· Reviews ·

Ensuring the Compliance of Raw Herbal Materials stemmed from China with *European Good Agricultural and Collection Practice*

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Abstract: A "simplified" European procedure now allows the registration of traditional herbal medicines as medicinal products even without the support of clinical data. This procedure entails the requirement that those products comply with *European Good Manufacturing Practice* for medicinal products, which in turn implies that the raw herbal materials comply with the European guidelines for *Good Agricultural and Collection Practice*. On the basis of a comparison between *European Good Agricultural and Collection Practice* and *China Good Agricultural Practice*, as well as direct observation made at sites in China, we issue some recommendations to facilitate good communication between the Chinese producer and European pharmaceutical customer, with a view to ensure full compliance with European expectations.

Key words: *China Good Agricultural Practice*; *Europe Good Agricultural Practice*; *Good Agricultural and Collection Practice*; medicinal products; raw herbal materials

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European "simplified" procedure for traditional herbal medicines and requirement for compliance with *Good Agricultural and Collection Practice*

On March 31, 2004, the European Union issued the "Directive 2004/24/EC of the European Parliament and of the Council" (European Parliament and Council, 2004) to offer a reasonably convenient way to register traditional herbal medicines as medicinal (drug) products. A "simplified" procedure is being put in place to allow applicants to demonstrate the efficacy and safety of such products on the basis of evidence that does not necessarily involve clinical trials. Requirements as to product quality would be the same as for any other types of medicinal products, though. Those requirements include compliance with the *European Guide for Good Manufacturing Practice* (Eudralex Volume 4), which, in its Annex Seven (European Commission, 2008), requires the compliance of the cultivation, collection, harvesting, cutting, and drying operations of raw herbal materials with the *European Guidelines for Good Agriculture and Collection Practice* (GACP) (Committee on Herbal Medicinal Products, 2005).

Raw herbal materials purchased from sources outside the European Union are naturally expected to comply with those rules just as well as materials of European origin, but it might be expected that plantations in China would not find it easy to keep up-to-date with European requirements. China has its own set of *Good Agricultural Practice* (GAP) guidelines (State Drug Administration, 2002), which bears many similarities and also some divergences with European GACP. Those divergences have the potential to affect the compliance status of the plantations.

Awareness of those divergences is therefore essential to determine the respective responsibilities of producer and purchaser, and ensure that no misunderstanding leading to non-compliance would occur. To that end, we established correspondences between the two sets of guidelines, with a greater focus on parts that are defined as critical by the Chinese State Food and Drug

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Administration (SFDA) Inspectorate (State Food and Drug Administration, 2003), and parts of the European guidelines that appear to reflect a higher degree of concern.

In addition to this comparison study, we also considered the observations we made during the inspections of two plantations, one processing site, twenty trading companies for raw herbal materials, and two for seeds in the region of Anguo, Hebei Province in March, 2009.

European GACP

The European GACP Guide came into effect on August 1, 2006. The chief aim of that document is to ensure consumers' safety. The introductory remarks underline two concepts at the core of current European thinking on pharmaceutical quality assurance: criticality and the paradigm that "quality must be built into the product" due to the natural limitations of the approach that exclusively consists in "testing quality in the product". The production and primary processing of the herbal materials are deemed to have a direct influence on the quality of the extract or preparation made from herbal materials. They should therefore be the object of critical focus. The impossibility to fully test the quality of the material calls for control over production conditions.

For those reasons, contamination control is the foremost concern. Contaminants might come in the form of microbes, pesticides, herbicides, fertilizers, fumigating agents, and heavy metals, etc. Their sources might be polluted soil, water, and equipment. European GACP requires proper control of contaminants both during production and in the product.

Another area of focus is the potential presence of adulterants, and the botanical identification of the species and varieties of collected herbal materials and seeds. European perception of the safety of traditional herbal medicinal products has been deeply affected by large-scale accidents, particularly the confusion between *Stephania tetandra* S. Moore (*Fenfangji*) and *Aristolochia fangchi* Y. C. Wu ex L. D. Chow et S. M. Hwang (*Guangfangji*) that seriously harmed patients in Belgium in 1991 (Nortier and Vanherweghem, 2002) and France in 2000 (Nortier *et al*, 2000). Unsurprisingly, the GACP text insists that "the presence of different species, varieties or different plant parts has to be controlled during the entire production process, and such adulteration should be avoided" (State Drug Administration, 2002).

