Chapter 9
Coding Reports Involving Herbal Medicines in a Pharmacovigilance Database

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9.1 Background

Many pharmacovigilance centres worldwide receive spontaneous reports for herbal medicines (including unapproved/unlicensed products) in addition to reports for conventional medicines. Herbal medicines include *herbs*, *herbal materials*, *herbal preparations* and *finished herbal products*. In some countries, the term 'herbal' medicines may also be used to describe products that contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials) [1]. Spontaneous reports involving herbal medicines have to be stored in pharmacovigilance databases that are mainly developed for storing, coding, assessing, analysing and transferring data to other databases in the context of conventional medicines. The major aim of pharmacovigilance is the early detection of signals of previously unrecognized adverse (drug) reactions (ADRs). Early signals may be strengthened by combining the experiences reported in various countries. Coding herbal medicines so that they may be identified and assessed on different levels (e.g. medicinal plant species, part of the plant used, type of extract, specific manufacturer's product, particular chemical constituents, mode of action and indication) is needed both for national and global pharmacovigilance activities.

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J. Barnes (ed.), *Pharmacovigilance for Herbal and Traditional Medicines*,
https://doi.org/10.1007/978-3-031-07275-8_9

9.2 Challenges in Coding and Classifying Herbal Medicinal Products

It can be challenging to store reports on herbal products in a database without the fixed structure that is in place for regular drugs, while still needing to code and be able to analyse reports at all the different hierarchical levels, such as plant species, specific plant part used, type of extract and specific manufacturer's product (proprietary) name. For licensed medicines, the WHO Collaborating Centre for Drug Statistics Methodology in Oslo has devised, and maintains, the Anatomical Therapeutic Chemical (ATC) classification system. In the ATC system, the active substances in a medicine are classified into different groups according to the organ or body system on which they act, as well as their therapeutic, pharmacological and chemical properties [2]. Also, for registered medicines, other important information, such as batch/lot number, is often available.

While nomenclature for conventional medicines is (usually) unambiguous, nomenclature for herbal products is particularly complex. This can be particularly challenging in pharmacovigilance, especially when trying to code and analyse reported ADRs associated with a particular plant species, specific herbal substance, and/or specific manufacturer's product [3]. Herbal product nomenclature lacks uniformity and several types of names are currently in use: botanical or scientific names (and synonyms) of medicinal plants; common or vernacular names; Latinised pharmaceutical names or plant pharmacopoeial names (where they exist); for some ingredients and products, the pinyin name, which is often used in traditional Chinese medicine (TCM) [4]. Further, product labels may be written in a language that is different to the one usually used by the pharmacovigilance centre handling the report, particularly for some products that users may obtain through internet purchases.

Herbal 'prescriptions' (such as those compounded and supplied by a traditional medicine practitioner), and product packaging and/or labels may list one or more of these names depending on the source and regulatory status of the product. Some 'prescriptions' or other crude preparations of plant material may have no label at all. Where present, names must be interpreted with care as even the scientific names may be incorrect, or synonyms may be used, sometimes incorrectly. The common or vernacular name is the least precise, as the same name may be used for plants from completely different genera or species. A single vernacular name may refer to several different plants; these plants may have other vernacular names in different geographical areas, and a single plant may have several vernacular names. Moreover, a single plant may be called by different names in different communities. Thus, botanical identification by a specialist is necessary in these cases. Plant common names may be misleading or confusing if used for raw plant material or on labels of unlicensed herbal products, and so should be avoided. To avoid ambiguity, it is desirable that the genus, species, botanical authority and part of the plant are described on the herbal product label, or on packaging in the context of raw material [5]. In a pharmacovigilance setting, this information should also be added to the ADR report data in a pharmacovigilance database.

Ambiguous vernacular and pharmaceutical names, scientific synonyms and the incorrect use of scientific names can cause confusion and could result in attributing reported ADRs to the 'wrong' plant. Unravelling the diversity of nomenclature used in suspected ADR reports is time-consuming, and it is not always possible to be certain regarding precisely which plant species, plant parts, types of extracts and so forth might be involved in an ADR [3]. An example illustrating how plant nomenclature can be difficult comes from the plant family Aristolochiaceae, used in TCM, where at least three systems of nomenclature can be identified [6].

