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HERBAL MEDICINAL PRODUCTS IN GERMANY AND EUROPE: EXPERIENCES WITH NATIONAL AND EUROPEAN ASSESSMENT

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The German Medicines Act (AMG) and the Council Directive 65/65 European Economic Community (EEC) apply fully to herbal medicinal products. This was confirmed by the European Court of Justice in 1992. A marketing authorization according to Article 4 of Council Directive 65/65 EEC granted by the competent authority is obligatory if herbal remedies are sold as finished medicinal products. The applicant must document quality, safety, and efficacy of its product. The term "herbal remedies" includes medicinal products containing exclusively plant material or vegetable drug preparations as active ingredients. Homoeopathic preparations or isolated constituents such as Menthol or Digitoxin are not considered herbal remedies. Herbal drugs are included in the German Pharmacopoeia DAB '96 and in the European Pharmacopoeia. Specific aspects of quality control of herbal remedies are described in the EEC Note for Guidance "Quality of Herbal Remedies" and, on a national level, in the "Guidelines for the Testing of Drugs" following Article 26 AMG.

The criteria for the evaluation of safety and efficacy apply to herbal remedies in the same way as they apply to other medicinal products with comparable indications. The complex composition of herbal active ingredients, however, must be taken into account. Because herbal remedies can rely on long-term use and experience, bibliographic data can be used in the assessment according to Article 4 No. 8 a, ii of Council Directive 65/65 EEC. On a national level a definition of bibliographic data is set out in Article 22 (3) AMG and in the 5th section of the "Guidelines for the Testing of Drugs" following Art. 26 AMG. The review of old medicinal products on the German market has resulted in monographs on active ingredients of herbal origin providing a positive or a negative assessment of the safety and efficacy of these compounds. Herbal remedies with "traditionally used" labeling do not comply with the European Union (EU) criteria. For this reason they are only acceptable on national markets and with strictly limited indications and special labeling.

Key Words: Herbal medicinal products; Safety; Efficacy

INTRODUCTION

THE DISCUSSION ON HERBAL remedies has a long history in Germany and within the EEC Commission. In Germany, the Parliament decided to include specific regulations in its 1976 Medicines Act. One result was to establish the so-called Commission E and to prepare monographs for herbal remedies. At the European level a working group for "medicinal products of plant origin" was established in March 1978. The result of 10 years of discussion was the Note for Guidance "Quality of Herbal Remedies" of No-

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vember 1988. A consensus on medical questions was far from being reached at that time. In October 1990, the European Scientific Cooperative on Phytotherapy (ESCOP) presented the first series of draft core summary of product characteristics (SPC) on herbal remedies. This activity stimulated a constructive discussion of the question. The Committee for Proprietary Medicinal Products (CPMP) adopted final core SPCs for four laxatives in May 1994. No final agreement was achieved on core SPCs for Matricariae flos and Valerianae radix, though a relatively advanced state has been reached so that they may be useful in the context of national applications in some Member States.

There has been no concrete progress from 1994 until March 1996 when the industry presented a new series of proposals for core SPC guidelines. It should be noted that these texts were prepared with substantial financial support by the commission. It is questionable, however, if these ESCOP proposals will be discussed in the same framework as the previous one. Today, there is a new situation in the EU: there are new procedures for marketing authorizations, there is a new agency to coordinate activities, and there are three new Member States with different experiences which have not participated in previous discussions on herbal remedies. The function of CPMP and CPMP working parties have changed and CPMP and European Medicines Evaluation Agency (EMEA) decided not to continue work within the field of herbal and over-the-counter (OTC) remedies. Thus, results of future discussions are difficult to predict.

THE LEGAL STATUS OF HERBAL REMEDIES

The legal requirements and the definition of terms related to the problem, however, are clear and beyond any doubt. It is clear that herbal remedies are medicinal products as defined in Article 1 of Council Directive (CD) 65/65 EEC (Table 1). They are neither foods—most of them have no nutritional value or pleasant taste, nor cosmetics. Decisions of the European Court of Justice support this interpretation (1,2). Divergent legislation in some Member States has been changed meanwhile. Member States which may have believed that they had no "herbal problem" have discovered that herbal medicinal products are on their markets; others found out that the number of products had been underestimated. Questions of assessment of herbal remedies and OTC products have become increasingly important, especially with the decentralized procedure and the mutual recognition of marketing authorizations within Europe. This is why the EU Council declared on December 6, 1995 that the wider and growing use of medicinal plants in the EU has to be considered (3). It expressed possible concern that the heterogeneity of the commercial presentation of herbal remedies could have a negative impact on public health and on the free movement of goods. The EU Commission was called on to study the situation.

