approved by regulatory agencies [e .g . United States Food and Drug Administration (FDA)], where requirements for quality control are

described in detail in federal regulations known as current Good Manufacturing Practice (GMP) (e .g . 21 CFR 210)[6], and address issues such as active ingredient identity, purity, potency, as well as final product sterility, stability, and numerous other criteria . This ensures that all participants within a regulated study receive comparable intervention, and participants are protected from contaminants in the products studied, and that results from different studies using the same intervention may be compared . Recently, the FDA issued a "Guidance for Industry Botanical Drug Products"[7], to address some of the quality control issues specific to herbal products such as those used in CHM . For example, this document discusses the importance of providing information regarding the harvest location, growth conditions, stage of plant growth at harvest, harvest time, collection, washing, drying, and preservation procedures, and handling, transportation, and storage conditions . Some of these issues are discussed below .

In a healing system such as CHM that has been utilized for thousands of years, many aspects of practice have evolved over generations and are maintained due to tradition . This is an important challenge to overcome when discussing improvements to quality control of interventions in CHM, and is highlighted by the issue of individualized therapy . Practitioners of CHM have long used raw medicinal plants to prepare customized treatments for their patients based on several factors, including clinical presentation, patient constitution, and practitioner training . In addition to these variables, a particular CHM intervention may be further customized according to its preparation form (e .g . decoction, tea, etc .) and disease progression with treatment (e .g . improved, with no change, etc .) . But for RCTs, one of the basic requirements is to standardize every element of the interventions to prevent biasing the results . From our review, only one trial mentioned quality control of herbs . And although 54 trials used factory-made CHM products, there was no indication of quality control measures undertaken by the manufacturers . This represents an important barrier to implementing quality control for each CHM product in RCTs . Numerous other elements must also be considered when discussing the implementation of quality control of CHM products . These must begin with standardization of the raw herbal ingredients used to prepare the CHM products and extend to preparation of the final CHM products . A few of these aspects are briefly discussed below .

4 .2 Elements related with the quality control of CHM in clinical trial

4 .2 .1 Species of herbs

A particular herb used in CHM may have different subspecies . For example, *Radix glycyrrhizae* is used in Zemaphyte for atopic dermatitis[4] . But there are two sources for this herb, including the dried root and rhizome of *Glycyrrhiza uralensis* Fisch ., *Glycyrrhiza inflate* Bat . or *Glycyrrhiza glabra* L .[8] . Although the plants all contain the active ingredients dycyrrhizin and glycyrrhetinic acid, their ratios are different and this may affect their functions . For quality control, it is therefore necessary to specify the subspecies of the herbs used in CHM to standardize the identity and content of their active ingredients .

4 .2 .2 Location of production

The location of production for the raw herbal medicinal plants may affect their quality . Practitioners have traditionally selected herbs from specific producing areas, such as *Flos Carthami* from Tibet or *Flos Chrysanthemi* from Zhejiang province, where these herbs are considered of high quality . There is weak evidence to date to support this tradition . One study reported that the content of the active ingredient saponin was higher in *K . Scoparia* fruits produced in Bozhou, Anhui province, than those from Baoding, Hebei province, and Heilongjiang province[9] . Further research may clarify this aspect of CHM . For quality control, the location of production needs to be standardized for a particular CHM product .

4 .2 .3 Collection of herbs

Different parts of a medicinal plant may have different functions . For example, ginseng leaf is the dried leaf of *Panax ginseng* C . A . Mey . (*Fam . Araliaceae*), with the action of nourishing qi and lung, expelling summer-heat and promoting fluid secretion . *Radix ginseng* is the dried root of *Panax ginseng* C . A . Mey . (*Fam . Araliaceae*), with the action of reinforcing the vital energy, remedying collapse and restoring the normal pulse, benefiting spleen and lung, promoting the production of body fluid and calming the nerves . Thus it is necessary to state the part of the medicinal plants used in the CHM product .

