L.N. 324 of 2007

MEDICINES ACT
(CAP. 458)

Medicines (Marketing Authorisation) Regulations, 2007

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

Title.

1. The title of these regulations is the Medicines (Marketing Authorisation) Regulations, 2007.

Interpretation.

2. (1) For the purposes of these regulations –

"abuse of medicinal products" means persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects;

"Annex I" means Annex I of Directive 2003/63/EC and its subsequent amendments;

"the Act" means the Medicines Act;

"the Agency" means the European Medicines Agency established by Regulation (EC) No 726/2004;

"the Authority" means the Medicines Authority established under article 4 of the Act;

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

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

"common name" is the international non-proprietary name recommended by the World Health Organisation, or if it does not exist, the usual common name;

"co-ordination group" means the co-ordination group set up in accordance with Article 27 of Directive 2001/83/EC as amended by Directive 2004/27/EC;

"global marketing authorisation" means the marketing authorisations containing the initial marketing authorisation and

all variations and extensions thereof, as well as any additional strengths, pharmaceutical forms, administration routes or presentations authorised through separate procedures and under a different name, granted to the marketing authorisation holder of the initial authorisation;

"homeopathic medicinal product" means any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles;

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

"medicinal product" shall have the same meaning as defined by the Medicines Act;

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

"provisional marketing authorisation" means a marketing authorisation issued by the Licensing Authority for products present on the market in Malta up till the 30th November, 2002 and for which a valid application for a marketing authorisation has been received by the Medicines Authority;

"reference Member State" means the Member State which, for a given medicinal product, has produced the assessment report, which serves as the basis for the mutual recognition procedure and the decentralised procedure;

"representative of the marketing authorisation holder" means the person commonly known as local representative, designated by the marketing authorisation holder to represent him in the Member State concerned;

"risk-benefit balance" means an evaluation of the positive therapeutic effects of the medicinal product"in relation to the risks relating to the quality, safety and efficacy of the medicinal product as regards patients' health or public health;

"risks related to use of the medicinal product" means any risk relating to the quality, safety or efficacy of the medicinal

product as regards patients' health or public health or any risk of undesirable effects on the environment;

"strength of the medicinal product" means the content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form;

"the Superintendent" means the Superintendent of Public Health.

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

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

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

(c) medicinal products intended for research and development trials but without prejudice to the provisions of the Clinical Trials Regulations 2004 or of Directive 2001/20/EC of the European Parliament and of the Council of the 4th April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;

L.N. 490 of 2004.

(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, except for plasma which is prepared by a method involving an industrial process;

(g) medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

Application.

3. (1) The provisions of these regulations shall apply to medicinal products for human use intended to be placed on the market

in Malta and either prepared industrially or manufactured by a method involving an industrial process.

(2) In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a "medicinal product" and within the definition of a product covered by other community legislation, the provisions of these regulations shall apply.

Authorisation for placing on the market.

4. (1) (a) Subject to the following provisions of this regulation, no medicinal product may be placed on the market in Malta unless there is in respect of that product a valid marketing authorisation issued by the Licensing Authority in accordance with these regulations or in accordance with procedures laid down in Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency), read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, and such placing on the market is in accordance with the terms and conditions of such marketing authorisation.

(b) When a medicinal product has been granted an initial marketing authorisation in accordance with the preceding paragraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall only be granted an authorisation in accordance with the preceding subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of regulation 7(1).

(c) The provisions of subregulations 1(a), and (b) shall also apply to radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.

(d) A marketing 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, kits or radionuclide precursors in accordance with the manufacturer's instructions.

(e) 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.

(f) The Licensing Authority may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

(g) Products having a provisional marketing authorisation shall be allowed to remain on the market until such time as the Licensing Authority may establish.

(h) The marketing authorisation holder shall be responsible for marketing the medicinal product and the designation of a representative shall not relieve the marketing authorisation holder of his legal responsibility.

(2) (a) In the absence of a marketing authorisation or of a pending application for a medicinal product which is authorised in another Member State in accordance with Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use, and any amendments thereto, the Licensing Authority may for justified public health reasons authorise the placing of the said medicinal product on the market in Malta.

