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Quality Control of Medicinal Vegetable Drugs (**)

Quality control is one of the principal acquisitions of the recent development in the field of drug safety. In fact, *safety*, in the use, and *efficacy*, in the effects, are parameters useful to evaluate the right therapeutic employment of each drug; by the comparison of these parameters, we can define the *risk-to-benefit ratio*, that is the basic motivation for a useful administration in humans.

At any rate, the quality control represents one of the most important data to define the usefulness of a drug in therapeutic practice and strongly contributes to avoid eventual dangerous consequences of a dissociated evaluation of efficacy and safety. Many factors can be considered as potential determinants of these parameters and phases, through which this evaluation is attained, present several variables especially when it has to do with plant drugs.

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The health authorities of each country, through the Official Pharmacopoeiae or the Community Pharmacopoeiae, such as the "European Pharmacopoeia" [1], guarantee that medicinal vegetable drugs, listed in these Pharmacopoeiae, as well as all other drugs included in them, possess "a minimum level of quality", for which they are able to induce safe and constant therapeutic effects, in comparison with eventual potential risks, during the whole defined or expected duration of the therapy.

Statements indicated by Pharmacopoeiae fix the quality levels below which a drug cannot be accepted for use, in an extemporaneous pharmaceutical preparation "magistral", as well as in an official preparation, that is made up by a manufacturer (not in a pharmacy open for the public), to be, then, sold in a pharmacy.

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In fact, unlike the former Pharmacopoeiae, modern Pharmacopoeiae are no longer collections of prescriptions, or descriptions of pharmaceutical preparations, but they have been transformed substantially to become a collection of prescriptions, general methods and requirements for good production and quality control of drugs and pharmaceutical preparations. In other words, they have taken over, more and more, the nature and the function of a "drugs analytical codex", to be used as a guide by manufacturers, by operators, who have to verify that product quality is within the fixed safety limits, and by pharmacists, who have an irreplaceable role when a drug is passed from the production to the distribution: all things in order to guarantee good remedies with a rational therapeutic use.

Specifications, acceptable on an international level, for the quality control of many drugs, and consequently also for the plant drugs, are indicated in the « International Pharmacopoeia » by the World Health Organization (WHO). But, these requirements and the recommended analysis methods do not have necessarily a legal status in each country, unless this is indicated explicitly by the pertinent legislation; they are just suggestions, so that each country can fix some national specifications on a common basis. So, each state, member of the WHO, is authorized to include a translation of all these recommendations, or just of some of them, in its National Pharmacopoeia.

The first and the second editions of the « International Pharmacopoeia » [2], have found inspiration regarding analytical methods for quality control, especially in some national or regional Pharmacopoeiae, which employ complex analysis methods, (needing sophisticated apparatus) and specialized technicians. About medical vegetable drugs, these techniques cannot be always employed in the place of origin of the plants, from which drugs are derived, or in the centres where dry drugs are collected and sent to industrial laboratories, where they are used, for example, to prepare extracts, or as constituents of specialized official pharmaceutical preparations, the so-called « medicinal specialties ».

In the present third edition (1980-81) [3], the International Pharmacopoeia leaves room, as much as possible, for traditional chemical methods of assay, which are not so fast as the modern physico-chemical methods, but can provide reliable results, and in addition it indicates some very easy methods of extraction and separation, which can have a great practical utility for the control of raw vegetable drugs.

Today the role of modern Pharmacopoeiae is becoming more and more important, because specifications and methods listed in them can be consulted and used by all organizations or operators who are interested and allow to carry out independent quality evaluations, especially for drugs, in every phase, from the collection to the introduction on the market; in other words, before, as well as after, their introduction in the process of production, until the therapeutic use of the pharmaceutical preparation.

