Médicaments à base de plantes dans le contexte réglementaire européen

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Résumé

En Europe, les médicaments à base de plantes connaissent un regain d'intérêt important : ils représentent, selon des données récentes

Depuis lors, les compétences de l'Agence ont été élargies à la Norvège et l'Islande, deux pays non-membres de l'Union Européenne. L'an prochain tout le système de réglementation sera l'objet d'une révision par l'institution politique, en parallèle avec la discussion sur la création d'une agence de sécurité alimentaire. Enfin, actuellement, un des principaux thèmes de réflexion est l'élargissement de l'Union Européenne à au moins 10 pays d'Europe Centrale et Orientale.

Depuis quelques années, les autorités nationales compétentes et l'Agence Européenne d'Evaluation des Médicaments appliquent les mêmes réglementations obligatoires. Il s'agit à la fois de réglements à caractère quasi fédéral, comme ceux de la "Food and Drug Administration" aux Etats-Unis mais aussi de directives devant être transposées dans les législations nationales et enfin d'une pharmacopée européenne, convention non pas seulement de l'Union Européenne mais du Conseil de l'Europe et qui regroupe une quarantaine de pays d'Europe Centrale, Occidentale et Orientale.

En dehors de ces règles à caractère impératif, l'Agence émet beaucoup de notes explicatives, de texte pour les fabricants et les cher-

- la deuxième procédure est une reconnaissance mutuelle pour les médicaments plus conventionnels. Cela commence par une évaluation nationale qui doit être ensuite reconnue. En cas de désaccord entre les pays concernés, l'Agence Européenne effectue un arbitrage ;
- ensuite, il y a une autorisation nationale pour les produits qui n'ont qu'une vocation nationale ou locale. C'est le cas de beaucoup de plantes médicinales, en Allemagne par exemple.

L'autorisation unique européenne pour les médicaments nouveaux aboutit à une seule autorisation et un seul régime de prescription mais cela ne concerne ni le remboursement par la sécurité sociale ni la réglementation des prix.

Le travail de l'Agence a débouché sur l'autorisation de 140 médicaments innovateurs depuis 1995. Le plus spectaculaire est la diminution de 6 à 1 an du temps nécessaire à un nouveau médicament pour arriver sur le marché européen.

Très récemment, après une longue campagne de persuasion et avec

Son rôle consiste à clarifier l'interprétation des textes ordinaires et d'influencer le législateur lorsqu'il s'agit de les adapter aux cas particuliers des médicaments à base de plantes. La tendance dans les états membres est de créer un régime dérogatoire sous la pression des évènements mais sans harmonisation européenne.

L'Agence, qui n'a pas vocation de s'occuper de ces médicaments, a néanmoins créé en 1997 un groupe de travail ad hoc (Working Group on Herbal Medicinal Products) sur les médicaments à base de plantes, dont la présidence est assurée par le Docteur Konstantin Keller de l'Institut Allemand des Médicaments (Bipharm). Ce groupe est composé d'experts et des représentants des Etats Membres, du Parlement Européen, de la Commission, ainsi que d'observateurs de la Pharmacopée Européenne basée à Strasbourg (Figure 2).

En 1999, le Conseil d'Administration de l'EMEA a souhaité donner un caractère permanent à ces activités en en faisant un groupe de

graphies scientifiques. Mais cela fait l'objet de controverses importantes entre les comités scientifiques classiques et le groupe particulier sur les médicaments à base de plantes (Figures 3, 4 et 5).

Les futurs aspects réglementaires ne sont pas du ressort de l'Agence mais elle se sert du groupe de travail sur les médicaments à base de plantes pour formuler des voeux et émettre des propositions ; la Commission Européenne à Bruxelles vient d'annoncer une nouvelle initiative à propos de la réglementation des suppléments minéraux et vitaminés dans l'alimentation. Ce sera un nouveau thème de réflexion et de discussion proche du domaine pharmaceutique et espérons que cette proposition contribuera à délimiter plus clairement *la frontière entre les médicaments et les autres produits.*

L'EMEA a développé un site internet où l'on peut accéder aux rapports de nature générale, aux rapports publics d'évaluation de médicaments nouveaux mais également aux travaux du groupe sur les

Herbal medicines in the framework of European regulations

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Résumé

Herbal medicines have experienced renewed interest in Europe. According to recent statistics, the corresponding turnover is about 4 billion euro, half of it for Germany and a quarter for France.
1'400 medicinal plants have been recorded in the various preparations authorized in France. This growing interest is spreading, not only in the public at large, but also among doctors who prescribe more and more of these products though there is no obligation to do so.