4 .2 .4 Processing method

According to CHM theories, even herbs of the same subspecies grown in the same location may exhibit different functions when prepared according to different processing methods, enhancing or weake-

ning certain therapeutic effects . For example, raw *Radix rehmanniae* is mainly used to purge heat, cool the blood, and promote the generation of body fluids in CHM[8] . However, its processed counterpart *Radix rehmanniae preparata* is considered effective for enriching rather than cooling the blood . Similarly, *Radix et rhizoma rhei* is used to cause catharsis, purge heat, reduce heat in blood, counteract toxicity, eliminate blood stasis, and to stimulate menstrual discharge . If it is processed with wine, its function will focus on removing toxic heat from the blood in the upper portion of the body; while carbonized, it will focus on reducing heat in blood, removing blood stasis, and arresting bleeding . This may be due to different processing methods affecting the chemical structure or activity of active compounds in herbs, such as water, alcohol, acetone or combination extraction methods, though research is lacking in this area of CHM[9] . Similarly, the final preparation form resulting from the processing method may affect the use of CHM in RCTs . For example, steeping time of tea will affect strength, whereas prescribing large quantities of tablets taken multiple times per day may reduce compliance . For quality control, investigators must therefore weigh the advantages and disadvantages of various preparation forms when selecting the CHM products to use in their studies .

4 .2 .5 Screening for contamination of CHM products

The issue of contamination in CHM interventions is crucial to the discussion of quality control . Heavy metals, including mercury, lead, arsenic, copper, and cadmium, have the potential for acute toxicity with exposure to large doses, in addition to chronic toxicity with prolonged or repeated exposure to lower doses . Contamination is likely associated with the environmental conditions in which the herbal plants are grown, such as soil that naturally contains high levels of heavy metals, fields located near sources of industrial pollution, etc . Preparation of the raw herbs with utensils, cookware, or other manufacturing equipment containing heavy metals may also be responsible for contamination . Such sources of heavy metals must be investigated and minimized[10] .

Pesticides are among the most widely used chemicals in the world, and also among the most dangerous contaminants to human health . Currently over 2 .5 million tons of such chemicals costing over 30 billion US dollars are applied during cultivation of crops, vegetables, herbs, etc ., for pest control virtually in every country over the world . During the preceding century most of the herbs used in CHM were still collected in the wild using careful cultivation techniques and no pesticides . However, certain cultivators are now using large quantities of pesticides to minimize potential crop loss due to pests . Exposure to pesticide residues can result in many different adverse health consequences, from acute problems such as skin rashes and asthma attacks, to chronic problems including emphysema and cancer[11] . Regulations must therefore be developed to minimize the contamination of pesticides in CHM products .

Mycotoxins refer to the toxic metabolites generated by molds and fungi, which may grow freely in cereals, sugars, and protein-rich biological materials .Herbs used in CHM with these properties (e .g . *Angelicae sinensis*, *Choxiang*, etc .) will provide favorable conditions for the growth of molds and fungi and hence pose a risk of mycotoxin contamination . This potential may be further increased due to improper storage of herbs at elevated temperatures or humidity levels facilitating rapid growth of mycotoxins . Other microbial contaminants, including *Escherichia coli* and *Salmonella sp* . may also be introduced inadvertently as practitioners or manufacturers prepare CHM products in non-sterile conditions . For quality control, the sterility of the CHM products should be tested .

4 .2 .6 Combination products

Many CHM products contain multiple herbs and other ingredients that are believed to enhance their desired therapeutic effects and work synergistically . Preparing these combination products presents a challenge since individual ingredients may require different processing methods to achieve the desired effects . And also different preparation processing for one fixed prescription may affect the quality of final products used in clinical trials, thus potentially affecting the results . Thus, the effects of combination products must be further investigated . And reports of trials should give detailed information about selection of such formation .

4 .3 How can we control the quality of CHM products for clinical trials

The quality control of CHM for clinical trial should be a systematic procedure . The key steps required to achieve these goals are discussed below .