In addition to the difficulties with nomenclature, there may be many 'unknowns' about herbal products, such as the lack of reported exact ingredients. Herbal practitioners, such as herbalists, often prescribe compound and/or dispense preparations containing herbal mixtures, and preparations or products in processed or powdered forms, which may make identification of a product difficult in cases where ADRs occur. These issues are common to all forms of traditional medicines used in traditional medicine systems globally. This raises many questions about how to code and classify these kinds of products and preparations.

The product information and package leaflet (where present, i.e. usually only for approved/authorized/registered herbal medicinal products) constitute an important source of information for health practitioners and patients/consumers, as a guide for rational use and correct administration of herbal medicines. Where regulations exist, licensed products are required to carry information on ingredients, dosage, indications and cautions, contraindications and potential interactions on their labels [7]. In the absence of regulations, this information may be absent from the product label, or may be substantially incomplete. In some African countries, although herbal medicines are often the main form of primary healthcare, there is an absence of herbal medicines on National Essential Medicines lists. A lack of standard treatment guidelines or a national herbal medicines pharmacopoeia is a major challenge for the implementation of coding and classification for these products.

Another challenge is that even if the plant used is declared on the product's label, the plant part may not be specified. Different plant parts contain different chemical constituents; for optimal pharmacovigilance causality assessment and coding, it is important to know which part(s) of the plant was/were used in the manufacturing process. In addition, for some traditional medicines, information on how the herbal material is prepared, e.g. with honey, or 'cooked', is also often lacking. The use of oil, vinegar and honey for their biological activities, or to aid the processing of traditional herbal medicines, is well documented [8].

Finished herbal products are herbal preparations comprising one or more herbal ingredients. Finished herbal products, particularly those formulated as tablets, capsules, and liquid dose forms, may contain excipients in addition to the active (herbal) ingredients. However, finished herbal products to which chemically defined active compounds have been added, including synthetic compounds and/or isolated chemical constituents from herbal materials, are not usually considered to be herbal (or, at least, do not meet regulatory definitions for herbal products, depending on the country) [1]. The use of non-herbal 'natural' substances in herbal products, such as animal parts (for example, powdered animal horns, animal thyroid hormone),

vitamins/minerals, or the addition of conventional medicines to a herbal product, present substantial difficulties for coding these products. In many cases, particularly with the latter category, these non-herbal substances are undeclared on the product label and are, therefore, adulterations. There are numerous examples in the literature where such adulterations have led to serious harm in patients [9]. It is very important to be able to code these products in a pharmacovigilance database, so that they can be easily recognized and flagged as adulterated products.

9.3 Current Approaches in Coding and Classification

9.3.1 Botanical Nomenclature

The Uppsala Monitoring Centre (UMC), Uppsala, Sweden, the Royal Botanic Gardens at Kew, UK, and the Department of Systematic Botany, Uppsala University, Uppsala, Sweden, have collaborated on botanical nomenclature in pharmacovigilance and have specified the following criteria [3]:

- A plant name should indicate only one species of plant.
- The source for this name must be authoritative.
- The name should indicate which part of the plant is used. The collaboration has proposed that using the binomial name for each plant species that is included as an ingredient of an herbal medicinal product is best practice for avoiding confusion about the precise plant(s) used. In botanical nomenclature, there is only one 'accepted' scientific name for each plant species in a given taxonomy, with only one accepted spelling: these names are unique and refer to only one species [3]. A scientific botanical name has three parts: a genus (generic) component, a species epithet (specific name) and an author's name (usually abbreviated). The genus name and the species epithet are in Latin and are italicized, for example, *Hypericum perforatum* L.

The binomial name alone gives no information on which part of the plant is used. As mentioned above, having information about the plant part used and its chemical composition (as far as possible) is important for a comprehensive causality assessment to be undertaken. However, the packaging of an herbal medicine may lack this important information. Also, the extraction and processing methods used in the preparation of herbal products are not captured by using the binomial name for a plant. This information, where provided, allows the type of extract (and, therefore, its chemical composition) to be considered, along with similar information from other reports, and thus should, ideally, be included in the report [1].

As discussed above, for spontaneous reports for herbal products, best practice for naming the ingredient(s) of herbal products associated with suspected ADRs is to use the binomial name for the herbal substances, i.e. including both the genus and species epithets, together with the botanical author (e.g. *Hypericum perforatum* L.).

