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Commission E in the German Drug Approval Process: Briefing Notes

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COMMISSION E IN THE GERMAN DRUG APPROVAL PROCESS:

BRIEFING NOTES

Summary

In Germany, physicians are permitted to prescribe herbal drugs, and they do so frequently.

In Germany, herbal drugs are approved for marketing through the same agency that authorizes the approval of chemical entities, the Federal Institute for Pharmaceutical Drugs and Medicinal Products.[1] This German Institute insists that benefit/risk evaluations be made for each herbal drug but recognizes that herbal drugs are different. Therefore, their evaluation is based:

1) on the assumption that the medical propensities of an herb can be determined, on the basis of various empirical data. However, this evaluation generally does not require a breakdown of the dug into its chemical components. Instead, the plant itself, as used for curative purposes, is the pharmaceutical component under review; and

2) on the reliance of experts who practice herbal medicine, either as physicians or as practitioners of an alternative or traditional form of medicine outside of conventional medicine. Commission E, an advisory body for the agency, is composed of such experts.

Commission E has attracted worldwide attention through its publication of some 350 monographs on curative herbs. Since 1995, Commission E has stopped the preparation of monographs. Since then, the Commission is solely engaged in advising on the authorization of new drugs or old drugs which still can be marketed on the basis of a grandfather clause. Before 1995, the herbal monographs were sufficient to justify the marketing of herbal drugs. Since 1995, the applying drug manufacturer must prove the efficacy of the drug, and the monographs alone may no longer sufficient, if there have been new scientific discoveries. However, Commission E still bases its decisions in part on the practical experience of its herbal experts, as is required by law.[2]

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[1] The telephone number of the Institute and of other institutions that may provide information is included in *Appendix I.*

[2] Information on the composition and the workings of Commission E has been obtained by telephone from Dr. Wissinger, Deputy Chief of the Division for Herbal Drugs of the Federal Institute for Pharmaceutical Drugs and Medicinal Products in Berlin.

The general status of herbal drugs in Germany

In Germany, herbal medications are pharmaceutical drugs, and they are governed by the Act on Pharmaceutical Drugs of 1976,[3] generally in the same manner as chemical entities, aside from the differences in their approval described below. In accordance with the overall regulatory scheme, herbal drugs can be over-the-counter or prescription drugs; and they may fall into the category of drugs that can be sold in pharmacies only or they may be permitted to be sold elsewhere.

German physicians prescribe herbal drugs frequently, and German patients are also in favor of herbal medications. They may request them from their physicians, or use them as self-treatment, or upon the advice of non-medical healing practitioners. Herbal drugs are desirable because they have few side effects. They are gentle, and they may effect several bodily functions and thereby activate circulations. They work slower and have to be taken for longer periods. For these reasons, their effectiveness may be difficult to prove in laboratory or clinical tests.[4]

The current work of Commission E

Commission E was created in the 1977, as an advisory body to assist the German Federal health authorities in the marketing approval for herbal medications.[5] Commission E currently consists of some 20 experts and most of them have practical experience in the treatment of human disease through herbal medications. Among these experts are licensed physicians who rely to a large extent on herbal methods in their medical practice as well as healing practitioners. The latter are individuals who are not physicians but who are nevertheless licensed by the German states to practice their healing arts.[6] Healing practitioners apply many traditional healing methods, among them herbal cures. In addition to these practicing health professionals, Commission E also has experts on pharmacology, toxicology, biometrics, and related disciplines.

At the present time, the Commission is involved in the approval of both grandfathered (see below) and new herbal drugs. Each drug is evaluated according to the same criteria that apply to chemical entities by focusing the efficacy, a risk/benefit analysis, side effects and synergistic effects, counter-indications, etc. This process always involves a review of the existing literature; but, depending on the drug, it also may involve case histories, expert opinions, and other proof that the applicant may be asked to furnish. In reaching a judgment, the Commission also relies on the practical therapeutic experience of its members.

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[3] Arzneimittelgesetz (AMG), repromulgated Oct. 19, 1994, BUNDESGESETZBLATT (BGBl., official law gazette of the Federal Republic of Germany) I, p. 3019, as amended.

[4] Included as *Appendix II* is a consumer information leaflet that is a package insert of *Crataegut* Tropfen, a frequently used preparation of hawthorne extract that is used as self-medication for heart ailments.

[5] Bekanntmachung, Apr. 13, 1977, Bundesanzeiger No. 79 (Apr. 27, 1977), as amended by Bekanntmachung, Apr. 22, 1982, Bundesanzeiger, No. 80 (Apr. 29, 1982).

[6] On the basis of a Federal Act of 1939, Heilpraktikergesetz, Feb. 17, 1939, REICHSGESETZBLATT I, p. 251.