The first step will be to standardize important elements of the herbs used in CHM, such as the exact species and subspecies, ideal growing location, environmental conditions, harvesting methods, etc .,

to ensure the quality of the raw materials produced from the herbs . In the People's Republic of China, the government has already implemented guidelines for the cultivation of CHM materials with reference to the origin of growth for over 70 medicinal plants in five major provinces . These guidelines discuss issues of seed selection and storage, site selection for cultivation base, fertilizer application, water sources and usage, pesticides monitoring, harvesting practices including packaging, storage, field sanitation and product transport . The Good Agricultural Practice (GAP) for Chinese crude drug guidelines will be essential towards achieving this objective .

The second step will be to standardize the processing method for the raw materials produced from herbs according to GAP guidelines . The need for this was highlighted in the updated *Chinese Pharmacopoeid*[8] . That text discussed 75 commonly used CHM products containing materials processed made from herbs . Over 90% of these products did not specify a standard method of processing[8] . To standardize processing of CHM, a committee of experts must be established to develop standard operating procedures (SOPs) outlining specific steps to be followed during the processing of herbs and raw materials used in CHM . These SOPs should then be regularly updated as new data become available .

The third step will be to standardize the preparation procedure of the final products, whether they may be pills, tablets, powders, granules, oral liquids, teas, syrups, capsules, etc . This has already been implemented for licensed herbal products, for which the government has already implemented GMP guidance for CHM products in mainland China . This guidance established a minimum national requirement for CHM products, from selection of raw materials to the quality control system for the final products . To ensure their continuing relevance, these GMP guidelines must be continually updated and referred to as current GMP (CGMP) to identify them as dynamic . Without such guidelines and standardization of the preparation procedure of the final product used in RCTs of CHM, the internal and external validity of results from such studies will be questioned . Another challenge posed by the GMP guidelines is that they only apply to the small fraction of CHM products that have sought regulatory approval . Extending their scope to include all CHM products will not likely be feasible .

The fourth step will be to qualitatively and/ or quantitatively evaluate the quality of CHM based on one or more selected biomarkers . Some of the important distinctions of CHM products are that they made from herbs rather than synthesized in a laboratory under controlled conditions, that use is based on a long history of clinical use rather than basic science research, and that herbs are administered both singly and in combination . This makes identification of the active ingredient(s) - the starting point for standardization - very challenging without devoting enormous resources to this endeavor . An alternative would be to select one or several chemical components or pharmacologically active components from the CHM product for further study . These compounds would then be the subject of the guidelines to qualitatively and/ or quantitatively evaluate their identity, purity, potency, etc . By focusing the guidelines on the active ingredients present in the final product, minor variations present in the raw materials and processing methods that do not affect the final active ingredients would be less crucial . A pitfall to this approach is that misidentification of the active ingredient(s) could result in CHM products that are no longer efficacious . In this regard, it is necessary to determine most of the chemical constituents of herbs used in CHM in order to ensure the reliability and repeatability of pharmacological and clinical application, to understand the bioactivities and possible side effects of active compounds, and to enhance product quality[12,13] .

In fact, the concept of phyto-equivalence was developed in order to ensure consistency of CHM products[14] . According to this concept, a chemical profile, such as a chromatographic fingerprint for CHM or its product, should be constructed and used as the reference by which the quality of CHM products may be measured . The combination of fingerprints from both raw herbal materials and final products would be required to validate each step of the processing method . Spectroscopic or chromatographic methods are commonly used techniques to examine the chemical fingerprints of various compounds using the fundamental attributions of“ integrity ”, “ fuzziness ”, “ sameness ”, and“ differences ” so as to chemically represent the CHM materials under investigation[12] . With the use of chromatographic fingerprints, authentication and identification of CHM materials and their products can be achieved (“ integrity ”) even if the identity and/ or content of the chemically characteristic constituents are not ascertained in the CHM materials . The chromatographic fingerprints can illustrate both the

“sameness” and “differences” between various samples successfully and achieve the goal of quality control. However, establishing and maintaining reliable chromatographic fingerprints that represent pharmacologically active and chemically characteristic components of CHM products is not a trivial task and will require considerable resources.

