Proposal for a second directive on the harmonization of laws and regulations governing branded pharmaceuticals

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Proposal for a second directive on the harmonization of laws and regulations governing branded pharmaceuticals

(Submitted by the Commission to the Council on 24 February 1964)

Explanatory Memorandum

I. GENERAL

The present directive, which is complementary to the directive issued by the Council of Ministers on 5 November 1962, is intended to amplify it by laying down certain provisions concerning the testing of branded pharmaceuticals.

As stated in the explanatory memorandum of the first directive, the problem of tests is one of the most important that have to be solved before there can be fuller harmonization of the regulations governing the offer for sale of branded pharmaceuticals in the Member States.

In making the present proposal the Commission is acting in response to the recommendations of the European Parliament and the Economic and Social Committee which, on being consulted concerning the text of the first directive, urged the Executive to pursue the work of harmonization that had been undertaken in this field.

The aim of this second directive is, in fact, to narrow the more outstanding disparities between the regulations applicable in the different Member States, and so to facilitate the mutual recognition of licences for sale of branded pharmaceuticals, which is the ultimate objective.

This directive contains two sets of provisions prompted by two distinct, but complementary, considerations. It defines the obligations laid upon manufacturers of branded pharmaceuticals by way of guaranteeing the quality of their products, both at the production stage and at the time when the application is made for a licence for sale. The relevant provisions are contained in Chapters I and III.

It was also considered necessary to define the scope of the functions of administrative bodies responsible for the protection of public health. These are concerned with:

1) Action taken before the licence for sale is issued, and in particular the examination of the application, so as to make certain that the conditions for granting these licences, as set out in the directive of 5 November 1962, have been fulfilled.

2) General supervision by the authorities during the manufacturing process and when the branded pharmaceuticals are offered for sale.

The relevant provisions are contained in Chapters II and IV.

The directive also contains special provisions concerning notification of the competent authorities' decisions to the persons concerned, and the communication of certain of these decisions to the authorities in other Member States: these provisions are contained in Chapter V.

Finally the directive contains provisions concerning implementation and transitional arrangements; among these, Article 13 is of special importance. It is examined in the second part of this Explanatory Memorandum, in which the directive is discussed in detail article by article.

II. COMMENTARY ON THE ARTICLES

Chapter I

Application for licence for sale

The provisions in this chapter are complementary to those in the directive of 5 November 1962. In particular, the chapter contains certain detailed regulations concerning the documentation to be submitted in accordance with Article 4 of that directive.

Article 1

Under the terms of this article, the manufacturer or any other person applying for a licence to sell a branded pharmaceutical must submit to experts, whom he may nominate, the documents specified in Article 4 of the first directive, points 7 and 8. These concern the methods of testing used by the manufacturer, and the results of various trials made by him before deciding to market the product. It should be noted that while the manufacturer has the prerogative of choosing the experts, he is not entirely free, in that he may only choose persons with a certain competence in this field, and the authorities have the power not to approve this choice if the expert is not sufficiently competent.

Article 2

This article sets out the functions of the experts mentioned in Article 1.

Their first duty is to give an opinion on the testing methods used by the manufacturer and on the results they yield.

The object is to ensure that the manufacturer's methods provide a satisfactory test of the product.

Secondly, the experts are asked to give their opinion on the trials the manufacturer has carried out to prove the harmlessness of the product and its therapeutic potency.

Article 3

The intention of this provision is clear. Failure to observe the provisions laid down in Articles 1 and 2 will incur the same penalty as failure to comply with the rules laid down in Article 4 of the first directive concerning the documentation submitted in support of the application for a licence: this penalty consists in rejection of the application.

The severity of the penalty underlines the importance attached to the work of the experts

Chapter II

Examination of the application for a licence for sale

This chapter deals with the powers vested in national authorities to satisfy themselves that branded pharmaceuticals fulfil the conditions laid down.

Article 4

This article deals with the powers of examination enabling the authority to decide whether to grant a licence or refuse it.