One thing is clear: if the criteria for herbal remedies should be less stringent, namely in the sense of "traditionally used products with no proven or plausible efficacy," the definition of medicinal products in CD 65/65 is to be discussed anew and maybe even changed. Such a change would have a substantial impact on many other medicinal products cov-

TABLE 1
European Court of Justice
Judgment of October 28, 1992

"1. . . . a product *recommended or described as having prophylactic or therapeutic properties is a medicinal product* within the meaning of the first subparagraph of *Article 1 (2) of CD 65/65 EEC* . . . even if it is generally regarded as a foodstuff and in the current state of scientific knowledge has no known therapeutic effect;

2. . . . a product *whose therapeutic properties are described* only in documentation such as a brochure sent on demand . . . after sale, or by the manufacturer, or the supplier of the product, or *by a third party* may, where in the latter case the third party is not acting totally independently of the manufacturer or supplier, may be described as a medicinal product . . . "

ered by EU directives until now. An exclusion of herbal remedies would lead to the paradoxical situation that homeopathic remedies would be included, while herbal remedies would be excluded. Such a substance-related exclusion would lead to a revival of the so-called "exclusion products," whereas it has been the political will and the commission's goal to overcome the problem of exclusion products by the inclusion directives of 1991/1992. A substance-orientated exclusion could not eliminate all herbal remedies and the curious situation would appear that Belladonna or Senna leafs would have to be declared as herbal "nonherbals." Therefore, such an approach is in the Federal Institute for Drugs and Medical Device's view neither reasonable nor acceptable.

THE EEC MARKET FOR HERBAL REMEDIES

Herbal remedies are indeed a relevant factor in EU harmonization efforts. They are not just a German problem that would originate from the "lingering influences of 19th century romanticism" (4). An investigation conducted in the Member States in 1991 revealed the impressive number of about 1,400 herbal drugs used in the EEC. When the study focused on those drugs that were used in half of the responding Member States (five out of a possible 10), there are still 145 herbal drugs (Table 2) (6,7). Even if this number is a rather broad brush, due to problems with defining a given drug, this shows that herbal drugs are indeed a major problem for harmonization in the EU. The commission, on the call of the EU Council, decided to repeat this inquiry and it can be expected that the number of relevant herbal drugs will continue to increase.

Herbal remedies are a relevant economic factor as well. Sales of herbal remedies in the EU were reported in 1994 to amount to a value of six billion dollars (United States) (Table 3). Increases until 1998 are estimated to be 8% per year. In the sector of herbal OTCs, Germany holds the biggest share with $2.5 billion followed by France with $1.6 billion and Italy with $600 million. Every citizen of the EU spends $17.4 per year for herbal remedies (8,9,10).

Because of their legal status as medicinal products, finished drugs of herbal origin must be authorized according to Article 4 of CD 65/65 EEC. Applicants must document quality, safety, and efficacy of their products in compliance with CD 75/318 EEC. At a European level, the definitive result of the assessment process of a medicinal product is the summary of product characteristics (SPC). While SPCs for new chemical entities are no real problem in centralized procedures, consensus on SPCs for generic applications will pose a major problem, especially in cases of well-known old medicinal products, maybe with a long tradition as OTC products. In these cases not only the individual application is to be checked, but former decisions on similar products are to be discussed to overcome differences among Member States. Harmonization of old products at the EU level may result in a deharmonization of national markets with many problems for the industry and national authorities. Finally, consumers will be confronted with very similar or identical products but different medical information depending on the origin and type of authorization. This will be particularly relevant for those countries where herbal remedies had a food-like status in the past. This situation may explain why there are only four officially accepted core SPCs on herbal laxatives. The underlying problem, however, is not a specifically herbal one (there is only one core SPC on chemically defined OTCs, ie, bisacodyl), on the contrary, the legal framework and the scientific requirements for herbal remedies are clearly set out.

PROBLEMS AND EXPERIENCES WITH HERBAL REMEDIES

Identifying the Market

The term herbal remedies applies to medicinal products whose active ingredients consist exclusively of plant material or vegetable drug preparations, for example, powdered vegeta-

TABLE 2
Most Relevant Herbal Drugs

Achillea millefolium	Herba	Fraxinus excelsior	Cortex
Acorus calamus	Rhizoma	Fraxinus excelsior	Folium
Aesculus hippocastanum	Semen	Fucus vesiculosus	Thallus
Agar		Fumaria officinalis	Herba
Agrimonia eupatoria	Herba	Geranium robertianum	Herba
Agrimonia procera	Herba	Glycyrrhiza glabra	Radix
Agropyron repens	Rhizoma	Hamamelis virginiana	Folium
Alchemilla vulgaris	Herba	Harpagophytum procumbens	Radix
Allium cepa	Bulbus	Hedera helix	Folium
Allium sativum	Bulbus	Humulus lupulus	Glandula
Aloe species (barbadensis, capensis, ferox)	Succus (sicc.)	Humulus lupulus	Strobuli
		Hydrastis canadensis	Rhizoma
Alpinia officinarum	Rhizoma	Hypericum perforatum	Herba
Althaea officinalis	Flores	Hyssopus officinalis	Herba
Althaea officinalis	Folium	Illicium verum	Fructus
Althaea officinalis	Radix	Inula helenium	Rhizoma
Anethum graveolens	Fructus	Juniperus communis	Fructus
Angelica archangelica	Radix	Krameria triandra	Radix
Arctium lappa	Radix	Lamium album	Flores
Arctostaphylos uva-ursi	Folium	Laurus nobilis	Folium
Armoracia rusticana	Radix	Lavandula angustifolia	Flores
Arnica montana	Flores	Levisticum officinale	Radix
Artemisia absinthium	Herba	Linum usitatissimum	Semen
Atropa bella-donna	Folium	Lobelia inflata	Herba
Barosma betulina	Folium	Malva sylvestris	Flores
Betula pendula	Folium	Malva sylvestris	Folium
Calendula officinalis	Flores	Marrubium vulgare	Flores
Capsella bursa-pastoris	Herba	Marrubium vulgare	Herba
Capsicum annuum	Fructus	Melaleuca species	Atheroleum
Carum carvi	Fructus	Melissa officinalis	Folium
Cassia angustifolia	Folium	Mentha piperita	Aetheroleum
Cassia senna	Folium, Fructus	Mentha piperita	Folium
		Menyanthes trifoliata	Folium
Centaurium erythraea	Herba	Myristica fragrans	Semen, Arillus
Cephaelis ipecacuanha	Radix	Myroxylon balsamum var. pereirae	Balsamum
Chamomilla recutica	Flores		
Chondrus crispus	Thallus	Olea europaea	Folium
Cimicifuga racemosa	Rhizoma	Olea europaea	Oleum
Cinnamomum aromaticum	Cortex	Origanum vulgare	Herba
Citrus limon	Aetheroleum	Panax ginseng	Radix
Cnicus benedictus	Herba	Papaver rhoeas	Flores
Cola nitida	Semen	Passiflora incarnata	Planta tota
Commiphora molmol	Gum-Resin	Peumus boldus	Folium
Coriandrum sativum	Fructus	Pimpinella anisum	Fructus
Crataegus laevigata	Folium	Pimpinella anisum	Fructus, Aetheroleum
Crocus sativus	Stigma		
Curcuma longa	Rhizoma	Pinus species	Aetheroleum (Terpentin)
Cynara scolymus	Folium		
Drosera rotundifolia	Herba	Plantago ovata	Semen
Equisetum arvense	Herba	Podophyllum peltatum	Rhizoma, Resina
Eucalyptus species	Aetheroleum		
Ferula asa-foetida	Gum-Resin	Polygonum aviculare	Herba
Ficus carica	Fructus	Potentilla erecta	Rhizoma
Filipendula ulmaria	Flores, Herba	Primula veris	Radix
Foeniculum vulgare var. vulgare	Aetheroleum	Prunus cerasus ssp. acida	Stipites
		Prunus spinosa	Flores
Foeniculum vulgare var. vulgare	Fructus	Quercus robur	Cortex
		Quillaja saponaria	Cortex

