

L.N. 426 of 2003

**MEDICINES ACT, 2003.
(ACT NO. III OF 2003)**

Medicines (Marketing Authorisation) Regulations, 2003

IN exercise of the powers conferred by article 106 of the Medicines Act, 2003, the Minister of Health, has made the following regulations:-

1. (1) The title of these regulations is the Medicines (Marketing Authorisation) Regulations, 2003. Title and commencement.

(2) These regulations shall come into force on the 1st May, 2004.

2. For the purposes of these regulations - Interpretation.

“the Act” means the Medicines Act;

“the Authority” means the Medicines Authority established under article 4 of the Act;

“the Agency” means the European Agency for the Evaluation of Medicinal Products established by Regulation (EEC) No 2309/93;

“the Commission” means the Commission in accordance with Council Decision 1999/468/EC of 28th June, 1999;

“the Community” means the European Union, previously referred to as the European Community and the European Economic Community;

“imported” means a medicine brought into Malta for the purpose of being placed on the market;

“Licensing Authority” means the Licensing Authority referred to in article 3 of the Act;

“medicines” and “medicinal products” means medicinals for human use;

“Member State” means a State which is a member of the European Union and shall also include Iceland, Norway and Liechtenstein;

“provisional market authorisation” means a market authorisation issued by the Licensing Authority for products present on the market in Malta up till the 31st November, 2002;

“reference Member State” means the Member State, which is granted the market authorisation on which an application for a market authorisation is based;

“risk to public health” means all risks with regard to the quality, safety and efficacy of the medicinal products;

“Superintendent” means the Superintendent of Public Health.

(2) The provisions of these regulations shall not apply to:

(a) any medicinal product which is prepared in a pharmacy in accordance with a medicinal prescription for an individual patient, commonly known as the magistral formula;

(b) any medicinal product which is prepared in a pharmacy in accordance with prescriptions of a pharmacopoeia and is intended to be supplied directly to patients served by the pharmacy in question, commonly known as the official formula;

(c) medicinal products intended for research and development trials;

(d) intermediate products intended for further processing by an authorised manufacturer;

(e) any radionuclides in the form of sealed sources;

(f) whole blood, plasma or blood cells of human origin.

Application.

3. The provisions of these regulations shall apply to industrially produced medicinal products for human use intended to be placed on the market in Malta.

Placing on the market.

4. No medicinal product, radionuclide generators, radionuclide kits, radionuclide precursor radiopharmaceutical and industrially prepared radiopharmaceuticals, may be imported, placed on the market or otherwise sold in Malta unless, there is in respect of that product, a

valid market authorisation, issued by the Licensing Authority in accordance with Council regulation No. (EEC) 2309/93 of 22 July 1993, and such importation, placing on the market or sale is in accordance with the terms and conditions of such market authorisation:

Provided that a market authorisation shall not be required in the case of a radiopharmaceutical prepared at the time of its use by a person or by an establishment duly authorised to use such medicinal products in an approved health care establishment exclusively from authorised radionuclide generators, radionuclide kits or radionuclide precursors in accordance with the manufacturer's instructions:

Provided further, that the Licensing Authority may, in exceptional cases, subject to any condition it deems fit, allow the use of a medicinal product which does not have a marketing authorisation:

Provided further that, products having a provisional market authorisation shall be allowed to remain on the market until such time as the Licensing Authority may, in respect of such products, issue a market authorisation.

5. (1) A market authorisation may only be granted or renewed if the General Conditions applicable to authorisations and the conditions set out under Directive 2001/83/EC on the Community Code relating to medicinal products for human use and subsequent amendments thereto, are fulfilled as follows:-

Grant or renewal of
market
authorisation.