Specifications registered in the Official Pharmacopoeiae and relative to vegetable drugs described in them represent statements necessary to control the quality of these drugs. So the *quality control* (F.U. IX, vol. I, p. 4) is consti-

tuted by all those various operations able to guarantee that drugs, and products derived from them, correspond to the specific requirements of identity, genuineness, activity and other characteristics. These statements must be able to guarantee the efficacy of a drug, with greatly reproducible pharmacological effects in the clinical utilization.

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The *pharmacologically active content* of vegetable drugs and of pharmaceutical preparations derived from them represents a very important characteristic of the quality of these medicinal products.

Pharmacopoeiae describe methods for the quantitative analysis of these contents and fix, in each monograph, minimum and maximum limits of acceptability, needed to obtain uniform actions and effects, or limits, beyond which a sample must be discarded. However, people who have to use drugs may employ also methods different (for example, more sensitive) from those described in the Pharmacopoeiae; in other words, one may use, to carry out an assay or a determination, a method employing the high-performance liquid chromatography (HPLC), instead of a non-specific titrimetric method, or of the thin-layer chromatography (TLC). But, in case of dispute, probative analysis methods are only those described by the corresponding Pharmacopoeia.

About the numerous other drugs, not listed in the Pharmacopoeia but used in therapy or employed in industries to make up specialties or specialized preparations, methods already known in literature must be used.

However, they have to be verified, uniformed and described with full details, to carry out comparable results; in addition, these methods must be confirmed by official authorities. So, an "International Codex of officinal drugs derived from plants" needs to be created by experts from several nations, coordinated by an international organism, that might be the WHO.

It is well known that the content of active principles in each vegetable drug is not constant, varying sometimes in a large measure, depending on geographical source and habitat in which the plant yielding the drug grows, on cultivation conditions (if the plant is cultivated), on the vegetative stage and the season during which the plant is harvested, on drying and storing methods, and on other conditions or factors which, in smaller or greater measure, exert their influence.

In addition, we have to take into consideration that the therapeutically active principle of a drug, because it is one of the metabolic products of the plant, is always present with other substances, produced through other metabolic pathways, or with intermediate products of the metabolic reaction chain yielding the active principle itself. Generally, these substances induce a pharmacological action different in their intensity, or in their quality too, and, sometimes, completely opposite to that induced by the therapeutically important principle. Their separation during extraction processes, to titrate the therapeutically active principle, is not always easy. However, it may be useful to be able to individuate, and also estimate quantitatively, these substances, especially when they would

induce undesirable or dangerous effects. And also if these substances induce functional modifications in the nature of the chief active principle, it is always useful to be able to define quantitative ratios of the principal active constituent to the secondary ones.

The search for and the assay of these substances are needed when their presence is certain in pharmaceutical preparations, because they cannot be eliminated through extraction processes. If this presence, because of dangerous or undesirable effects in the organism, may be a source of risk, it is necessary to fix precise maximum limits. All these requirements are a part of the analytical controls described by Pharmacopoeiae, about drugs listed in them.

These problems always come to the attention of Committees entrusted to elaborate Pharmacopoeiae, and do not always have an easy solution.

To take an example, one can talk about drugs employed very commonly and registered in the largest part of National Pharmacopoeiae in force; analytical controls demanded by the European Pharmacopoeia, with reference to these drugs, have been accepted by all Member States of the Convention pertinent to the Pharmacopoeia named above.

"Belladonna" (leaves and flowering tops of *Atropa belladonna* L.), as our Pharmacopoeia and many other National Pharmacopoeiae in force demand, does not have to contain less than 0.30% total alkaloids (calculated as hyoscyamine) in the drug dried at 100-105°C. Similarly, "Hyoscyamus" (leaves and flowering tops of *Hyoscyamus niger* L.) does not have to contain less than 0.05% total alkaloids, and "Stramonium" (leaves and flowering tops of *Datura stramonium* L.) does not have to contain less than 0.25% total alkaloids.

It is well known that these alkaloids consist mainly of the atropine-hyoscyamine group, together with a smaller quantity of hyoscyne (scopolamine), in different proportions in different drugs.

