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REGISTRATION OF PHARMACEUTICAL SPECIALITIES

by

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The definition of a pharmaceutical speciality is given as follows in the "Report on a European Technical Meeting on the Quality Control of Pharmaceutical Preparations, Warsaw 1961", Wld Hlth Org. techn. Rep Ser., 1962, 249,p.4: "A pharmaceutical speciality is a simple or compound drug ready for use and placed on the market under a special name or in a characteristic form."

It is of course important for public health and international commerce that legislation dealing with the registration of pharmaceutical specialities in a country be drafted so as to correspond to legislation enacted in another country, in order to facilitate acceptance of pharmaceutical specialities already registered in that country. It should be of interest in this connection to examine the legislation of a few exporting and importing countries. The International Digest of Health Legislation, published quarterly by WHO, contains pharmaceutical laws and regulations of different countries and constitutes a remarkable source of information.

In Vol. 20, No. 3, p. 509 et seq. the Medicines Act 1968 of the United Kingdom is published in extenso. Clause 7 of the Act requires a "product licence" to be held before a medicinal product, whether produced in the United Kingdom or imported, is marketed. Clause 19 states the factors that must be taken into account in relation to the grant or

refusal of licenses, i.e. safety, efficacy and quality in relation to product licenses, the facilities and control arrangements in relation to manufacturers' licenses, and premises and storage facilities in relation to wholesale dealers' licenses. Concerning the quality of medicinal products, the following information is useful to authorities responsible for public health: (a) the qualitative and quantitative composition declared in the commonly accepted nomenclature; (b) details of analytical methods and possibly certain useful indications on the method of preparation; (c) physico-chemical constants if not already known; (d) the therapeutic indications and dosage; (e) the recommended method of selling (prescription, etc.); (f) samples in sufficient quantity for analysis; (g) information concerning label, package and publicity (advertising).

For products already on the market, upon application before a date fixed for the purpose, an applicant is entitled, on furnishing basic particulars, to be granted a license by right. Clause 27 makes it clear the considerations listed in clause 19 are not relevant factors in relation to the granting of a license by right, and provides for representation to a person appointed by the licensing authority where refusal or partial refusal is proposed. Clause 53 enables prohibiting the sale, supply or importation of specified medicinal products after prior consultation, except in cases of urgency, with the appropriate committee or the Medicines Commission.

It may be of interest to quote how from the Food and Drug Regulations of Canada the following two statements concerning the quality of imported pharmaceutical specialities: "No person shall import into Canada for sale a drug in dosage form unless the person seeking to import the drug has available in Canada information and evidence that the conditions prescribed in section C.01.052 [1] have been met in respect of that drug and at the Director's request furnishes to him such information and evidence".

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(1) This section of the Regulations deals with good practices and quality Control in the manufacture of drugs.

"No person who imports a drug in dosage form into Canada shall sell any lot or batch of that drug unless (a) each lot or batch of the drug in dosage form has been tested in Canada by an acceptable method to ensure identity, potency and purity for its recommended use; or (b) evidence is available in Canada, satisfactory to the Director, that each lot or batch of the drug in dosage form has been adequately tested in the country of origin."

In that country drug importers are thus required to have in their possession satisfactory evidence that the drugs imported are manufactured, controlled and tested in a like manner to those produced in Canada. A "Guide for imported drugs manufacturing facilities and controls" has also been published by the Canadian Department of Health and Welfare in 1969 in order to indicate the information and evidence required to enable the Directorate to judge the compliance of drug importers with these two regulations. Such a Guide, placed at the disposal of exporters, facilitates their task, and other countries may wish to issue similar information to firms or agents importing pharmaceutical products designed to be marketed in their countries.

In the United States, the Food, Drug and Cosmetic Act (as amended in May 1966 and revised in August 1966) requests that every person who owns or operates an establishment "engaged in the manufacture, propagation, compounding or processing of a drug or in the wholesaling, jobbing or distributing of any depressant or stimulant drug shall register with the Secretary his name, places of business, and all such establishments. (Sec. 510c)."