These powers include in the first place the examination of documents, including opinions given by the experts. If on examination it is found that the conditions for obtaining a licence have not been fulfilled, the authority is obliged to withhold the licence. It is possible, however, that the documents supplied by the applicant may have an omission or leave room for doubt on certain points. If such shortcomings are not of overriding importance in assessing the documentation, it would appear excessive for a refusal to follow automatically. Allowance has therefore been made for supplementary information or tests to be requested from the manufacturers. This option should only be used in exceptional cases at the discretion of the authorities.

Provision is also made whereby the competent authorities may use their discretion, again in exceptional cases, to order the tests to be repeated by a government laboratory or a laboratory chosen by them, by the same methods as the manufacturer claims to have used. In this way the authority, should there be any doubt, can satisfy itself that the product conforms to the stated formula.

Article 5

Under this article the competent authorities must ascertain that the manufacturers possess the testing facilities necessary to use the methods described in the documentation. Although this checking by the authorities is prescribed by law in some countries as part of the procedure for licences to manufacture medicinal products, it was considered necessary, pending the harmonization of national regulations on this point, to include the principle in the present directive. The rule is that the manufacturer must himself possess, that is to say on his own premises, these testing facilities.

However, in special cases and on adequate grounds, the competent authority may grant exemption from this regulation, the testing then being carried out by a specialized laboratory.

Chapter III

Testing of the branded pharmaceutical by the manufacturer

Article 6

This provision is an extension of Article 8 of the directive of 5 November 1962, which makes it compulsory for the manufacturer to carry out tests on finished products and supply proof that they have been carried out. Article 6 of the present directive extends this obligation to carrying out tests on the raw materials used, and on products during manufacture, when the nature of the products makes this necessary.

Article 7

As in the provisions of the directive of 5 November 1962 in respect of infringement of Article 8 thereof, failure to meet the requirements of Article 6 involves penalties. These penalties are, however, different from those laid down in the first directive, since infringement of Article 6 of the present directive is less serious. Failure to carry out or furnish proof of tests on finished products incurs the withdrawal or suspension of the licence for sale; the penalty for failure to carry out or furnish proof of tests on raw materials or during manufacture, will only be an order to cease or suspend production.

Chapter IV

Supervision

This chapter deals with the general supervisory duties of public health authorities in connection with the manufacture and sale of branded pharmaceuticals.

Article 8

The first paragraph states the object of inspections, which is to ensure that the legal provisions governing the production and sale of branded pharmaceuticals are observed. The persons carrying out these inspections must be members of the authority's staff. Their powers are specified in the third paragraph. It is laid down that these inspectors must have access to the manufacturing establishments, and also, when certain tests are carried out outside, in accordance with Article 5(2), to the laboratories carrying out these tests; they may take samples, and examine any documents relevant to the inspection. The right to obtain information on the manner in which the product is prepared has, however, been kept within limits; in order to safeguard manufacturing secrets, this power is limited to the descriptions given by the manufacturers in their application for a licence for sale.

Article 9

This is a measure to prevent branded pharmaceuticals already on the market from continuing to be distributed when they have incurred a penalty as provided in the directive of 5 November 1962 or in the present directive.

Chapter V

Miscellaneous

Article 10

This article does not appear to call for any special comment.

Article 11

This article does not appear to call for any special comment.

Article 12

This article provides for exchange of information between national authorities on the more important decisions which they are called upon to take concerning the sale of branded pharmaceuticals, so as to avoid discrepancies and possible repercussions thereof. This provision has been introduced in response to the recommendations of the Economic and Social Committee (see Opinion of 25 April 1963 — doc. 18/3) and international organizations such as the World Health Organization and the Council of Europe.

This provision can also be considered as inaugurating closer co-operation between national authorities.

Chapter VI

Implementing arrangements and transitional measures

Article 13

The need for general quality standards for medicinal preparations (as regards purity, stability, etc.), has been stressed on several occasions. Concurrently with work being done by the World Health Organization and the Council of Europe, the Commission has undertaken the preparation of a European pharmacopoeia.

The Commission also felt it desirable to take the initiative of studying, in collaboration with the competent authorities of the Member States and with the assistance of scientific circles in the Community, standardized methods for carrying out various tests on medicinal products (physico-chemical, biological, microbiological, pharmacological, toxicological and clinical tests), and for evaluating their results.