The quantitative assay of alkaloids is carried out by titrating the drug (titrimetric assay), because of their basic group, and so gives information on the quantitative ratio, in each drug, of atropine/hyoscyamine group-to-scopolamine, and does not allow to distinguish between hyoscyamine and its racemic atropine. Atropine is stabler than its levorotatory stereoisomer, and its effects on the autonomous nervous system (antimuscarinic effects) are significantly lower (about 50%).

The presence of an oxygen bridge between the carbon atoms in the 6 and 7 positions of the tropane nucleus of scopolamine is essential for its effects on the Central Nervous System (CNS), that are different from those induced by atropine. In fact, scopolamine induces more evident central effects (8-9 times higher); low amounts induce depressive effects (at therapeutic doses, scopolamine causes drowsiness, fatigue, amnesia) and, on the contrary, high doses induce excitatory effects on the CNS, such as restlessness. Atropine, at low doses, causes a moderate central excitation; with higher doses, these effects become more prominent, leading to restlessness, irritability, disorientation, hallucinations and delirium; with still larger doses excitatory effects are followed by deep depression with respiratory paralysis and death.

Thus, it is necessary not only to quantify the total amount of alkaloids contained in each drug to be used, but also to define the hyosциamine-to-scopolamine ratio. For this purpose, the European Pharmacopoeia demands the carrying out of an analysis by TLC, that makes known, with good approximation, this percentual ratio, comparing the chromatogram of an extract of the specimen tested with the chromatogram of a reference solution of pure alkaloids, in suitable concentrations and in the reciprocal ratio as they are found in nature. This ratio hyosциamine/scopolamine is approximately 20/1 for "Belladonna", 4/1 for "Hyoscyamus", 4/1 for "Stramonium". A similar assay is described, in our Pharmacopoeia in force, also for the fluid extract and the dry extract of "Belladonna", and, in the last VIII Edition, for the extracts of "Hyoscyamus" and "Stramonium".

By this assay, it is possible to evidence also eventual adulterations of officinal drugs. In fact, for example, in some other species of the genus *Atropa*, as *A. pallidiflora* and *A. acuminata* (Indian Belladonna), which can be marketed, leaves have a scopolamine content very much higher than that present in *A. belladonna*, going up to 15%, or even 30%, of the total alkaloid content.

In chromatograms of the extract of the drug tested, one can see some spots due to the presence of apo-atropine (originating from dehydration of atropine) and of tropan-3-ol (originating from alkaloid degradation), only when amounts of these extracts, applied on chromatographic plate, and corresponding to well known drug amounts, go up to limits fixed in the assay of the Pharmacopoeia, for each drug in the respective monograph. This requirement indicates that drugs themselves have been dried and conserved well, so that no detectable alteration of their therapeutically active principles has occurred. Excellent quality drugs satisfy these demands.

By this same assay, one can show also the conversion of hyosциamine to atropine, because, when sodium nitrite is sprayed on chromatograms, the reddish-brown spot becomes greyish-blue.

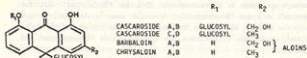
Many other examples of the quality control may be taken; however, I am going to talk only about "Cascara" and the "Liquorice" both very used drugs.

The quality analysis of the active principle contained in *Rhamnus purshiana* DC. bark (*Frangula purshiana* (DC.) A. Gray ex I. C. Cooper) demands a minimum amount of 8% hydroxyanthracene glycosides (calculated as cascarioside A); not less than 60% of this amount consists of cascariosides, also calculated as cascarioside A. The described assay method to be employed for the experimental control allows, in fact, to distinguish between cascariosides and hydroxyanthracene heterosides different from them. In fact, cascariosides (C-heterosides) are the glycosides best tolerated by the organism, and induce a laxative effect; on the contrary, O-heterosides, that have the "oses" connected by a glycosidic bond in the 6 or 8 positions, and also anthrones, induce a much stronger effect and colics may occur.