However, scientists sometimes disregard the studies mentioned in the literature and documentation for reference and the competent authorities are not prepared to acknowledge the qualities of herbal medicines

The complexity of preparations based on vegetable drugs might be taken as the cause of the ambiguous attitudes displayed by the national authorities in charge of issuing marketing authorizations when it comes to assessing the quality, safety and efficacy of these products.

The wide range of situations in the member states, some dramatic events such as the kidney accidents that occurred in Belgium five years ago or the interaction between St-John's wort and the anti-retroviral medicines, and popular interest had induced the European Agency for the Evaluation of Medicinal Products to address the issue of herbal medicines on request by the Parliament as they were aware that this situation might have negative repercussions on public health.
As this topic is not pivotal in the preoccupations of the Agency whose research is focused on innovative medicines, a taskforce was set up to investigate plant-based medicines.

General framework for the EU regulations on pharmaceuticals

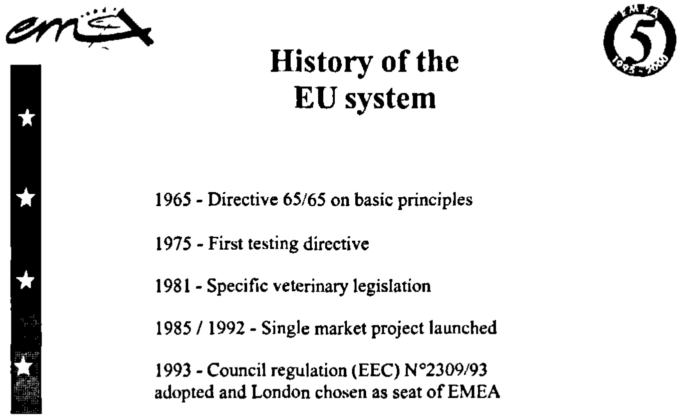
The objectives of the EU regulations for pharmaceuticals have been clearly outlined:

- protection and promotion of public health in Europe;
- creation of a single market for medicines;
- reinforcement of the potential for pharmaceutical research and development in Europe through enhanced international cooperation.

The history of EU regulations dates back to over 30 years, but this basic legislation was complemented with technical contents only in the 80s, and more specifically in the 90s when the EMEA was founded. In 1993 the heads of state of the various nations decided to establish the head office in London. The institution has been active since 1995 and its objective is to protect and promote public health in Europe by focusing on the regulations applying to innovative medicines, or so-called "high tech" drugs produced by biotechnology.

The scope of activity of the Agency has been extended in the meantime to Norway and Iceland, two countries which are not EU

Figure 1



History of the EU system

1965 - Directive 65/65 on basic principles

1975 - First testing directive

1981 - Specific veterinary legislation

1985 / 1992 - Single market project launched

1993 - Council regulation (EEC) N°2309/93 adopted and London chosen as seat of EMEA member states. The set of regulations will be submitted to a thorough revision by the body politic next year, parallel to a discussion on the creation of a food safety agency. finally, another issue currently under discussion is the enlargement of the EU to at least 10

In the past few years, the national authorities and the European Agency for the Evaluation of Medicinal Products apply the same mandatory regulations. These are not only regulations that have near to federal character, similar to that of the Food and Drug Administration in the USA, but also directives meant to be introduced into national legislation, and finally a European pharmacopoeia as a convention promoted by not only the European Union, but also the Council of Europe with some 40 countries of Western,

wide assessment which should then be validated by all. In the event of disagreement between the countries concerned, the European Agency comes up as an arbitrator;

whose scope of application is only one national or local. This

applies, for instance, to many medicinal plants used in Germany.

The European single authorization for the new drugs leads thus results in only one authorization and there is only one prescription mode; however, this regulation does not apply to either social security reimbursements or price control regulations.

Its role consists in clarifying the interpretation of the ordinary texts and to influence the legislator when it comes to adapt them to the particular cases of the drugs containing plants. The tendency in the Member States is to create a derogatory mode under the pressure of the events but without European harmonization.

