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REGULATIONS

Herbal medicine rule book

Can Western guidelines govern Eastern herbal traditions?

BY NATASHA GILBERT

In the early 1990s, thousands of women attending a slimming clinic in Belgium were accidentally given a weight-loss treatment containing the toxic herb *Aristolochia fangchi* rather than the anti-inflammatory agent *Stephania tetrandra*. For practitioners and adherents of herbal medicine, it was one of their worst nightmares: more than 100 of the women suffered kidney failure. Many later developed cancer of the urinary system.

This was partly a story of mistaken identity: Chinese herbs are traded using their common names, which can confuse Western practitioners of traditional medicine. In this instance, the term fang ji describes the roots of both *A. fangchi* and *S. tetrandra*. In addition, in traditional Chinese medicine, *Aristolochia* species are regularly interchanged with other plant species, further complicating the use of these herbs for Western doctors who may be unfamiliar with the language and with traditional practice.

The Belgian cases prompted the European Medicines Agency to create new regulations, which are considered to be some of the strictest in the world. Given the increasing popularity among Western populations of herbal medicinal products — around a third of UK adults use herbal products, for example — there is a pressing need to tackle safety issues while ensuring the availability of potentially useful therapies to patients.

But are Western medical agencies capable of regulating herbal medicines developed in Eastern traditions? And if not, what reforms are needed to make it possible?

NEW EUROPEAN DIRECTIVE

The Traditional Herbal Medicinal Products Directive (THMPD) came into force across the European Union (EU) in April 2011. The THMPD "aims to protect public health and at the same time secure the free movement of herbal products within the EU", according to the European Medicines Agency.

Under the directive, herbal medicines intended as treatments for minor health ailments must be registered as traditional-use products with the regulatory agency in every EU member state in which the product is to be sold (although each national regulatory agency is supposed to recognize licences already granted by other EU members). This system is designed to make it less likely that a product is sold as a traditional herbal medicine in one country and as something else in another. Before the THMPD, Europe had a patchwork of herbal medicine regulations. Some countries did not regulate traditional herbs at all; others classified herbal products as food supplements rather than medicines, and so subjected them to less scrutiny. Consequently, some traditional herbal products had been available to patients without the quality and safety guarantees that come with registration.

With the THMPD, criteria for whether a product is a medicine or a food supplement are consistent across all European member states. Moreover, these criteria apply to all manufactured herbal products whether they are sold in healthfood shops or pharmacies, or prescribed by doctors (as happens in Germany). The THMPD does not cover practitioners of herbal medicine, who are still permitted to mix herbal remedies from individual components for personal prescriptions.

Products are eligible for licence as a traditional herbal medicine only if they have been used to treat a specified health complaint for at least 30 years, including a minimum of 15 years in Europe. Herbal products are held to similar safety and quality standards as pharmaceutical drugs. What's different is how manufacturers are required to demonstrate efficacy. Rather than having to conduct original clinical trials, as pharmaceutical drug manufacturers must,

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makers of traditional herbal medicines are instead permitted to point to their long history of use. "Some of these medicines have been around for thousands of years," explains Dick Middleton, technical director at Schwabe Pharma UK in Buckinghamshire. "If they didn't work they would have disappeared by now."

WEIGHING UP THE RULES

Many Western herbal providers and manufacturers applaud the move to improve standards, and expect Europe's new rules will provide a fairer ground for competition among responsible herbal suppliers.

"We are supportive of the rules because they ensure herbal products are consistently of an acceptable standard and give patients accurate information," says Middleton. Schwabe Pharma UK — part of Dr Willmar Schwabe Pharmaceuticals, a German phytomedicine company based in Karlsruhe — has registered 18 traditional herbal medicine products with the UK's Medicines and Healthcare Products Regulatory Agency — the most by any company.

Other supporters of herbal medicine worry that the rules are too demanding and could ban some therapies on which people depend. Adam Smith, science and communications officer for the Alliance for Natural Health International (ANHI) in Dorking, United Kingdom, a non-governmental campaign group promoting the use of herbal medicines and other approaches to healthcare, fears that patients will lose out on some Asian medicines because they have not been used in Europe for the requisite 15 years, even though they have been consumed in East Asia for considerably longer.

ANHI also detects a perceived bias in the THMPD towards products developed in the West, which often contain just one herb. Traditional Asian products contain mixtures of several herbs — making it difficult, time consuming and expensive to meet the directive's requirement to identify and quantify the active botanical ingredients or other biological agents in a herbal product. "These technical assessments require expensive methods," says Smith. "The cost burden is a problem, particularly for small businesses," he adds.