Thus, the richer in cascariosides the drug is, the more it is esteemed for therapeutic use. In addition, an assay, carried out by TLC, allows to show the

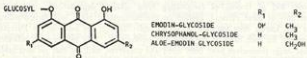
CASCARA - HYDROXYANTHRACENE GLYCOSIDES

C - HETEROSIDES

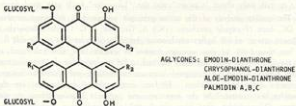


O - HETEROSIDES

ANTHRAQUINONE HETEROSIDES



DIANTHRONE HETEROSIDES



presence of free or bound anthrones, and, so, to eliminate the drugs in which the presence of these substances is demonstrated.

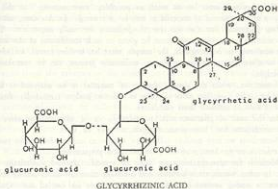
However, this assay excludes the necessity required by some precedent Pharmacopoeia, to use the drug only one year at least after collection, because during this period anthrones can change into dianthrones or anthraquinones. The same assay allows to show the eventual addition of barks of other not officinal species of *Rhamnus*, such as *R. cathartica* and *A. alpina*.

A few words also about the "Licorice" (*Liquiritiae radix*, F. Eur.) (*Glycyrrhiza glabra* L.). A good quality drug must contain at least 4% glycyrrhizinic acid or glycyrrhizin; but it does not have to contain glycyrrhetic acid, that is a degradation product originating from glycyrrhizinic acid and is able to induce mineralcorticoid-like side effects typical of this drug, for example edoema. The quantitative measurement of glycyrrhizinic acid is a spectrophotometric assay, after hydrolysis and separation (by TLC) of the beta-glycyrrhetic acid so originated. The presence of glycyrrhetic acid, eventually originating from hydrolysis following heating of the drug in the presence of water, or also from treatment with acid or basic solutions, to produce pure glycyrrhizin, is shown by TLC.

This last quick and easy test allows to discard a drug completely or partially devoid of glycyrrhizin, also without carrying out quantitative assay.

Requirements and tests described by the European Pharmacopoeia and modern Pharmacopoeia for a correct quality control of the most employed vegetable drugs result from a hard and accurate experimental joint-work done under the supervision of experts, in laboratories of several countries, and can be applied also to pharmaceutical preparations obtained from the above-mentioned drugs.

Joint researches and experiments are always in progress and may be really



useful, not only for pharmacological-therapeutic applications, but also for marketing and social reasons. The most important example is that of opium and its pharmaceutical preparations. One does not need to stress the importance of this drug, from a sanitary-pharmacological, but also social, viewpoint to which the demanded quality requirements are of great interest. Experiments in progress by the Committee for the European Pharmacopoeia are trying to elaborate a method which makes it possible to assay, besides morphine, also secondary opium alkaloids, codeine especially, and, in addition, thebaine, noscapine (narcotine) and papaverine. This method, employing the HPLC, might substitute gravimetric and titrimetric methods, generally demanded by Pharmacopoeiae in force, including the International one, by which morphine only or total alkaloids are determined. Thus, this method makes it possible to measure exactly, for the therapeutic activity, the content of the several active principles, in addition to morphine. Then, because the ratio among the alkaloids contained in the drug is modified in specimens coming from different geographical sources, this method can help to know the place of origin of the drug, in the case of an illicit trade.

* * *

Characteristics of a drug or a product must be examined and investigated through data obtained by quantitative analyses carried out in one or more specimens taken from the material whose quality one would like to know or to control. To assess the reliability of data obtained by a particular assay method, we must not forget the importance of the process following the sampling, that is generally not described by Pharmacopoeiae.

In the case of raw vegetable drugs, which are generally "not homogeneous products", processes must be fixed for each kind of drug, trying as much as possible to employ constant rules for standardizing the sampling.