TABLE 2
Continued

Rhamnus frangula	Cortex	Thymus vulgaris	Herba
Rhamnus purshianus	Cortex	Tilia cordata	Flores
Rheum officinale	Radix	Trigonella foenum-graecum	Semen
Rosa canina	Fructus	Urtica dioica	Radix
Rosa centifolia	Flores	Vaccinium myrtillus	Folium
Rosmarinus officinalis	Folium	Valeriana officinalis	Radix
Rubus fruticosus	Folium	Verbascum phlomoides	Flores
Rubus idaeus	Folium	Verbascum thapsus	Flores
Salvia officinalis	Folium	Verbena officinalis	Herba
Sambucus nigra	Flores	Viburnum prunifolium	Cortex
Silybum marianum	Fructus	Viola odorata	Flores
Silybum marianum	Herba	Viola tricolor	Flores
Solidago virgaurea	Herba	Viola tricolor	Herba
Tamarindus indica	Fructus	Vitis vinifera	Folium
Taraxacum officinale	Radix	Zea mays	Stipites
Thymus serpyllum	Herba	Zingiber officinale	Rhizoma

ble drugs, vegetable secretions, essential oils, or extracts. Homeopathic preparations are excluded as are chemically defined substances such as menthol, thymol, or eugenol. This notion of herbal remedies has a broad international basis since the world Health Organization (WHO) defined the term herbal remedies in the same way (11).

Even if herbal drugs are widely used for self-medication, the term herbal remedies is not automatically linked to an OTC status. In Germany and France, a relevant portion of medical prescriptions is made up by herbal remedies (10,12) (Table 4). Some herbal remedies, for example, Belladonna leaves, are prescription-only medicines.

TABLE 3
EU Sales of Herbal Remedies (IMS 1994)

	Million US $	p. capita (US $)
Germany	2,500	37.0
France	1,600	28.0
Italy	600	10.5
United Kingdom	300	5.0
Spain	230	6.0
Netherlands	100	6.5
Belgium	40	4.0
Others	130	4.5
Total	5,500	17.4

Regulating the Market

In dealing with the scientific assessment of herbal remedies, agencies are regularly confronted with two types of problems:

1. The huge number of products on the market, and
2. The criteria which have to be applied to these drugs.

Since 1978 when the German Medicines Act came into force, every finished drug has been liable to registration by the Federal Institute for Drugs and Medical Devices (formerly the Federal Health Office). Even products produced in individual pharmacies or health food stores and sold outside these places on a regional market have been covered by this regulation. Owing to this situation and to the fact that different dosage forms were counted separately, the office was confronted with about 148,000 registered finished drugs in 1978. Of these drugs, 126,000 were still registered in 1989. The impressive number of about 67,000 of 126,000 registered finished drugs contained herbal constituents. Forty thousand of these products were herbs used for tea infusions and these products were typically sold outside pharmacies. All these herbal medicines were produced on the basis of about 1,100 different botanical drugs.

TABLE 4
Drug Sales in Germany in 1994

Prescription only		
	Value (Billion US $)	Packages
	20.8 (+5%)	652 Million
Nonprescription		
	Value (Billion US $)	Packages
Prescribed by physician	5.4	369 Million
Self-medication	5.6	723 Million
Herbal Remedies West Germany 1994		
	Value (Billion US $)	
Prescribed by physician	1.4 (+6%)	
Self-medication	1.1 (±0)	
Total US $ 2.5 Billion (23% of nonprescription market)		

Being confronted with a market of 148,000 medicinal products will present a problem to any administration. The institute's strategy to overcome this problem was to follow two lines: the introduction of standardized marketing authorization, and the review of old drugs, in addition to the individual marketing authorization.