Chinese GAP

The current version of the *Chinese GAP Guidelines* was released by SFDA on April 17, 2002 (State Drug Administration, 2002). On September 19, 2003, the SFDA published a list of 104 Inspection Criteria of GACP, out of which 19 criteria are considered to be critical (State Food and Drug Administration, 2003). Not complying with one critical criterion and/or more that 20% of non-critical criteria would disqualify the applicant for GAP certification.

The scope of the *Chinese GAP Guidelines* includes the cultivation and collection of plant and animal species and varieties used for medicinal purposes. The text shows a particular concern for the sustainable use of natural resources.

The quality of soil, air, and water is emphasized. Fertilizers should preferably be organic, to the exception of human waste. Cultivation and harvest conditions receive much attention, thus concurring with the paradigm of "building quality into the product."

Similarities and divergences

Both the European and Chinese guidelines share an emphasis on cultivation conditions and the protection of endangered species. The scope, aims, and focus of the two sets of rules are compared in Table 1. The contents in more detail are compared in Table 2. Overall, Chinese GAP can be considered to be equivalent to European GACP. This is the most obvious case with respects to cross-contamination control and traceability of materials.

Among the differences of note is the fact that, while the Chinese rules require the identification of the plant material, the European text more exactly requires the control of the presence of adulterants, e.g. the proper identification of the totality of the material. Another divergence is that fumigating agents are not mentioned in the Chinese text. Also, the European GACP expects that quality agreements be concluded between producer and responsible buyer.

As Table 1 makes obvious, the *Chinese GAP Guidelines* adds animal substances to their scope. This difference is the result of the relative prevalence of

Table 1 Comparison on the scope, aims, and focus between European GACP and Chinese GAP

Items	European GACP	Chinese GAP
scope	agricultural production and collection of medicinal plants/herbal substances	production and quality management of Chinese crude drugs from plant or animal origin
aims	ensuring consumers' safety by establishing appropriate quality standards	regulating the production of Chinese crude drugs, ensuring their quality, and facilitating the standardization and modernization of traditional Chinese medicines
focus	hygienic production careful handling of herbal substances reduction of contamination to a minimum botanical identification of herbal material	control on pesticide residues, heavy metals, and microbial contamination botanical identification of herbal species and varieties sustainable use of natural resources

using plant material in European traditional medicine. European importers of crude drugs of animal origin can therefore justify their use of Chinese GAP as reference standard.

Also of note is the fact that the Chinese guidelines, if read literally, restrict their scope to "Chinese" crude drugs. This apparent restriction is no more than the consequence of the common use of a Chinese phrase (*Zhongyao*) that confuses drugs from plant/animal origin with "Chinese medicines" — in contrast with "Western medicines" (*Xiyao*), which actually designate drugs manufactured by chemical synthesis. All crude natural drugs marketed in China should comply with Chinese guidelines for GAP no matter whether they can be called Chinese or not. This is sufficiently demonstrated by the following definition of "Chinese crude drugs" provided in Article 55 of the Chinese guidelines: "The raw medicinal materials from the parts of medicinal plants or animals, which are collected and primarily processed" (State Drug Administration, 2002). Materials unrelated to traditional Chinese medicine (TCM), or obtained from non-Chinese sources, are not excluded from such definition. Comparison between European GACP and Chinese GAP is shown in Table 2.

As shown in Table 2, the European expectations regarding the conditions of cultivation and processing must, as should be expected in view of the international nature of the European Union, be met in ways that take regional or national standards for water, soil, and air into account.

The Chinese National Standards for water (National Standards of the People's Republic of China, 1992) and soil (National Standards of the People's Republic of China, 1995) quality are appropriate. Compliance with Directive 2008/50/EC on ambient air quality (European Parliament and Council, 2008) is not expected for the cultivation of herbal medicinal products, as it rather aims to protect human health from polluted inhaled air. The European purchaser should nevertheless be aware that air pollution by heavy metals is less tightly controlled in China (National Standards of the People's Republic of China, 1996). Knowledge of local industries and past outbreaks of contamination is recommended.