"Every establishment in any State registered with the Secretary pursuant to this section shall be subject to inspection pursuant to section 704 and shall be so inspected by one or more officers or employees duly designated by the Secretary at least once in the two-year period beginning with the dates of registration of such establishment pursuant to this section and at least once in every successive two-year period thereafter. (Sec. 510 h)."

Concerning establishments situated in foreign countries and exporting to the United States, the following paragraph is of significance: "Any establishment within any foreign country engaged in the manufacture, preparation, propagatinn, compounding, or processing of a drug or drugs shall be permitted to register under this section pursuant to regulations promulgated by the Secretary. Such regulations shall include provisions for registration of any such establishment upon condition that adequate and effective means are available, by arrangements with the government of such foreign country or otherwise, to enable the Secretary to determine from time to time whether drugs manufactured, prepared, propagated, compounded, or processed in such establishments, if imported or offered for import into the United States shall be refused admission on any of the grounds set forth in section 810 (a) of this Act (Sec. 510 i)".

Moreover, "the Secretary of Health, Education and Welfare shall furnish to the Secretary of the Treasury a list of establishments registered pursuant of subsection (i) of section 510 and shall request that if any drug manufactured, prepared, propagated, compounded or processed in an establishment not so registered are imported or offered for import into the United States, samples of such drugs be delivered to the Secretary of Health, Education, and Welfare with notice of such delivery to the owner or consignee who may appear before the Secretary of Health, Education, and Welfare and have the right to introduce testimony. If the article is not in accordance with the specification or forbidden within the originating country or adulterated or misbranded, or in violation of section 505 ("New Drugs"), then such article shall be refused admission or its delivery shall in certain cases be authorized under sufficient bond by the owner or consignee and offered for sale after relabeling or other necessary action." (Sec.801 (a) and (b).

In France, Article L 601 of the "Code de la Santé publique" contains the following provisions (27 September 1967): "L'autorisation de mise sur le marché d'une spécialité n'est accordée que lorsque le fabricant justifie: 1) qu'il fait procéder à la vérification de l'innocuité du produit dans des conditions normales d'emploi et de son intérêt thérapeutique ainsi qu'à son analyse qualitative et quantitative, 2) qu'il dispose effectivement d'une méthode de fabrication et de procédés de contrôle de nature à garantir la qualité du produit au stade de la fabrication en série."

And article L 605: "Les justifications y compris celles relatives à l'étiquetage des spécialités qui doivent être fournies à l'appui des demandes d'autorisation de mise sur le marché et qui comprennent obligatoirement la vérification par des experts agréés ou désignés par le ministre des affaires sociales de l'existence des propriétés définies à l'article 601 ci-dessus."

Article 201 makes it possible for the administration to verify whether the laboratory has effectively the means to ensure an adequate quality of the product.

In many countries authorization to have a pharmaceutical speciality on the market is valid for a limited number of years, usually five years.

The classification of medicinal products according to their mode of dispensation to the public - on prescription not renewable, on prescription renewable, over the counter in pharmacies, or in other places - should preferably be done by a panel of experts, medical, pharmacological and pharmaceutical specialists, carefully selected and nominated by the health authority.

In order to ensure an adequate control of the quality of exported pharmaceuticals it should be possible to register all pharmaceuticals either sold on the market of an exporting country, or only manufactured for export. Of course, this would mean in certain cases allowing registration of drugs manufactured according to specifications of countries importing these products. Attention is drawn on this occasion to the Specifications for quality control proposed in the second edition of the International Pharmacopoeia and to subsequent WHO proposed specifications.

The exchange of information on analytical procedures between official control laboratories should also be developed as is the case, for instance, at annual meetings of the Commission of Official Control Laboratories of the International Pharmaceutical Federation.

For registration and labelling the use of the international non-proprietary names proposed by WHO for pharmaceutical substances is of great advantage in facilitating international commerce in pharmaceutical specialities and for the protection of public health.