(a) an application for market authorisation shall be made to the Licensing Authority which shall refer such application to the Authority for processing;

(b) a marketing authorisation may only be granted to an applicant established in the Community;

(c) the application shall be accompanied by the following documents and particulars to be submitted in accordance with Annex I of Directive 2003/63/EC:-

(i) the name or corporate name and permanent address of the applicant and, where applicable, of the manufacture;

(ii) the name of the medicinal product;

(iii) the qualitative and quantitative particulars of all the constituents of the medicinal product in usual terminology, but excluding empirical chemical formulae, with mention of

the international non-proprietary name recommended by the World Health Organisation (WHO) where such name exists;

(iv) a description of the manufacturing method;

(v) therapeutic indications, contra-indications and adverse reactions;

(vi) posology, pharmaceutical forms method and route of administration and expected shelf life;

(vii) if applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the medicinal products for the environment;

(viii) a description of the control methods employed by the manufacturer (qualitative and quantitative analysis of the constituents and of the finished product, special tests, such as sterility tests, tests for the presence of pyrogenic substances, the presence of heavy metals, stability tests, biological and toxicity tests, controls carried out at an intermediate stage of the manufacturing process);

(ix) results of physico-chemical, biological or microbiological tests, toxicological and pharmacological tests and clinical trials;

(x) a summary, in accordance with regulation 8, of the product characteristics, one or more specimens or mock-ups of the outer packaging and the immediate packaging of the medicinal product with a package leaflet;

(xi) a document showing that the manufacturer is authorised in his own country to produce medicinal products; and

(xii) copies of any authorisation obtained in another Member State or in a third country to place the medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with the provisions of these regulations is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with regulation 8 or approved by the competent authorities of the

Member State. Copies of the package leaflet proposed. Details of any decision to refuse authorisation, whether in the community or in a third country, and the reasons for such a decision.

(2) The information under paragraph (c) of subregulation (1) hereof shall be updated on a regular basis.

6. In the case of an application for a market authorisation for a radionuclide generator, the application shall also contain:

Application for radionuclide generator.

(i) a general description of the system together with a detailed description of the components of the system which may affect the composition or quality of the daughter nucleid preparation; and

(ii) qualitative and quantitative particulars of the eluate of the sublimate.

7. (1) The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he shows to the satisfaction of the Authority that :

Details to be provided.

(a) either the medicinal product is essentially similar to another already authorised in Malta, and that the holder of the marketing authorisation of such similar product has consented to the toxicological, pharmacological and, or clinical references contained in the file of such product being used for the purpose of examining the application in question; or

(b) the constituent or constituents of the medicinal product have a well established medicinal use, with recognised efficacy and an acceptable level of safety by means of a detailed scientific bibliography; or

(c) the medicinal product is marketed in Malta and is essentially similar to another product which has been authorised within the Community, in accordance with the Community provisions in force, for not less than six years, which period shall, in the case of high technology, be extended to ten years:

Provided that where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed, or is to be administered by different routes or in different doses, the results of appropriate toxicological and pharmacological tests and or the appropriate clinical trials must also be provided.

(2) In the case of new medicinal products which contain known constituents not hitherto used in combination for therapeutic purposes, the results of toxicological and pharmacological tests and of clinical trials relating to that combination must be provided, provided that it shall not be necessary to provide references relating to each individual constituent.

Summary of
product
characteristics.

8. The summary of the product characteristics shall contain the following information:-

a) the name of the medicinal product;

b) the qualitative and quantitative composition in terms of the active substance and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product, in such manner that the usual common name or chemical description shall be used;

c) pharmaceutical forms;

d) pharmacological properties and, in so far as this information is useful for therapeutic purposes, pharmacokinetic particulars;

e) clinical particulars:

(i) therapeutic indications,

(ii) contra-indications,

(iii) adverse reactions (frequency and seriousness),

(iv) special precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient,

(v) use during pregnancy and lactation,

(vi) interaction with other medicaments and other forms of interaction,

(vii) posology and method of administration for adults and, where necessary, for children,

(viii) overdose (symptoms, emergency procedures, antidotes),

(ix) special warnings

(x) effects on ability to drive and to use machines;

(f) pharmaceutical particulars:

(i) major incompatibilities,

(ii) shelf life, when necessary after reconstruction of the medicinal product or when the immediate packaging is opened for the first time,

(iii) special precautions for storage,

(iv) nature and contents of the immediate packaging,

(v) special precautions for disposal of unused medicinal products or waste materials derived from such medicinal products, if appropriate;

(g) name or corporate name and permanent address of the marketing authorisation holder;

(h) for radiopharmaceuticals, full details of internal radiation dosimetry, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

9. The Authority shall take all the necessary measures to ensure that the documents and particulars listed in the preceding regulations are drawn up and signed by experts with the necessary technical or professional qualifications. Experts to formulate and sign documents.

