

REGULATING HERBAL PRODUCTS

- A Historical Canadian Perspective

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Several years before the Natural Products Section, of which I was the Head, was cancelled in 1993, and prior to elimination of the entire Bureau of Drug Research of Health & Welfare Canada (HWC), I circulated a Discussion Paper entitled *A Drug Identification Number (DIN) Ought to Mean Something* and proposed that Natural Products should not be granted DINs but rather TMNs (Traditional Medicine Numbers) – unless there were acceptable clinical trials in support of specific therapeutic claims for marketed product forms. At the time, I successfully promoted the granting of the first such DIN to feverfew (*Tanacetum parthenium*) whole leaf for prevention of migraine attacks. Then all other DINs for herbal products had been granted based on acceptance of the claims of traditional medicine; however, most of these products bore little resemblance to products prepared by traditional methods, which are mostly whole plant material or water extracts. Nevertheless, the regulatory authority granted DINs to a variety of preparations, including combination products, with no assurance of botanical identity or consistent method of preparation. Several instances of adverse reactions were observed during that period, resulting from adulteration and/or substitution; however, the adverse effects were relatively mild, despite the occasional need for hospitalization in more serious cases such as *contamination* by tropane alkaloid – containing plant material – likely belladonna (*Atropa belladonna*), also known as Deadly nightshade, which was indicated in 5 different plants resulting in hallucination, CNS and respiratory depression. A widely publicized case of botanical *substitution*, popularly described as *The Hairy Baby Case* resulted from Chinese silk vine (*Periploca sepium*) being consumed by a pregnant nurse in Toronto, instead of the apparently innocuous intended eleuthero (labeled ‘Siberian ginseng’).

In 1990, in Belgium, the formula of an established slimming regimen was modified by inclusion of extracts of two Chinese herbs imported from Hong Kong where there was no legal regulation of Traditional Chinese Medicine (TCM). One of the intended herbs was *Han Fang Ji* (*Stephania tetrandra*) but that supplied was *Guang Fang Ji* (*Aristolochia fangchi*) which contains aristolochic acid a

neurotoxin, known also to be mutagenic and carcinogenic, in laboratory animals; prolonged ingestion of slimming treatment, administered by doctors untrained in herbal medicine, led to more than 100 cases of kidney failure in women in Belgium and France.

The foregoing examples, as well as more recent occurrences of adverse health effects (AHEs), including *reports* of serious adverse reactions to purported black cohosh (*Actaea racemosa*) products, popular for treatment of menopausal complaints, reveal some related aspects of herbal regulation: notably, almost invariably, occasions of adulteration/substitution are revealed by observation of AHEs reported via the medical community, as for example, the case of serious effects attributed to a specific black cohosh product; a subsequent analytical investigation resulted in recall of such products from at least 7 companies supplied with the wrong plant species (e.g. *A. podocarpa*).

IQ

The underlying situation responsible for all these observed AHEs is the failure of the regulatory system to ensure proper botanical, identity, and the quality of marketed plant products simple declarations of manufacturers on licence application forms and elaborate product labels *cannot assure identity and quality*.

In the current climate, judicious consumer choice can only be advanced by education regarding medicinal effects, their relation to the type of preparation, and, arguably, most importantly, knowledge of the experience and scientific competence of manufacturers.

Quality assurance (QA) is aided by promotion of Good Manufacturing Practices (GMPs) which, if effectively enforced, should address most purity issues, including contaminants such as pesticides and pollutants, toxic metal (e.g. As, Cd, Hg, Pd), bacteria, molds and mycotoxins, processing impurities and solvent

residues, as well as adulteration with undeclared, pharmaceuticals. Quality issues may also involve botanical identity and the use of incorrect plant parts.

Identity

At present, the predominant methods for botanical identity testing rely on morphological features or phytochemical profiles. Historically, morphological identification could be reliably depended upon macroscopic examination of whole plants and / or plant parts, essentially intact after harvest, by an experienced botanist or trained herbalist. However, a botanist at the herbarium of the University of Texas, Austin wrongly identified a voucher specimen as German chamomile (*Matricaria recutita*), claimed to be of Argentinian origin and to contain 7.3% of antheotulid, a noxious highly allergenic sesquiterpene lactone: examination of the specimen by German researchers revealed the plant material to be actually derived from Dog's chamomile (*Anthemis cotula*); *M. recutita* contains variable, but much lower levels of antheotulid. Commercial raw material can be available in various forms, from cut and powdered, otherwise untreated, plant parts, to extracts using a variety of solvents, making definitive taxonomic diagnosis, even using microscopy and relying increasingly on phytochemical procedures, mainly chromatographic and spectroscopic/spectrometric. Largely reliable, well-established chemical separation techniques can provide distinctive profiles without necessarily identifying individual phytochemical compounds. However, complete reliance on chemical profiles for botanical identification is problematic since marker compounds may exhibit wide variation in presence/concentration of the naturally-occurring chemical constituents of plants. Definitive comparative data on plant-to-plant, population-to-population and species-to-species are prerequisite to reliable taxonomic diagnoses. Also, the preponderance of processed botanical material in the herbal supply chain precludes the broader reliable application of morphology-based identity testing, and by default the herbal community relies largely on phytochemical measurements to ascertain sample identity.

DNA

DNA-based approaches appear to be particularly useful for deconstructing plant mixtures to confirm the identity of components in blended herbal products. Nucleotide-based methodology has been used to overcome many of the shortcomings associated with morphological and chemical identification techniques, including identification of both single herb and mixed plant preparations: St. John's wort (*Hypericum perforatum*) has been effectively differentiated from morphologically and chemically similar species, as have other species such as Korean/Chinese or Asian ginseng from American ginseng (*Panax* spp.), and Chinese from Japanese star anise (*Illicium* spp.). Further, the time and cost surrounding DNA-based analytical techniques have steadily decreased over the last 20 years: data collection which once required days or weeks can now be completed in a matter of hours, with service pricing in the neighborhood of morphological and phytochemical methods.

A Prescription for Improved Regulation

Following the resuscitation in 2004, after more than a decade of virtual dormancy of HWC herbal regulatory programs, the renovated HC established the Natural Health Products Directorate (NHPD) to replace the NPDD (Non-Prescription Drugs Directorate), replacing herbal DINs with NPNs. A website since developed publishes plant species monographs (<http://webprod.hc-sc.gc.ca/nhpid-bdipsn/monosReq.do?lang=eng>) and also elaborates extensive specifications required for licensing finished products. However, a seminal – and critical – deficiency of NHPDs regulatory process is the lack of a confirmatory aspect, respecting both botanical identity and chemical analysis.

Suggested Initiatives

1. A Registry of Certified Growers (obedient to Good Agricultural and Collection Practices - GACP) / Suppliers, based on established competence in Botanical Authentication of Raw Material, who can be identified at all subsequent stages of supply and processing.
2. Certification of Analytical Laboratories qualified to conduct chemical testing of both raw material and finished products (The most recent refinements of analytical methodology should be provided in a timely manner to prospective license applicants).
3. A schedule of rotational random manufacturer product testing should be established (such as operated biannually in France); product candidates ought to be prioritized for selection, as in the earlier Natural Products program, on the basis mainly of sales volume, severity of associated health conditions and recognition of past incidences of adulteration / substitution.
4. Development of a data base of DNA analytical profiles, as an aid to charactering herbal products, especially the components of blended finished products.

References

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