(b) The medicinal product referred to in paragraph 2(a) has to comply in particular with the requirements of the provisions regarding the classification of medicinal products, laid down in the Medicines Act, and any regulations made thereunder, and the following regulations:

L.N. 380 of 2005.

(i) the Medicinal Products (Advertising) Regulations,2005,

L.N. 393 of 2005.

(ii) the Medicinal Products (Labelling and Packaging) Regulations, 2005,

L.N. 61 of 2006.

(iii) the Pharmacovigilance Regulations, 2006 and,

L.N. 386 of 2005.

(iv) the Wholesale Distribution of Medicinal Products Regulations, 2005.

(c) Any authorisation issued under this regulation shall for the purposes of articles 99 to 104 of the Medicines Act be deemed to be a marketing authorisation.

(d) Before granting such an authorisation the Licensing Authority shall:

(i) notify the marketing authorisation holder in the Member State in which the medicinal product concerned is authorised, of

its intention to grant an authorisation under subregulation (2) hereof, and

(ii) request the competent authority in that Member State to furnish a copy of the assessment report, and of the marketing authorisation in force.

(e) (i) The medicinal product to be placed on the market in Malta shall be that authorised by the Member State referred to in paragraph (a) of this subregulation.

(ii) An authorisation under this sub-regulation hereof cannot be used as the basis for a licence in terms of the Parallel Importation of Medicinal Products Regulations, 2004. L.N. 437 of 2004.

(iii) An authorisation under this sub-regulation cannot be used as a reference for an application submitted in accordance with regulation 7.

(f) The holder of the authorisation in Malta granted in accordance with this sub-regulation, shall ensure that:

(i) the medicinal product is in accordance with the marketing authorisation issued by the Member State referred to above, and includes any variations in particular those affecting the summary of product characteristics, labelling and package leaflet of the medicinal product as approved in the said Member State, and submits the updated documentation to the Medicines Authority;

(ii) he implements without any delay actions relating to issues concerning the medicinal product which have resulted in a product or batch recall as may apply to the medicinal product authorised in the Member State referred to above.

(g) In the case of a medicinal product, where the wholesale distributor is not the authorisation holder for the medicinal product in Malta, the distributor shall, in respect of the product he is distributing in Malta, furnish to the Medicines Authority an authenticated copy of the said authorisation together with a letter of access issued by the authorisation holder granting the wholesale distributor the use of such an authorisation.

Grant or renewal of marketing authorisation.

5. (1) A marketing 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:

(a) an application for marketing 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:

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

(ii) the name of the medicinal product;

(iii) qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the World Health Organisation, where an INN for the medicinal product exists, or a reference to the relevant chemical name;

(iv) evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged;

(v) a description of the manufacturing method;

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

(vii) posology, pharmaceutical form, method and route of administration and expected shelf life;

(viii) 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 potential risks presented by the medicinal product for the environment;

(ix) description of the control methods employed by the manufacturer;

(x) results of pharmaceutical (physico-chemical, biological or microbiological) tests, pre-clinical (toxicological and pharmacological) tests, clinical trials.

A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce.

A statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of the Clinical Trials Regulations, 2004 and of Directive 2001/20/EC of the European Parliament and of the Council of the 4th April, 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products on human use; L.N. 490 of 2004.

(xi) a summary, in accordance with regulation 8, of the product characteristics, a mock-up of the outer packaging, containing the details provided for in the Medicinal Products (Labelling and Packaging) Regulations, 2005, and of the immediate packaging of the medicinal product, containing the details provided for in those regulations, together with a package leaflet in accordance with those same regulations;

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

(xiii) 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 Directive 2001/83/EC, as amended, 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 in accordance with the Medicinal Products (Labelling and Packaging) Regulations, 2005, or as approved by the competent authorities of the Member State. Details of any decision to refuse authorisation, whether in the Community or in a third country, and the reasons for such a decision;

(xiv) a copy of any designation of the medicinal product as an orphan medicinal product under Regulation (EC) No 141/2000 of the European Parliament and of the Council

of 16 December 1999 on orphan medicinal products, accompanied by a copy of the relevant Agency opinion;

(xv) proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country;

(2) The information under sub-regulation (1)(c)(xiii) hereof shall be updated on a regular basis.

