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Phytotherapy in Brazil: recovering the concepts

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Abstract: This article shows the evolution of the Brazilian legislation in recent years in the area of herbal products and discusses the concept of phytotherapy in Brazil, bringing information about how it works in Europe.

Article

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In the last ten years, the Brazilian legislation for herbal medicines has evolved a lot in many aspects, which was a mandatory precondition to promote us to another level, a better level, getting closer to international guidelines. We can mention several rules that demonstrate clearly such progress, such as the amplification of registration forms (herbal medicines registration in Brazil has evolved a lot since Ordinance 22/1967 and RDC 14/2010 currently effective) (Anvisa, 2010), improved control of raw material and herbal medicines, creation of laws to standardize stability studies (RE 1/2005) (Anvisa, 2005), guidance to validate analytical and bioanalytical methods (RE899/2003) (Anvisa, 2003), guidance to perform herbal pre-clinical toxicity studies (RE 90/2004) (Anvisa, 2004) and standardized package inserts for herbal medicines (RDC 47/09) (Anvisa, 2009).

Currently, there are several initiatives on the way to continue this evolution process, so we are in a regulatory expansion phase for raw materials, creating specific rules for pharmaceutical herbal raw material, such as, Good Practice (CP 63/09) rules, the creation of Good Pharmaceutical Practice for medicinal plants and herbal drugs, creation of Farmácias Vivas (Living Pharmacies) (Ordinance 886/10) (Ministério da Saúde, 2010) and Good Practice for medicinal plant and herbal medicine processing in Farmácias Vivas (CP 85/10).

The initiatives are many, a government movement took place in order to stimulate the use of herbal medicines in the country and was approved by the *National Policy of Medicinal Plants and Herbal* Medicines - PNPMF (Decree 5.813/06) (Brasil, 2006) , the approval of the program and creation of the National Committee of Medicinal Plants and Herbal Medicines (Ordinance 2960/08) (Ministério da Saúde, 2008) and the approval of National Policy on Integrative and Complementary Practices at the SUS (Public Health System) (Ordinance 971/2006) (Ministério da Saúde, 2006).

In 2009 the Ordinance 2982 was published in which the rules have been approved to perform and finance the Pharmaceutical Care in Primary Care and brings out in Attachment II a list of eight herbal and homeopathic drugs and in 2010, the national medicinal plant list has been disclosed, a list of SUS interests (RENISUS list) (Ministério da Saúde, 2009).

The PNPMF approval, therefore, has motivated a series of other regulations and initiatives in a way to support the policy and create a technical base in order to guide and standardize the herbal medicines in Brazil.

In order to continue to mention examples that demonstrate this evolving process, we can comment on the mobilization of the Brazilian Pharmacopoeia in the sense to support the policy and so, several releases were performed during 2011 such as the publication of the National Herbal Form (RDC 60/11) (Anvisa, 2011), new monographs in the Brazilian Pharmacopoeia 5th edition and the Memento Brasileiro de Fitoterápicos (*Memento of Brazilian Herbal Medicines*) which is in progress, among others.

Recently, the Ordinance MS No. 533 was also published in March 28th, 2012 which establishes the list of drugs and raw materials of the National List of Essential Medicines (RENAME) in the Sistema Único de Saúde (SUS) scope (Ministério da Saúde, 2012). This ordinance

presents in item 88.1, regarding herbal medicines, twelve plants species with indications and presentations established.

This cannot be undone and the herbal medicine will occupy a bigger space in the Brazilian market in the future and we need a regulatory and technical framework that allows its future development. Although the search for improvement is a continuous process, there is still need for further progress and, in some situations, when we take a look at the market, we realize that there is no consensus regarding the herbal concept. Many people see a herbal extract or a herbal medicine the same way they see a synthetic one and we know that there is a huge difference between these two categories of products.

When we talk about Brazilian regulations in the herbal segment, it is common to mention the legislation that regulates the herbal medicine registration in Brazil (current RDC 14/2010) is based on international rules, mainly, European rules, where the knowledge on medicinal plants and products arising from them are ancient. Regulatory bodies are always interested in taking advantage of the existing knowledge from other cultures and harmonizing the rules, whenever possible.