10. It shall be the duty of experts to:- Duty of experts.

(a) to perform tasks falling within their respective disciplines (analysis, pharmacology and similar experimental sciences, clinical trials) and to describe objectively the results obtained (qualitatively and quantitatively);

(b) to describe their observations in accordance with Annex I of Directive 2003/63/EC, and to state, in particular:

(i) in the case of the analyst, whether the medicinal product is consistent with the declared composition, giving any substantiation of the control methods employed by the manufacturer;

(ii) in the case of the pharmacologist or the specialist with similar experimental competence, the toxicity of the medicinal product and the pharmacological properties observed;

(iii) in the case of the clinician, whether he has been able to ascertain effects on persons treated with the medicinal product which correspond to the particulars given by the applicant in accordance with the provisions of these regulations, whether the patient tolerates the medicinal product well, the posology the clinician advises and any contra-indications and adverse reactions; and

(c) where applicable, to state the grounds for using the bibliography referred to under regulation 7(1)(b) hereof.

Reports by experts.

11. Detailed reports by the experts shall be deemed to form part of the particulars accompanying the application submitted by the applicant.

Processing of application.

12. It shall be the duty of the Authority to ensure that an application for a marketing authorisation is processed within a period of 210 days from the date of its submission:

Provided that this period shall be suspended when the processing of the application stops for any reason deemed necessary by the Authority, which reason shall be communicated in writing to the applicant.

Application already under examination in a Member State.

13. In those cases where an application is already under examination in a Member State, the Authority shall suspend the examination of the application, await an assessment by the aforementioned State and inform that State and the applicant of its decision to suspend.

Duties of the Authority on receiving the report.

14. The Authority shall within 90 days of receipt of the aforementioned assessment report, either recognise the decision and the summary of product characteristics as approved by that Member

State or, if it deems that there is a risk to public health, it shall inform the applicant, the Agency and the reference Member State and other Member State concerned by the application:

Provided further, that the provision of this regulation shall not be applicable to medicinal products present on the market in Malta up till the 30th November, 2002.

15. In order to examine the submitted application, the Authority:- Examination of application.

(a) shall verify whether the particulars submitted by the applicant are in terms of the provisions of these regulations and examine whether any condition for issuing a market authorisation are complied with;

(b) may submit the medicinal product, its starting materials and, if need be, its intermediate products or other constituent materials, for testing by a State laboratory or by a laboratory designated for that purpose in order to ensure that the control methods employed by the manufacturer and described in the particulars accompanying the application are satisfactory, in which case the period of 210 days referred to under regulation 12 is suspended;

(c) may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items and, in such case, the 210 days referred to under regulation 12 hereof shall be suspended until such time as the supplementary information required has been provided. Likewise, these time limits shall be suspended when the applicant is given the opportunity of an oral or written explanation.

16. (a) When the marketing authorisation is issued it shall be subject to the general conditions in the Schedule to these regulations and the holder shall be informed by the Authority of the summary of the product characteristics as approved by it. Information to holder.

(b) The Authority shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorisation is issued or subsequently.

(c) A copy of the authorisation together with the summary of the product characteristics shall be forwarded to the Agency.

(d) It shall be duty of the Authority to draw up an assessment report and comments on the dossier as regards the results of the analytical and pharmacotoxicological tests and the clinical trials of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

Exceptional
circumstances.

17. (1) In exceptional circumstances, and following consultation with the applicant, an authorisation may be granted subject to certain specific obligations, including:-

(a) the carrying out of further studies following the granting of authorisation; and

(b) the notification of adverse reactions to the medicinal product.

(2) Such exceptional decisions may be adopted only for objective and verifiable reasons and shall be based on one of the causes referred to in part 4 (G) of Annex I of Directive 2003/63 EC.

Duties of
authorisation
holder.

18. After an authorisation has been issued, the authorisation holder must, in respect of the methods of manufacture and control, take account of any scientific and technical progress and introduce any changes which may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods accepted by the Authority.

Validity of market
authorisation.