Standardized Marketing Authorization

Medicines or groups of medicines which do not pose a direct or indirect risk to the health of man or animal could be exempted from the requirement for an individual marketing authorization according to Article 36 of the Medicines Act. To assure quality, safety, and efficacy of such products each medicinal product referring to this procedure must comply exactly with a monograph of a standardized marketing authorization published by the Federal Ministry of Health. The monographs include analytical test requirements and also the texts for labels and package leaflets. Two hundred seventy nine monographs of standardized marketing authorizations have been published mainly for such herbal remedies as herbal teas. If an applicant refers to such a monograph it does not need not to present any documentation to the Federal Institute for Drugs and Medical Devices. Compliance with the requirements of the monograph is controlled by the local inspection authority. If the drug will be sold in pharmacies only, the producer will only have to inform the institute that it refers to the monograph.

Review of Active Principles

The review of existing products started in 1978 and was stopped by an amendment to the Medicines Act in August 1994. The review was focused on active ingredients and not on individual products, because of the large number of products on the market. The concept of the procedure was to establish clear, a priori criteria for active ingredients and to make it transparent to industry which products would have a chance to be authorized.

The institute thinks that these two approaches have been a success: The number of products covered by a standardized marketing authorization is estimated to be 25,000. The number of finished medicinal products of herbal origin, which are going to be checked individually, has decreased to 5,381. Three hundred and thirty monographs prepared by Commission E cover more than

80% of the herbal medicinal products on the German market.

CRITERIA FOR THE ASSESSMENT OF HERBAL REMEDIES

Points of conflict in the assessment of quality, safety, and efficacy of herbal remedies are the criteria to be applied, especially in the case of safety and efficacy.

Quality

Herbal remedies represent complex biological mixtures, and achieving a reproducible pharmaceutical quality could appear to be a problem. The EU Council asked the commission to study any tests required to ensure the quality of raw materials and medicinal plant preparations. The EEC Note for Guidance "Quality of Herbal Remedies," however, already provides a well-defined framework for quality testing (13) (Table 5). It is without question that consistent quality of products of vegetable origin can only be assured if the starting materials are defined rigorously and in great detail. An exact definition and the control of all steps of the manufacturing process are necessary to assure consistent quality of a herbal medicinal product. Member States refer to these regulations in granting marketing authorizations to herbal products. The Note for Guidance can guarantee a reproducible quality of a specific herbal product. If a European harmonization of multisource products is wanted, uniform definitions of vegetable drugs in all Member States are needed. The European Pharmacopoeia reflects the high standard of phytotherapy in Europe and provides a worldwide unique collection of official, high-standard monographs on herbal drugs. One advantage of this pharmacopoeia is that it is published in all languages of the EU, and the Spanish, Portuguese, and French editions, beside the English texts, are relevant for many countries outside Europe. Quality requirements are, therefore, transparent for any third country producing herbal raw materials for export to EU Member States. Group 13 of the European Pharmacopoeia Commission, responsible for the monographs on herbal drugs, agreed to adopt the CPMP list of the most important herbal drugs in its priority ratings for future work. There are 60 monographs already included in the European Pharmacopoeia. Forty five draft monographs have been published in Pharmeuropa for comments. This cooperative approach will greatly facilitate harmonization of herbal remedies.

TABLE 5
QUALITY: Note for Guidance "Quality of Herbal Remedies," November 1988

A—Qualitative and Quantitative Particulars of the Constituents
B—Method of Preparation
C—Control of Starting Materials
D—Tests Carried out at an Intermediate State
E—Tests on the Finished Product
F—Stability

Quality assessment of herbal remedies does not pose fundamental problems in practice, because of the high standards and long scientific tradition phytochemistry and pharmacognosy have in the Member States. More controversy is found when safety and efficacy of herbal remedies are addressed. Reasons for the divergent opinions are the different traditions in administrative practice (some Member States have considered herbal remedies as food-like products), problems associated with the acceptance of bibliographic data, difficulties in the assessment of typical OTC products with minor indications, and, maybe, reservations toward everything that comes from traditional, nonmodern, and nonmainstream academic medicine. National agencies, however, not only must provide service to the industry but their primary task is consumer's and public health protection. The topics agencies must deal with are partly determined by consumers who wish to have access to safe and effective herbal and other OTC medicines. There are at least two types of herbal remedies or OTC consumers:

1. Consumers who use herbal remedies for self-medication because they are recom-

mended by their doctors or by pharmacists, even for the treatment of more serious indications, and even though they are not or no longer reimbursed by health insurance, and

2. Consumers who prefer to use herbal remedies because they are representatives of an alternative lifestyle who fully trust in their grandmothers' or herbal books' advice and who, therefore, prefer natural products.

Both types of consumer must be informed, even if the latter may pretend that they, rather than the health professionals, are the competent authority. In a situation such as this scientific fundamentalism will be seen by many of the industry's compatriots as an administrative attack against holistic medicine, it will block any dialogue and, finally, will put consumers who have access to the product, at least to botanical drugs, at risk.