In some countries the number of specialities on the market is enormous, up to 40,000 in one instance. There is a tendency to try and remove some of them from the market, however the screening for safety and efficacy should take a long time. In this connection it is interesting to watch the "National Academy of Sciences - National Research Council Drug Efficacy Study" undertaken in the United States for the Food and Drug Administration for drugs marketed between 1938 and 1962. Ten thousand claims for some 2,800 drugs, about 85 percent prescription drugs and 15 percent sold over the counter, were studied and evaluated by the Academy during a two-year period, and in about seven percent of the cases it was found that there was no "substantial evidence" to claims of effectiveness.

There is a marked endeavour in certain groups of countries to harmonize pharmaceutical legislation in order to facilitate and accelerate the registration of new pharmaceutical specialities once they have already found their way on the market of one of the countries of the group. A good example is in the Nordic countries of Europe. While each country has its own legislation on drugs and its own registration procedures there exists a strong cooperation. As reported by Dr. H. Hellberg of the National Pharmaceutical Laboratory of Stockholm, Sweden (Journal of the A.O.A.C., Washington, Vol. 51, No. 1 1968) the controlling bodies inform each other of drugs for which registration is sought. They report to each other about that evaluation of the preparations from pharmacological, toxicological, clinical and pharmaceutical standpoints which is carried out by their investigating bodies. Lastly they communicate to each other the decisions of the administrative authority. It is also possible for the investigating bodies to consult one another from time to time in order to achieve the best and most uniform evaluations. Results of random tests carried out on the specialities held in stock are also exchanged. While at present evidence of deficiencies cannot be used as a reason for administrative action outside the country in which they are found, such evidence leads, however, to renewed investigations in the other countries where the preparation is sold. Moreover, common problems are discussed and plans to unify actions are made at annual conferences.

Close cooperation is also achieved between inspectors of pharmaceutical manufacturing establishments, using common rules and requirements. A common Nordic registration of specialities is, however, still not thought possible. The unification of traditionally different legislation is a legal problem and there are in the different countries regulations of a more politico-economic nature which are rather difficult to change. However, most of the Nordic countries belong to the European Free Trade Association which is working toward close cooperation in the exchange and registration of drugs.

Of importance in this direction towards common legislation for the registration of pharmaceutical specialities are the three Directives issued by the six countries of the European Economic Community. The first aims at the free circulation of specialities between countries of this Common Market and deals also with labelling. Everyone of its member states is now required to adopt the same definition in law for a pharmaceutical speciality and each state should have the same basic system for authorizing the marketing of a medicament or speciality. The two main points of the second directive deal with the control by the manufacturer during manufacture and the manner in which an application for marketing should be dealt with. The problem of the selection of experts required to give their opinion on the methods of control and tests for safety and efficiency is still under discussion.

A draft third directive provides for the mutual recognition of authorization for marketing. A temporary provision would state that each country takes appropriate measures to ensure that pharmaceutical specialities are manufactured or controlled under the authority of a pharmacist as is already the case in France. This is also under discussion.

Other draft directives are concerned with specialities to be imported from countries outside the E.E.C., with the object of avoiding a situation which would lead to the progressive transfer of the manufacturing industry to countries leaving more freedom to their pharmaceutical industry and business and having less control.

The opinion has, however, been expressed that in order to achieve the desired result of having a member-state accept pharmaceutical specialities made in another member-state, there should preferably exist a joint competent agency in which all members of the Common Market are represented. "Manufacturers should be allowed to submit drug applications directly to this agency, which should be equipped and staffed adequately to fully examine the applications and be given responsibility to deliver or refuse permits for placing the drugs concerned on the Common Market". (Drug Regulations in Common Market Countries, P. Siderius, Journal of the A.O.A.C.(Vol.51,No.1,1968).

It will probably not be possible for many years to establish a supra-national authority of this kind, but it is important to try and harmonize legislations concerning the registration of pharmaceutical specialities in the best interest of public health and international commerce.

There is no doubt that efforts in this direction will be considerably helped if they are undertaken under the authority and with the assistance of the World Health Organization.