However, for many marketed products or traditionally prepared products, it is not always possible to determine to which species (within the genus) the stated ingredient corresponds. In these instances, the term 'spp.' substances (e.g. *Aloe* spp.) is used. 'Spp.' indicates that the genus is known, but not the precise species, where more than one species exists for the genus in question [10]. This occurs with several other popular herbal substances, such products containing 'echinacea'; where this is not further described, and in the context of ADR reports, 'Echinacea spp.' must be used.

9.3.2 The Herbal Anatomical Therapeutic Chemical (ATC) Classification System

For conventional medicines, the ATC coding system, where drugs are divided into different groups in accordance with the organ or system on which they act, and their chemical, pharmacological, and therapeutic properties, has been in use since 1976; the system was initially developed as a tool for drug utilization research with the aim of improving the quality of drug use [11]. In this system, conventional medicines are divided into fourteen main groups ('first' level), with pharmacological/therapeutic subgroups ('second' level). The third and fourth levels are chemical/pharmacological/therapeutic subgroups and the fifth level is the chemical substance [2].

In 1991, de Smet proposed a new method for the classification of herbal medicines [12, 13], based on the ATC system. This Herbal-ATC (HATC) classification provides a scientific framework for a harmonized, global nomenclature and therapeutic classification of herbal substances and combinations of them for herbal medicines [14].

By placing an 'H' before the existing ATC classes at the "0-level" of the code, a system is produced that is compatible with the regular ATC classification and which can be used for classifying herbal medicines [12, 13]. The first level comprises 14 anatomical groups designated by the letters A–V. These are the same in both the ATC and the HATC systems. The Uppsala Monitoring Centre (UMC) has further developed this classification tool to permit the inclusion of individual herbal products in the global WHO database of ADR reports for pharmacovigilance purposes. The HATC classification, unlike the regular ATC system, is based on botanical science, pharmacognosy, phytochemistry, literature search, and documented traditional use, rather than chemistry and evidence-based medicine (as for conventional medicines). It is linked to botanical synonyms and vernacular names via the substance register of the WHODrug Global® dictionary, which contains all ingredients, herbal and chemical, of medicinal products mentioned on spontaneous reports of suspected ADRs in the global WHO database [15]. The UMC always aims to assign codes on the fourth level of the ATC-code (chemical subgroup). Often a herbal product may have several indications/uses and, therefore, will appear in several

places in the HATC classification. For instance, *Aesculus hippocastanum* (horse chestnut) fruit is used to treat haemorrhoids [16], the leaves are used in arthritis and rheumatism [17], and seeds are used as an anti-varicose therapy [17].

In data-analyses, the hierarchical HATC structure supports both the broader overview and in-depth analysis, by allowing grouping and aggregation of data on different levels of specificity [18]. The structure of the HATC coding system is shown below (Table 9.1), using as an example the complete classification of preparations of *Aloe ferox* Mill. dry leaf juice, which is used as a laxative [14, 18].

For pharmacovigilance centres using the WHODrug Global® dictionary, maintained by the UMC, the HATC code can be used as it is included in this dictionary. Users of this dictionary can look up herbal products based on proprietary name or on product ingredients. The system identifies the 'preferred names' of ingredients of products listed on ADR reports in the global WHO database. The logic for identifying 'preferred names' for herbal substances follows, as far as possible, that for identifying preferred chemical substance names in the WHODrug Global® dictionary. There is a system checklist for cross-referencing of botanical and vernacular names used as names of ingredients. In cases where only the product name is known in a report, the UMC searches its global ADR database to see if there are existing reports for the same product and where the ingredients are already coded. If the product is not already in the global WHO ADR database, it will be added, together with the available information [1].

Although the HATC coding system represents a valuable attempt at coding herbal medicines, it may not be perfect for covering all types of herbal medicinal products [1]. For instance, traditional Chinese medicines often have indications/uses that are not listed in the ATC classification, such as 'Yin Deficiency' or 'Qi-deficiency' [19], and are, therefore, difficult to capture with the HATC.