Two interconnected series of studies are consequently in progress, the results of which should have a favourable influence from both the public health and economic points of view.

From the public health angle, the work on the pharmacopoeia and on test procedures is unquestionably of interest, because of the advantages and guarantees that any normalization brings to the scientific sector, and also because these studies will enable all manufacturers of pharmaceuticals in the Community to make use of the most advanced technical knowledge.

On the economic side, the compilation of a pharmacopoeia will be particularly valuable as regards rationalizing production; so far as test procedures are concerned, they will enable those who carry out tests of medicinal products to know the rules for carrying out tests (their duration, the means applied, etc.) and for assessing and presenting the results.

All this work will also add to the efficiency of the competent authorities' tests of medicinal products, and to a large extent avoid discrepancies in assessing the results of tests submitted with an application for a licence to sell a branded pharmaceutical.

Establishing the standards and procedures provided for in this article will call for complex studies over a long period. Continual revision will also be necessary. However, it seemed advisable to stress the gradual nature of this work and the need to apply the first results as soon as possible, in the interests of both public health and production, by setting a date for the first phase.

Article 14

Paragraph 1 of this article does not appear to call for any special comment. Paragraph 2 was included to enable the Commission to be informed reasonably promptly of any plan drawn up by Member States in the fields covered by the present directive, so that the Commission may present its comments.

Article 15

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Article 16

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Proposal for a second directive on the harmonization of laws and regulations governing pharmaceutical products

(Submitted by the Commission to the Council)

The Council of the European Economic Community,

Having regard to the provisions of the Treaty establishing the European Economic Community, and particularly Articles 100 and 155 thereof;

Having regard to the directive on the harmonization of laws and regulations governing pharmaceutical products of 5 November 1962;

Having regard to the proposal of the Commission;

Having regard to the opinion of the European Parliament;

Having regard to the opinion of the Economic and Social Committee;

Whereas disparities in certain national laws have the effect of hindering trade in pharmaceutical products within the Community, and whereas this affects the establishment and operation of the Common Market;

Whereas the directive of 5 November 1962 laid down certain principles with a view to achieving the harmonization of laws concerning the sale of branded pharmaceuticals;

Whereas it is important to pursue the harmonization begun by the directive of 5 November 1962 and to ensure that the principles laid down by that directive are applied;

Whereas among the remaining disparities, those affecting the testing of branded pharmaceuticals are of primary importance;

Whereas with a view to reducing these disparities, it is important to establish rules which manufacturers of branded pharmaceuticals must observe in testing their products, and to define the duties to be carried out by national authorities to ensure that legal requirements are observed;

Whereas so as to ensure the operation and development of the Common Market the Commission must be able to exercise certain powers for the execution of the directive of 5 November 1962,

Has issued the present directive:

Chapter I

Application for licence for sale

Article 1

Member States shall take the necessary measures to ensure that the particulars and supporting documents referred to in Article 4(2), points 7 and 8 of the directive of 5 November 1962 shall be referred by the applicant to experts having the necessary technical or professional qualifications before being submitted to the competent authorities.

Article 2

The experts mentioned in Article 1 shall give their opinion:

1. On the methods of testing referred to in Article 4(2), point 7 of the directive of

5 November 1962 and the results obtained by these methods:

2. On the results of physico-chemical, biological, micro-biological, pharmacological, toxicological and clinical tests carried out.

Article 3

In the event of infringement of the provisions of Articles 1 and 2 of the present directive, Article 5(2) of the directive of 5 November 1962 shall be applicable.

Chapter II

Examination of application for licence for sale

Article 4

The Member States shall take the necessary measures to ensure that the competent authorities shall, within the time-limits laid down in Article 7, paragraph 1, point 2, and paragraph 2 of the directive of 5 November 1962 examine the application in order to satisfy themselves that the conditions for obtaining a licence for sale have been fulfilled.