The specimen must be, as much as possible, "representative" of the material, or of the amount of material to test or to control. In this case, not only sampling processes, but also the size of specimens are really important. Thus, the possibility to be withdrawn must be given to each constituent of the sample to be analyzed; in other words, the sample must be, besides casual, sufficiently large to allow that also foreign matter, eventually present, can be contained in the sample.

Sometimes, when the size of the lot of material to be analyzed is large, it may be useful to collect more samples, in order to analyze statistically obtained data and then to estimate their variability.

In the case of pharmaceutical preparations or of extracts, processes and recommendations for "homogeneous products" may be used.

Sometimes we may need to collect one sample to analyze during the process of extraction or production of the pharmaceutical preparation.

Methods for quantitative assay must be reproducible and statistically uniform. In other words, their accuracy and precision must not differ among several analyses or among several laboratories where analyses are carried out. Quanti-

tative evaluation of results and of their uncertain degree is, in fact, necessary when active principles concentration is determined, both to know the deviation from the required concentration and to obey the statements fixing high and low limits accepted for the real concentration of the product tested.

About drugs containing essential oils, our Pharmacopoeia, and the European one, describe an apparatus for the determination of the essential oils in vegetable drugs and, for each drug, all specifications (drug amount to be distilled, time and rate of steam distillation) are indicated, in order to carry out reproducible and constant results.

It is known that these essential oils consist of a mixture of many volatile constituents: qualitative and quantitative ratios among these constituents in the essential oil determine its aromatic and medicinal properties.

In Pharmacopoeiae, some physical (for example, specific density, optical rotation, refractive index) and chemical (ester value, content in carbonyl compounds and others) characteristics are required, all in accordance with official values published by international organizations for the study and the control of essential oils, as the ISO, the AFNOR, the UNICHIM, etc. However, the consistence with these values demonstrates only in a very approximate way the constancy of the qualitative and quantitative composition of the essential oil, also if it seems to be in conformity with requirements of Pharmacopoeiae.

Today, it is possible, by gas-chromatographic methods, to give a determinant contribution to the quality control of essential oils.

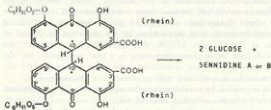
In fact, one can compare the chromatogram of an essential oil, tested for a quality control, with that of a genuine essential oil which, through the analysis of many specimens, may be regarded as a "standard" chromatogram. So, it is possible to identify and measure, among so many constituents, those which are particularly important for their aromatic and medicinal properties, controlling in a more precise way the conformity with the required quality.

Research groups, working on monographs about essential oils included in Pharmacopoeiae, are going — for a better quality control — toward the use of this method comparable with standard samples, already used successfully in TLC for substances identification.

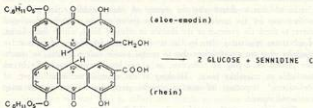
In addition to determining the content of therapeutically active principles, another way for the quality control, is, as shown in the examples mentioned above, to check the presence or the absence in officinal drugs, within fixed limits, of substances originating often by fission or enzymatic degradation of main active principles, that are modifications due to several causes such as, firstly, an unsuitable process of drying or collection, or a too long storing, especially in an unsuitable or unhealthy place. Thinking of the example mentioned above, of "Belladonna", important information may be given the chromatographic assay mentioned above.

With reference to this problem, the availability of *pure reference substances* is particularly important. They are needed to make up reference solutions to be employed, for example, in quantitative analyses for comparative measurement of absorbance, or in TLC for semi-quantitative determinations. When, sometimes,

it is impossible to get chemically pure substances, one can use suitable dry extracts, whose high content of active principles has been already determined by spectrophotometric or chromatographic assays; these extracts may be employed as reference substances in several assays. In fact, in accordance with the European Pharmacopoeia, a known extract of this kind is employed to recognize and distinguish, in leaves and fruits of Alexandria Senna (*Cassia senna* L. = *C. acutifolia* Delile) and of Tinnevely Senna (*Cassia angustifolia* Vahl), the four most important sennosides present in these two drugs: sennosides A and B, which are homodanthrones of rhein, and sennosides C and D, which are heterodanthrones of rhein and aloemodin.