The HATC can be considered a valid approach if a herbal medicinal product implicated in a spontaneous report consists of a single medicinal plant ingredient, where the part used is known (i.e. provided), the active principle/constituent(s) is/are known, the dose taken is known, and the product always meets the same quality criteria. This is often the case in certain countries where herbal medicines fall under legislation that governs and that guarantees all these requirements. In practice, there are many marketed or traditionally prepared herbal products available that contain multiple herbal (and, sometimes, non-herbal) ingredients and it is not always

Table 9.1 Herbal-Anatomical Therapeutic Chemical (HATC) classification system structure, using *Aloe ferox* Mill. dry leaf juice as an example [14]

Level 0	Herbal Remedy designated by letter H
Level 1	A—Alimentary tract and metabolism (first level, anatomical main group)
Level 2	A06—Drugs for constipation (second level group, therapeutic main group)
Level 3	A06A—Drugs for constipation (third level group, therapeutic/pharmacological subgroup)
Level 4	A06AB—Contact laxatives (fourth level group, therapeutic/pharmacological/chemical subgroup)
Level 5	A06AB5001—Aloe ferox Mill., dry leaf juice (fifth level group, individual crude drug)

possible to identify them all. In many countries, herbal medicines are used in the form of raw or crude herbal substances, also making it difficult to apply the HATC system to coding their ingredients. Also, the quality of these products and preparations varies, and it is not possible to capture this with the HATC system.

In the UMC database, the ATC code V90—'unspecified herbal and traditional medicine'—is assigned to every product given an herbal ATC code, or if no ATC (herbal or chemical) is suitable for products with at least one herbal ingredient. The ATC V90 is not included in the official ATC codes. The UMC aims to avoid assigning 'V90' only. However, there are situations, such as multi-ingredient products with ingredients that cannot all be identified, where it is impossible to identify an appropriate HATC code, and so the ATC V90 code is used. The WHODrug Global® dictionary also contains substances used in traditional methods of processing herbal products, such as 'honey', 'oil' and 'vinegar', that can be used as coded ingredients.

9.3.3 Other Coding Methods

WHO HATC codes are not universally used by all pharmacovigilance centres. For pharmacovigilance centres that do not use the WHODrug Global® dictionary, it is difficult to use the HATC because, without the use of a WHO drug dictionary, the herbal ATC codes are not automatically linked to substance and product-level.

There are also other reasons for using different coding systems. For instance, in the pharmacovigilance centre in Morocco (WHO Collaborating Centre for Strengthening Pharmacovigilance Practices) the HATC classification is not used because of some of the limitations mentioned above. For recording and coding the identity of herbals, mainly consisting of raw materials, the Moroccan Pharmacovigilance Centre uses the binomial nomenclature as described above. In addition, after a comma, the part of the plant used is added, if this is specified in the spontaneous report (e.g. *Aesculus hippocastanum*, seeds). For unlicensed finished herbal products found in pharmaceutical dosage forms, the Moroccan Pharmacovigilance Centre classifies them by name (with binomial nomenclature of the herbal medicine if specified) with the country of origin of the product and ingredients listed on the product label. The Moroccan Pharmacovigilance Centre has developed an MS Excel® herbal medicines database according to VigiFlow® (a management system for recording, processing and sharing reports of adverse effects) which meets its needs and its own specifications to have all information available to analyse data. To assist with coding accuracy, the Moroccan centre has a single reporting form covering all medicinal products, with an adaptation for herbal medicines raw material to specify the part of the plant used, the type of extract, and the dose used. All Moroccan herbal medicine reports, now around 3000, are in the VigiFlow® database with all needed information. Each report can be flagged if there is a suspicion that it involves an adulterated product containing undeclared conventional medicines. Products suspected to be adulterated, along with a sample where available, are analysed by the Centre Anti Poison et de Pharmacovigilance laboratory.

The Netherlands Pharmacovigilance Centre (Lareb) has developed a reporting database, PV Report, where reports relating to conventional medicines and non-registered/unapproved products can be stored, coded and analysed. As Lareb currently uses a specific Dutch drug dictionary, the HATC is not available. Reports involving registered herbal medicinal products are coded with the regular ATC-coding system (for instance, a registered *Valeriana officinalis* product has the ATC code N05CM09).