(3) The documents and information concerning the results of the pharmaceutical and pre-clinical tests and the clinical trials referred to in sub-regulation (1)(c)(x) hereof, shall be accompanied by detailed summaries in accordance with regulation 9.

Application for radionuclide generator.

6. In the case of an application for a marketing authorisation for a radionuclide generator, in addition to the requirements set out in regulations 5 and 7(1), the application shall also contain:

(a) 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

(b) qualitative and quantitative particulars of the eluate or the sublimate.

Details to be provided.

7. (1) (a) (i) By way of derogation from regulation 5 (1)(c)(x), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 of Directive 2001/83/EC and its subsequent amendments for not less than six years in Malta or in the Community.

(ii) Sub-regulation (1)(a)(i) shall also apply if the reference medicinal product was not authorised in Malta. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the Licensing Authority, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised, together with the full composition of the reference product and if necessary other relevant documentation:

Provided that the Licensing Authority shall within one month provide any information requested by the competent authority of another Member State in respect of a reference medicinal product authorised in Malta:

Provided further that for the purposes of this regulation:

"reference medicinal product" means a medicinal product authorised under regulation 4, in accordance with the provisions of regulation 5 or authorised under article 8 of Directive 2001/83/EC as amended;

"generic medicinal product" means a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and, or efficacy. In such cases, additional information providing proof of the safety and, or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

(b) In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided above or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in any active substance, therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.

(c) Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines.

The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

(d) In addition to the provisions laid down in sub-regulation (1)(a), where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.

(e) Conducting the necessary studies and trials with a view to the application of sub-regulation (1)(a),(b),and (c) and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.

(f) The periods of protection provided for in sub-regulation (1)(a), (b), (c) and (d) shall not apply to reference medicinal products for which an application for authorisation has been submitted before the date of coming into force of these regulations.

(2) By way of derogation from regulation 5 (1)(c)(x), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I. In that event, the test and trial results shall be replaced by appropriate scientific literature.

(3) In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with regulation 5(1)(c)(x), but it shall not be necessary to provide scientific references relating to each individual active substance.

(4) Following the granting of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, pre-clinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

8. (1) The summary of the product characteristics shall contain, in the order indicated below, the following information: Summary of product characteristics.

(a) name of the medicinal product followed by the strength and the pharmaceutical form;

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

(c) pharmaceutical form;

(d) clinical particulars:

(i) therapeutic indications,

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

(iii) contra-indications,

(iv) special warnings and 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) interaction with other medicinal products and other forms of interactions,

(vi) use during pregnancy and lactation,

(vii) effects on ability to drive and to use machines,

(viii) undesirable effects,

(ix) overdose (symptoms, emergency procedures, antidotes);

(e) pharmacological properties:

(i) pharmacodynamic properties,

(ii) pharmacokinetic properties,

(iii) preclinical safety data;

(f) pharmaceutical particulars:

(i) list of excipients,

(ii) major incompatibilities,

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

(iv) special precautions for storage,

(v) nature and contents of container,

(vi) special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate;

(g) marketing authorisation holder;

(h) marketing authorisation numbers;

(i) date of the first authorisation or renewal of the authorisation;

(j) date of revision of the text;

(k) for radiopharmaceuticals:

(i) full details of internal radiation dosimetry;

(ii) 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.

(2) For the authorisations referred to under regulation 7, those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms which were still covered by patent law at the time when a generic medicine was marketed need not be included.

Experts to formulate and sign documents.

9. (1) The applicant shall ensure that, before the detailed summaries referred to in the regulation 5 (3) are submitted to the

Licensing Authority, they have been drawn up and signed by experts with the necessary technical or professional qualifications, which shall be set out in a brief curriculum vitae.

(2) Persons having the technical and professional qualifications referred to in the preceding sub-regulation shall justify any use made of scientific literature under regulation 7(2) in accordance with the conditions set out in Annex I.