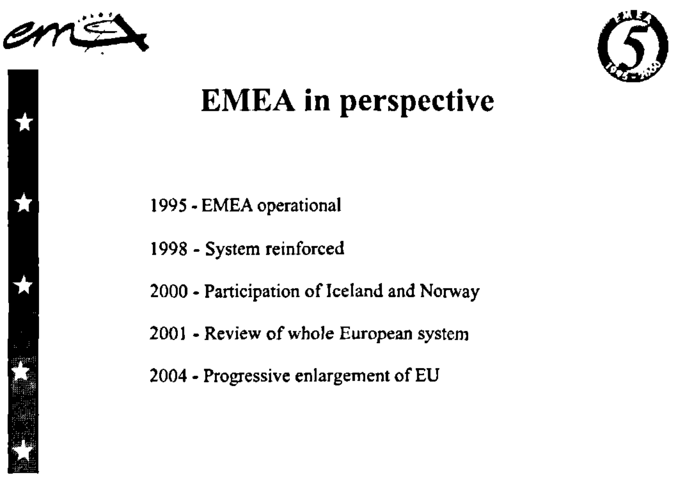
The Agency, whose scope of activities does not include dealing with this type of drugs, has nevertheless created in 1997 an ad hoc working group (Working Group on Herbal Medicinal Products) to deal with the issue of plant-based drugs; this committee is currently chaired by Doctor Konstantin Keller of the German Drug Institute (Bipharm). This group is composed of experts and representatives delegated by the Member States, MEPs, members of the European Commission, and observers of the European Pharmacopoeia whose office in Strasbourg (Figure 2).

In 1999, the Board of directors of EMEA made moves to give permanent character to the activities of this group by giving up ths status of an ordinary working group; they also adopted new members from the Central and Eastern European countries and also experts from Norway and Iceland. In 1999, the group likewise established contacts with Société Européenne d'Ethnopharmacologie, ESCOP and other associations interested.

The work that has been accomplished since 1997 made it possible to suggest new orientations and requirements relating to quality, safety and the effectiveness of plant-based drugs, from the point of view of manufacturing, and also cultivating and collecting.

Concerning safety, the group issued a memo with information and explanations about the testing protocols in pharmacology and toxicology. Research is less advanced as far as efficacy is concerned; however, a memo on possible combinations of plant-based drugs has already been published.

Figure 2



EMEA in perspective

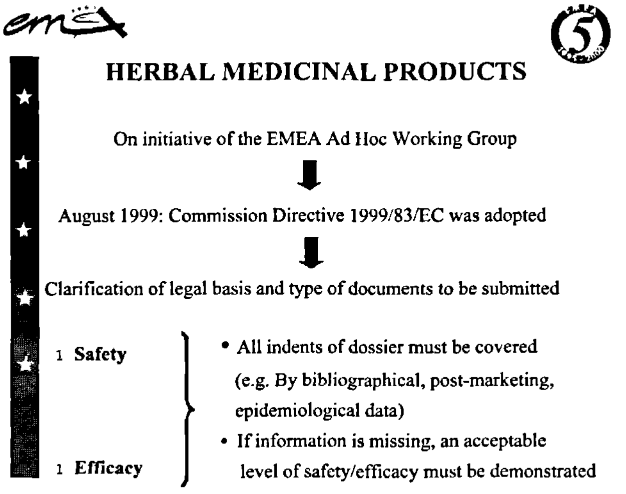
1995 - EMEA operational
1998 - System reinforced
2000 - Participation of Iceland and Norway
2001 - Review of whole European system
2004 - Progressive enlargement of EU

The group is currently working in two areas: on the one hand, examining proposals and leads related to the potential efficacy of drugs as reported in bibliographical data; on the other hand, drafting notes on products specifications, i.e. scientific monographs. But this is the subject of very controversial debating between the traditional scientific committees and the specific group working on plant-based drugs (Figures 3 and 4).

The legal dimension of the issue is outside the scope of competence of the Agency. All the same, the Agency turns to the working group dealing with herbal medicinal products to make suggestions and table proposals. the European Commission in Brussels has just announced a new initiative in connection with the regulations applying to mineral and vitaminised additives in food products. This will another theme for thought and discussion, closely related to pharmaceutical issues. We hope that this proposal will help us draw clearer borderlines between medicinal products proper and the other products.

EMEA has developed an Internet site where specialists can have access to reports of general character, assessment reports on new drugs published by public organisations, and also the proceedings of the work group on plant-based drugs.
Specific quality standards have also been taken up in the Website. They are to be integrated into the series entitled "Regulations applying to Medicinal Products within the European Community" published by the European Commission.
Other policy papers are still under examination; they are meant to reduce in the short term the uncertainties related to a demonstration of the efficacy of herbal medicinal products, thus ensuring a high level of consumer protection and safety.