This is why the German Parliament repeatedly stated that especially in the sector of herbal and OTC medicines the long-term therapeutic experience and the particularities of therapy with complex natural mixtures must be respected in administrative decisions and that at the same time, consumers must be protected from fraudulent and dangerous medicinal products. The European Parliament and parliaments from other Member States came to identical or essentially similar conclusions.

Council directives provide a framework for the assessment of safety and efficacy of well-known herbal and OTC products if they are applied with the aim of protecting public health, and not in just a formalistic way. Proof of safety and efficacy is not only provided by new pharmacological and toxicological studies or recent double blind randomized clinical trials. According to Art. 4 No. 8a) ii) of CD 65/65 EEC, published literature must be considered in the case of well-known medicinal products, a category which herbal remedies usually belong to. As long as publications give sufficient evidence that the product in question has a well-established medicinal use with recognized efficacy and an acceptable level of safety it is not necessary to repeat all the tests and trials. The situation of herbal remedies is in this aspect identical to that of other known drugs occasionally used for minor indications.

The terms well-established medicinal use, recognized efficacy, and acceptable level of safety are open for interpretation by assessors in agencies; they include the obligation for a case-by-case assessment. Evidently, such an individual judgment will pose problems to EU harmonization and mutual recognition, because well-established criteria are lacking in this area. Maybe this is the reason why the Scotia-decision of the European Court of Justice (ECJ) received so much attention (14).

In his judgment of October 5, 1995 the ECJ had to answer the question: can a marketing authorization be granted by the competent authority if the application under Article 4 (8) a) ii of CD 65/65 does not contain a detailed reference to published scientific literature and if expert reports complying with the CD 75/319 EEC are absent? The Court stated that the abridged procedure in no way relaxes the requirements of safety and efficacy which must be met by medicinal products. If an applicant wants to use the abridged procedure, it must demonstrate by scientific literature that the requirements set out by CD 75/318 are met. The competent authority is not allowed to decide to which extent an applicant must satisfy these criteria.

The institute does not believe that this decision contrasts with the possibility to accept bibliographic data and documented well-established use for herbal and OTC products under the conditions of Article 4 No. 8 a ii. It should be noted, however, that all items in the annex of CD 75/318 EEC must be addressed in the expert report and in the documentation. Relevant aspects which cannot be covered by scientific literature must be covered by appropriate new studies, especially if it is a question of safety. For example, it is not reasonable to require animal studies on the acute toxicity of Peppermint tea, but the problem of Peppermint-tea

toxicity must be discussed by the experts on the basis of its widespread use and experience.

Safety

Concern about the safety of herbal remedies is growing worldwide, with the main concern focusing on appropriate quality control and proper labeling of ingredients (15,16,21). This aspect is of particular importance for those countries which, until now, have not had full control of their markets with herbal remedies; most of the cases of intoxication or of problems come from such countries. Many herbal remedies can rely on long-term use documented in the literature and the question arises as to whether an acceptable level of safety can be based on widespread and well-established use, despite the fact that, from a formal point of view, nonclinical tests are incomplete or not in accordance with today's state of the art. This question was addressed by the CPMP in the context of mutual recognition of marketing authorizations. Development of criteria for safety assessments of well-known medicinal products with a broad use on national markets is ongoing and a draft paper was published in April 1996. Nonclinical testing of old substances should be directed toward the study of effects that are difficult or even impossible to detect clinically. Such effects are reproductive toxicity, genotoxicity, and carcinogenicity. These criteria and the discussion of the underlying problem come one step closer to a more precise definition of the type and contents of bibliographic safety data presented in abridged or bibliographic applications. They come one step closer to a more realistic approach to the existing markets with products which are neither new chemical entities nor high tech products.

After more than 18 years of experience with the review and medical assessment of herbal medicines in Germany, it can be said that products devoid of any risks are rare. Clear definitions of herbal drugs and their preparation is fundamental to safe use. For each preparation it must be assured that it really has a well-established use. It is difficult, for example, to find a link between an herbal tea or a tincture and an extract prepared by supercritical carbondioxide. Because of the high standards of analytical phytochemistry, there are examples where data are available on unwanted ingredients or negative markers. In these cases, reasonable suspicion can result from the pharmacognostic characterization of an herbal drug, and more toxicological data may be necessary before researchers can agree on the safety assessment of an herbal medicinal product. Examples are the content of emodin in Senna, or cytotoxic valepotriates in Valerian root or estragole in fennel oil (17). In contrast to many chemically defined products indicators can be found for a traditional reproductive toxicology: herbal drugs are described in textbooks to have abortive properties and they may be used for birth-control in ethnomedicine. Such data may serve as negative markers as well. In these cases, there are reasonable grounds to ask for more detailed studies.

It should be noted that more than 4,000 herbal medicinal products on the German market have been subject to pharmacovigilance actions since 1978 and that many of them had to be withdrawn from the market or their use had to be restricted (Table 6). At the European level, one important result of the discussions on safety aspects in the former CPMP was a list of herbal drugs that pose more severe risks but have no proven benefit, so that at the present state of knowledge they do not qualify for authorization (Table 7) (6). Examples are drugs with pyrrolizidinic alkaloids, Secale cornutum, or Teucrium chamaedris. Drugs with a particularly high risk require a more detailed discussion concerning the benefit to risk ratio, among them comfrey preparations for external use, and herbal drugs with cardiac glycosides and with alkaloids, for example, Atropa belladonna or Cephaelis ipecacuanha.