Although the concept is not always interpreted the same way and in the case with the Brazilian legislation some parts are very different. There are some examples that can be mentioned, however, it is possible to start with the situation described as follows. When the simplified registration (RDC 17; RE 89/2000) (Anvisa 2000a,b) was created, which has been characterized by an improvement process, it started to determine an analytical marker in the specification of the extract and the respective dose according to such marker. This helped the market a lot to improve the quality control, analytical methodologies, to standardize extracts (active herbal raw material) and, probably, it was the reason to a great revolution in the market at the time and it was a great step in improving quality. However, as the time passes by, we realize that part of the market started to see the extract by its marker and what used to be a quality control parameter, was regarded as the total quality of the extract.

Not that other parameters are being disregarded (such as chromatographic profile, ratio herbal drug: extract, species variability etc.), but herbal medicines and extracts are a complex matrix and when focusing mainly on the marker standard the risk is to lose the whole concept.

In order to improve the analysis of this matter, it is important to remember the marker concept that at first is about a "compound or compound class of chemicals present in the herbal raw material, preferably having a correlation with the therapeutic effect and that is used both as reference in the herbal raw material quality control and in the herbal medicine" - (RDC 14/2010). Therefore, the marker is a substance or substance group that can be related to the effect, so, they are not necessarily proven to be responsible for the activity. Thus, they cannot be considered "active ingredients".

This way, a mistake can be made when determining the medicinal dose according to the marker in the simplified registration. When we talk about plants/ herbal drugs there is not always a scientific proof about the active ingredient. This information exists for a few plants, as for example frângula (anthraquinones), belladona (alkaloids), horse chestnut (aescin), sene (sennoside), milk thistle (silymarin). There are plants in which a substance or a substance class is related to the activity, such as the hypericum (hypericin and pseudohypericin) case.

If we remind ourselves that the herbal drug and its derivatives are complex matrixes and with several substances interacting with each other in a synergic way, all of this makes sense again, *i.e*., when we talk about herbals in most of the time the active ingredient is the total extract and not a substance or an isolated fraction.

It is possible that when getting anxious for better control of the materials, desiring more result accuracy and better answers in relation to efficacy and product safety, was created a distance to the herbal concept and approach to regard this as a synthetic substance, which can create big problems for the quality of herbal material.

Other examples can be shown that lead to this path. For instance, the creation of restricted ranges for analytical markers in specifications of plant extracts with the same severity used for synthetic products, which can represent a mistake in a situation that the active constituent in unknown.

It is necessary to balance the controls and parameters to be controlled and/or monitored, taking into account the matrix being worked on, *i.e*., the herbal drug as a whole.

We can also mention, as a complicated matter to determine for the same extract two or three markers with a restricted range. The plant does not produce substances in the same relation and to create this kind of control makes the industry work even harder and, at the same time, favors the extract adulteration.

The same thing can be said about the focus on the analytical marker instead of the extract in the registration process and the extraction process. This is also a situation that favors the adulteration and disfavors the control of the process, because, most of the times, the quality of the extract, in this situation, is measured by the marker and not by the composition of the total extract. When it comes to active ingredient, this *modus operandi* makes sense, but when it comes to a marker and, normally, aiming only the analytical quality control, a severe mistake is made.

It is important to emphasize the relevance of the relation between herbal drug: native extract (the amount of native extract = the content of extractable matter) and chromatographic profile, both for quality of the extract as for the herbal product efficacy, and this does not disqualify

the importance of the quantitative analysis of the marker that represents an important step in quality control for herbal raw materials.

However, it is known that the less knowledge about the therapeutic action of the constituents in herbal drugs, the bigger is the need for using qualitative methods to evaluate the quality, such as, *fingerprint* whether by TLC or by HPLC.

Therefore, the first question to be asked is: Is the active constituent known or not? Since we do not know it in the majority of the cases, the whole extract will be regarded as the active ingredient.

One of the most important parameters to be observed in the extract is its composition (native extract content that represents the extract without excipients) and the DER native (Drug Extraction Ratio native), in addition to all items that compose the specification of the product such as extraction solvent and raw material quality, as well as the manufacture process, taking into account that it must be validated.