Figure 3



HERBAL MEDICINAL PRODUCTS

On initiative of the EMEA Ad Hoc Working Group
⬇
August 1999: Commission Directive 1999/83/EC was adopted
⬇
Clarification of legal basis and type of documents to be submitted

1 **Safety**
1 **Efficacy**

- All indents of dossier must be covered (e.g. By bibliographical, post-marketing, epidemiological data)
- If information is missing, an acceptable level of safety/efficacy must be demonstrated

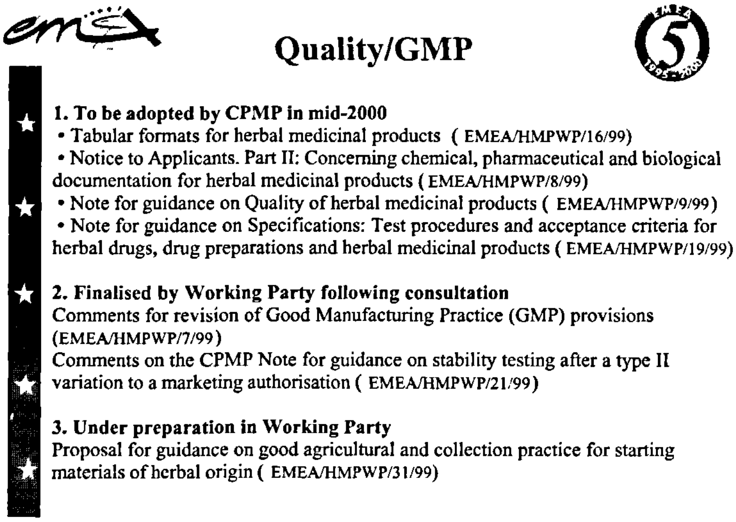
Conclusion

The stock of herbal medicinal products represents a major asset and a heritage for Europe and the rest of the world and it should be preserved with the utmost care.

For its research and technical work, the Agency relies on the work of ESCOP in Europe and W.H.O. for the rest of the world; it has set up a specific working group for that purpose. The United States – in particular biotech corporations - have recently shown growing interest in herbal medicinal products as these drugs are likely to assume to strengthen their position in the revolution currently developing in the field of life sciences.

The Website address is as follows:
http://www.eudra.org/emea.html

Figure 4



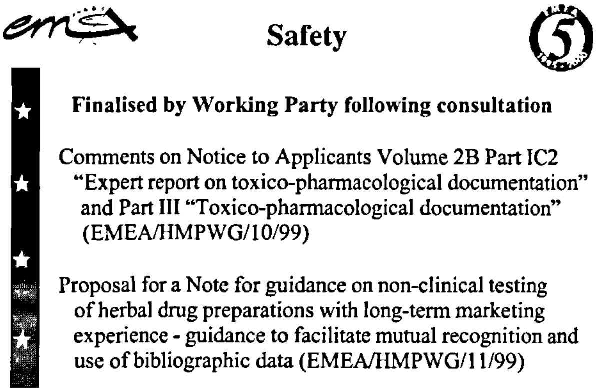
Quality/GMP

1. To be adopted by CPMP in mid-2000
- Tabular formats for herbal medicinal products (EMEA/HMPWP/16/99)
- Notice to Applicants. Part II: Concerning chemical, pharmaceutical and biological documentation for herbal medicinal products (EMEA/HMPWP/8/99)
- Note for guidance on Quality of herbal medicinal products (EMEA/HMPWP/9/99)
- Note for guidance on Specifications: Test procedures and acceptance criteria for herbal drugs, drug preparations and herbal medicinal products (EMEA/HMPWP/19/99)

2. Finalised by Working Party following consultation
Comments for revision of Good Manufacturing Practice (GMP) provisions (EMEA/HMPWP/7/99)
Comments on the CPMP Note for guidance on stability testing after a type II variation to a marketing authorisation (EMEA/HMPWP/21/99)

3. Under preparation in Working Party
Proposal for guidance on good agricultural and collection practice for starting materials of herbal origin (EMEA/HMPWP/31/99)

Figure 5



Safety

Finalised by Working Party following consultation

Comments on Notice to Applicants Volume 2B Part IC2 "Expert report on toxico-pharmacological documentation" and Part III "Toxico-pharmacological documentation" (EMEA/HMPWG/10/99)

Proposal for a Note for guidance on non-clinical testing of herbal drug preparations with long-term marketing experience - guidance to facilitate mutual recognition and use of bibliographic data (EMEA/HMPWG/11/99)