This list demonstrates that discussion of drug risks is hardly possible without the pres-

TABLE 6
Pharmacovigilance Problems

Year	# of Products	Reason
1981	336	Aristolochic acid
1985	11	Sugar in teas for children
1987	59	Vinca minor
1988	1	Echinacin (parenteral)
1990	2	Dionaea muscipula
1990	2,817	Pyrrolizidinic alkaloids
1991	14	Ginkgo biloba (parenteral)
1991	95	Rauvolfia/Aflatoxins
1992	1,427	Anthranoids (Step I)
1992	1,427	Anthranoids (Step II)
1992	159	Rubia tictorum
1992	7	Teucrium chamaedris
1993	2	Ginkgo biloba (i.v. infusion)
1994	44	Sassafras albidum
1995	1	Safrole

ence of plausible benefits. Therefore, a systematic risk evaluation must include the plausible proof of efficacy. A traditionally used label will only defer the problem of assessment to the consumer, who is probably the least capable of well-founded decision making.

Efficacy

A medicinal product is essentially characterized by its indications. In some Member States herbal remedies are generally labeled traditionally used products whereas other Member States use a so-called regular indication. CDs do not, however contain such a category as traditional efficacy; on the contrary, they apply to herbal remedies in the same way as to any other medicinal product. A traditional use label is not acceptable on the basis of EC directives but it might be used for products limited to national markets. On a free European market, however, such strictly national products are a pure illusion. After all, it is not clear what the basis of a traditionally used label should be: marketing authorizations granted though efficacy that cannot be demonstrated from bibliographic data do not comply with CD 65/65 EEC. If a well-established medicinal use can be taken from published data, the label "traditional" could be seen as discrediting, especially as this term is not used in chemically defined substances with comparable conditions. Considering that herbal remedies are often used by way of self-medication, comprehensive patient information is crucial. This includes unambiguous information on indications and adverse reactions, contraindications, interactions as well as details of the route of administration and dosage. The CPMP debate on toxicological requirements for old substances opened up the discussion for a more realistic view of the existing market of old medicinal products that have been reviewed in national procedures. Such discussions are also needed in the field of efficacy assessment.

Indeed, it is a problem for herbal remedies that there are many active constituents accepted in the literature to be safe and effective although there are no new clinical studies complying with current criteria. But this is a problem for many other well-established OTC drugs as well. In the regulations under Article 26 of the German Medicines Act (19) the term bibliographic data mentioned in the EEC directive is stated more precisely as:

- Controlled clinical trials,
- Other clinical trials,
- Field studies,
- A collection of single cases, allowing a scientific evaluation, or
- Scientifically documented medical experience, for example, scientific literature and expertise of scientific medical associations.

The data presented must be such that an assessment of safety and efficacy of the product is possible. They are required to correlate with the severity of indications claimed for the product and the risks of the active constituents. In the years from 1978–1994 a pluridisciplinary expert group for herbal remedies, the so-called Commission E, made a review of herbal drugs on the German market (Table 8). In 1984, it proposed the following additional criteria for the evaluation of long-

TABLE 7
Herbal Drugs with Serious Risks without any Accepted Benefit
(Not acceptable for revision)

Aconitum all species
parts: all parts
reason: contains aconitine and other toxic alkaloids, benefit not proven

Angelica archangelica L.
parts: fruit, herb
reason: contains phototoxic furanocumarins, benefit not proven

Aristolochia all species
parts: all parts
reason: contains aristolochic acids, strong carcinogen, genotoxicity, benefit not proven

Artemisia cina (BERG.) WILLKOMM.
parts: flower-bud
reason: contains the toxic lactone santonin, benefit/risk negative

Berberis vulgaris L.
parts: bark, root bark, root
reason: contains the alkaloid berberine

Borago officinalis
parts: herb, flowers
reason: contains pyrrolizidine-alkaloids with genotoxic, carcinogenic and hepatotoxic properties

Bryonia all species
parts: root
reason: cytotoxic cucurbitacines, drastic laxative and emetic

Chenopodium ambrosioides L. var. anthelminthicum (L.) A.GRAY
parts: essential oil
reason: contains the toxic principle ascaridole, benefit/risk negative

Chrysanthemum vulgare (L.) BERNH.
parts: flower, herb
reason: may contain essential oil with the neurotoxic thujone

Citrullus colocynthis (L.) SCHRAD.
parts: fruit
reason: contains cytotoxic cucurbitacines, drastic laxative

Claviceps purpurea (FR.) TULASNE
parts: Secale cornutum (Sclerotium)
reason: contains toxic ergot-alkaloids. benefit/risk negative

Convolvulus scammonia L.
parts: resin
reason: drastic laxative with irritant properties

Croton tiglium L.
parts: seed, fatty oil from seed
reason: drastic laxative, contains tumor-promoting phorbol diesters

Cynoglossum officinale L.
parts: herb
reason: contains pyrrolizidine-alkaloids with genotoxic, carcinogenic and hepatotoxic properties

Dryopteris filix mas (L.) SCHOTT
parts: rhizome
reason: the constituents drug are highly toxic, severe intoxications may occur when absorption is increased, benefit/risk is negative

Exogonium purga (WEND) BENTH.
parts: root, resin
reason: drastic laxative with irritant action

Juglans regia L.
parts: Fruit-shell
reason: may contain the naphtoquinone juglone which is mutagenic and possibly carcinogenic. no benefit proven