19. An authorisation shall be valid for five years and shall be renewable for five-year periods, on an application by the holder at least three months before the expiry date, and after consideration by the Authority of a dossier containing in particular, details of the data on pharmacovigilance and other information relevant to the monitoring of the medicinal product.

Civil and criminal
liability.

20. An authorisation shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the marketing authorisation holder.

Refusal of
marketing
authorisation.

21. (1) The marketing authorisation shall be refused if, after verification of any particulars and documents submitted to it, the Authority deems that :

a) the medicinal product is harmful in the normal conditions of use, or

b) its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or

c) its qualitative and quantitative composition is not as declared.

(2) Authorisation shall likewise be refused if the particulars and documents submitted do not comply with the provisions of these regulations.

22. (a) (i) Before submitting an application for the recognition of a marketing authorisation in Malta, the holder of the authorisation shall inform the Authority in a reference Member State that an application is to be made in accordance with this regulation and shall notify it of any additions to the original dossier. Mutual recognition.

(ii) The holder of the authorisation shall submit an application to the Authority and shall testify that the dossier is identical to that accepted by the reference Member State, or shall identify any additions or amendments it may contain. In the latter case, the holder shall certify that the summary of the product characteristics proposed by him in accordance with regulation 8 is identical to that accepted by the reference Member State in accordance with regulation 16 hereof.

(iii) The Authority shall recognise the marketing authorisation granted by the reference Member State within 90 days of receipt of the application and the assessment report. It shall inform the reference Member State which granted the initial authorisation, the other Member States concerned by the application, the Agency, and the marketing authorisation holder:

Provided that this shall not apply when the Authority has reason to believe that the marketing authorisation of the medicinal product may present a risk to public health. In such case the Authority shall inform the reference Member State, the applicant, any other Member State concerned with the application and the Agency, giving reasons for its decisions and advising what action to be taken to correct any defect in the application.

(iv) The Authority shall endeavour to reach an agreement with all the Member States concerned regarding the action to be adopted. If agreement is not reached within 90 days the matter shall then be referred to the Agency.

(v) The Authority and any other Member State concerned shall also provide the Committee within 90 days of receipt of the application, with a report giving the reasons for disagreement. This report shall be copied to the applicant who on receipt of such report shall forward to the Committee a copy of the information and particulars referred to under regulations 5, 7(1) and 8.

(b) (i) In those cases where Malta is the Reference Member State, the Authority may require the applicant to provide it with all the particulars and documents necessary to enable it to check that the dossiers filed are identical.

(ii) The Authority, upon request by the holder of the authorisation shall prepare an assessment report in respect of the medicinal product concerned, or, if necessary, shall update any existing assessment report. The Authority shall prepare the assessment report, or update it within 90 days of the receipt of the request.

(iii) The Authority shall then forward the assessment report to the Member State or Member States concerned at the same time as the application is submitted.

Application for
variation.

23. A market authorisation holder may apply to vary the marketing authorisation and such application shall be submitted to that Authority and to all other Member States which have previously authorised the medicinal product concerned.

Referral to the
Agency.

24. When the Licensing Authority is of the opinion that the variation, suspension or withdrawal of the marketing authorisation is necessary in the interest of public health it shall refer the matter to the Agency:

Provided that when urgent action needs to be taken in the interest of public health the Licensing Authority may suspend the marketing and use of the medicinal product concerned and inform the Commission and other Member States within 24 hours giving reasons for its decision.

SCHEDULE

Regulation 16 (a).

General Conditions applicable to Authorisations

1. The authorisation holder shall report to the Authority any change of name and/or address and any change of address at which there is carried on a business to which the authorisation relates.

2. The authorisation holder shall ensure that any product to which the authorisation relates is manufacture only in accordance with the methods set out in, or furnished in connection with, his application for the authorisation and that the specification of the constituents and of the finished product are in accordance with the information contained in, or furnished in connection with the said application, except insofar as may otherwise be approved by the Authority.

3. The authorisation holder shall not issue, or cause another person to issue, or consent to the issue of any advertisement or recommendation, relating to any product to which the authorisation relates, which contains particulars as to the uses, nature or effects of such product or warnings or precautions in use concerning such product, unless the terms of the advertisement or recommendation, insofar as they relate to such particulars, warnings, or precautions in use correspond to or differ only to an extent that is not material from those specified in the authorisation.