SENNOSIDE A or B



SENNOSIDE C or D

Reference substances, not always easy to find, are necessary also for trying to identify major adulterations of essential oils, whose constituents are known to be, often, many tens.

Useful information for the quality control comes also from results of some non specific tests, for example ashes values, water loss on drying (at 100-105°C), determination of water soluble extractive ("Liquorice", "Gentian" or, for some particular drugs, viscosity, swelling index, or some biological assays, such as bitterness value for bitter drugs ("Gentian").

* * *

The problem of vegetable drug quality control involves also that of control of contamination by pesticides (weedkillers, insecticides, fungicides, heavy metals), of microbial contamination, and, eventually, contamination by radionuclides.

Also if the importance of some substances employed to protect and improve the vegetable production and to protect stored products, is undoubted, we must take into consideration possible dangerous effects induced by residues of these substances, eventually present.

Few years ago, some authors (Schilcher [4], in Germany, 1982; Atindehou and coworkers [5], in France, 1981) published some results of their investigations, carried out for this purpose, on drugs and their extractive preparations, withdrawn from the market. More than 50% of drugs tested showed the presence of heavy metals or residues of organophosphorus pesticides. In addition, in about 1/3 of these specimens of drugs, which were among the most commonly used, amounts of residues found exceeded limits fixed by regulations for foodstuffs. Also the pharmaceutical preparations tested showed 1/5 to 1/3 of residues of pesticides contained in the drugs used.

Since it is impossible to prohibit, in a generalized and extremist way, the use of phyto-pharmaceutical products, because of consequences induced by the presence of residues of these substances in foodstuffs used for human and animal feeding, it is desirable that in a short time regulations will be created to fix, for vegetable drugs as well as for foodstuffs, the maximum amount, as ppm, of each pesticide allowed in the drugs and in extracts obtained from these drugs, and also (this is a very important particular, too) the deadline for employing pesticides before harvesting.

About microbial contamination, several factors may determine the presence of microorganisms and their diffusion in the plant kingdom, that is due especially to cultivation and harvesting conditions, as well as storage and transport conditions.

The permanence of viable microorganisms on plant aerial parts is influenced by temperature, humidity, direct exposure to sunlight, and, also, by plant morphology and physiologic characteristics, that are presence of hairs and emergences, chemical composition of outer layers, presence in the surface of polysaccharidic mucous substances which can facilitate the adhesiveness and the microbial

survival at a low acidity. A high enough bacterial and mycotic contamination in vegetable drugs from different geographic origin has been demonstrated also recently by many authors [6, 7, 8, 9].

In the "Farmaco-Biologico" Department of the School of Pharmacy at Messina some years ago a study about bacterial contamination of several medicinal plants (*Datura innoxia* Mill., *D. stramonium* L., *D. metel* L., *Nicotiana tabacum* L., *Nerium oleander* L., *Laurus nobilis* L., *Lavandula angustifolia* Mill., *Rosmarinus officinalis* L., *Ruta graveolens* L.) was carried out. It employed plants cultivated in the Department itself or harvested in several parts of the land, and tested both wet, immediately after the harvesting, and dry. Regarding the size and the presence of a microbial contamination in these plants, it was observed that the most important factors seem to be the distance from the ground and the anatomy of the part used of the plant, besides, obviously, those factors related to harvesting methods.

Further processes undertaken to produce pharmaceutical preparations — for example infusions, decoctions, macerations — decrease the microbial contamination because of exposure to heat, methods of preparation or the different nature of contaminants, more or less sensitive to heating; but if a product is largely contaminated from the beginning of the process, an abundant residual amount of bacterial contamination is present in the finished product. In addition, there is the risk coming from the persistence of substances inducing toxic effects, such as endotoxins from Gram-negative bacteria, and mycotoxins. Strains of *Aspergillus*, able to produce aflatoxins, ochratoxins and sterigmatocystine, have been found in "liquorice root" (Hitokoto and coworkers, 1978) [10], in sage leaves and Tormentilla rhizomes (*Potentilla tormentilla* Neck) (Lutomski and coworkers, 1980) [11].