As the majority of the existing products in the market are approved by simplified registration and points score registration, therefore, the traditional use is based on plants or extracts mentioned in official literatures, when changing focus in some products to mainly analytical marker standards, it is possible to lose these references and the efficacy matter can be jeopardized. The simplified product registration and all other registration forms, always indicates daily dosage based on analytical marker content. This is usually not and adequate way and can provide wrong dosage of genuine extract. For both the "quantified and other" extracts categories, the active substance is the genuine extract and dosage should always be established in active substance.

Thus, all these matters were mentioned and one question can be asked: do you think the phytotherapy concept the way it is being worked in Brazil could not be aligned to the one practiced internationally? In order to complete this analysis, the following paragraphs will provide information about the phytotherapy concept in Europe and how the extracts are classified.

Concepts in Europe

DER native is the ratio between herbal drug and genuine extract (extract without excipients). Therefore, the DER native is the amount of material that can be extracted (dry residue - extractable matter) that is obtained with a proper extraction solvent and a validated extraction process. There is also in the European literature the DER concept (without the word "native") and in this case, it is about the ratio between the herbal drug (raw material) and the extract (finished product/ non native extract). However, the most developed amount is of DER native, because it is related to the plant proportion in relation to the genuine extract.

Extract classification

In Europe, the extracts are classified in three forms, according to the European Pharmacopoeia 7.6 edition (EP, 2012) and Herbal Medicinal Products (Gaedke & Steinhoff, 2003):

Standardized extracts

Extracts in which compounds have known therapeutic activity (*active*). In this type, the amount of native extract (genuine) is variable. The native or genuine extract is the extract without excipients. The extract is adjusted within the range defined for the active. Adjustment is carried out with inert excipients or by blending of production batches with a higher or lower content of therapeutically active constituents, resulting in a variable amount of native herbal drug preparation (native extract). Ex. belladonna

Quantified extracts

Extract adjusted within a defined range of compounds, which relation with the activity is proved through clinical trials. Therefore, the compounds are generally accepted to contribute to the therapeutic activity. They are known as active markers. In this type, the amount of native extract (genuine) is constant. Adjustment can only be achieved by blending of batches of extracts with the same specification and on the basis of a constant amount of native herbal extract. Ex. *Ginkgo biloba.*

Other extracts

These extracts are mainly defined by their manufacturing process (state of the drug to be extracted, solvent, extraction conditions) as well as their specification. In this case the active substance is the native extract and the amount of native extract is constant. There is no adjustment for a constituent or group of constituents. In this type, the constituents with known therapeutic activity or active markers (which are related to the activity) are not known. There is indication of the analytical markers and in this case the contents are batch-specific, informative, or it is recommended to have a minimum content referred to. Ex. valerian.

Existing monographs in the European Pharmacopoeia - current edition is possible to confirm this classification not only in "Extracts" found in "General Monographs", but also in the titles of monographs.

The monographs whose extracts are classified as *Standardized* have this word in the title, the same occurs for the monographs whose extracts are classified

as *Quantified*, as in the case of titles where there is no mention of the classification, they belong to *Other*.

Thus, out of the 43 extracts with monographs in the European Pharmacopoeia Edition 7.6, it can be observed the existence of fifteen extracts classified as *Standardized* and four extracts classified as *Quantified*. The others would be considered as *Other*.

Within this classification and from my point of view, we can say that many of the plants and market extracts fit in the second and third classes (possibly the major part in the third class), since the active principle (recognized as responsible for the therapeutic activity) or active marker (activity related substances) is not always known.

As information, there is a guide (*Guideline on declaration of Herbal Substances and Herbal Preparations in herbal medicinal products/traditional herbal medicinal products*) of European Medicines Agency (EMA, 2010), where rules are established for the labeling of these products according to the classification of the extract. And in case of Other Extracts class, it is not allowed to declare on the label the name and content of the marker (*analytical marker*).

Charter 1 summarizes the classification of the extracts into categories, which, particularly, I find it very interesting and easier to understand. From this classification, we might reflect on its application within the concept of herbal raw materials and herbal medicines in Brazil.