(3) The detailed summaries shall form part of the file which the applicant submits to the Licensing Authority.

Specific provisions applicable to homeopathic medicinal products.

10. (1) The Authority shall ensure that homeopathic medicinal products manufactured and placed on the market within the Community are registered or authorised in accordance with regulations 10 and 11. In case of registrations sub-regulations 22(1)(a) to (f) shall apply.

(2) The Authority shall establish a special simplified registration procedure for the homeopathic medicinal products referred to in sub-regulation (3).

(3) Only homeopathic medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure:

(a) they are administered orally or externally;

(b) no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto;

(c) there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more then one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

The classification for the dispensing of the medicinal product, shall be determined by the Authority at the time of registration.

The criteria and rules of procedure provided for in regulations 12, 17, 18, 19, 20 and 21. and articles 4(4), 112, 116 and 125 of Directive 2001/83/EC, as amended, shall apply by analogy to the special, simplified registration procedure for homeopathic medicinal products with the exception of the proof of therapeutic efficacy.

(4) An application for special, simplified registration may cover a series of medicinal products derived from the same homeopathic stock or stocks. The following documents shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the products concerned:

(a) scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered;

(b) dossier describing how any homeopathic stock or stocks is obtained and controlled, and justifying its homeopathic use, on the basis of an adequate bibliography;

(c) manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentization;

(d) manufacturing authorisation for the medicinal product concerned;

(e) copies of any registrations or authorisations obtained for the same medicinal product in other Member States;

(f) one or more mock-ups of the outer packaging and the immediate packaging of the medicinal products to be registered;

(g) data concerning the stability of the medicinal product.

Saving.

11. Homeopathic medicinal products, other than those referred to in regulation 10 (3), shall be authorised and labelled in accordance with regulations 5, 7 and 8.

Processing of application.

12. It shall be the duty of the Authority to ensure that the procedure for granting a marketing authorisation for medicinal products is completed within a maximum of 210 days after the submission of a valid application:

Provided that applications for marketing authorisations in two or more Member States in respect of the same medicinal product shall be submitted in accordance with the mutual recognition and decentralised procedures.

Application already under examination in a Member State.

13. Where the Authority notes that another marketing authorisation application for the same medicinal product is being examined in another Member State, the Authority shall decline to assess

the application and shall advise the applicant that the mutual recognition and decentralised procedures apply.

Duties of the Authority on receiving the report.

14. Where the Authority is informed in accordance with regulation 5(1)(c)(xiii) that another Member State has authorised a medicinal product, which is the subject of a marketing authorisation application in Malta, it shall reject the application unless it was submitted in compliance with the mutual recognition or decentralised procedures.

Examination of application.

15. (1) In order to examine the application submitted in accordance with regulations 5 and 7 of these regulations, the Authority –

(a) shall verify whether the particulars submitted by the applicant are in terms of the provisions of these regulations and examine whether the conditions for issuing a marketing 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 an Official Medicines Control Laboratory or by a laboratory designated for that purpose by the Authority in order to ensure that the control methods employed by the manufacturer and described in the particulars accompanying the application in accordance with regulation 5(1)(c)(ix) are satisfactory;

(c) may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items listed under regulations 5(1)(c) and 7, in which case, the two hundred and ten days referred to under regulation 12 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 providing an oral or written explanation.

(2) The Authority:

(a) shall verify that manufacturers and importers of medicinal products coming from third countries are able to carry out manufacture in compliance with the particulars supplied pursuant to regulation 5(1)(c)(v) and, or to carry out controls according to the methods described in the particulars accompanying the application in accordance with regulation 5(1)(c)(ix);

(b) may allow manufacturers and importers of medicinal products coming from third countries, in justifiable cases, to have

certain stages of manufacture and, or certain of the controls referred to in regulation 15(2)(a) carried out by third parties; in such cases, the verifications by the Authority shall also be made in the establishment designated.

Information to holder.