In the approval process for an herbal preparation, both the approving agency, the Federal Institute for Pharmaceutical Drugs and Medicinal Products, and Commission E are guided by the assumption that the herb itself has certain propensities and the entire herb (or the preparation made therefrom) is the compound to be evaluated. No effort is made to break down this evaluation process to the chemical components of the herb. Instead, it is recognized that there is no scientific explanation as to why certain drugs have curative propensities although it is scientifically provable or proven that they do.

The monographs prepared by Commission E

An important part in the approval of many herbal drugs is played by the 350 monographs that were prepared and published by Commission E from the time of its creation until 1994. These give a pharmaceutical profile of the more commonly used herbs. These monographs were used to justify the approval of herbal preparations that had been in existence before 1978, the effective date of the 1976 Act on Pharmaceuticals, and the approval of which had been grandfathered by the new Act.

With the reform of 1994, Commission E stopped producing further monographs and has since focused solely on the approval of old and new drugs, upon individual application of the producer. Although the monographs are still used in this process as part of the scientific documentation, both by the Commission and by the approving authority, additional proof of the usefulness of the drug may be required from the applicant, either because of new uses or new preparations of a particular herb, or because the monograph may no longer represent state-of-the art knowledge. In contrast to the procedures before the 1994 reform, the producer now has the burden of proof for the evaluation of the herbal drug.

The legislative mandate for Commission E

Commission E for herbal drugs is one of several advisory commissions for the approval of drugs. Commission A deals with drugs that do not fall into any of the special therapy groups. Commission B was engaged in the preparation of monographs for grandfathered chemical entities. Commission C deals with the approval of antroposophic drugs, yet another alternative form of medicine in Germany; and Commission D deals with homeopathic drugs. Yet another Commission deals with over-the-counter medications of mild efficacy (see below). For prescription drugs, the legislative mandate for these Commissions and their work is found in § 25, ¶ 6, of the Act on Pharmaceutical Drugs which translates as follows:[7]

> Before the approval of a proprietary drug that requires a prescription in accordance with § 49, an approval commission must be heard. The hearing shall cover the content of the document supplied by the applicant, the opinions of experts, including those requested by the authorities, the positions taken by consulted experts, the result of the examination, and the reasons for the decision, or the evaluation by opposing experts. If the Federal authority deviates from the findings of the hearing, it shall present the reasons for the difference. The Federal Ministry for Health shall appoint

[7] For non-prescription drugs of an herbal or other alternative nature the special commissions for these therapies must also be involved [AMG, § 25. ¶ 7].

> the members of the approval commissions upon the proposal of the associations of the healing professions, that is the representative associations of physicians, dentists, veterinarians, pharmacists, healing practitioners, and pharmaceutical manufacturers. *The appointments shall consider the special propensities of certain drugs. Appointed to the approval commissions shall be experts who have scientific knowledge as well as practical experience in the areas of application, with regard to specific substances, and for the alternative practices of medicine [Italics supplied].*

The attitude toward herbal medications as the philosophical basis for Commission E

This statutory recognition of alternative forms of medicine dates back to the creation of the Act on Pharmaceutical Drugs in 1976, when Germany adopted an approval system for drugs, in contrast to the formerly existing mere registration system. At that time, advocates of alternative and traditional forms of medicine were concerned that the scientific approval criteria for drugs would make it impossible for herbal drugs and other alternative drugs to gain approval and that thereby herbal medications would become illegal and be driven from the market.

In a Committee Report on the bill for the 1976 Act on Pharmaceutical Drugs, [8] the Committee affirmed that conventional medicine is not the only form of medicine practiced in Germany. Instead, there is a plurality of medical doctrines, and these are based on different theories and methods. The Pharmaceutical Act should not be used to drive alternative therapies and their drugs from the market by letting one medication doctrine impose its state of the art concept on the other doctrines. The Committee continued that the rules for determining efficacy of a drug for the market authorization should reflect the plurality of scholarly doctrines on drugs.

The fate of herbal drugs in the current drug-approval proceedings

Herbal medicines have strong popular support. Many physicians prefer to prescribe or recommend them in general. Two thirds of the German population prefer them. Fifty percent of the 2,000 most frequently prescribed drugs are herbal drugs. Nevertheless, there is some hostility among the medical establishment, the social Health insurers and the drug companies.[9] Current drug law has been shaped by this tension between herbalists and conventional medicine, first through the making of allowances for their approval in 1976, and second, in 1994, through the changes in the approval process which require more scientific information from the producer. This new policy may have had positive effects on the quality control and scientific justification of the herbal drugs but also may have driven many of them from the market. The required documentation now costs U.S. $700,000, a large sum for the small businesses that produce herbal drugs. In 1978, some 67,000 herbal drugs were on the market. This number has dwindled to 57,000 (plus 20,000 teas) in 1997. Currently, 700 herbals have passed the marketing authorization. Four thousand are in application and 1,000 will disappear from market in 2005. (In addition, there are also some 20,000 teas that don't need

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[8] Ausschussbericht, Aug. 24, 1976, reprinted in A. Cloesel & W. Cyran, ARZNEIMITTELRECHT M2 (Stuttgart, 1988-).