A standardization of an extract in Europe is related to the therapeutic activity of the relevant constituents. In most cases, in *Other extracts* and *Quantified Extracts*, the native extract (= extractable matter) is considered the active ingredient. Consequently, the composition of the extract (ratio of the native extract: excipients) is fixed, having the same proportion of native extract for each batch (for example, extract 80% native extract). Only the *Standardized Extract* having constituents with proven therapeutic activity are adjusted for these constituents. As a result, the native extract : excipients ratio is variable.

In Brazil, not always the standardization of the extracts is related to the therapeutic activity of the relevant constituents. Standardization provides ranges for the markers regardless of their contribution to the therapeutic activity. As a result, the proportion of native extract (extract without excipients) is always variable.

It is important to emphasize that presenting a range for the active ingredient and dosage on the basis of this is not what is being questioned, because in this case (*Standardized Extract*) it is proven that sustenance is responsible for the effect. Within this, mandatorily the amount of native extract is variable (it is not possible to create a range for the amount of active ingredient with a constant quantity of native extract) and the active content will be constant within the range established as mentioned in the table above (adjusted with excipients or with a blending of batches of extracts).

In case of *Quantified extracts*, a range is allowed, though related to clinical trials (and therefore studies that confirm the relationship of that substance with the activity). As discussed before, in this scenario the amount of native extract is also constant. For achieving the batch to batch consistency within establish ranges for marker standard(s) is only permitted blending of batches, because only in this way keeps the composition of native extract constant.

For extracts classified as "Other" the amount of native extract in final extract composition is fixed and thus nor blending or adjustment with excipients is permitted. By this, marker standard is either batch specific or as normally established by a minimum content. If establishing range for "other" extracts, the amount of native extract (extractable matter) will be affected and hence the efficacy of the

Charter 1. Classification of extracts.

Assessment	Extract concept		Extract adjustment	Extract type
Pharmacological/therapeutic relevance	Amount			
	Marker	Native extract		
Constituents with known therapeutic activity	Constituents with known therapeutic activity Constant	Variable	1. inner carrier material 2. blending of batches	Standardised
Constituents which are generally accepted to contribute to the known therapeutic activity	Active marker Range[1]	Constant	Blending of batches	Quantified (pharmacol/clinically tested extract)
Constituents with known therapeutic activity or active markers of the herbal substance/preparation are not known	Analytical marker Variable (min content if appropriate)	Constant	None	Other

Source: Regulatory Department SaRA- Finzelberg GmbH & Co.Kg.

extract.

Thus, the question discussed in this article is the fact that in most cases, they talk about a marker and no active ingredient, therefore, the decisive question to be asked is: What is the type of extract (classification) *i.e.*, is the active ingredient known or not? And so, this classification would determine the features of this extract and how it can be worked into the final product.

These concepts related to classification of the extracts are still discussed in Europe and there are forums that take place periodically to discuss improvements and optimizations, however it is worth knowing and assessing their relevance to our reality.

In Europe, the DER native is also necessary to inform for calculating the daily dose of the extract. So this determination is not based on the substance alone, but also in the relationship between herbal drugs and genuine extract (native extract).

The purpose of this paper is to contribute with information about the concept of herbal medicine in Europe and perceptions of how we have worked in Brazil and then after assessing, try to get the best parts of the concept and adapted in our legislation.

The interest is in allowing our market to have herbal medicines containing extracts consistent with the literature data and, consequently, the expected effectiveness and safety.

Currently these concepts are already being discussed in Brazil and the objective here is to disseminate this information so that there is an understanding of how it works out in Europe and the possibility to redeem these concepts for improving to the way that these concepts are being handled today.

As a conclusion, it is important to remember that, even if the literatures and scientific papers are being used for the registration of herbal medicines, this is based on external knowledge and big part of this is derived from Europe. We also need to understand these concepts and external assess and consider whether these concepts are suitable for the Brazilian market; since they take into accout different categories of extracts relating the chemical constituents and therapeutic activity and all are based on extract as active material.

Brazil have shown a big evolution over its production of scientific papers these recent years, but currently we still don´t have enough information about Brazilian herbal drugs and extracts for product registration purposes. This scenario might certainly change in the future, however it takes a long time to build this up.

It is worth saying that my perception is that ANVISA and especially the groups that deal with the registration of herbal medicine are open to discussions and at the same time seeking to harmonize knowledge, which is very important.

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