Pesticide and herbicide maximum residue limits differ from water, soil, and air standards in which they should be aligned, not on standards defined in the regions of production, but on standards determined by the authorities of the countries and regions of use. Good communication will therefore be needed between the European purchaser and its Chinese supplier to ensure that European residue limits are complied with. It should be an essential part of the quality agreement required by the European authorities. The *Regulations for Pesticides Management of the People's Republic of China* requires local authorities to provide guidance on pesticide use (People's Republic of China State Council, 2001). The European purchaser may request to be informed on such guidance.

Both sets of guidelines require extensive record-keeping. Records of field use, batch mixing, fumigating agents, and audits are required in Europe but not in China.

Compliance issues observed at plantations

Table 2 Comparison of major areas between European GACP and Chinese GAP

Major areas	European GACP	Chinese GAP
cultivation and processing conditions	The soil should be free from chemical and human waste contamination.	The soil should respond to the "Quality Standard Grade 2" (GB15618-1995) (National Standards of the People's Republic of China, 1995), which includes limits for Cd, Hg, As, Cu, Pb, Cr, Zn, Ni, hexachlorobenzene, and dichlorodiphenyltrichloroethane (DDT). The use of house garbage, industrial wastes, hospital refuse, and feces are strictly prohibited.
	Remark: Europe GACP includes no requirements as to air quality, but Directive 2008/50/EC specifies limits for inhaled contaminants, including Pb (0.5 μg/m^3 averaged yearly), As, Cd, Ni, benzene and benzo(a)pyrene (European Parliament and Council, 2008).	The air quality should meet the Ambient Air Quality Standard Grade 2 (GB3095-1996) (National Standards of the People's Republic of China, 1996). This standard includes limits for Pb (1.0 μg/m^3 averaged yearly, and 1.5 μg/m^3 averaged quarterly) and benzo(a)pyrene, but not for As, Cd, Ni, and benzene.
	Irrigation water should comply with regional standards.	Water should meet the "Standards for Farm Irrigation Water" (GB5084-92) (National Standards of the People's Republic of China, 1992), which contain limits for coliforms, heavy metals, and other chemicals.
	During harvest, contamination with soil particles and toxic weeds should be avoided. The harvest should be protected from contamination from chemicals, soil, pest, and previous crops.	Machines and tools for collection should be kept clean and free of contamination, and stored in a dry place inaccessible for insects, rodents, poultry, and livestock.
	The drying conditions should be controlled; Drying on the ground is not recommended.	Drying should be timely and by means of appropriate methods that protect the crude drugs from contamination. *Remark: Drying on the ground, a common method, is not expressly discouraged.*
	Packaging should be in clean and dry, preferably new, sacks, bags or cases.	The packaging materials should be clean, dry, uncontaminated, and undamaged, and should conform to the quality requirements for crude drugs. *Remark: The use of new sacks, bags, and cases is not expressly recommended.*
	Containers and machines in contact with the product should be clean from chemicals and previous harvests. Storage and distribution conditions, including the presence of pest and the use of fumigating agents, should be under control.	The use of anti-oxidant and preservatives should preferably be avoided. If used, they must conform to national requirements on food additives. Pest must be controlled. The crude drugs should be placed on shelves. *Remark: There is no requirement to control the use of fumigating agents.*
pesticides and herbicides	Pesticide and herbicide applications should be avoided as far as possible. Regional and/or national regulations on maximum residue limits in the *European Pharmacopoeia*, *European Directives*, *Codex Alimentarius*, etc., should be observed.	If necessary, a minimal effective amount of pesticides of high-efficacy, hypo-toxicity, and low-residue can be used according to the *Regulations for Pesticides Management of the People's Republic of China* (People's Republic of China State Council, 2001).