We believe that international guidelines similar in intent to those developed by the ICH for pharmaceutical products are the best way to implement quality control not only in RCTs but also for mass marketed, commercially available CHM products. Developing such guidelines will be a timely endeavor requiring the participation of numerous stakeholders including CHM practitioners, researchers, scientists, and policy makers from several countries. The goal of these guidelines—whether voluntary or mandatory—will be to standardize CHM products with quality control measures to ensure their consistency and safety.

5 LIMITATIONS

The primary limitation of this review is that results regarding the quality control in RCTs of CHM only apply to the 167 RCTs selected. It is therefore possible that the sample of RCTs selected for this study is not representative of all RCTs of CHM, thus limits the generalization of our results.

6 CONCLUSION

The issue of quality control of the interventions used in RCTs of CHM has largely been ignored despite its importance in establishing the internal and external validity of clinical studies, as well as their conclusions regarding the safety and efficacy of the treatments examined. In order to improve this situation in future RCTs of CHM, it is necessary to establish and enforce guidelines governing each step of the preparation process for CHM products. Such guidelines must standardize quality control of raw materials, processing methods, and final products in CHM.

7 RECOMMENDATIONS

Quality control of CHM is a systematic procedure. From the raw material to the final products given to the participants in clinical trials, we recommend the following steps. (1) To control the quality of the raw materials, including species of herbal plants, production area, and contamination with heavy metals, pesticide residues, mycotoxin and microbial contents. And we recommend selecting the raw materials from GAP-compliant farms. (2) To control the quality of processing method for herbal plants used in the prescription with standard operation procedures. (3) To control the quality of preparation procedure for whole prescription, with optimized procedures used throughout the preparation process. (4) To ensure the consistency of batch preparation of CHM materials, using procedures such as chemical fingerprinting.

For the final preparation of the CHM product, decoction is not a good formation for use in clinical trials due to difficulties in quality control. Formations such as granule, powder, capsule, tablet and pill are recommended.

Development and implementation of guidelines such as the GAP for Chinese Crude Drugs, and current GMP specific to CHM products will help standardize the quality of CHM used in RCTs. These guidelines should include raw material specifications (herb subspecies, producing location, environmental conditions, etc.), processing methods (raw material quantities, preparation equipment, etc.), and testing of final product (detection about heavy metals, pesticide residues, mycotoxin, microbial contents, etc.), and these guidelines will finally benefit the quality of RCTs.

As for the publication of RCT results with CHM, the following information should be provided: (1) Name of the CHM, including synonyms, chemical names, etc; (2) Raw material species and subspecies, productionlocation, desired environmental conditions, etc; (3) Description of the CHM, including appearance, color, texture, gross internal structures, odor, taste, etc; (4) Identification—morphological and microscopic identification; (5) Processing methods—targeted at the standard procedure for processing; (6) Tests (to safeguard against hazardous contamination and other abnormality)—heavy metals, pesticide residues, microbial levels, mycotoxins, drug adulterants. Permissible limits should be set for each of the above parameters; (7) Chemical fingerprint—targeted at entire representative chemical profiles, if applicable.

REFERENCES

1 Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J Intern Med, 2002, 252(2): 107-113.

2 Ernst E. Toxic heavy metals and undeclared drugs in Asian herbal medicines. Trends Pharmacol Sci, 2002, 23(3): 136-139.