16. (a) When the marketing authorisation is issued it shall be subject to the conditions as specified in the Marketing Authorisation, the Act and any regulations made thereunder as well as to any conditions that the Licensing Authority may deem necessary, and the holder shall be informed by the Authority of the summary of the product characteristics as approved by it.

(b) The Authority shall:

(i) 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;

(ii) make publicly available without delay the marketing authorisation together with the summary of the product characteristics for each medicinal product which it has authorised;

(iii) draw up an assessment report and comments on the file as regards the results of the pharmaceutical and pre-clinical 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;

(iv) make publicly accessible the assessment report, together with the reasons for its opinion, after deletion of any information of a commercially confidential nature. The justification shall be provided separately for each indication applied for.

Exceptional circumstances.

17. In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to meet certain conditions, in particular concerning the safety of the medicinal product, notification to the Authority of any incident relating to its use, and action to be taken. This authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I. Continuation of the authorisation shall be linked to the annual reassessment of these conditions. The list of these conditions shall be made publicly accessible, together with deadlines and dates of fulfilment.

Duties of authorisation holder.

18. (1) After an authorisation has been issued, the authorisation holder must, in respect of the methods of manufacture and control provided for in regulation 5(1)(c)(v) and (ix), 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. These changes shall be subject to the approval of the Authority.

(2) (a) The authorisation holder shall forthwith supply to the Authority any new information which might entail the amendment of the particulars or documents referred to in regulations 5(1)(c), 7 and 8 or Article 32(5) of Directive 2001/83/EC, and its subsequent amendments or Annex I of that Directive.

(b) In particular, he shall forthwith inform the Authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned.

(3) In order that the risk-benefit balance may be continuously assessed, the Authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable.

(4) After a marketing authorisation has been granted, the holder of the authorisation shall inform the Authority of the date of actual marketing of the medicinal product for human use in Malta, taking into account the various presentations authorised. The holder shall also notify the Authority if the product ceases to be placed on the market in Malta, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product.

(5) Upon request by the Authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide it with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions.

Validity of marketing authorisation.

19. (1) Without prejudice to sub-regulations (4) and (5), a marketing authorisation shall be valid for five years.

(2) The marketing authorisation may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the Authority. To this end, the marketing authorisation holder shall provide the Authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, at least six months before the

marketing authorisation ceases to be valid in accordance with sub-regulation (1).

(3) Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the Authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal in accordance with sub-regulation (2).

(4) Any authorisation granted by the Authority which within three years of its granting is not followed by the actual placing on the market of the authorised product in Malta shall cease to be valid.

(5) When an authorised product previously placed on the market in Malta is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid.

(6) The Authority may, in exceptional circumstances and on public health grounds grant exemptions from sub-regulations (4) and (5) provided that such exemptions are duly justified.

Civil and criminal liability.

20. An authorisation or licence for placing a medicinal product on the market shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the marketing authorisation holder who has placed such medicinal product on the market in any European Union or European Economic Area state. Such manufacturer or marketing authorisation holder shall in particular remain liable for any deficiencies in quality, safety and efficacy of such medicinal products.

Refusal of marketing authorisation.

21. (1) The marketing authorisation of a medicinal product shall be refused if, after verification of the particulars and documents listed in regulations 5 and 7 it is clear that:

(a) the risk-benefit balance is not considered to be favourable, or

(b) the therapeutic efficacy of the medicinal product is insufficiently substantiated by the applicant, or

(c) the qualitative and quantitative composition of the medicinal product is not as declared.

(2) Authorisation shall likewise be refused if any particulars or documents submitted in support of the application do not comply with the provisions of regulations 5 and 7.

(3) The applicant or the holder of a marketing authorisation shall be responsible for the accuracy of the documents and the data submitted.

Mutual recognition and decentralised procedure.

22. (a) With a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, including Malta, an applicant shall submit an application to the Authority, based on a dossier identical to that submitted in the other Member States. The dossier shall contain the information and documents referred to in regulations 5, 7 and 8. The documents submitted shall include a list of Member States concerned by the application.

The applicant shall request one Member State to act as "reference Member State" and to prepare an assessment report on the medicinal product in accordance with paragraphs (b) and (c) hereof.