Negretti (1983) [12] showed the existence of microbial contamination also in some phytotherapeutic products, such as tinctures, fluid and dry extracts, and essential oils.

The European Pharmacopoeia (II ed., 1983) states requirements for the microbial contamination control of products not required to comply with the test for sterility and tests for specific microorganisms (enterobacteria and some other Gram-negative bacteria). The Italian Pharmacopoeia, IX ed. (1985, vol. I, p. 309) gives information about required microbiological characteristics of pharmaceutical preparations for parenteral, topic and oral administration (powders, capsules, tablets, syrups, elixirs, etc.); but it states no particular requirements for vegetable drugs.

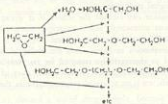
Drugs must be devoid of Enterobacteria (*Salmonella*, *Escherichia coli*), *Pseudomonas aeruginosa*, *Streptococcus aureus*.

Limits, almost generally accepted, about contamination with viable microorganisms (not pathogenic), per gram of drug, must be values with a magnitude order not higher than 10^6 .

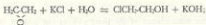
This value is an index of a contamination level, acceptable in practice, and points out a large enough contamination. Instead, strict limits must be stated and applied to finished products, both for pharmaceutical and for cosmetic use.

However, it is always convenient to limit values of the initial microorganism amount in raw materials, before immission into the transformation process. This can help to eliminate a potential contamination of the finished product or remaining endotoxins and mycotoxins, and also to avoid long and heavy successive processes, having poor efficacy if the product is too largely contaminated since the beginning.

To treat preventively vegetable drugs with dry heat or in autoclave or with X, ultraviolet or gamma rays, to destroy eventually present parasites, bacteria and mycetes is often not cheap in practice. One of the decontamination methods, sometimes used, is the treatment with *ethylene oxide*. However, this method is not devoid of disadvantages [15]. Since it is a strongly reactive epoxide, it interacts with many substances present in vegetable drugs, as, for example, alkaloids, amines, essential oils, lactones, etc., producing their modifications. Drugs containing lipids or peptides, following treatment with ethylene oxide, produce, if shaken with water, a persistent foam, because of formation of surface-active compounds. Drugs containing pyridine (tobacco) or purine (coffee, cacao, etc.) alkaloids, anthraquinonic or cardiac glucosides, or essential oils show a little decrease of their activity. Ethylene oxide acts on spores, avoiding their encapsulation. In drugs, with the residual water, glycol and polyethylene-glycoethers [12]



and especially chloro-2-ethanol, can be produced [13]



in addition, chloroethyl esters can be produced following the interaction of chloro-2-ethanol with organic acids present:



Its heavy reactivity, shown also in irreversible protein alkylation and block of many enzymatic and metabolic processes, the toxicity of its transformation

products [13] and its known mutagenic activity [15] are related with a great concern regarding an eventual residue of this gas or its conversion products in processed drugs. So, a direct consequence of the use of ethylene oxide is the necessity to fix strict technical conditions to be observed for its proper use, and to state limits, in processed drugs, for residues of both the gas itself and its transformation products.

* * *

As appears from what is said above, several and different problems occur continually and must be faced and solved in practice, to get a real evaluation of the quality of vegetable drugs, from the harvesting until their distribution as a simple pharmaceutical form — solid or liquid, in a suitable container — or as an extractive compound to be used as a constituent of a complex pharmaceutical preparation.

The first control must be carried out on the raw drug organized (leaf, flower, fruit, seed, bark, root) or unorganized (excreta or secreta from the plant: juice, essential oil, gum, oil, etc.), immediately when it arrives in the store, and, then, during the period of storage, until it is used.

For this purpose, a precise schedule is needed to be followed in its analytical course, developing through three phases: morphological evaluation, chemical evaluation, biological evaluation.