[9] A group of social health insurers issued a report that discredited the effectiveness of many herbal medications -- some of these statements had to be retracted after lawsuits.

approval.[10] In 2005, it appears that herbal drugs that the 1,000 herbal drugs that will no longer be marketable as drugs might be marketable as foods or as cosmetics. There is still uncertainty over the fate of these drugs, which is a pending political issue.

The more stringent approval system of 1994 may have been enacted not only because of a more rigorous understanding of the need for scholarly documentation but also by the requirements to terminate the transition from a registration to an authorization system that was commenced with the enactment of the Act on Pharmaceutical Drugs in 1976. Drugs already existing on January 1, 1978, the effective date of the new Act, could continue to be marketed if an application for their approval was filed; and by 1990, an extension of the application was filed, together with the documentation for a (new) approval.[11] Drugs that have been registered as not applying for approval can be marketed until 2005, and then they must disappear from the market.

For certain over-the-counter drugs of a low efficacy, yet another special scheme was created in 1994.[12] These can be approved by a special Commission that is largely composed of family practitioners. These drugs must, however, bear an inscription that is something of a disclaimer . It must state that the drug is traditionally used to strengthen, or to make a person feel better, or to support the function of an organ, for preventive purposes, or as a drug of mild efficacy. The fate of these drugs after 2005 is still undetermined.

Influence of European Community Law on German Drug Law

Germany has to comply with the European harmonization directives for medicinal products. The most important of these are Directive 65/65 EEC, and Directive 75/319 EEC, on the authorization process in general, as expanded in 1989, by Directive 89/341. In addition, Directive 75/318 on the testing of medicinal products for human use, sets the standards for the evaluation of drugs. In 1991 Directive 75/318 was extensively rewritten by Directive 91/507,[13] and the deadline for transforming this directive into national law was January 1, 1995. It appears that this implementing deadline caused the Germans to reform their laws and practice with regard to the approval of herbal medicines.

This reform has preserved some of the special rules for herbal drugs, in particular the reliance on herbal practitioners in the evaluation, but it has made the approval process more stringent, partly in an effort to terminate the transitional phase of the Act of 1976 and to achieve the goal of having all drugs scientifically evaluated and approved.

Although Germany cooperates with EU law on pharmaceuticals, there may be a tension between the German herbal traditions and the overall drug regulation system of the EU. There also

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10 P. Thorbrietz, *Steiniger Weg zur neuen Medizin*, DIE WOCHE 26 (Feb. 13, 1998).

11 AMG, § 109, ¶ (3).

12 AMG, §§ 109 & 109a.

13 Sept. 26, 1992, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES L No. 270/32.

appears to be a tension between the German constitutional provisions on personal and professional freedom and the fundamental goals of freedom of movement and European Union trade.[14]

Conclusion

The German attitude toward herbal medications is based on longstanding traditions that have never been totally abandoned in favor of conventional medicine. The approval process for drugs is based on the assumption that conventional medicine does not have an exclusive claim for determining what a scientific method is. It appears that the Germans are intent on maintaining a favorable climate for the approval of herbal medications, even though the process has become more expensive for the small producers since the fall of 1994. On the whole, since 1976, the rules for herbal drug approval have been a compromise between the proponents of traditional medicine who would have preferred that these drugs not be regulated at all and the proponents of conventional medicine and the chemical pharmaceutical industry which would have preferred to regulate herbal drugs as stringently as chemical entities.

The shift in policy in 1994 has led to a more thorough examination of herbal drugs, and the proof for their effectiveness must be made by the manufacturer. Nevertheless, the practical experience with drugs still is an important evaluation criterion. Herbal drugs that have been approved under the new policy may have more credibility with conventional physicians who are skeptical of traditional medicine. There appears to be a widespread opinion that more research is needed, for which there seems to be scarcity of funds.

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[14] L. Dietze, *Zum gesundheitlichen Vertrauensschutz*, M. Heinze, FESTSCHRIFT FÜR WOLFGANG GITTER 223 (Wiesbaden, 1995).

APPENDIX I

German addresses of potential interest:

Bundesinstitut für Arzneimittel und Medizinprodukte
Berlin.
Phytomedical experts: Dr. Keller and Dr. Wissinger
Tel. 30454830

Naturopathic Medical Association
Freudenstadt Tel: 74412151
Bismarkstr. 3
Zentralverband der Ärzte für Naturheilverfahren.

Hufeland Gesellschaft für Gesamtmedizin
Karlsruhe
Tel. 721/886276(-77)

Kooperation Deutscher Heilpraktikerverbände
Bonn Tel 228/611049

Bundesverband der pharmazeutischen Industrie
Frankfurt
Tel: 692556

European Council for Plurality in Medicine in Karlsruhe and Brüssel