Juniperus sabina L.
parts: herb
reason: toxic herb, no benefit proven

Ledum palstre L.
parts: herb
reason: contains essential oil which is a potent irritant of the GI-tract, kidneys and urinary tract. no benefit proven

(*continued*)

TABLE 7
Continued

Mallotus phillipinensis (LAM.) MÜLLER-ARG.
parts: gland and trichomes (Kamala)
reason: drastic laxative which may cause severe gastroenteritis, diarrhea and vomiting when taken in higher dosages; benefit/risk negative

Ocimum basilicum L.
parts: essential oil
reason: contains high amounts of estragole which is genotoxic and a carcinogen in rodents. no benefit proven

Petasites hybridus (L.) GAERT. MEYER et SCHREB.
parts: leaf
reason: contains pyrrolizidine-alkaloids with genotoxic, carcinogenic and hepatotoxic properties

Petroselinum crispum (MILL.) Nym. ex A. W. HILL
parts: fruit
reason: contains significant amounts of essential oil with toxic apiole. Apiole and the fruits are used for self-induced abortions

Pulsatilla vulgaris MILLER
parts: herb
reason: higher doses may irritate the kidneys and urinary tract and pregnancy is an absolute contraindication. no benefit proven

Ruta graveolens L.
parts: herb, leafs
reason: causes phototoxic reactions, genotoxic, used for self induced abortions, resulted in fatal intoxications. no benefit proven

Rubia tinctorum L.
parts: root
reason: contains lucidin with genotoxic and probably carcinogenic activity. no benefit proven

Sassafras albidum (NUTT.) NEES
parts: wood, root
reason: contains essential oil with carcinogenic and genotoxic safrole. no benefit proven

Senecio all species
parts: herb, root
reason: contains pyrrolizidine-alkaloids with genotoxic, carcinogenic and hepatotoxic properties

Strychnos nux-vomica L.
parts: seed
reason: contains alkaloids, especially strychnine. benefit/risk negative

Symphytum all species, internal use
parts: herb, leaf, root
reason: contains pyrrolizidine-alkaloids with genotoxic, carcinogenic and hepatotoxic properties. no benefit proven

Teucrium chamaedris L.
parts: herb
reason: hepatotoxicity

Tussilago farfara L.
parts: flower, root
reason: contains pyrrolizidine-alkaloids with genotoxic, carcinogenic and hepatotoxic properties. no benefit proven

Vinca minor L.
parts: herb, leaf
reason: hematological changes (leucocytopenia, lymphocytopenia, reduced globuline levels) have been observed in rabbits. no benefit proven

Drugs with Toxic Principles, where a More Detailed Discussion Concerning the Benefit/Risk Ratio is Necessary:

1. Drugs with pyrrolizidine-alkaloids where a use is accepted under special precautions/labeling:

Symphytum officinale L., external use
parts: leafs, herb, root
restrictions: use only on unbroken, intact skin, use during pregnancy requires medical advice, use no longer than 6 weeks per year, temporarily tolerable dose (TTD) 100 µg PA/day

Tussilago farfara L.
parts: leaf
restriction: contraindicated during pregnancy and lactation, use no longer than 6 weeks per year, temporarily tolerable dose (TTD) 1 µg (herbal tea 10 µg) PA/day

Petasites hybridus (L.) GAERT. MEYER et SCREB.
parts: rhizome
restriction: contraindicated during pregnancy and lactation, use not longer than 6 weeks per year, temporarily tolerable dose (TTD) 1 µg PA/day

For these drugs a limitation of the toxic principle and a strict definition of the conditions of use is necessary

A similar approach is necessary for herbal drugs with small amounts of toxic constituents and accepted uses, for example, estragole in (sweet) fennel

2. Drugs with cardiac glycosides
for example:
Adonis vernalis L.
Convallaria maialis L.
Digitalis species
Nerium oleander L.
Urginea maritima (L.) BAKER
Strophanthus species

For these drugs a detailed benefit/risk assessment is necessary

3. Drugs with alkaloids
for example:
Atropa belladonna L.
Cephaelis ipecacuanha KARSTEN
Datura stramonium L.
Ephedra sinica STAPF
Hyoscymaus niger
Pausinystalia yohimbé (K. SCHUM.) PIERRE
Rauwolfia serpentina (L.) BENTHAM ex KURZ

For these drugs a detailed benefit/risk assessment is necessary

TABLE 8
Commission E

Articles 25 (5) and 25 (7) Medicines Act:
Experts with special theoretical knowledge and practical experience with herbal remedies
12 Members + 12 Substitute Members: • Pharmacy (1) • Pharmacology/Toxicology (1) • Clinical Pharmacology (1) • Medical Statistics (1) • Medical Practice (8) (Physicians, Pharmacists, nonmedical Practitioners)

term experience with herbal drugs: without new controlled clinical trials, evidence of safety and efficacy is accepted as plausible if:

- An herbal drug is mentioned in the standard literature or well-documented review articles,
- There are clinical trials which are not conclusive alone but are supported by supplementary experimental data, or
- There is well-documented knowledge on traditional use that is supported by significant experimental studies.

Traditional use without supplementary data or experimental data alone cannot be accepted as sufficient evidence of efficacy. An example of this approach is the drug Manna which consists mainly of mannitole. Mannitole is not fully absorbed in the gut and, therefore, it can be used as an osmotic laxative. In this case, the traditional use has a pharmacologically plausible basis. The situation is different with the fruits of Ficus carica, mainly consisting of saccharose, which have no laxative effect. The amount of fiber is quite low, so it is not a bulk forming laxative. A laxative action of this drug, at least at therapeutic dosages, is not plausible even if the traditional use is documented in the literature (20). The assessment of other gums which are highly (>70%) fermentable, for example, Pectin, Gum arabic, or Tragacanth, could be done on a similar basis (18).