The first evaluation can exclude the others if it shows the drug as not corresponding to those microscopic and macroscopic characteristics necessary to identify the drug itself certainly as that declared.

The chemical evaluation excludes, also, the biological one if the sample does not correspond to characteristics required for its identification and purity (spectrophotometric or chromatographic characteristics, assay of residues of pesticides or heavy metals, etc.), or to stated concentrations in therapeutically active principles.

The biological evaluation completes the examination permitting to guarantee both the pharmacological activity and the absence of microbial contamination.

A complete operative schedule for the quality control of a tested raw drug can be summarized as follows:

Drug

Botanic nomenclature of the plant yielding the drug

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- 1) Indications on geographical source, material amount and packing
Indications on harvesting date (if wild or cultivated plants)
Indications on eventual processes following immediately harvesting and their related methods (hand or mechanical), on methods of drying, packing and storage.
 - 2) Morphologic control: — appearance, colour, odour
— macroscopic characteristics of identification
— microscopic and histochemical characteristics
— eventual sophistications or adulterations

- 3) Chemico-analytical control: — Identification reactions
— Chromatographic characteristics
— Spectrophotometric characteristics
— Physico-chemical characteristics
— Assay of active principles
— Loss in weight at room temperature
— Loss in weight at 100-103° C.
— Ash values
— Assay of residues of pesticides, heavy metals and contaminants
- 4) Biological control: — Pharmacological activity
— Bacterial amount
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Results of principal assays carried out would have to be marked on the label of the drug package.

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General principles and rules for good production and quality control, described by Pharmacopoeiae, can be regarded, in conclusion, as a basic guide, because on their ground one can set practically the suitable processes good for each requirement.

The quality control of a vegetable drug or of a corresponding pharmaceutical preparation consists, after all, of the following steps, in accordance with statements for a good manufacture required by Pharmacopoeiae (F.U. IX, vol. I, 1985, p. 13):

- 1) execution of all tests and assays required by Official Pharmacopoeiae, regarding genuineness, authenticity and activity, in a specimen of vegetable drug, to be employed in pharmacy or for pharmaceutical uses;
- 2) to decide and carry out, if it is necessary, other tests and assays, in addition to those required by official Pharmacopoeiae;
- 3) to accept or discard a tested drug sample, because of analysis results;
- 4) to analyze, accept or discard, if it is necessary, a product specimen taken during the manufacturing process;
- 5) to analyze, accept or discard a preparation ready to be marketed;
- 6) to assess the adequacy of storage conditions of drugs and their corresponding extractive and pharmaceutical preparations;
- 7) to assess the stability and therapeutic effectiveness of the drug during storage, also whether storage conditions are good;
- 8) in consequence of all observations described above, to fix the deadline for a therapeutic use of the drug or the correspondent preparation tested.

Obviously, the conformity of a medicinal drug with requirements fixed by Pharmacopoeiae (with reference to drugs registered in them) is really important; but it cannot always, by itself, guarantee the quality of the product. In fact, these statements do not have to be regarded as regulations to be applied just

when the drug is harvested or arrives in the store, or also in the case of pharmaceutical preparations obtained from these drugs, when the manufacturing process is completely done. It is necessary that strong and reproducible effects of a drug are guaranteed during the whole utilization period. So, the quality control is completely related to the life of the drug or its pharmaceutical preparations. For this purpose, other requirements and specifications can sometimes be necessary to integrate the statements of monographs of Pharmacopoeiae; in addition, specifications, as complete as possible, must be fixed for drugs not registered in Pharmacopoeiae.

Thus, the compilation of an INTERNATIONAL CODEX, specific for the quality control, is hoped for because it is becoming more and more necessary.

The quality control of medical drugs is strictly related to the problem of health, that is an unrenounceable right, enjoyed by each man and, through him, by the entire society.

Beneficial effects, which physicians and patients expect from drugs, depend especially on their quality characteristics and on a rigid control.

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