Middleton agrees that conducting scientific analyses are "tough" — even for products containing just one herb, such as echinacea (for colds), St John's wort (depression and anxiety) and feverfew (migraines) — all registered under the THMPD. Attempting to determine the biochemical characteristics of the ingredients in mixtures of up to 14 herbs sometimes found in traditional Chinese medicines can be an "endless story", says Rob Verpoorte, a pharmacologist and molecular biologist at Leiden University in the Netherlands, who studies medicinal plants. This biochemical requirement is a likely reason that, of the 350 herbal medicines that had been licensed under the THMPD by December 2010, none were from an East Asian background. The European Medicines Agency says it predicts a "substantial increase" in registrations in an updated assessment due in December 2011, but again few of these are expected to be from East Asian traditions.

Removing all but essential ingredients could simplify the analysis, suggests Arnold Vlietinck, a pharmaceutical scientist at the University of Antwerp, Belgium, and chairman of the regulatory affairs committee of the Society for Medicinal Plant and Natural Product Research, based in Bonn, Germany. For example, he says, other herbs are sometimes added to preparations to improve the look and taste.

In the longer term, ANHI suggests dispensing with the THMPD entirely and developing a new European regulatory framework for traditional medicinal products that is distinct from the existing regimens for food and medicine. This new framework would deal with all medicinal herbal preparations — including over-the-counter products and those prescribed by practitioners, as well as products on sale in some countries as food supplements.

AMERICAN DIET

In the United States, the regulatory requirements for herbal medicinal products are simpler than in Europe. US herbal products are generally regulated as dietary supplements, meaning that standards are lighter. Manufacturers do not need to analyse the biological and chemical properties of their herbal products, and there is no need to register them with the Food and Drug Administration (FDA). This laissez-faire regulation only goes so far, though. Sellers of herbs in the US are permitted to make only limited health assertions. In particular, US regulations prohibit the claim that any herbal product prevents disease. Moreover, US manufacturers are responsible for making sure that the information on the herbal product label is truthful and not misleading, which the FDA monitors — alongside reports of adverse effects from the use of dietary supplements.

GRACIA LAM

This simpler system is not without problems, says Darrell Rogers, communications director at ANHI's US branch, based in Washington, DC. Herbal products formulated to treat more serious ailments — a category that covers many traditional Asian preparations — fall between the regulatory cracks. If products are marketed as food supplements, their makers cannot make claims about the conditions they aim to treat — and people suffering from particular maladies will be unaware of these potentially beneficial treatments. To make therapeutic claims, the products have to register as medicinal drugs and undergo the FDA's rigorous, expensive and lengthy drug approval process — which, like the European regulations, requires complex biochemical analyses and three phases of clinical trials. It's not surprising that only one herbal medicine has achieved this status: sinecatechins, a tea polyphenol for the topical treatment of cervical warts. But these are something of a special case, and are registered as a 'botanical' — a separate classification from synthetic, chemically pure drugs.

One pharmacologist attempting to get an Asian medicine approved by the FDA is Yung-Chi Cheng at Yale University in New Haven, Connecticut. For the past 11 years, Cheng has been investigating PHY906, a 1,800-year-old Chinese formulation of four herbs that has the potential to alleviate the vomiting and cramps caused by chemotherapy for gastrointestinal cancer. With the latest analytical technologies available to him, Cheng has made good progress: he has completed phase I clinical trials of the herb and is soon to start phase II. Cheng is investigating the concoction's effects on three tissue types — splenic, hepatic and the gastrointestinal tumour tissue — to see if it works differently. Cheng's research has revealed some surprises: the herbal mixture not only relieves sickness during chemotherapy but also seems to enhance the patient's response to treatment[1]. "When the chemical goes into the body it doesn't only act on one organ, it also affects others and might help the final outcome of the patient," he adds.

Cheng says his experience highlights the need for more research into traditional Asian medicines — and for a change in attitude, both from regulators and some scientists. He had a lot of negative feedback about his compound, he says, before he finally got it published. "The mainstream science journals take one look at it, see it is a mixture and reject it," he says.

Work like Cheng's shows that traditional Asian medicines could provide important new avenues for treatment. But without an appropriate regulatory framework, these could be lost to science. Getting Eastern and Western medical traditions to meet will require political and cultural changes as much as scientific ones. ■

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1. Lam, W. *et al. Sci. Transl. Med.* **2,** 45ra59 (2010).

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