All reports involving non-registered herbal medicinal products are flagged in the Lareb database as 'herbal'. If known, the product name and the manufacturer are stored. All active ingredients are coded with their binomial plant names using an in-house built dictionary that allows for additions if the herbal medicine involved has not been reported to Lareb previously. If known, the part of the plant used, extract type and dosage are also stored with the report. The system also allows for the addition of names of vitamins and minerals, or other non-herbal ingredients, as ingredients for an herbal product itself. In the summary of the report, additional information can be added. In cases where information is not available, for instance, for reports where a product is simply described as 'valerian', the 'spp.' substance is coded. Each report can be flagged if there is a suspicion it is an adulterated product with undeclared registered medicinal ingredients. Products with these suspected adulterations, for which a sample is available, are sent for laboratory testing to the National Institute for Public Health and Environment (RIVM) in the Netherlands. If a product indeed contains an undeclared ingredient, this is described in the narrative and summary of the report. Test-results are stored with the report.

9.4 Solutions Towards Better Coding

It is important for pharmacovigilance centres to identify the specific herbal product(s) involved in a spontaneous report, including label and manufacturer information, specific ingredients and dose used. Also, assessment of reports would benefit substantially from having results of analysis of the suspect product(s) used, for contamination and adulteration, or species identification, where possible [7, 20]. If possible, national pharmacovigilance centres could collaborate with pharmacognosy departments of universities, and with botanists or botanical garden staff, regarding taxonomic (botanical and chemical) identification and botanical and vernacular nomenclature [20]. Of course, the reporter of the information plays an important role here as they are the primary source of information for a pharmacovigilance centre for obtaining precise information about products involved for a particular report. Having a reporting form in place with additional questions that prompt the reporter for specific information for herbal drugs, such as that designed by the WHO, or used by the Moroccan Pharmacovigilance Centre, can ensure that reports are more complete to start with. Also, asking specific follow-up questions to reporters can help to make the report as complete as possible, which enables more precise coding. If the finished herbal product(s) concerned, or its raw materials,

were imported from other countries, the drug regulatory authority of the exporting country may be able to provide helpful information [20]. This, of course, requires comprehensive, reliable traceability throughout the supply chain for herbal medicinal products from field to finished product.

9.4.1 Coding Options

The ultimate goal of coding spontaneous reports involving herbal products as precisely as possible is to be able to search for and aggregate reports in order to detect signals of safety concerns. This approach can be undertaken either on a national level and/or in a global database, such as that maintained by the WHO-UMC. Despite the limitations mentioned, the HATC coding system as developed by the UMC is a valuable option for centres already using the WHODrug Global® dictionary. It should be noted that not all countries who are members of the WHO Programme for International Drug Monitoring use the HATC [21].

For countries not using the HATC, coding on multiple levels for herbals in a pharmacovigilance database is needed in order to perform searches and signal detection: the herbal product name; the herbal ingredients described using binominal nomenclature; for each ingredient, the part of the plant used, and the preparation method; the other ingredients in the product should all be coded. If a product contains non-herbal ingredients, such as vitamins or animal parts, these should also be coded. Storing a photograph of the product or the original packaging can be useful to be able to differentiate between products and also helpful if a manufacturer changes the ingredients of a product over time [20].

In addition to coding systems for medicinal products, there are other systems for coding of adverse drug reactions, such as MedDRA®, the Medical Dictionary for Regulatory Activities [22]. The MedDRA® coding system also includes terms for ‘herbal interaction’, ‘herbal supplement’ and ‘herbal toxicity’.

9.5 Final Considerations

Herbal medicines have their own specificities and characteristics that are different from those for conventional drugs. This creates challenges in coding the precise details and ingredients of implicated herbal products for spontaneous reports of suspected ADRs in pharmacovigilance databases. Pharmacovigilance systems were developed according to the principles and conditions for conventional medicines and require modifications to address the specific features of herbal medicines. This is even more the case for medicinal plants, or parts of plants, used in the form of fresh or dried plant material (crude or raw material), in the form of herbal teas, for plants that are sold in bulk quantities, and for other plants without essential information on their label or for herbal products without national legislation regarding

quality, efficacy and safety [23]. Inaccurate coding at a national pharmacovigilance centre level makes it difficult to conduct further analysis later at both the national and global levels [24]. Independent of the method used, the coding of the product in a pharmacovigilance database should be as accurate as possible, without losing information and, equally important, without implying more about the precise herbal ingredients of a product than is actually known.

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