4. The authorisation holder shall inform the Authority of any material change that has been made; or is proposed to be made in the particulars contained in or furnished in connection with the application, in relation to any product to which the authorisation relates, that is to say:-

4.1 in the composition of the product, or of any of its constituents,

4.2 in the specification of the product or of any of its constituents,

4.3 in the methods of manufacture of the product or of any of its constituents,

4.4 in the methods and procedures described in the application for ensuring compliance with such specification,

4.5 in the arrangements described in the application for storage of the product,

4.6 in the recommended uses, routes of administration or dosage schedules,
or

4.7 in the method of retail sale, supply or sales promotion.

5. The authorisation holder shall notify the Authority of any change proposed to be made in the labelling or package leaflet relating to any medicinal product to which the authorisation relates. Any such change not connected with the summary of product characteristics, which have not been opposed by the Authority within 90 days following the said notification shall be deemed to be approved by the Authority and may be put into effect by the authorisation holder.

6. The authorisation holder shall inform the Authority of any additional information received by him which may alter the validity of data provided in support of the application, or may further the understanding of the substance and its effects or may alter the directions for use of the medicinal product which is the subject of the authorisation.

7. The authorisation holder shall keep a record of reports of adverse effects associated with the use of the product to which the authorisation relates. The record shall be available for inspection by a person authorised by the Authority who may take copies thereof. The authorisation holder shall furnish to the Authority a copy of any such report of which he has a record or of which he is aware.

8. The authorisation holder shall keep available for inspection by a person authorised by the Authority durable records of his arrangements -

8.1 for obtaining materials for the purpose of the manufacture by him or on his behalf of any product to which the authorisation relates, and

8.2 for procuring the manufacture, importation, storage, sale or supply of any such product, and

8.3 for the tests to be carried out on any such product or on the materials used for its manufacture,

and shall permit the person so authorised to take copies of, or to make extracts from, such records. The records shall be retained for a period of five years from the date on which the relevant batch of the product was released for sale or was imported by or on behalf of the authorised holder.

9. The authorisation holder shall keep such documents as will facilitate the withdrawal or recall from sale or supply of any product to which the authorisation relates.

10. The authorisation holder, on being informed by the Authority that any product to which the authorisation relates has been found -

10.1 to be harmful under normal conditions of use, or

10.2 to be lacking in therapeutic efficacy, or

10.3 not to be in accordance with the information contained in or furnished in connection with the application for such authorisation, or furnished in compliance with any of the condition set out in this Schedule, as regards the qualitative or quantitative composition of the product, or

10.4 not to be in accordance with any conditions, other than those set out in this schedule, which are specified in the authorisation,

shall, if so directed by the Authority withhold from sale all batches of the product or such batch as may be specified by the Authority, and so far as may reasonably be practicable, immediately recall all supplies of the product or of such batch of the product as has already been issued.

11. The authorisation holder shall comply with the condition set where the controls on the product to which the authorisation relates, or on any of its constituents, in the course of its manufacture as indicated in or in connection with his application for the authorisation or in compliance with the conditions set out in this Schedule, have not been carried out.

12. The authorisation holder shall notify the Authority of any decision to withdraw from sale or supply any product to which the authorisation relates and shall state the reason for the decision.

13. The authorisation holder shall on request by the Authority -

13.1 furnish from such batch or batches as may be specified a sample of any product to which the authorisation relates for the purpose of test, examination or analysis, or

13.2 furnish full particulars of the tests which have been applied to such batch or batches of such product as may be specified and the result of such tests.

14. The authorisation holder shall, if requested by the Authority, withhold from sale any batch or batches in respect of which a sample is, or particulars are, requested to be furnished until a certificate authorising the sale of the batch or batches has been issued to him by the Authority.

15. The authorisation holder shall ensure that -

15.1 the product to which the authorisation relates is not sold unless it has been manufactured in the premises in respect of which any undertaking has been given.

15.2 such product has been manufactured in such premises and in such circumstances as to comply with any conditions specified in such undertaking.

16. The authorisation holder shall in the event of the authorisation being revoked surrender it to the Authority.