Maybe this approach could be a starting point for developing guidance to the interpretation of the terms of Article 4 No. 8 a, ii for herbal remedies. A consensus is needed if arbitration in decentralized procedures is to be avoided. One key to the solution of these problems could be core SPC guidelines on active principles or even groups of substances. As the time for the mutual recognition procedures is very strict, it will not be possible to discuss all problems related to an application. Problems can be expected especially in those cases where divergence is great, for example, herbal remedies and many other OTC remedies. Biological products such as herbal remedies pose specific problems in assessment and need special experience and expertise for evaluation due to their complex composition. One herbal preparation is considered one active constituent even if it is composed of many different chemically defined substances. In some cases, where the active ingredients of herbal preparations are well known, a reproducible therapeutic activity can be assured by a standardization of these active ingredients, an example of which is sennosides in Senna. In most cases it is not possible to clearly associate one active ingredient with the therapeutic effect. Even in those cases where an active ingredient is known, the therapeutic activity may be influenced by other constituents of the herbal preparation, for example, tannins, flavonoids, or saponins, which may enhance, prevent, or prolong absorption or modify metabolism. As a consequence, every assessment of efficacy must be based on the individual herbal drug preparation. This may result in one assessment for a number of similar preparations covered by one monograph of the European Pharmacopoeia. In cases where bibliographic data are presented, posology and therapeutic effect must be correlated to the particular preparation. This is why an assessment of such preparations requires a pluridisciplinary approach of pharmacists, toxicologists, and medical assessors. It is hardly imaginable that a consensus can be reached without prior discussions and experience. Concern of individual Member States about the decision will lead to time-

consuming arbitration procedures. It was an important step against arbitration when the CPMP decided to accept existing core SPC guidelines and to focus discussion on indications, posology, contra-indications/special warnings, and shelf-life. Unfortunately, such guidelines are practically absent for most OTC and herbal products. After all that is known about the situation, it does not seem reasonable to postpone all these open questions to arbitration. A platform is needed to discuss these problems and to exchange experiences with the assessment of herbal drugs. Identical problems in the EMEA and the CPMP have already led to the creation of a special group, the Mutual Recognition Facilitating Group. The group will try to answer open questions with single applications or harmonization of SPCs. These activities demonstrate that decisions on efficacy that are based on bibliographic data and the consequences derived from this approach are not a specific herbal problem. There could be a forum to discuss such questions.

Fixed Combinations

One additional, mainly efficacy-related, problem with the scientific acceptance of herbal remedies is the fear of completely chaotic fixed combinations and the revival of ancient Theriak (Table 9). The problem of OTC-fixed combinations on the market was addressed in discussions on the new EU Note for Guidance on fixed combinations as well. Clear criteria for well-known fixed combinations are still lacking. It is right to say that the use of fixed combinations is one characteristic aspect of phytotherapy, yet in the institute's experience irrational combinations are not found more frequently in phytotherapy than in any other segment of the market, especially in the OTC market. It is possible to apply strict and consistent criteria in the assessment of well-known herbal medicines. Theriak's approach of "it really works" will not be acceptable. As in the case of any other product, benefits and risks of herbal combinations must be balanced and compared to those of single ingredients. There must be a clear indication for the combination and each constituent must contribute to this indication. Dosage and function of each constituent are to be justified by the applicant. The result of review in Germany demonstrates that the number of constituents will decrease and most of the products will be accessible to a scientific evaluation once criteria are set out clearly.

TABLE 9
Theriak Andromachi
(Antidotum Mithridaticum)

≥64 consituents with Opium, Vipers, Squill, Rhubarb, Ruta, Saffron, Valerian, Myrrh, Angelica, Asphalt, Vitriol, Blood of Ducks . . . .
"It really works?"

Andromachos 1st century AD
Mithridates Eupator 120–163 BC

SUMMARY

In summary, the following points should be stressed. The legal and terminological framework for herbal remedies in the EU is clear. Proper labeling and a consistent quality of herbal remedies is a prerequisite in public health protection. Quality criteria are set out in the European Pharmacopoeia and in the EEC Note for Guidance. The problem lies in the interpretation of open terms such as well-established use and acceptable safety and the apparent lack of guidance in interpreting these open terms for widespread OTC and herbal products. The unease of some Member States with this situation is expressed by discussions on toxicological requirements and criteria for fixed combinations of this part of the pharmaceutics market, but EMEA's and CPMP's resources are mainly focused on a limited number of products with new active principles and high-tech products. It is well known that there is a great difference in the assessment of these products in the Member States and that the share of these products of the pharmaceutics market is relevant. "Sit

and wait" does not seem to be a reasonable approach to determine results that are a substantial response to the industry's and consumers' demands. Scientific fundamentalism will do more harm than benefit to consumers' health. Herbal remedies have a well-defined position in the market of medicinal products; it is possible to assess quality, safety, and efficacy on the basis of the existing directives if bibliographic data are accepted in an unbiased way. The best way to protect public health from risks associated with botanical drugs is to make well-tested and adequately labeled herbal medicinal products available.

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