(b) Where the medicinal product has already received a marketing authorisation at the time of application, if Malta is a concerned Member State, the Authority shall recognise the marketing authorisation granted by the reference Member State. To this end, the marketing authorisation holder shall request the reference Member State either to prepare an assessment report on the medicinal product or, if necessary, to update any existing assessment report. If Malta is the reference Member State, the Authority shall prepare or update the assessment report within 90 days of receipt of a valid application. The assessment report together with the approved summary of product characteristics, labelling and package leaflet shall be sent to the concerned Member States and to the applicant.

(c) In cases where the medicinal product has not received a marketing authorisation at the time of application, the applicant shall request the reference Member State to prepare a draft assessment report, a draft summary of product characteristics and a draft of the labelling and package leaflet. If Malta is the Reference Member State, the Authority shall prepare these draft documents within 120 days after receipt of a valid application and shall send them to the concerned Member States and to the applicant.

(d) If Malta is a concerned Member State, within 90 days of receipt of the documents referred to in paragraphs (b) and (c) hereof, the Authority shall approve the assessment report, the summary of product characteristics and the labelling and package leaflet and shall inform the reference Member State accordingly. If Malta is the reference Member State, the Authority shall record the agreement of all parties, close the procedure and inform the applicant accordingly.

(e) The Authority shall adopt a decision in conformity with the approved assessment report, the summary of product characteristics and the labelling and package leaflet as approved, within 30 days after acknowledgement of the agreement.

(f) If, within the period laid down in paragraph (d) hereof, the Authority cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of potential serious risk to public health, it shall give a detailed exposition of the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant. The points of disagreement shall be forthwith referred to the coordination group. Within such co-ordination group, the Authority shall use its best endeavours to reach agreement on the action to be taken and it shall allow the applicant the opportunity to make his point of view known orally or in writing. If, within 60 days of the communication of the points of disagreement, all Member States reach an agreement, if Malta is the Reference Member State, the Authority shall record the agreement, close the procedure and inform the applicant accordingly and paragraph (e) hereof shall apply:

Provided that if Member States fail to reach an agreement within the co-ordination group, within such 60-day period, and if the Authority has approved the assessment report, the draft summary of product characteristics and the labelling and package leaflet of the reference Member State, the Authority may, at the request of the applicant, authorise the medicinal product without waiting for the outcome of the procedure laid down in Article 32 of Directive 2001/83/EC as amended by Directive 2004/27/EC. In that event, the authorisation granted shall be without prejudice to the outcome of that procedure.

Referral to Committee for Medicinal Products for Human Use.

23. (1) If two or more applications submitted in accordance with regulations 5, 7 and 8 have been made for marketing authorisation for a particular medicinal product, and if Member States have adopted divergent decisions concerning the authorisation of the medicinal product or its suspension or revocation, the Authority, the Commission or the applicant or the marketing authorisation holder may refer the matter to the Committee for Medicinal Products for Human Use, hereinafter referred to as the Committee, for the application of the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83 as amended by Directive 2004/27.

(2) In order to promote harmonisation of authorisations for medicinal products authorised in the Community, the Authority shall, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics should be drawn up.

(3) The Authority or the Commission, in agreement with the Agency and taking into account the views of interested parties, may refer these products to the Committee in accordance with sub-regulation (1).

(4) The Authority or the Commission or the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Community are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83/EC as amended by Directive 2004/27/EC, before any decision is reached on a request for a marketing authorisation or on the suspension or revocation of an authorisation, or on any other variation to the terms of a marketing authorisation which appears necessary, in particular to take account of the information collected in accordance with the Pharmacovigilance Regulations, 2005.

(5) The Authority or the Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the applicant or the marketing authorisation holder.

(6) The Authority and the applicant or the marketing authorisation holder shall supply the Committee with all available information relating to the matter in question.

Application for variation.

24. (1) A marketing authorisation holder may apply to vary the marketing authorisation, which has been granted in accordance with regulations 22 and 23, and such application shall be submitted to the Authority and to all other Member States which have previously authorised the medicinal product concerned.