3 Bian ZX, Li YP, Moher D, *et al* . Improving the quality of randomized controlled trials in Chinese herbal medicine, Part Ⅰ: clinical trial design and methodology . Zhong Xi Yi Jie He Xue Bao, 2006, 4(2): 120-129 .
4 Sheehan MP, Rustin MHA, Atherton DJ, *et al* . Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis . Lancet, 1992, 340(8810): 13-17 .
5 Pharmacopoeia Commission of the Ministry of Public Health of PRC . Chinese Pharmacopoeia . Beijing: Chemical Industry Press, 1988 .
6 Code of Federal Regulations, Title 21, Volume 4, Part 210, Revised April 1, 2005 . http:// www .gpoaccess . gov/ cfr/ index .html .
7 U .S . Department of Health and Human Service Food and Drug Administration, Center for Drug Evaluation and Research (CDER) . Guidance for industry botanical drug products . http:// www .fda .gov/ cder/ guidance/ 4592fnl .htm . February, 2006 .
8 Pharmacopoeia Commission of the Ministry of Public Health of PRC . Chinese Pharmacopoeia . 5th ed . Beijing: Chemical Industry Press, 2005 .55-56, 132 .
9 Liu GY, Yan X, Li W, *et al* . Influence of different processing technique on the contents and analgesic effect in Radix Paeoniae Alba . Pharm J Chin PLA, 2005, 21 (3): 167-169, 185 .
10 Chan TY, Chan JC, Tomlinson B, *et al* . Chinese herbal medicines revisited: a Hong Kong perspective . Lancet, 1993, 342(8886-8887): 1532-1534 .
11 Calvert GM, Plate DK, Das R, *et al* . Acute occupational pesticide-related illness in the US, 1998-1999: Surveillance findings from the SENSOR-pesticides program . Am J Ind Med, 2004, 45(1): 14-23 .
12 Raven PH, Evert RF, Eichhorn SE . Biology of Plants . 6th ed . New York: W .H . Freeman and Company, 1999 .
13 Tyler VE . Phytomedicines: Back to the future . J Nat Prod, 1999, 62(11): 1589-1592 .
14 Welsh WJ, Lin W, Tersigni SH, *et al* . Pharmaceutical fingerprinting: evaluation of neural networks and chemometric techniques for distinguishing among same-product manufacturers . Anal Chem, 1996, 68 (19): 3473-3482 .

Received 2005-12-07

“第二届亚太地区男科学论坛”会讯

论坛基本信息

主办单位:亚洲男科学会 《亚洲男科学杂志》
中国科学院上海药物研究所

主　　题:关爱男性生殖健康:从科学研究到公众参与

时间地点:2006 年 10 月 26-30 日 上海

主　　席:王一飞(亚洲男科学会执行主席,中华医学会生殖分会主任委员,亚洲男科学杂志主编)

报名参会必备信息

参会注册网站:
http:www .conference .ac .cn/ APFA .htm

摘要递交网址:
http:// 2apfa .asiaandro .com/ login .asp

会议联络方式:
电话:(021)54922824
传真:(021)54922825
E-mail: apfa@sibs .ac .cn

9 个学术专题

1 .男性生殖健康:全球及地区展望;
2 .后基因组时代的男科学;
3 .男性节育:现状及新途径;
4 .男性不育与辅助生殖技术;
5 .中老年男子的生殖内分泌问题;
6 .前列腺与男性健康;
7 .男性性功能的基础与临床;
8 .生殖道感染,HIV 及爱滋病;
9 .传统医学与男科学。

论坛特色

1 .参会代表将获得 2006 年国家级继续医学教育Ⅰ类学分 20 分;
2 .英文摘要将刊登在《亚洲男科学杂志》增刊上;
3 .开辟一个“中国专场”,方便国内学者无语言障碍交流;
4 .开设“男子不育诊疗规范化培训班”(暂定名);
5 .主要发言配同声翻译;
6 .面向公众的大型免费男性生殖健康咨询活动;
7 .同步举办“男科医药产品展览会”,展示国内外男科学领域的先进仪器和药品。

特别提醒:
注册费优惠截止日:2006 年 5 月 30 日
国内代表:1500 元(优惠价)/ 1800 元(非优惠价);**在读学生**:900 元(优惠价)/ 1000 元(非优惠价)
摘要投递截止日:2006 年 6 月 30 日

论坛第二轮通知已发布,公布了论坛主要议程和学术报告主题,敬请联系会务组或访问会议网站获得第二轮通知!