(To be continued)

(Continued Table 2)

Major areas	European GACP	Chinese GAP
identification of material and presence of adulterants	The presence of different species, varieties or different plant parts has to be controlled during the entire production process, and such adulteration should be avoided. Personnel should receive adequate botanical training. Source material for seeds should be accurately identified.	Species, subspecies, varieties or cultivars of medicinal plants and animals reared, cultivated or existing in the wild should be clearly identified and recorded in the Chinese adopted name and Latin name. *Remark: There is no requirement to control the presence of botanical adulterants.*
material traceability	Labeling and batch assignment should take place as early as possible to enable traceability of materials to their sources. Seeds should be traceable to accurately identified material.	On each package of the crude drugs, the product name, specification, production site, batch number, packaging date, and the name of producer should be indicated and a sign for qualified products should be marked. Production records should include the origin of seeds, strains, and propagation materials.
documentation and communication	Documentation should include: all quality-affection processes and procedures; producers; growth and harvest extraordinary circumstances; processing steps; field records; use of fertilizers, pesticides, herbicides, growth promoters and fumigating agents; geographic location; batch mixing; audit reports. *Remarks: Field Records and Batch Mixing Records are specific European requirements, which reflect a special European concern for adulteration resulting from previous crops and mixing operations.* *Records of growth promoters and fumigating agents are not required in China. Audit reports are an additional European requirement.*	Detailed records for the entire production process of each crude drug should be documented, which should include: 1. Origin of seeds, strains and propagation materials; 2. Production techniques and process: a. Seeding time, quantity and area of medicinal plants; seedling, transplantation, and the type, application schedule, quantity and usage of fertilizer; sort, quantity, application schedule and usage of pesticide, micro-biocide or herbicide; b. Records related to medicinal animals; c. Collection time and yield, fresh weight and processing, drying and drying loss, transport and storage of medicinal parts; d. Meteorological information, microclimate records; e. Quality evaluations of crude drugs: description of macroscopic characters of crude drugs and records of test.
	Agreements between producers and buyers with regard to quality such as content of active principle, macroscopical and olfactory properties, limit values for microbial contamination, chemical residues and heavy metals, interval of time between last pulverization and harvest, etc. *Remark: Guidelines on quality and specifications have been provided by the European Medicines Agency* (European Medicines Agency, 2008a; 2008b).	*Remarks: Such agreements are not formally expected in China.* *Specifying the interval of time between last pulverization and harvest is an interesting requirement, which might have to be supplemented by information on precipitations during that interval.*

and trading sites

The plantation sites inspected in Hebei Province were satisfactorily managed according to the *Chinese GAP Guidelines*. Such positive observation was in stark contrast with the situation at trading sites. All the traded materials that we inspected showed several critical deviations from compliance with Chinese guidelines. None of them could be traced to their sources by the customer, no matter whether the trader was certified for *Good Supply Practice* (GSP) or not. Traded products

were identified on the basis of their medicinal names only, as the botanical identification was consistently lacking. The practice to spread products on the bare ground outdoors for drying is widespread. Seeds were traded with no traceability and botanical identification either. We observed the use of bags recycled from the chemical industry to package seeds at four trading companies. At all trading sites, storage was on the bare floor instead of shelving. None of the sites implemented any pest control. The use of pesticides, fertilizers, herbicides, and fumigation agents at the materials source was nowhere documented. Despite the fact that one of the traders was also certified for *Good Manufacturing Practice* (GMP), no certificates of analysis were available anywhere.

Conclusion and recommendations to help ensuring GACP compliance

It might be difficult to ensure the compliance with European GACP of herbal materials obtained from traders on the Chinese market, as the traditional supply chain shows severe non-compliance issues with Chinese GAP, GSP, and GMP guidelines. Direct sourcing from, or direct communication with, plantations compliant with Chinese GAP must be strongly recommended.

Compliance, rather than the exact equivalence of the two sets of rules, is the most critical question facing the European purchaser of medicinal herbal material grown in China. Where equivalence is not ensured, the use of quality agreements, as expected by the European guidelines, can resolve local differences, particularly with respects to the use of chemical agents (pesticides, herbicides, fumigating agents, etc.), and the detection of adulterants and other contaminants.

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