(2) Where the Authority considers that a variation of a marketing authorisation which has been granted in accordance with the provisions relating to the mutual recognition or decentralised procedure, or its suspension or withdrawal is necessary for the protection of public health, the Authority shall forthwith refer the matter to the Agency for the application of the procedures laid down in Articles 32, 33 and 34 of Directive 2001/83/EC as amended by Directive 2004/27/EC:

Provided that, without prejudice to regulations 23(4), (5) and (6), in exceptional cases, 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 not later than the following working day, giving reasons for its decision.

This regulation shall apply by analogy to medicinal products authorised by the Authority following an opinion of the Committee

given in accordance with Article 4 of Directive 87/22/EEC before 1 January, 1995.

Applications to be considered in accordance with regulation (EC) No 726/2004.

25. Applications for marketing authorisations which have been referred to the Committee for Proprietary Medicinal Products before the 1 January, 1995 in accordance with Article 2 of Directive 87/22/EEC and in respect of which the Committee concerned has not given an opinion by 1 January, 1995, shall be considered in accordance with Regulation (EC) No 726/2004.

Regulation 22(1)(f) second paragraph, regulation 23 and Articles 32 to 34 of Directive 2001/83/EC and its subsequent amendments, shall not apply to homeopathic medicinal products referred to in sub-regulations (1), (2) and (3) of regulation 10.

Classification of medicinal products.

26. (1) When a marketing authorisation is granted, the Authority shall specify the classification of the medicinal product into:

(a) a medicinal product subject to medical prescription,

(b) a medicinal product not subject to medical prescription.

To this end, the criteria laid down in regulation 27(1) shall apply.

(2) The Authority may fix sub-categories for medicinal products which are available on medical prescription only. In that case, they shall refer to the following classification:

(a) medicinal products on medical prescription for renewable or non-renewable delivery;

(b) medicinal products subject to special medical prescription;

(c) medicinal products on "restricted" medical prescription, reserved for use in certain specialised areas:

Provided that where the Authority does not designate medicinal products into sub-categories, it shall nevertheless take into account the criteria referred to in sub-regulations (2) and (3) of regulation 27 in determining whether any medicinal product shall be classified as a prescription-only medicine.

Medicinal products subject to medical prescription.

27. (1) Medicinal products shall be subject to medical prescription where they:-

(a) are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision, or

(b) are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or

(c) contain substances or preparations thereof, the activity and any adverse reactions of which require further investigation, or

(d) are normally prescribed by a doctor to be administered parenterally.

(2) For the sub-category of medicinal products subject to special medical prescription, the Authority shall take account of the following factors:

(a) the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971, or

(b) the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or

(c) the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in sub-regulation (b), as a precautionary measure.

(3) For the sub-category of medicinal products subject to restricted prescription, the Authority shall take account of the following factors:

(a) the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment;

(b) the medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere, or

(c) the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.

(4) The Authority may waive application of sub-regulations (1), (2) and (3) having regard to:

(a) the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging; and, or

(b) other circumstances of use which it has specified.

Medicinal products not subject to a prescription.

28. Medicinal products not subject to prescription shall be those which do not meet the criteria listed in regulation 27 of these regulations.

List of medicinal products.

29. The Authority shall draw up a list of the medicinal products subject to medical prescription, specifying, if necessary, the category of classification, and it shall update this list annually.

Amendment of classification.

30. (1) When new facts are brought to its attention, the Authority shall examine and, as appropriate, amend the classification of a medicinal product by applying the criteria listed in regulation 27 of these regulations.

(2) Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the Authority shall not refer to the results of those tests or trials when examining an application by another applicant or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised.

Repeals L.N. 387 of 2004.

31. The Medicines (Marketing Authorisation) Regulations, 2004 are hereby repealed.

Ippubblikat mid-Dipartiment ta' l-Informazzjoni (doi.gov.mt) — Valletta — *Published by the Department of Information (doi.gov.mt) — Valletta*
Mitbugh fl-Istamperija tal-Gvern — *Printed at the Government Printing Press*

Prezz/*Price*
Lm1.04 (€2.42)