To this end, the competent authorities:

1. Shall check the particulars submitted in accordance with Article 4 of the directive of 5 November 1962 and shall verify that the opinions given by the experts in accordance with Article 2 of the present directive are comprehensive and conclusive;

2. May request the manufacturer to supply additional information or carry out additional tests;

3. May submit the product to a State laboratory or a laboratory designated for this purpose to repeat the tests carried out by the manufacturer, by the methods described in the documentation in accordance with Article 4(2), point 7, of the directive of 5 November 1962.

When the competent authorities exercise the prerogative mentioned in point 2 of the foregoing paragraph, the time-limits laid down in Article 7, paragraph 1, point 2 and paragraph 2 of the directive of 5 November 1962 shall be waived.

Article 5

The Member States shall take the necessary measures for the competent authorities to check that the manufacturers are able:

1. To make the tests by the methods described in the documentation and mentioned in Article 4(2), point 7, of the directive of 5 November 1962;

2. In exceptional cases, good cause being shown and provided the competent authorities are in agreement, to have some of the tests prescribed in point 1 above carried out on their own responsibility.

Chapter III

Tests of branded pharmaceuticals by the manufacturer

Article 6

The Member States shall take the necessary steps to ensure that the holder of a licence to sell a branded pharmaceutical shall be obliged to furnish proof, whenever requested, that tests on raw materials have been carried out and also tests in the course of production in so far as the latter are necessary for a manufacturing process in accordance with the regulations in force.

Article 7

The Member States shall take the necessary steps to ensure that the production of a branded pharmaceutical shall be temporarily or permanently stopped if, after receiving a formal notice, the holder of the licence for sale cannot furnish the proof specified in Article 6.

Chapter IV

Supervision

Article 8

The competent authorities shall ensure by carrying out inspections that the regulations concerning the production and sale of branded pharmaceuticals are complied with.

The inspections referred to in the foregoing paragraph shall be carried out by the appropriate personnel of the competent authorities.

The above-mentioned personnel must be empowered:

1. To visit manufacturing establishments and laboratories responsible for carrying out tests on behalf of the manufacturer in accordance with the provisions of Article 5, point 2;

2. To take samples;

3. To take note of all documents relevant to the object of the inspections, apart from descriptions of methods of preparation when these descriptions go beyond those contained in the documentation submitted in support of the application for a licence for sale in accordance with Article 4(2), point 4, of the directive of 5 November 1962.

Article 9

The Member States shall take the necessary measures to ensure that deliveries of the branded pharmaceutical shall be forbidden and that the product shall be withdrawn from the market, in cases where:

1. When used under normal conditions, the product appears to be harmful;

2. The product is deficient in therapeutic potency or the applicant supplies inadequate proof of it;

3. The product has not the qualitative and quantitative composition claimed for it;

4. Tests on the finished product have not been carried out;

5. Production has been stopped in pursuance of Article 7 of the present directive.

Chapter V

Miscellaneous provisions

Article 10

Any decision taken under the terms of the present directive shall be accompanied by a precise statement of grounds. It must be notified to the person concerned, with an indication of the procedure for appeal under the existing law and of the time-limit within which such appeal must be lodged.

Article 11

No order for the permanent or temporary stoppage of manufacture, ban on deliveries of the product, or withdrawal from the market may be made except for the reasons stated in the present directive.

Article 12

Member States shall take the necessary measures to ensure that decisions to refuse or withdraw licences for sale, to stop manufacture permanently or to withdraw products from the market, and the grounds therefor shall immediately be brought to the notice of the other Member States.

Chapter VI

Arrangements for implementation and transitional measures

Article 13

On publication of the present directive, the Commission, in collaboration with the competent authorities of the Member States, shall undertake the establishment of common standards and of procedures for the testing of medicinal preparations as provided for in Article 4(2), point 8, of the directive of 5 November 1962.

Article 14

The Member States shall enact the necessary laws and regulations to conform with the provisions of the present directive within twelve months of its notification and shall inform the Commission immediately.

The Member States shall inform the Commission, in time for it to submit comments, of any further draft laws or regulations which they may contemplate adopting in the matters covered by the present directive.

Article 15

The regulations provided for by the present directive shall be applicable to products which have been granted a licence for sale by virtue of previous provisions two years after the notification referred to in Article 14.

Article 16

The present directive is addressed to the Member States.